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# Synthesis, Fungistatic, Protistocidal, and Antibacterial Activity of 1-(3-Amino-2-Hydroxypropyl)Indoles

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**Abstract**—A series of new indole derivatives containing the 3-amino-2-hydroxypropyl group at the nitrogen atom has been synthesized by the ring-opening of the oxirane cycle of 1-oxiranylmethylindoles. Their antibacterial, fungicidal, and protistocidal activities have been studied. Most of the synthesized compounds have been shown to exhibit a high protistocidal activity that several times exceeds that of the reference drug, baikoks (toltrazuril).

*Keywords*: indole, oxiranes, chalcones, 1,2-amino alcohols, antibacterial, fungistatic, protistocidal activity
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## INTRODUCTION

In recent years, there has been an increased interest in indoles that contain the 1,2-amino alcohol fragment at position 1. Compounds that are described in this paper are indole-containing chalcones with the 3-amino-2-hydroxypropyl residue at the indolyl nitrogen atom. Chalcones of the indole series that contain the amine residues at the $N^1$ position are known to be selective inhibitors of norepinephrine reuptake. They are promising for the treatment of temperature dysregulation, depression, and some pain disorders including fibromyalgia and lower back pain [1]. On the other hand, indoles that contain the amino alcohol residues at position 1 can be used for the treatment of cancer since they are inhibitors of polo-like kinases, attractive anticancer drug targets, which stimulate oncogenesis [2]. Similar compounds are nonpeptide inhibitors of HIV-1 protease [3]. There are many compounds with antibacterial [4–7] and fungistatic [8] activities among other indole derivatives.

We showed earlier that $N^1$-3-amino-2-hydroxypropyl derivatives of 3-(2-carbonylvinyl)indole based on oxiranes (**III**) exhibit antiarrhythmic and local anesthetic activities that exceed those of the known widely used preparations, i.e., novocaine, lidocaine, and marcaine [9]. Moreover, we revealed the antiplatelet activity of thiophene-containing amino alcohol, which was higher than that of the reference preparations, aspirin and clopidogrel [10].

Despite the discovery of many types of biological activity of indoles that contain the 3-amino-2-hydroxypropyl group at the nitrogen atom and the unsaturated ketone residue at position 3, their fungistatic, protistocidal, and antibacterial activities have not yet been investigated. We have synthesized new aminohydroxyalkyl indole derivatives (**IVa–e**) by the previously developed method [11]. The prepared compounds have been tested for the above activities.

## RESULTS AND DISCUSSION

The compounds were synthesized according to the following scheme. Indole-3-aldehyde (**I**) was used as the starting material. Its interaction with methyl aryl ketones leads to chalkones of the indole series (**IIa–c**) [12]. Thiophene-containing chalkone (**IId**) was prepared according to the modified method described in [13]. The introduction of the oxiranylmethyl fragment in chalcones (**IIa–d**) was performed through the generation of the indolyl anion by the action of sodium hydride in DMSO. The subsequent reaction occurs as *N*-alkylation with epibromohydrin. Resulting 1-oxyranylmethyl indole derivatives (**IIIa–d**) interacted with amines with the formation of 1,2-amino alcohols (**IVa–e**).

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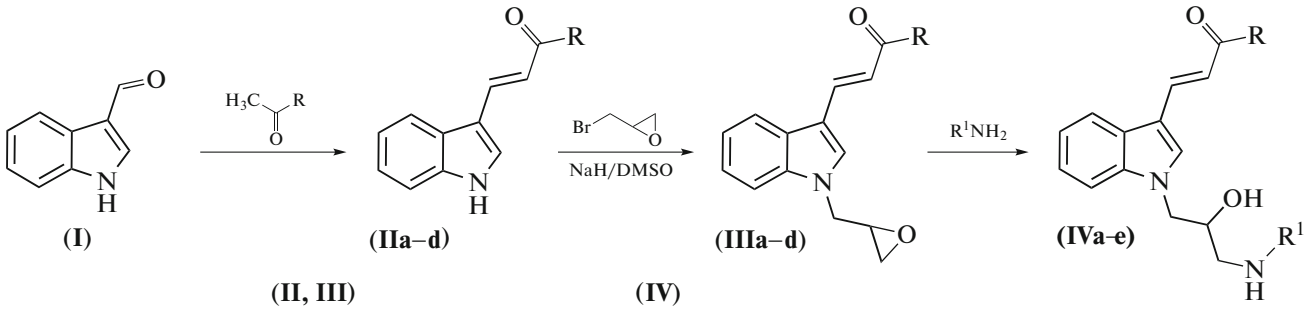



**(I)** **(IIa–d)** **(IIIa–d)** **(IVa–e)**

**(II, III)**

**a:** R = Ph
**b:** R = 4-$CH_3C_6H_4$-
**c:** R = 4-$CH_3OC_6H_4$-
**d:** R = thienyl-2

**(IV)**

**a:** R = Ph, $R^1$ = cycloheptyl
**b:** R = 4-$CH_3C_6H_4$-, $R^1$ = cycloheptyl
**c:** R = 4-$CH_3OC_6H_4$-, $R^1$ = cycloheptyl
**d:** R = thienyl-2, $R^1$ = cycloheptyl
**e:** R = thienyl-2, $R^1$ = 1-methylbenzimidzolyl-2

