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1,2,3-Triazole-Containing 1,5,6,7-Tetrahydro-4*H*-indazol-4-ones and 6,7-Dihydrobenzo[*d*]isoxazol-4(5*H*)-ones: Synthesis and Biological Activity

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Abstract—Triazole-containing 1,5,6,7-tetrahydro-4*H*-indazol-4-ones and 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones were synthesized by cyclocondensation of 2-[(1*H*-1,2,3-triazol-1-yl)acetyl]cyclohexane-1,3-diones with phenylhydrazine (4-fluorophenylhydrazine) or hydroxylamine, respectively. Structure and composition of the obtained compounds were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy methods and by data of elemental analysis. Cytotoxic and cytostatic activities of the series of obtained compounds were investigated *in vitro* against human hepatocellular carcinoma cells HepG2, mammary adenocarcinoma cells MCF-7, and laryngeal cancer cells Hep2.

Keywords: 1,5,6,7-tetrahydro-4*H*-indazol-4-ones, 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones, 1,2,3-triazoles, 2-[(1*H*-1,2,3-triazol-1-yl)acetyl]cyclohexane-1,3-diones, cytotoxic activity, cytostatic activity

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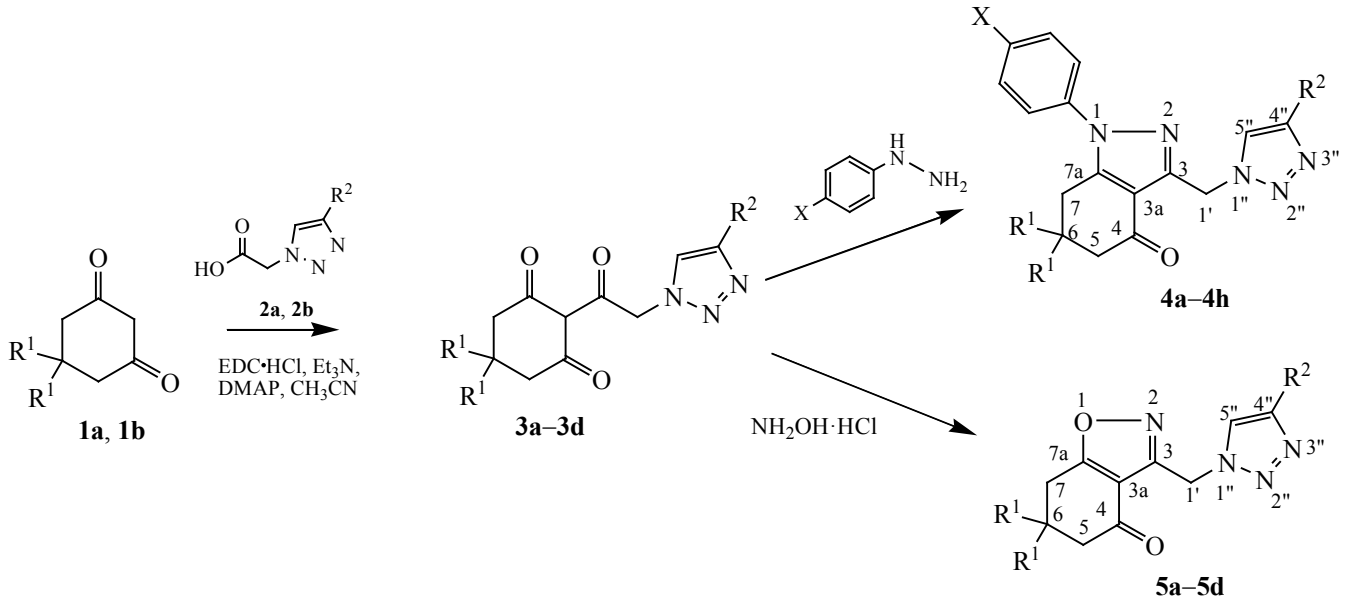
In the field of search and synthesis of new bioactive molecules, the chemistry of heterocyclic compounds plays an important role. Compounds having five-membered nitrogen- and oxygen-containing heterocycles, such as triazole [1–4], indazole [5–9], and benzisoxazole [10–12], have a wide range of biological activity. A number of compounds containing a triazole [13], indazole [14], or benzisoxazole [15] structural fragment are used in many modern drugs, including antitumor, antiviral, anti-inflammatory, antibacterial, and other pharmaceuticals. Some drugs are at the stage of clinical trials, such as the antitumor drug SNX-5422, the pharmaceutical substance of which contains a derivative of tetrahydroindazolone [16]. The 1,2,3-triazole cycle is often used to create new hybrid molecules with an increased therapeutic potential [17, 18]. This heterocyclic system can serve not only as a linker for combining pharmacophore fragments, but also acts as a pharmacophore itself. Thus, the combination of indazolone and triazole or benzisoxazolone and triazole fragments into a single hybrid molecule can lead to compounds with high biological activity. Triazole-containing 1,5,6,7-tetrahydro-4*H*-indazol-4-ones and 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones are not described in the literature.

The aim of this work is the synthesis of triazole-containing 1,5,6,7-tetrahydro-4*H*-indazol-4-ones and 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones.

