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Study of the anticancer activity of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide toward human tumor cells *in vitro*

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Aim. *In vitro* study and characterization of anticancer activity of new heterocyclic derivative — *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide. **Methods.** The cell culture; MTT assay. **Results.** We synthesized *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide, which possessed diuretic, cardioprotective, and anti-inflammatory effects. Here, we investigated its cytotoxicity effect towards the tumor cell lines of various tissue origins: liver (HepG2), breast (MCF-7), lung (A549), cervical (KB3-1), and leukemia (HL-60) cells, as well as towards the non-tumor cells (HEK293 and NIH3T3). The IC_{50} values of the synthesized compound for tumor cells were in the range of 9.4–97.6 μg/mL. We found that the human hepatocellular carcinoma HepG2 cells were the most sensitive to the action of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide with the IC_{50} value of 9.4 μg/mL. The studied derivative slightly inhibited the growth of the pseudo-normal HEK293 and NIH3T3 cells. **Conclusions.** The anti-proliferative activity of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide dropped in the order: hepatocarcinoma > leukemia > breast carcinoma cells. Thus, we revealed in the molecule of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide a combination of the diuretic, cardioprotective, anti-inflammatory and anticancer activities, which is of great significance for this agent as a potent anticancer medicine.

Keywords: *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide, cytotoxicity *in vitro*, anticancer activity.

Introduction

Cancer is a multifaceted global health issue that continues to demand action. According to the World Health Organization, cancer is responsible for one in six deaths, which makes it the second most common cause of death globally [1, 2].

The role of chemotherapy in cancer treatment is undeniable. However, despite the rapid development of modern medical chemistry, the effectiveness of anticancer drugs remains low. To a large extent, this is due to the non-specificity of their action, the resistance of tumors, and insufficient study of the mechanisms of the pathogenesis of the disease. Most of the obtained compounds do not find clinical application due to their high toxicity, poor solubility in water, non-selective action, and a number of other side effects [3].

Over the past decades, there has been significant progress in understanding of the mechanisms of pathogenesis of various diseases, from the demarcation of genes to the cellular pathways that are crucial for the development of diseases. The state of the disease usually includes various pathological processes that are interconnected through a complex network, so the multifactorial nature is observed in severe chronic diseases, including cancer. Today, the prevailing concept is the so-called "single hit", when the targeted biologically active molecules act on a certain, usually one biological target. However, over time, a more complex polypharmacological approach appeared, which assumes that the same substance simultaneously affects different metabolic pathways and biological targets are involved in different stages of the development of this or that (or several) pathologies [4–7].

It is known that many drugs used for the treatment of cancer cause several disorders in the part of the cardiovascular system. The search for new BARs with both antitumor and cardioprotective effects is promising. The biological mechanisms that account for both diseases require a comprehensive study of the possible application of some anticancer agents for the therapy of cardiovascular diseases and vice versa [8].

Therefore, the search for novel effective and safe anticancer agents with multi-target action is urgent.

Many compounds containing a five-membered heterocyclic ring exhibit exceptional chemical properties and diverse biological activities. The analogues of nitrogen-containing heterocycles are an extremely important class of the organic substances that are widely used in medicinal chemistry since more than 60 % of drugs and more than 85 % of biologically active substances described in the literature contain a nitrogen-containing heterocycle in their structure [9].

Thiadiazoles have unique properties that make them useful frameworks in medicinal chemistry. Being the bioisosteres of pyrimidines and oxadiazole [10], their derivatives can potentially interact with DNA and RNA. Being mesoionic compounds, thiadiazoles can easily penetrate cell membranes. The thiadiazole-containing compounds exhibited a wide range of activities (anti-inflammatory, antibacterial, antifungal, antiviral, cardioprotective, and antidiabetic) [11–16]. It was reported the anticancer activity of thiadiazole derivatives [17–20]. Noteworthy, the substances containing thiadiazole have entered the clinical trials, either alone or in conjunction with the already-approved anticancer medications [21–23].

Recently, we have synthesized a derivative of thiadiazole — the compound *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide (Fig. 1), which, as described earlier, has diuretic, cardioprotective and anti-inflammatory effects [24, 25] .

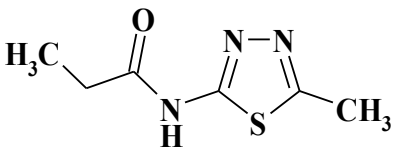

Fig. 1. The structure of N-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide

Here, we addressed the investigation of the anticancer potential of the *N*-(5-methyl-[1,3,4] thiadiazol-2-yl)-propionamide. A combination of the cardioprotective, anti-inflammatory, and anticancer activities in one molecule is of great significance, since a very potent anticancer drug, Doxorubicin, is extremely cardiotoxic, which limits its applications as an anticancer remedy [26, 27].