**Scheme.**

Since compounds (**IIIa–d**) contain the asymmetric carbon atom, protons of the oxiranylmethyl substituent are nonequivalent, and each of five of them appears in the $^1$H NMR spectra as a separate peak. For example, the signals of the methylene doublet of protons at the indole nitrogen atom appear as two doublets at 4.14–4.19 ppm, which corresponds to their splitting on each other and on the proton at the tertiary carbon atom. The signal of the latter is a multiplet at 3.35–3.38 ppm. The signals of the methylene protons of the epoxy ring are registered as two signals, i.e., the doublet of doublets at 2.42–2.52 ppm and the multiplet at 2.79–2.90 ppm.

The structure of amino alcohols (**IVa–e**) is confirmed by the spectral data. Their IR spectra contain the bands in the region of 3101–3339 $cm^{-1}$, which are characteristic of the OH and NH groups. This indicates the opening of the oxirane ring of starting materials (**IIIa–d**). The signals of the $NCH_2$-group of the introduced alkyl amine appear in the $^1$H NMR spectra as the doublet of doublets at 2.42–2.81 ppm. The multiplet of the proton at the tertiary carbon atom attached to the hydroxyl group is in the region at 3.85–4.27 ppm. The signals of the methylene protons at the indole nitrogen atom appear as the eight-line multiplet at 4.15–4.22 ppm, which corresponds to their splitting on each other due to the presence of the chiral center and on the proton at the tertiary carbon atom. In addition, the $^1$H NMR spectra contain the signals of the indole protons and protons of the attached amines.

In addition to the compounds described above, amino alcohols that contain the 1,3-indandione residue (**Va–c**) [14] (Table 1) were also tested for their biological activity because these compounds have a similar structure to compounds (**IVa–e**).

The results on the biological activity of compounds (**Va–c**) and (**IVa–e**) are summarized in Table 1. Some of the studied compounds exhibit the pronounced activity against fungi and bacteria although they are twice inferior to the reference preparations except for the compound (**IVe**), which is comparable in its efficiency with furaszolidon against *S. aureus* (strain P-209). Compounds (**IVa–e**) and (**Vb**) have a high protistocidal activity in the *C. steinii* model and several times exceed the reference preparation in efficiency. The compound (**IVe**) that contains the 1-methyl-2-aminobenzimidazole fragment acts at ten times lower concentration than the control. The degree of the protistocidal activity depends on both the structure of the chalcone fragment and, to a greater extent, the structure of the substituent at the indole nitrogen atom. Compounds (**IVa–d**) and (**Vc**) that contain the cycloheptylamine fragment exhibit a high activity. The displacement of this fragment by the more lipophilic *N*-phenylpiperazine residue leads to a complete loss of the activity of compound (**Va**). Compound (**IVe**) that contains the hydrophilic 1-methyl-2-aminobenzimidazole residue demonstrates the maximal activity. The studied compounds contain fragments of both the lipophilic chalcone and hydrophilic amino alcohol (which is partially ionized even at neutral pH values). This fact allows us to make an assumption about one of the possible ways the compounds act: probably, their surface-active properties disorganize the membrane functions of microorganisms.

The studied group of the compounds is promising for the search of efficient protistocidal preparations. The most expedient is the synthesis of compounds with other 2-aminobenzimidazole derivatives and substituted guanidines.

**Table 1.** Biological activity of indole derivatives (**IVa–e**) and (**Va–c**)

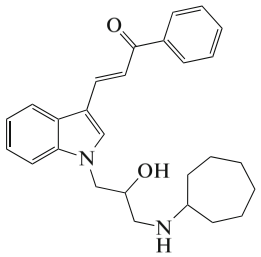
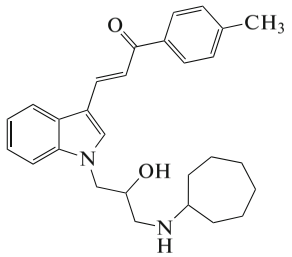
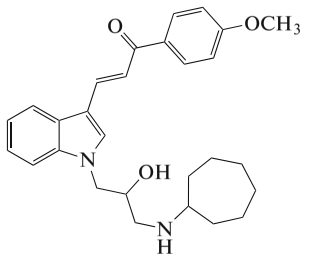
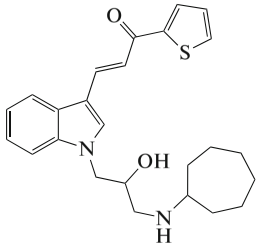
| Code | Formula | Activity type | | | |
|---|---|---|---|---|---|
| | | protistocidal against *Colpoda steinii* | fungistatic against *Penicillium italicum* | antibacterial against *Staphylococcus aureus* | antibacterial against *Escherichia coli* |
| | | minimal active concentration, μg/mL | delay zone, mm | delay zone, mm | delay zone, mm |
| **(IVa)** |  | 0.9 | 10 | 10 | 10 |
| **(IVb)** |  | 0.9 | 10 | 6 | 0 |
| **(IVc)** |  | 7.8 | 10 | 6 | 10 |
| **(IVd)** |  | 1.9 | 10 | 0 | 8 |