At present, a number of strategies have been developed for the synthesis of indazoles [19], benzisoxazoles [20], and their derivatives. Due to the presence of three electrophilic centers (one *exo*-cyclic and two *endo*-cyclic carbonyl groups) and high reactivity, cyclic triacylmethanes can be used to construct various heterocyclic structures [21]. It is known that 2-acylcyclohexane-1,3-diones

Scheme 1.



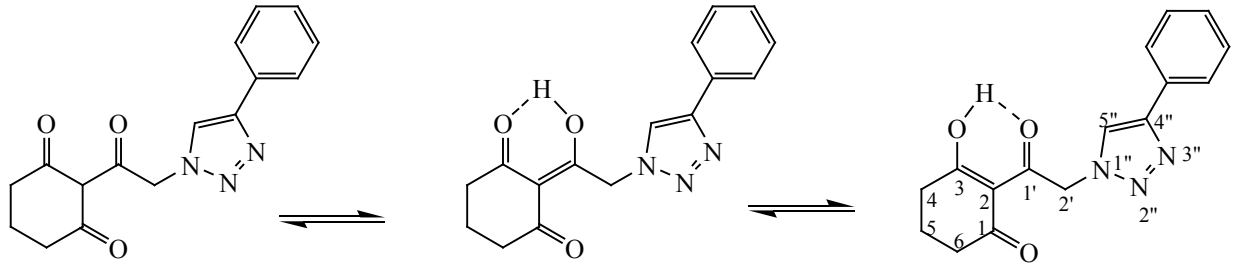
R^1 = H (**1a**), Me (**1b**); R^2 = Ph (**2a**), R^2 = C_5H_{11} (**2b**); R^1 = H, R^2 = Ph (**3a**); R^1 = Me, R^2 = Ph (**3b**); R^1 = H, R^2 = C_5H_{11} (**3c**); R^1 = Me, R^2 = C_5H_{11} (**3d**); R^1 =X = H, R^2 = Ph (**4a**); R^1 = H, R^2 = Ph, X = F (**4b**); R^1 = Me, R^2 = Ph, X = H (**4c**); R^1 = Me, R^2 = Ph, X = F (**4d**); R^1 =X = H, R^2 = C_5H_{11} (**4e**); R^1 = H, R^2 = C_5H_{11}, X = F (**4f**); R^1 = Me, R^2 = C_5H_{11}, X = H (**4g**); R^1 = Me, R^2 = C_5H_{11}, X = F (**4h**); R^1 = H, R^2 = Ph (**5a**); R^1 = Me, R^2 = Ph (**5b**); R^1 = H, R^2 = C_5H_{11} (**5c**); R^1 = Me, R^2 = C_5H_{11} (**5d**).

interact with *N*,*N*- and *N*,*O*-dinucleophiles to give the corresponding indazolones and benzisoxazolones [22]. To synthesize new derivatives of tetrahydroindazolones and dihydrobenzisoxazolones containing a triazole fragment, we used 2-[(1*H*-1,2,3-triazol-1-yl)acetyl]cyclohexane-1,3-diones as block synthons (Scheme 1).

By *C*-acylation of cyclohexane-1,3-diones **1a**, **1b** with triazolylacetic acids **2a**, **2b** according to the procedure proposed by us earlier for the preparation of 2-(tetrazolylacetyl)cyclohexane-1,3-diones [23], we obtained 2-acylcyclohexane-1,3-diones **3a**–**3d** containing a triazole ring in the side acyl chain in 75–80% yield. Reaction of 2-[(1*H*-1,2,3-triazol-1-yl)-acetyl]cyclohexane-1,3-diones **3a**–**3d** with a small excess of an equimolar mixture of phenylhydrazine hydrochloride or 4-fluorophenylhydrazine and sodium hydroxide in ethanol for 48 h at room temperature led in high yield (71–87%) to the heterocyclization products of intermediate hydrazones, indazolones **4a**–**4h**. Cyclocondensation of 2-[(1*H*-1,2,3-triazol-1-yl)acetyl]-cyclohexane-1,3-diones **3a**–**3d** with hydroxylamine was used to obtain 6,7-dihydrobenzisoxazolones **5a**–**5d**. Treatment of triketones **3a**–**3d** with an equimolar mixture of hydroxylamine hydrochloride and sodium hydroxide for 8 h at room temperature in ethanol gave the target benzisoxazolones **5a**–**5d** in 61–81% yield.

The structure and composition of synthesized compounds **3a**–**3d**, **4a**–**4h**, **5a**–**5d** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy and elemental analysis data. In the ^{1}H NMR spectra of triketones **3a**–**3d**, along with the signals of the hydrogen atoms of CH_2 and CH_3 groups, there are a proton signal at the carbon atom of the triazole ring in the form of a singlet in the range of 7.29–7.81 ppm and a signal of the enol proton in the form of a broadened singlet in the downfield region of order 16.41–16.45 ppm, which indicates the tricarbonyl system enolization and a strong hydrogen bond. In the ^{13}C NMR spectra of compounds **3a**–**3d**, in the region of 195.6–197.5 ppm, there are signals of carbon atoms of carbonyl groups. The carbon signal of the carbonyl group of the cycle appears in the region of 195.6–195.8 ppm (C^1), the signal of the carbon of the enolized carbonyl group,

Scheme 2.



in the region of 195.6–196.7 ppm (C^3), and the signal of the carbonyl group of the acyl chain $C^{1'}$, in the region of 196.6–197.5 ppm ($C^{1'}$). The results are consistent with the data obtained earlier for related triketone systems [23, 24]. To further confirm the structure of the synthesized triketones **3a**–**3d**, two-dimensional ^1H, ^{13}C, and ^{15}N NMR spectra were recorded for 2-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetyl]cyclohexane-1,3-dione **3a** (Scheme 2).