**Table 1.** (Contd.)

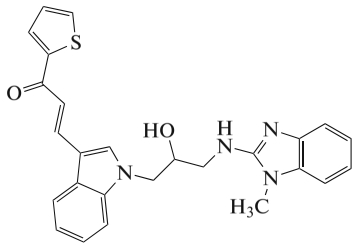
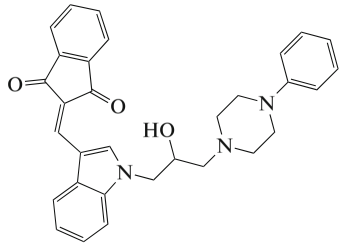
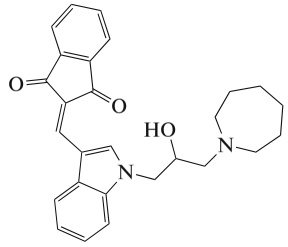
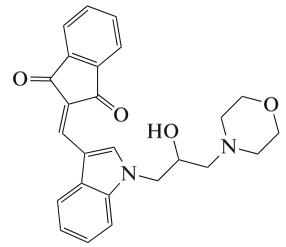
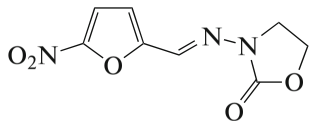
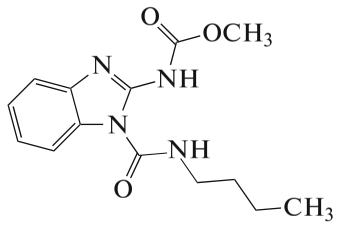
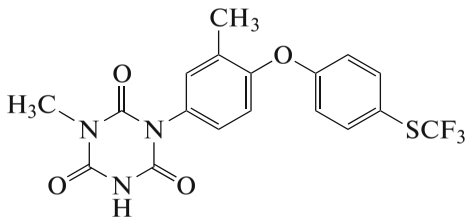
| Code | Formula | Activity type | | | |
|---|---|---|---|---|---|
| | | protistocidal against *Colpoda steinii* | fungistatic against *Penicillium italicum* | antibacterial against *Staphylococcus aureus* | antibacterial against *Escherichia coli* |
| | | minimal active concentration, μg/mL | delay zone, mm | delay zone, mm | delay zone, mm |
| **(IVe)** |  | 0.48 | 10 | 18 | 6 |
| **(Va)** |  | >500 | 0 | 8 | 12 |
| **(Vb)** |  | 0.9 | 0 | 0 | 12 |

**Table 1.** (Contd.)

| Code | Formula | Activity type | | | |
|---|---|---|---|---|---|
| | | protistocidal against *Colpoda steinii* | fungistatic against *Penicillium italicum* | antibacterial against *Staphylococcus aureus* | antibacterial against *Escherichia coli* |
| | | minimal active concentration, μg/mL | delay zone, mm | delay zone, mm | delay zone, mm |
| **(Vc)** |  | 500 | 0 | 0 | 12 |
| Furazolidone* |  | – | – | 19 | 20 |
| Benomyl* |  | – | 25 | – | – |
| Bycox* |  | 62.5 | – | – | – |

* Reference preparations

## EXPERIMENTAL

### *Chemical*

$^1$H NMR spectra (δ, ppm; *J*, Hz) were recorded on a Bruker DPX-250 spectrometer (250 MHz) using tetramethylsilane as the standard. The IR spectra were recorded on a Varian 3100 FT-IR spectrometer, Excalibur Series, in vaseline oil suspension. The melting points were measured in an open capillary on a Khimlabpribor PTP apparatus. The elemental analysis was performed on a CHNS Elementar Vario Micro cube analyzer. The reactions and purity of the compounds were monitored by HPLC on the Silufol UV-254 plates.

**(2*E*)-3-(1*H*-Indol-3-yl)-1-(2-thienyl)prop-2-en-1-one (IId)**. The mixture of indole-3-aldehyde (16.1 g, 0.11 mol), 2-acetylthiophene (16.5 g, 0.15 mol), and piperidine (4 mL) was refluxed in *n*-butyl alcohol (50 mL) for 8.5 h and stored overnight for crystallization. The precipitate was filtered and washed with *n*-butyl alcohol and hexane. The large yellow crystals were obtained in a yield of 21.9 g, 78%; mp, 162–163°C (164°C [13]). $^1$H NMR in DMSO-$d_6$: 7.18–7.33 (m, 3 H, C$\boldsymbol{H}_{\mathbf{Ar}}$), 7.45–7.53 (m, 1 H, C$\boldsymbol{H}_{\mathbf{Ar}}$), 7.57 (d, 1 H, *J* 15.5, CH=C***H***CO), 7.94–7.99 (m, 1H, C$\boldsymbol{H}_{\mathbf{Ar}}$), 8.05 (d, 1 H, *J* 15.5 Hz, C***H***=CHCO), 8.09–8.13 (m, 3 H, C$\boldsymbol{H}_{\mathbf{Ar}}$), 8.21–8.27 (m, 1 H, C$\boldsymbol{H}_{\mathbf{Ar}}$), 11.72 (br.s., 1 H, N***H***).

**3-{1-[(Oxiran-2-yl)methyl]-1*H*-indol-3-yl}-1-phenyl-2-propen-1-one (IIIa).** (2*E*)-3-(1*H*-indol-3-yl)-1-phenylprop-2-en-1-one **(IIa)** (1.24 g, 0.005 mol) was added under stirring to a 60% suspension of sodium hydride (0.24 g, 0.006 mol) in dry DMSO (5 mL). After 30 min when the hydrogen evolution was completed, epibromohydrin (2.08 g, 0.015 mol) was added. After 1 h of incubation, the dark red color of the solution changed to dark yellow. The mixture was kept overnight, followed by the dropwise addition of water (0.5 mL). The formed oil-like substance was dissolved by the addition of isopropyl alcohol (2–3 mL); crystallization was initiated by friction. The yellow precipitate was filtered, washed with methanol, and recrystallized from isopropyl alcohol (10 mL). Yield 0.91 g, 60%, mp 112–114°C. IR spectrum (ν, cm$^{-1}$): 1573 (C=C); 1637 (C=O). $^1$H NMR spectrum, ($CDCl_3$): 2.52 (dd, 1 H, *J* 2.6, 4.6, OC$\boldsymbol{H}_{\mathbf{2}}$); 2.86–2.90 (m, 1 H, OC$\boldsymbol{H}_{\mathbf{2}}$); 3.31–3.38 (m, 1 H, C***H***); 4.19 (dd, 1 H, 1 H, *J* 2.8, 15.2, NC$\boldsymbol{H}_{\mathbf{2}}$); 4.54 (dd, 1 H, *J* 2.8, 15.2, NC$\boldsymbol{H}_{\mathbf{2}}$); 7.38–7.50 (m, 8 H, $\boldsymbol{H}_{\mathbf{Ar}}$); 8.00–8.12 (m, 4 H, $\boldsymbol{H}_{\mathbf{Ar}}$ and C***H***=C***H***CO). Found, %: C, 79.21; H, 5.63; N, 4.70. $C_{20}H_{17}NO_2$. Calc., %: C, 79.19; H, 5.65; N, 4.62.

**(2*E*)-1-(4-Methylphenyl)-3-[1-(oxiran-2-ylmethyl)-1*H*-indol-3-yl]prop-2-en-1-one (IIIb)** was synthesized similar to the above method. Yield, 62%; mp, 127–128°C. IR spectrum (ν, cm$^{-1}$): 1575 (C=C); 1640 (C=O). $^1$H NMR spectrum, ($CDCl_3$): 2.48 (s, 3 H, C$\boldsymbol{H}_{\mathbf{3}}$), 2.42 (dd, 1 H, *J* 2.6, 4.6, –OC$\boldsymbol{H}_{\mathbf{2}}$–), 2.79–2.87 (m, 1 H, –OC$\boldsymbol{H}_{\mathbf{2}}$–), 3.26–3.35 (m, 1H, C***H***), 4.15 (dd, 1 H, *J* 5.6, 15.2, –NC$\boldsymbol{H}_{\mathbf{2}}$–), 4.50 (dd, 1 H, *J* 2.8, 15.2, –NC$\boldsymbol{H}_{\mathbf{2}}$–), 7.25–7.46 (m, 5 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 7.54 (s, 1 H, –2$\boldsymbol{H}_{\mathbf{ind}}$), 7.55 (d, 1H, *J* 15.6, CH=C***H***CO), 7.78–8.01(m, 3 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 8.05 (d, 1 H, *J* 15.6, C***H***=CHCO).

**(2*E*)-1-(4-Methoxyphenyl)-3-[1-(oxiran-2-ylmethyl)-1*H*-indol-3-yl]prop-2-en-1-one (IIIc)** was synthesized similar to compound **(IIIa)**. Yield, 77%; mp, 113–115°C. IR spectrum (ν, cm$^{-1}$): 1572 (C=C); 1641 (C=O). $^1$H NMR spectrum, ($CDCl_3$): 2.48 (dd, 1 H, *J* 2.6, 4.6, –OC$\boldsymbol{H}_{\mathbf{2}}$–), 2.79–2.86 (m, 1 H, –OC$\boldsymbol{H}_{\mathbf{2}}$–), 3.25–3.34 (m, 1 H, C***H***), 3.87 (s, 3 H, OC$\boldsymbol{H}_{\mathbf{3}}$), 4.14 (dd, 1 H, *J* 5.6, 15.2, –NC$\boldsymbol{H}_{\mathbf{2}}$–), 4.49 (dd, 1 H, *J* 2.8, 15.2, –NC$\boldsymbol{H}_{\mathbf{2}}$–), 6.60–7.04 (m, 2 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 7.25–7.62 (m, 4 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 7.53 (s, 1 H, 2-$\boldsymbol{H}_{\mathbf{ind}}$), 7.91–8.11 (m, 4H, $\boldsymbol{H}_{\mathbf{Ar}}$).