Thus, in the HMBC spectra, the *exo*-cyclic carbonyl group has a cross peak with methylene protons located outside the ring, the C^3 nucleus of the enolized carbonyl group interacts with the hydroxyl proton and protons at C^4, and the C^1 nucleus, in turn, gives a signal with protons at the atom C^6. It can be concluded that enolization is observed for the carbonyl group located in the cyclic molecule part, i.e. triketone **3a** is in the form **B**. The assignment of the signals of nitrogen nuclei of the triazole ring is based on the observation of the interaction of the $N^{3''}$ nucleus (351.0 ppm) with the *ortho*-protons of the aromatic ring, the $N^{1''}$ (239.6 ppm) and $N^{2''}$ (368.6 ppm) nuclei give cross peaks with the protons of the CH_2 group and the proton at the $C^{5''}$ atom, it is interesting that the $N^{3''}$ nucleus does not show a cross peak with the proton at the $C^{5''}$ atom. The establishment of differences between the nuclei $N^{1''}$ and $N^{2''}$ is based on the magnitude of the chemical shift: the nitrogen nucleus at the double bond is located in a weaker field.

The proton signal of the triazole fragment of indazolones **4a**–**4h** and benzisoxazolones **5a**–**5d** in the ^1H NMR spectra appears as a singlet in the region of 7.57–8.18 ppm, while the signal of the protons of the methylene group at the $C^{1'}$ atom appears in the region of 5.75–5.89 ppm. In the ^{13}C NMR spectra of indazolones **4a**–**4h**, the signal of the carbon atom of the carbonyl group (C^4) and the signals of the carbon atoms of the C–N (C^{7a}) and C=N (C^3) groups are observed in the ranges of 193.2–194.0, 149.7–150.7, and 147.8–148.4 ppm respectively, while the ^{13}C NMR spectra of benzisoxazolones **5a**–**5d** show signals at 192.2–193.0 (C^4), 181.8–182.4 (C^{7a}), and 155.0–155.3 ppm (C^3). According to the obtained spectroscopic data, the cyclocondensation of 2-[(1*H*-1,2,3-triazol-1-yl)acetyl] cyclohexane-1,3-diones **3a**–**3d** with phenylhydrazines or hydroxylamine proceeded at the most electrophilic *exo*-cyclic carbonyl group, as was established for other cyclic β-triketones [25–28].

The cytotoxic activity of triazole-containing tetrahydroindazolones **4c**, **4d** and 6,7-dihydrobenzisoxazolones **5b**, **5c** was assessed *in vitro* against human hepatocellular carcinoma HepG2, human mammary adenocarcinoma MCF-7, and human laryngeal carcinoma Hep2 using fluorescence microscopy on an IN Cell Analyzer 2200 device (GE Healthcare, UK).

The test compounds did not show pronounced cytotoxic activity against human tumor cells HepG2, MCF-7, and Hep2 in the concentration range of 1–100 μM (IC_{50} > 100 μM). Slight cell death (13% apoptotic cells and 7% dead cells) was observed at the effect of compound **4c** on MCF-7 cells. Compounds **4c**, **4d**, **5b**, **5c** showed moderate cytostatic properties (a decrease in the rate of cell division and, as a result, a decrease in the total number of cells compared to the control) at concentrations of 25, 50, and 100 μM (Fig. 1).

Thus, previously unknown triazole-containing 1,5,6,7-tetrahydro-4*H*-indazol-4-ones and 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones were synthesized starting

from 2-[(1*H*-1,2,3-triazol-1-yl)acetyl]cyclohexane-1,3-diones. The structure and composition of the obtained compounds were confirmed by spectral methods. The results of bioassays showed the promise of further search for compounds with cytostatic activity in this heterocycles series.

EXPERIMENTAL

^{1}H, ^{19}F, ^{13}C, ^{15}N NMR spectra were recorded on a Bruker-Biospin AVANCE 500 spectrometer with operating frequencies of 500.13, 470.59, 125.77, 50.70 MHz for ^{1}H, ^{19}F, ^{13}C, ^{15}N nuclei, respectively, using a 5 mm sensor (BBO) with Z-gradient. The spectra were registered at a sample temperature of 293 K for solutions in $CDCl_3$. The residual signal of the solvent was used as an internal standard for the ^{1}H and ^{13}C NMR spectra, and the signal of nitromethane was used as an internal standard for the ^{15}N NMR spectra. The signal of α,α,α-trifluorotoluene was used as an external standard for ^{19}F NMR spectra. Correlation spectra (HSQC, COSY, HMBC, NOESY) were recorded and processed using standard Bruker Biospin software. Melting points were determined on a Boetius block. Elemental analysis was performed on a Eurovector EA3000 CHNS-O analyzer. The reactions progress and the products purity were monitored by TLC on Silufol UV-254 plates (ethyl acetate–petroleum ether). Column chromatography was performed on silica gel (70–230 mesh) eluting with ethyl acetate–petroleum ether.

Triazolylacetic acids 2a, 2b. To a solution of 17.1 mmol (1.97 g) of methyl-2-azidoacetate in a mixture of 50 mL of *tert*-butanol and 50 mL of water was added 18.9 mmol (1.92 g) of phenylacetylene [or 18.9 mmol (1.82 g) of hept-1-yne] and then 23.6 mmol (0.64 g) copper sulfate pentahydrate (0.64 g) and 23.6 mmol (1.5 g) copper powder. The reaction mixture was stirred for 20 h. The precipitate was filtered off; the filtrate was evaporated under reduced pressure to half the original volume and was extracted with ethyl acetate (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, the solvent was removed. Column chromatography of the residue gave methyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate or methyl 2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)acetate as an oil in 93% and 85% yield, respectively.

To a solution of 16.0 mmol of the resulting methyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate or methyl 2-(4-pentyl-1*H*-1,2,3-triazolyl)acetate in a mixture of 50 mL of methanol and 50 mL of water was added 16 mmol (6.4 g) of sodium hydroxide. The reaction mixture was stirred for 24 h, methanol was removed, and the residue was acidified with 20% hydrochloric acid to pH 1. To isolate triazolylacetic acid **2a**, the formed precipitate was filtered off, washed with water, and dried in air to give 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetic acid **2a** in 93% yield as colorless crystals (mp 198–200°C). To isolate triazolylacetic acid **2b**, the formed precipitate was filtered off, washed with water, and dried in air to give 1.99 g (63%) of acid **2b**. The aqueous layer was extracted with ethyl acetate (3×30 mL), the combined organic layer was dried over anhydrous Na_2SO_4. After the solvent removing, 0.98 g (31%) of acid **2b** was additionally obtained. The total yield of 2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)acetic acid (**2b**) was 2.97 g (94%) as colorless crystals (mp 124–125°C). The physicochemical characteristics of triazolylacetic acids **2a**, **2b** coincide with the literature data [29, 30]. 2-[(1*H*-1,2,3-Triazol-1-yl)acetyl]cyclohexane-1,3-diones **3a**–**3d** were synthesized by analogy with the procedure described in [23].

2-[2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)acetyl]cyclohexan-1,3-dione (3a) was obtained from cyclohexane-1,3-dione **1a** and 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetic acid **2a**. Yield 80%, colorless crystals, mp 139–142°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 2.07 quintet (2H, CH_2, *J* 6.5), 2.56 t (2H, CH_2, *J* 6.6), 2.75 t (2H, CH_2, *J* 6.4), 5.88 s (2H, CH_2), 7.31–7.36 m (1H, H_{Ar}), 7.40–7.45 m (2H, H_{Ar}), 7.80 s (1H), 7.83–7.88 m (2H, H_{Ar}), 16.42 br. s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.2, 31.9, 38.1, 58.0, 112.4, 121.8, 125.9, 128.3, 128.9, 130.7, 148.0, 195.8 (C^1), 196.7 (C^3), 197.0 ($C^{1'}$). Found, %: C 64.72; H 5.13; N 14.18. $C_{16}H_{15}N_3O_3$. Calculated, %: C 64.64; H 5.09; N 14.13.

5,5-Dimethyl-2-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-acetyl]cyclohexane-1,3-dione (3b) was obtained from 5,5-dimethylcyclohexane-1,3-dione **1b** and 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetic acid **2a**. Yield 77%, colorless crystals, mp 136–138°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 s (6H, $2CH_3$), 2.42 s (2H, CH_2), 2.61 s (2H, CH_2), 5.89 s (2H, CH_2), 7.31–7.36 m (1H, H_{Ar}), 7.40–7.45 m (2H, H_{Ar}), 7.81 s (1H), 7.83–7.88 m (2H, H_{Ar}), 16.41 br. s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.3, 31.3, 45.4, 51.9, 57.9, 111.4, 121.8, 126.0, 128.3, 129.0, 130.7, 148.1, 195.6 (C^1, C^3), 196.6 ($C^{1'}$). Found %: C 66.53; H 5.94; N 12.96. $C_{18}H_{19}N_3O_3$. Calculated, %: C 66.45; H 5.89; N 12.91.