**(2*E*)-3-[1-(Oxiran-2-ylmethyl)-1*H*-indol-3-yl]-1-(2-theinyl)prop-2-en-1-one (IIId)** was synthesized similar to compound **(IIIa)**. Yield, 75%; mp, 142–144°C. IR spectrum (ν, cm$^{-1}$): 1573 (C=C); 1637 (C=O). $^1$H NMR spectrum, ($CDCl_3$): 2.49 (dd, 1 H, *J* 2.6, 4.6, OC$\boldsymbol{H}_{\mathbf{2}}$), 2.79–2.88 (m, 1H, OC$\boldsymbol{H}_{\mathbf{2}}$), 3.25–3.35 (m, 1H, C***H***), 4.15 (dd, 1 H, *J* 5.6, 15.2, NC$\boldsymbol{H}_{\mathbf{2}}$), 4.50 (dd, 1 H, *J* 2.8, 15.2, NC$\boldsymbol{H}_{\mathbf{2}}$), 7.13–7.50 (m, 5H, $\boldsymbol{H}_{\mathbf{Ar}}$ and CH=C***H***CO), 7.55 (s, 1H, 2-$\boldsymbol{H}_{\mathbf{ind}}$), 7.59–8.03 (m, 3 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 8.08 (d, 1H, *J* 15.5, C***H***=CHCO).

**(2*E*)-3-{1-[3-(Cycloheptylamino)-2-hydroxypropyl]-1*H*-indol-3-yl}-1-phenylprop-2-en-1-one (IVa).** The mixture of cycloheptylamine 0.2 g, 2 mmol) in toluene (3 mL) and compound **(IIIa)** (0.3 g, 1 mmol) in toluene (5 mL) was refluxed for 8 h, followed by the addition of *n*-hexane (2 mL). After incubation of the reaction mixture for 24 h, the precipitate was filtered and washed with *n*-hexane. The product was recrystallized from an ethyl acetate–ethanol mixture (7 : 1) as a yellow fine crystalline powder in a yield of 0.32 g (78%); mp, 131–132°C. Found, %: C, 68.48; H, 5.11; N, 12.47; S, 7.19. $C_{26}H_{24}N_4O_2S$. Calc., %: C, 68.40; H, 5.30; N, 12.27; S, 7.02. IR spectrum (ν, cm$^{-1}$): 1583 (C–C$_{\mathbf{Ar}}$), 1598 (C=C), 1647 (C=O), 3104 (NH), 3286 (OH). $^1$H NMR spectrum, ($CDCl_3$): 1.16–1.85 (m, 12 H, (C$\boldsymbol{H}_{\mathbf{2}}$)$_6$), 2.43 (dd, 1 H, *J* 8.68, 12.1, NHC$\boldsymbol{H}_{\mathbf{2}}$), 2.47–2.61 (m, 1 H, C***H***), 2.77 (dd, 1 H, *J* 3.7, 12.1, NHC***H***H), 3.88–4.02 (m, 1 H, ***CH***OH), 4.17 (qd, 2 H, NC$\boldsymbol{H}_{\mathbf{2}}$), 7.26–7.56 (m, 6 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 7.58 (d, 1 H, *J* 15.6, CH=C***H***CO), 7.94–8.03 (m, 4 H, $\boldsymbol{H}_{\mathbf{Ar}}$), 8.07 (d, 1 H, *J* 15.6, C***H***=CHCO).

**(2*E*)-3-{1-[3-Cycloheptylamino)-2-hydroxypropyl]-1*H*-indol-3-yl}-1-(4-methylphenyl)prop-2-en-1-one (IVb).** The mixture of cycloheptylamine 0.2 g, 2 mmol) in toluene (3 mL) and compound **(IIIb)** (0.32 g, 1 mmol) in toluene (5 mL) was refluxed for 5 h,

followed by the addition of *n*-hexane (5 mL). After incubation of the reaction mixture for 24 h, the precipitate was filtered and washed with *n*-hexane. The product was recrystallized from a toluene–heptane mixture (7 : 1) as a yellow fine crystalline powder in a yield of 0.33 g (76%); mp, 129–130°C. Found, % : C, 68.48; H, 5.11; N, 12.47; S, 7.19. $C_{26}H_{24}N_4O_2S$. Calc., %: C, 68.40; H, 5.30; N, 12.27; S, 7.02. IR spectrum (ν, $cm^{-1}$): 1591 (C–$C_{Ar}$), 1609 (C=C), 1650 (C=O), 3107 (NH), 3289 (OH). $^1$H NMR spectrum: 1.13–1.82 (m, 12 H, $(CH_2)_6$), 2.30–2.59 (m, 3 H, N*H*C*H*H, C*H*), 2.42 (s, 3H, $CH_3$), 2.75 (dd, 1 H, *J* 3.7, 12.1, NHC$H_2$), 3.87–3.99 (m, 1 H, C*H*OH), 4.15 (qd, 2H, *J* 5.4, 14.4, NC$H_2$), 7.21–7.43 (m, 5 H, $H_{Ar}$), 7.53 (d, 1 H, *J* 15.5, CH=C*H*CO), 7. 59 (s, 1 H, 2-$H_{ind}$), 7.88–8.00 (m, 3 H, $H_{Ar}$), 8.06 (d, 1 H, *J* 15.5, C*H*=CHCO).