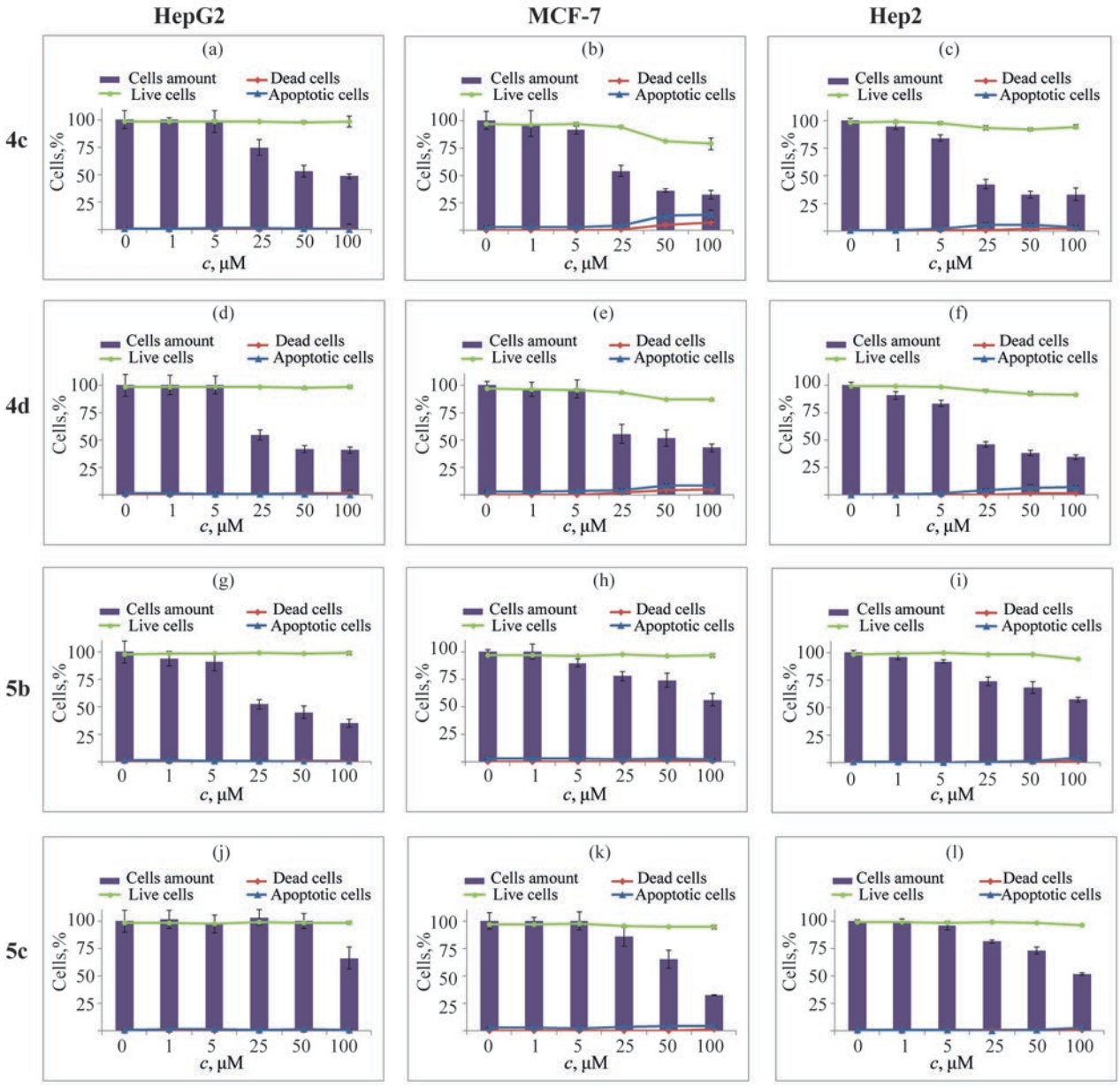


Fig. 1. Cytotoxic effect of compounds **4c** (a, b, c), **4d** (d, e, f), **5b** (g, h, i), **5c** (j, k, l) in relation to cell lines HepG2, MCF-7, and Hep2 after 48 h of exposure (data from three independent experiments).

2-[2-(4-Pentyl-1*H*-1,2,3-triazol-1-yl]acetyl)cyclohexan-1,3-dione (3c) was obtained from cyclohexane-1,3-dione **1a** and 2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)acetic acid **2b**. Yield 75%, colorless crystals, mp 68–71°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.85–0.91 m (3H, CH_3), 1.28–1.39 m (4H, CH_2), 1.63–1.74 m (2H, CH_2), 2.04 quintet (2H, CH_2, *J* 6.5), 2.53 t (2H, CH_2, *J* 6.6), 2.73 t (4H, CH_2, *J* 7.7), 5.78 s (2H, CH_2), 7.29 s (1H), 16.45 br. s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.1, 19.2, 22.5, 25.8, 29.2, 31.6, 31.9, 38.1, 57.8, 112.4, 122.7, 148.7, 195.7 (C^1), 196.6 (C^3), 197.5 ($C^{1'}$). Found, %: C 61.92; H 7.31; N 14.52. $C_{15}H_{21}N_3O_3$. Calculated, %: C 61.84; H 7.27; N 14.47.

5,5-Dimethyl-2-[2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)-acetyl]cyclohexane-1,3-dione (3d) was obtained from 5,5-dimethylcyclohexane-1,3-dione **1b** and 2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)acetic acid **2b**. Yield 75%, colorless crystals, mp 115–116°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.85–0.93 m (3H, CH_3), 1.11 s (6H, CH_3), 1.28–1.40 m (4H, CH_2), 1.68 quintet (2H, CH_2, *J* 7.5), 2.40 s (2H, CH_2), 2.58 s (2H, CH_2), 2.74 t (2H, CH_2, *J* 7.7), 5.79 s (2H, CH_2), 7.30 s (1H), 16.43 br. s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.1, 22.5, 25.8, 28.3, 29.2, 31.3, 31.6, 45.4, 51.9, 57.7, 111.3, 122.7, 148.7, 195.6 (C^1, C^3), 197.0 ($C^{1'}$). Found, %: C 63.85; H 7.86; N 13.10. $C_{17}H_{25}N_3O_3$. Calculated, %: C 63.93; H 7.89; N 13.16.

Triazole-containing 1,5,6,7-tetrahydro-4*H*-indazol-4-ones 4a–4h. To solution of 37 mmol of 2-(triazolylacetyl)cyclohexane-1,3-dione **3a–3d** in 15 mL of ethanol, 37 mmol (0.05 g) of phenylhydrazine hydrochloride [or 37 mmol of (0.06 g) of 4-fluorophenylhydrazine hydrochloride] and 37 mmol (0.02 g) of sodium hydroxide were added. The reaction mixture was stirred for 24 h at room temperature, and then 12.3 mmol (0.017 g) of phenylhydrazine hydrochloride and 12.3 mmol (0.01 g) of sodium hydrochloride [or 18.5 mmol (0.03 g) of 4-fluorophenylhydrazine hydrochloride and 18.5 mmol (0.01 g) of sodium hydroxide] were added and the reaction mixture was stirred for 24 h. Ethanol was removed, the residue was dissolved in 60 mL of chloroform, washed with diluted 1 : 10 hydrochloric acid (3×15 mL), water (2×15 mL), dried over anhydrous sodium sulfate. Chloroform was removed, and indazolones **4a–4h** were isolated by column chromatography of the residue (71–87% yield).

1-Phenyl-3-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)-methyl]-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4a). Yield 79%, colorless crystals, mp 146–147°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.13–2.21 m (2H, CH_2), 2.54–2.59 m (2H, CH_2), 2.96 t (2H, CH_2, *J* 6.1), 5.89 s (2H, CH_2), 7.27–7.32 m (1H, H_{Ar}), 7.35–7.45 m (3H, H_{Ar}), 7.46–7.52 m (4H, H_{Ar}), 7.80–7.86 m (2H, H_{Ar}), 8.18 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 23.5, 23.7, 38.2, 46.5, 117.6, 121.0, 123.9, 125.9, 128.0, 128.7, 128.8, 129.6, 131.0, 138.3, 146.2, 147.8, 150.7, 194.0. Found, %: C 71.45; H 5.13; N 18.90. $C_{22}H_{19}N_5O$. Calculated, %: C 71.53; H 5.18; N 18.96.

1-(4-Fluorophenyl)-3-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4b). Yield 71%, colorless crystals, mp 161–162°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.13–2.23 m (2H, CH_2), 2.52–2.60 m (2H, CH_2), 2.92 t (2H, CH_2, *J* 6.2), 5.87 s (2H, CH_2), 7.15–7.22 m (2H, H_{Ar}), 7.27–7.33 m (1H, H_{Ar}), 7.35–7.42 m (2H, H_{Ar}), 7.43–7.50 m (2H, H_{Ar}), 7.80–7.85 m (2H, H_{Ar}), 8.17 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 23.4, 23.7, 38.2, 46.5, 116.6 d ($^2J_{CF}$ 23.0), 117.6, 121.0, 125.8 d ($^3J_{CF}$ 8.8), 125.9, 128.1, 128.9, 131.0, 134.5 d ($^4J_{CF}$ 2.5), 146.3, 147.8, 150.7, 162.4 d ($^1J_{CF}$ 249.4), 193.9. ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –111.87 to –111.96 m (1F). Found, %: C 68.30; H 4.72; N 18.14. $C_{22}H_{18}FN_5O$. Calculated, %: C 68.21; H 4.68; N 18.08.

6,6-Dimethyl-1-phenyl-3-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4c). Yield 82%, colorless crystals, mp 71–74°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 s (6H, CH_3), 2.44 s (2H, CH_2), 2.81 s (2H, CH_2), 5.89 s (2H, CH_2), 7.27–7.31 m (1H, H_{Ar}), 7.35–7.40 m (2H, H_{Ar}), 7.40–7.45 m (1H, H_{Ar}), 7.45–7.52 m (4H, H_{Ar}), 7.80–7.85 m (2H, H_{Ar}), 8.16 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.5, 36.2, 37.2, 46.5, 52.3, 116.6, 120.9, 124.0, 125.9, 128.0, 128.7, 128.8, 129.6, 131.0, 138.3, 146.0, 147.8, 149.9, 193.4. Found, %: C 72.62; H 5.88; N 17.70. $C_{24}H_{23}N_5O$. Calculated, %: C 72.52; H 5.83; N 17.62.

6,6-Dimethyl-1-(4-fluorophenyl)-3-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4d). Yield 87%, colorless crystals, mp 84–87°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 s (6H, CH_3), 2.42 s (2H, CH_2), 2.76 s (2H, CH_2), 5.86 s (2H, CH_2), 7.14–7.21 m (2H, H_{Ar}), 7.24–7.31 m (1H, H_{Ar}), 7.34–7.41 m (2H, H_{Ar}), 7.41–7.48 m (2H, H_{Ar}), 7.78–7.84 m (2H, H_{Ar}), 8.14 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 28.5, 36.1, 37.0, 46.4, 52.2, 116.5, 116.5 d ($^2J_{CF}$ 22.9), 120.9, 125.8 d ($^3J_{CF}$ 8.8), 125.9, 128.1, 128.8, 130.9, 134.4 d ($^4J_{CF}$ 2.5), 146.0, 147.8, 149.9, 162.3 d ($^1J_{CF}$ 249.6), 193.3. ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –111.84÷–111.94 m (1F). Found, %: C 69.30; H 5.31; N 16.81. $C_{24}H_{22}FN_5O$. Calculated, %: C 69.38; H 5.34; N 16.86.