**(2*E*)-3-{1-[3-Cycloheptylamino)-2-hydroxypropyl]-1*H*-indol-3-yl}-1-(4-methoxyphenyl)prop-2-en-1-one (IVc).** The mixture of cycloheptylamine 0.2 g, 2 mmol) in toluene (3 mL) and compound (**IIIc**) (0.33 g, 1 mmol) in toluene (3 mL) was refluxed for 5 h. After incubation of the reaction mixture for 24 h, the precipitate was filtered and washed with toluene. The product was recrystallized from toluene as a yellow fine crystalline powder in a yield of 0.37 g (83%); mp, 138–139°C. Found, %: C, 68.48; H, 5.11; N, 12.47; S, 7.19. $C_{26}H_{24}N_4O_2S$. Calc., %: C, 68.40; H, 5.30; N, 12.27; S, 7.02. IR spectrum (ν, $cm^{-1}$): 1584 (C–$C_{Ar}$), 1601(C=C), 1647 (C=O), 3098 (NH), 3283 (OH). $^1$H NMR spectrum: 1.21–1.93 (m, 12 H, $(CH_2)_6$), 2.34–2.66 (m, 3 H, N*H*C*H*H C*H*), 2.81 (dd, 1 H, *J* 3.3, 12.4, NHC$H_2$), 3.92 (s, 3H, $OCH_3$), 3.93–4.06 (m, 1 H, C*H*OH), 4.22 (qd, 2H, *J* 5.7, 14.4, NC$H_2$), 6.92–7.10 (m, 1 H, $H_{Ar}$), 7.16–7.68 (m, 6 H, $H_{Ar}$, CH=C*H*CO), 7.97–8.20 (m, 4 H, $H_{Ar}$, C*H*=CHCO).

**(2*E*)-3-{1-[3-Cycloheptylamino)-2-hydroxypropyl]-1*H*-indol-3-yl}-1- (2-thienyl)prop-2-en-1-one (IVd).** The mixture of cycloheptylamine 0.2 g, 2 mmol) in *n*-butanol (3 mL) and compound (**IIId**) (0.31 g, 1 mmol) in *n*-butanol (3 mL) was refluxed for 6 h, followed by the addition of hexane (5 mL). After incubation of the reaction mixture for 24 h, the precipitate was filtered and washed with isopropyl alcohol. The product was recrystallized from isopropyl alcohol as a yellow fine crystalline powder in a yield of 0.32 g (76%); mp, 150–151°C. Found, %: C, 68.48; H, 5.11; N, 12.47; S, 7.19. $C_{26}H_{24}N_4O_2S$. Calc, %: C, 68.40; H, 5.30; N, 12.27; S, 7.02. IR spectrum (ν, $cm^{-1}$): 1563 (C–$C_{Ar}$), 1633(C=C), 1640 (C=O), 3049 (NH), 3101 (OH). $^1$H NMR spectrum: 1.20–1.83 (m, 12 H, $(CH_2)_6$), 2.42 (dd, 1 H, $J^1$ 8.7, $J^2$ 12.1, NHC$H_2$), 2.46–2.59 (m, 1H, C*H*), 2.75 (dd, 1 H, *J* 3.6, 12.1, NHC$H_2$), 3.85–4.01 (m, 1 H, C*H*OH), 4.16 (qd, 2H, *J* 5.5, 14.4, NC$H_2$), 7.07–7.20 (m, 1 H, $H_{Ar}$), 7.24–7.33 (m, 2 H, $H_{Ar}$), 7.39–7.43 (m, 1 H, $H_{Ar}$), 7.42 (d, 1 H, *J* 15.4, CH=C*H*CO), 7.55–7.66 (m, 2 H, $H_{Ar}$), 7.80–8.02 (m, 1 H, $H_{Ar}$), 8.08 (d, 1 H, *J* 15.4, C*H*=CHCO).