3-[(4-Pentyl-1*H*-1,2,3-triazol-1-yl)methyl]-1-phenyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4e). Yield 75%, colorless crystals, mp 44–46°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 0.82–0.89 m (3H, CH_3), 1.25–1.35 m (4H, CH_2), 1.63 quintet (2H, CH_2, *J* 7.6), 2.16 quintet (2H, CH_2, *J* 6.3), 2.50–2.57 m (2H, CH_2), 2.66 t (2H, CH_2, *J* 7.7), 2.95 t (2H, CH_2, *J* 6.1), 5.78 s (2H, CH_2), 7.37–7.43 m (1H, H_{Ar}), 7.43–7.50 m (4H, H_{Ar}), 7.64 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm:

14.1, 22.5, 23.5, 23.7, 25.7, 29.2, 31.5, 38.2, 46.3, 117.5, 121.9, 123.8, 128.6, 129.5, 138.3, 146.4, 148.3, 150.6, 193.9. Found, %: C 69.49; H 6.97; N 19.35. $C_{21}H_{25}N_5O$. Calculated, %: C 69.40; H 6.93; N 19.27.

3-[(4-Pentyl-1*H*-1,2,3-triazol-1-yl)methyl]1-(4-fluorophenyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4f). Yield 68%, colorless crystals, mp 42–45°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.82–0.90 m (3H, CH_3), 1.25–1.35 m (4H, CH_2), 1.63 quintet (2H, CH_2, *J* 7.3), 2.16 quintet (2H, CH_2, *J* 6.2), 2.53 t (2H, CH_2, *J* 6.4), 2.66 t (2H, CH_2, *J* 7.8), 2.91 t (2H, CH_2, *J* 6.2), 5.77 s (2H, CH_2), 7.11–7.20 m (2H, H_{Ar}), 7.40–7.48 m (2H, H_{Ar}), 7.64 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J,* Hz): 14.1, 22.5, 23.3, 23.6. 25.8, 29.2, 31.5, 38.1, 46.2, 116.5 d ($^2J_{CF}$ 23.2), 117.5, 121.9, 125.8 d ($^3J_{CF}$ 8.8), 134.5 d ($^4J_{CF}$ 2.5), 146.5, 148.4, 150.6, 162.3 d ($^1J_{CF}$ 249.4), 193.8. ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –112.00÷–112.10 m (1F). Found, %: C 66.21; H 6.39; N 18.44. $C_{21}H_{24}FN_5O$. Calculated, %: C 66.12; H 6.34; N 18.36.

6,6-Dimethyl-3-[(4-pentyl-1*H*-1,2,3-triazol-1-yl)-methyl]-1-phenyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4g). Yield 72%, colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.82–0.90 m (3H, CH_3), 1.09 s (6H, CH_3), 1.25–1.35 m (4H, CH_2), 1.63 quintet (2H, CH_2, *J* 7.3), 2.42 s (2H, CH_2), 2.67 t (2H, CH_2, *J* 7.7), 2.80 s (2H, CH_2), 5.79 s (2H, CH_2), 7.38–7.44 m (1H, H_{Ar}), 7.44–7.52 m (4H, H_{Ar}), 7.63 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.1, 22.5, 25.8, 28.5, 29.2, 31.5, 36.1, 37.2, 46.3, 52.3, 116.5, 121.8, 123.9, 128.6, 129.5, 138.3, 146.2, 148.4, 149.7, 193.3. Found, %: C 70.47; H 7.42; N 17.80. $C_{23}H_{29}N_5O$. Calculated, %: C 70.56; H 7.47; N 17.89.

6,6-Dimethyl-3-[(4-pentyl-1*H*-1,2,3-triazol-1-yl)-methyl]-1-(4-fluorophenyl)-1,5,6,7-tetrahydro-4*H*-indazol-4-one (4h). Yield 84%, colorless crystals, mp 87–88°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.80–0.90 m (3H, CH_3), 1.09 s (6H, CH_3), 1.24–1.35 m (4H, CH_2), 1.62 quintet (2H, CH_2, *J* 7.3), 2.41 s (2H, CH_2), 2.66 t (2H, CH_2, *J* 7.7), 2.75 s (2H, CH_2), 5.77 s (2H, CH_2), 7.12–7.20 m (2H, H_{Ar}), 7.39–7.47 m (2H, H_{Ar}), 7.62 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 14.1, 22.5, 25.7, 28.4, 29.2, 31.5, 36.1, 37.1, 46.2, 52.2, 116.5, 116.5 d ($^2J_{CF}$ 23.2), 121.8, 125.8 d ($^3J_{CF}$ 8.8), 134.4 d ($^4J_{CF}$ 2.5), 146.3, 148.4, 149.8, 162.3 d ($^1J_{CF}$ 249.4), 193.2. ^{19}F NMR spectrum: from –111.91 to –112.10 m (1F). Found, %: C 67.38; H 6.82; N 17.03. $C_{23}H_{28}FN_5O$. Calculated, %: C 67.46; H 6.89; N 17.10.

Triazole-containing 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones 5a, 5c. To a solution of 54 mmol (0.16 g) of 2-(triazolylacetyl)cyclohexane-1,3-dione **3a**, **3c** in 15 mL of ethanol was added 54 mmol (0.04 g) of hydroxylamine hydrochloride and 54 mmol (0.02 g) of sodium hydroxide. The reaction mixture was refluxed for 8 h, ethanol was removed. Column chromatography of the residue gave 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones **5a**, **5c** in 81 and 61% yields, respectively.