**(2*E*)-3-(1-{2-Hydroxy-3-[(1-methyl-1*H*-benzimidazol-2-yl)amino]propyl}-1*H*-indol-3-yl)-1-(2-theinyl)-prop-2-en-1-one (IVe).** 2-Amino-1-methylbenzimidazol 0.28 g (2 mmol) in *n*-butanol (3 mL) was added to the solution of compound (**IIIe**) (0.31 g, 1 mmol) in *n*-butanol (3 mL), and the reaction mixture was refluxed for 5 h. The resulting solution was halfway evaporated and left for 24 h. The precipitate was filtered and washed with isopropyl alcohol. The product was recrystallized from a butanol–DMF mixture (2 : 1) as a yellow fine crystalline powder in a yield of 0.36 g (79%); mp, 198–199°C. Found, %: C, 68.48; H, 5.11; N, 12.47; S, 7.19. $C_{26}H_{24}N_4O_2S$. Calc., %: C, 68.40; H, 5.30; N, 12.27; S, 7.02. IR spectrum (ν, $cm^{-1}$): 1614 (C–$C_{Ar}$), 1625 (C=C), 1639 (C=O), 3095 (NH), 3339 (OH). $^1$H NMR spectrum: 3.30 (s, 3 H, NC$H_3$), 3.82–4.12 (m, 2 H, C$H_2$), 4.12–4.27 (m, 2 H, N*CH*H, CH), 4.39–4.53 (m, 1 H, *NCH*H), 5.90 (br. s, 1 H, N*H*), 6.83–7.10 (m, 4 H, $H_{Ar}$), 7.17–7.36 (m, 3 H, $H_{Ar}$), 7.56 (d, 1 H, *J* 15.4, CH=C*H*CO), 7.60–7.69 (m, 1 H, $H_{Ar}$), 7.97–8.00 (m, 1 H, $H_{Ar}$), 7.99 (d, 1 H, *J* 15.4, C*H*=CHCO), 8.06–8.30 (m, 3 H, $H_{Ar}$).

Compounds (**Va–c**) (Table 1) were synthesized by the methods described in [14].

## BIOLOGICAL

**The protistocidal activity** was studied according to [15] on protozoa of the *C. steinii* species (field isolate from the collection of the laboratory of parasitology of the North-Caucasian Zonal Scientific Research Veterinary Institute, Russia). The study was performed in microplates for ISA. A mixture of boiled tap water and sterile distilled water (1 : 1, v/v) was used as a medium for cultivation of protozoa. A compound was initially diluted by distilled water in the presence of dimethylsulfoxide (DMSO). Serial dilutions of a compound were prepared as follows.

Solution 1. A compound (5 mg) was dissolved in 70% aqueous DMSO (50 μL) under stirring, followed by the addition in portions of distilled water (5 mL); the resulting concentration of the compound was 1000 μg/mL.

Solutions 2–12. Wells 2–12 were filled each with 150 μL of water (a mixture of equal volumes of boiled tap water and sterile distilled water). Solution 1 (150 μL) was added in well 2; after stirring; 150 μL of this solution was added in well 3, and this procedure was repeated up to the end of the row. Then, 150 μL of the solution from well 12 was removed after stirring. A three-day culture of *Colpoda steinii* (by 30 μL) was

added to each well. Well 1 contained 150 μL of solution 1 and 30 μL of protozoa suspension. The protozoa suspension was prepared so that each field of view under the microscope at low magnification contained 10–15 active species. After the introduction of protozoa, the plate was covered with a lid and left at room temperature (20–22°C) for 18–20 h.

The results were detected as follows. After stirring, an aliquot of 30 μL from the last wells of the row was taken by an automatic micropipette with a pink tip, applied on a clean microscope slide, and viewed from right to left under a microscope at low magnification (10 × 15). The presence or absence of living protozoa was noted. The first well containing no living species was considered as that with a minimal protistocidal concentration of the studied compound. The following solutions were used as controls:

—The control of the medium (boiled tap water + sterile distilled water), five wells.

—The control of the solvent (50 μL of 70% DMSO + 5 mL of distilled water and the subsequent serial dilutions as for the studied compounds), twelve wells.

—The reference preparation (baycox).

**The fungistatic activity** was studied according to the optimized method of agar diffusion using the *P. italicum* fungal culture [16]. The suspension of this culture (1 mL, 5 units of the optical bacterial turbidity standard) was applied on the solidified Saburo medium and evenly distributed over the medium surface. The excess of the culture was removed. The plates were dried for 20–30 min and marked for 3–6 sectors. One cardboard filter disk (GOST 6722-75, Division of new technologies of Pasteur Institute of Epidemiology and Microbiology) was placed on each sector. The studied compound (15 μg in 15 μL of suspension in distilled water) was applied to the disks. The plates were thermostated at 26°C for 72 h. The culture growth was monitored every day. After cultivation for 72 h, the size of the zone of fungal growth inhibition around the disk was evaluated. Benomyl was used as the reference preparation.

**The antimicrobial activity** was studied by the disc-diffusion method [17]. We used the Luria-Bertani dense nutrient medium, which was poured into Petri dishes, 25 mL in each. The dishes were dried for 10–20 minutes. Suspensions of the standard strains of *S. aureus* (P-209 strain) or *E. coli* (field 078 strain, five units of the optical bacterial turbidity standard) were loaded on the surface of Petri dishes with the nutrient medium. The suspension was evenly distributed over the medium surface. The excess of the culture was removed. The plates were dried for 20–30 min and marked for 3–6 sectors. One cardboard filter disk (GOST 6722-75, Division of new technologies of Pasteur Institute of Epidemiology and Microbiology) was placed on each sector. The studied compound (15 μg in 15 μL of suspension in distilled water) was applied to the disks. The plates were thermostated at 37°C for 24 h. The size of the delay zone of bacteria growth around the disk was evaluated. Furazolidone was used as the reference preparation.