3-[(4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-one (5a). Yield 81%, colorless crystals, mp 107–109°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.24 quintet (2H, CH_2, *J* 6.3), 2.49–2.57 m (2H, CH_2), 3.02 t (2H, CH_2, *J* 6.3), 5.84 s (2H, CH_2), 7.29–7.34 m (1H, H_{Ar}), 7.37–7.43 m (2H, H_{Ar}), 7.79–7.85 m (2H, H_{Ar}), 8.11 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.3, 23.1. 37.8, 44.3, 114.4, 121.1, 125.9, 128.3, 128.9, 130.6, 148.1, 155.1, 182.4, 193.0. Found, %: C 65.21; H 4.73; N 18.97. $C_{16}H_{14}N_4O_2$. Calculated, %: C 65.30; H 4.79; N 19.04.

3-[(4-Pentyl-1*H*-1,2,3-triazol-1-yl)methyl]-6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-one (5c). Yield 61%, colorless crystals, mp 69–70°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.80–0.92 m (3H, CH_3), 1.25–1.37 m (4H, CH_2), 1.59–1.69 m (2H, CH_2), 2.24 quintet (2H, CH_2, *J* 6.4), 2.50–2.55 m (2H, CH_2), 2.64–2.71 m (2H, CH_2), 3.01 t (2H, CH_2, *J* 6.3), 5.75 s (2H, CH_2), 7.58 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 22.4, 22.5, 23.1, 25.7, 29.1, 31.5, 37.8, 44.1, 114.4, 122.0, 148.8, 155.3, 182.3, 192.8. Found, %: C 62.40; H 6.93; N 19.38. $C_{15}H_{20}N_4O_2$. Calculated, %: C 62.48; H 6.99; N 19.43.

Triazole-containing 6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-ones 5b, 5d. To a solution of 37 mmol (0.12 g) of 5,5-dimethyl-2-(triazolylacetyl)cyclohexane-1,3-dione **3b**, **3d** in 15 mL of ethanol was added 37 mmol (0.03 g) of hydroxylamine hydrochloride and 37 mmol (0.02 g) of hydroxide sodium. The reaction mixture was refluxed for 8 h, kept at room temperature for 16 h, an additional 37 mmol (0.03 g) of hydroxylamine hydrochloride and 37 mmol (0.02 g) of sodium hydroxide were added, and the resulting reaction mixture was refluxed for 8 h. After removing the solvent, the target 6,7-dihydrobenzo[*d*]-isoxazol-4(5*H*)-ones **5b**, **5d** were isolated by column chromatography in 71 and 67% yields, respectively.

6,6-Dimethyl-3-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)-methyl]-6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-one (5b). Yield 71%, colorless crystals, mp 156–157°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.15 s (6H, CH_3), 2.42 s (2H,

CH_2), 2.87 s (2H, CH_2), 5.85 s (2H, CH_2), 7.28–7.34 m (1H, H_{Ar}), 7.36–7.43 m (2H, H_{Ar}), 7.78–7.84 m (2H, H_{Ar}), 8.10 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.5, 36.0. 36.8, 44.4, 52.2, 113.4, 121.0, 126.0, 128.3, 128.9, 130.6, 148.1, 155.0, 181.9, 192.3. Found, %: C 67.15; H 5.68; N 17.44. $C_{18}H_{18}N_4O_2$. Calculated, %: C 67.07; H 5.63; N 17.38.

5,5-Dimethyl-3-[(4-pentyl-1*H*-1,2,3-triazol-1-yl)-methyl]-6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-one (5d). Yield 67%, colorless crystals, mp 37–40°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.84–0.90 m (3H, CH_3), 1.15 s (6H, CH_3), 1.26–1.36 m (4H, CH_2), 1.58–1.69 m (2H, CH_2), 2.41 s (2H, CH_2), 2.65–2.71 m (2H, CH_2), 2.86 s (2H, CH_2), 5.76 s (2H, CH_2), 7.57 s (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.1, 22.5, 25.7, 28.5, 29.2, 31.5, 36.0, 36.8, 44.2, 52.3, 113.3, 121.9, 148.8, 155.2, 181.8, 192.2. Found, %: C 64.42; H 7.60; N 17.64. $C_{17}H_{24}N_4O_2$. Calculated, %: C 64.53; H 7.65; N 17.71.

Studies of cytotoxic activity were carried out on three cell lines: HepG2 (human hepatocellular carcinoma), MCF-7 (human mammary adenocarcinoma), and Hep2 (human laryngeal carcinoma), which were purchased from the State Research Center of Virology and Biotechnology "VECTOR." Cell viability was assessed by double staining with Hoechst 33342 fluorescent dyes and propidium iodide (PI) according to the standard method. Cells were seeded on 96 well plates and cultured in IMDM medium in a CO_2 incubator at 37°C. After 24 h, the compounds dissolved in DMSO were added in the concentration range of 1–100 μM and incubated for 48 h. Cells were stained with fluorescent dyes—Hoechst 33342 (Sigma-Aldrich) and propidium iodide (Invitrogen)—for 30 min at 37°C. Recording was performed on an IN Cell Analyzer 2200 (GE Healthcare, UK) in automatic mode, at least 4 fields per well. The obtained images were analyzed using the In Cell Investigator program to determine live, dead and apoptotic cells in the entire population. The result is presented as the percentage of cells from three independent experiments ± standard deviation.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY INFORMATION

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