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## REFERENCES

1. Kim, C.Y., Mahaney, P.E., McConnell, O., Zhang, Y., Manas, E., Ho, D.M., Deecher, D.C., and Trybulski, E.J., *Bioorg. Med. Chem. Lett.*, 2009, vol. 19, pp. 5029–5032.
2. Liu, M., Huang, J., Chen, D.-X., and Jiang, C., *Bioorg. Med. Chem. Lett.*, 2015, vol. 25, pp. 431–434.
3. Di Santo, R., Costi, M., Artico, M., Massa, S., Ragno, R., Marshall, G.R., and La Colla, P., *Bioorg. Med. Chem.*, 2002, vol. 10, pp. 2511–2526.
4. Biradar, J.S., Rajesab, P., and Somappa, S.B., *J. Chem.*, 2014, Article ID 579612. http://dx.doi.org/.10.1155/2014/579612.
5. Gali, R., Banothu, J., Gondru, R., Bavantula, R., Velivela, Y., and Crooks, P.A., *Bioorg. Med. Chem. Lett.*, 2015, vol. 25, pp. 106–112.
6. Gupta, R., Jain, A., Madan, Y., and Menghani, E., *J. Het. Chem.*, 2014, vol. 51, pp. 1395–1403.
7. Saundane, A.R., Verma, V.A., and Katkar, V.T., *J. Chem.*, 2013, Article ID 148412. http://dx.doi.org/10.1155/2013/148412.
8. Singh, G.S., Al-kahraman, Y.M.S.A., Mpadi, D., and Yasinzaic, M., *J. Het. Chem.*, 2015, vol. 52, pp. 614–619.
9. Suzdalev, K.F., Den'kina,, S.V., Galenko-Yaroshevskii, P.A., Varlashkina, I.A., Cherednik, I.L., Sheikh-Zade, Yu.R., Taran, O.A., Takhchidi, Kh.P., Sakhnov, S.N., Dol'skaya, O.A., Lisitsyna, N.P., Bguasheva, B.A., and Bogus, S.K., 3-[1-(2-Hydroxy-3-piperidin-1-yl-propyl)-1*H*-indol-3-yl]-1-phenyl-propenone hydrohalides having a local anesthetic and antiarrhythmic activity, RF Patent no. 2408592, *Chem. Abstr.*, 2011, vol. 154, p. 125248.
10. Kucheryavenko, A.F., Spasov, A.A., Tian, M., and Suzdalev, K.F., *Bull. Exp. Biol. Med.*, 2017, vol. 162, no. 6, pp. 758–761.
11. Suzdalev, K.F. and Babakova, M.N., *Russ. J. Org. Chem.*, 2005, vol. 41, pp. 243–246.

12. Zhungietu, G.I., Budylin, V.A., and Kost, A.N., *Preparativnaya khimiya indola* (Preparative Chemistry of Indol), Chișinău: ShTIINTsA, 1975, p. 197.

13. Tsukerman, S.I., Nikitchenko, V.M., Bugai, A.I., and Lavrushin, V.F., *Khim. Geterotsikl. Soed.*, 1969, no. 2, pp. 268–272.

14. Popov, L.D. and Suzdalev, K.F. *Russ. J. Org. Chem.*, 2016, vol. 52, no. 6, pp. 858–861.

15. Fetisov, L.N., Zubenko, A.A., Bodryakov, A.N., and Bodryakova, M.A., *Materialy mezhdunarodnogo parazitologicheskogo simpoziuma "Sovremennye problemy obshchei i chastnoi parazitologii"* (Proc. Int. Parasitology Symposium "Modern Problems of General and Special Parasitilogy"), Saint Petersburg, 2012, pp. 70–73.

16. *Rukovodstvo po eksperimental'nomu (doklinicheskomu) izucheniyu novykh farmakologicheskikh veshchestv* (Guide on Experimental (Preclinical) Investigation of New Pharmacological Substancies), Khabriev, R.U., Ed., Moscow: Meditsyna, 2005, pp. 582–585.

17. Semina, N.A., Sidorenko, S.V., Rezvan, S.P., Grudinina, S.A., Strachunskiim L.S., Stetsyuk, O.U., Kozlov, R.S., Eidel'shtein, M.V., Ved'mina, E.A., Stolyrova, L.G., Vasova, I.V., and Sereda, Z.S., *Opredelenie chuvstvitel'nosti mikroorganizmov k antibakterial'nym preparatam. Metodicheskie ukazaniya. MUK 4.2.1890–04* (Determination of Microorganism Susceptibility to Antibiotics. Methodology Guidelines. MUK 4.2.1890–04), Moscow: Meditsyna, 2004.

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