Materials and Methods

All reagents and solvents were purchased from commercial suppliers and were used directly without further purification. Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland), and were uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer (Perkin-Elmer, Waltham, MA, USA) and were within ±0.4 % of the theoretical values. The 500 MHz 1H and 100 MHz ^{13}C NMR spectra were recorded on Varian Unity Plus 500 (500 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). The LC-MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA).

The compound was synthesized, as described previously [24].

Synthesis of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide. In a conical flask, 5 mmol of 2-amino-5-methyl-1,3,4-thiadiazole are dissolved under heating in anhydrous dimethylformamide with the addition of anhydrous dioxane, cooled to 80 °C, 5 mmol of 3-ethylamine are added, and with stirring, a solution of 5.5 mmol of propionyl chloride in anhydrous dioxane, heated for 10 minutes at a temperature of 90 °C, stirring occasionally, cooled, diluted with water, acidified with dilute hydrochloric acid, recrystallized from acetic acid. Light beige crystalline powder is obtained, insoluble in water, and soluble in dimethylformamide and dimethylsulfoxide. from melting point mp 258–260 ºC, output Yield: –98.6 %. The composition and structure of the synthesized compound were proven using physicochemical methods, in particular PMR spectroscopy and elemental analysis. The obtained results indicate the conformity of the synthesized compound with the claimed one.

1H NMR (400 MHz, DMSO-d6+CCl4), δ, ppm: 1.08 (t, 3H, J = 7.2 Hz, CH3CH2CO), 2.45 (q, 2H, J = 7.4 Hz, CH3CH2CO), 2.59 (s, 3H, CH3), 12.23 (s, 1H, NH).

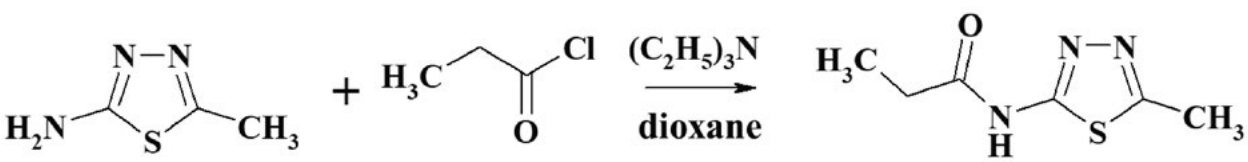

Fig. 2. The schema of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide synthesis

Anal. Calc. for C6H9N3OS %: C, 42.09; H, 5.30; N, 24.54.

Found %: C, 42.31; H, 5.48; N, 24.76.

The stock solution of the compound at 50 mg/mL concentration was prepared in dimethyl sulfoxide (DMSO, Sigma-Aldrich, USA). Before adding to cells, further dilutions were prepared using a culture medium. Doxorubicin (Dox, Actavis, Romania) was used as a positive control drug.

Cells culture. The human myeloid leukemia HL-60 cells, human hepatocarcinoma HepG2 cells were from a collection at the Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine (Kyiv, Ukraine). The human breast adenocarcinoma MCF-7 cells, human lung carcinoma A549 cells, human epidermoid cervix carcinoma KB3-1 cells, human embryonic kidney HEK293 cells, and murine fibroblast cell line NIH3T3 were from Cell Collection of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (Kyiv, Ukraine).

The HL-60 and KB3-1 cells were grown in the RPMI-1640 (BioWest, France) medium, HepG2, MCF-7, A549, HEK293, and NIH3T3 cells — in Dulbecco's modified Eagle's medium (BioWest, France). The culture medium was supplemented with 10 % of fetal bovine serum (BioWest, France). The cells were cultivated at 37 ºC in the atmosphere of 5 % CO_2 and 95 % air.

MTT assay for evaluation of cell proliferation. The antineoplastic activity of the synthesized compound and Doxorubicin towards the tumor and non-tumor cells was examined using the MTT test (EZ4U, Biomedica, Austria). Cells were seeded overnight into 96-well plates in 100 μL at concentrations of 5,000 cells/well (substrate-dependent cells) or 10,000 cells/well (suspension HL-60 cells). Aliquots of 100 μL of experimental compounds (0–100 μg/mL) were added to the culture medium. The 72 h term of compound exposure was used in order to analyze the possible cytotoxic activity of studied compounds without time-related limitations. The MTT reagent (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) was added to the cells following the manufacturer's recommendations (EZ4U, Biomedica, Austria). The results of the reaction were determined by an Absorbance Reader BioTek ELx800 (BioTek Instruments Inc., USA) at 490 nm and 630 nm. The relative amount of untreated (control) cells was taken as 1. The half-maximal inhibition concentration (IC_{50}) of tested compounds was calculated as the drug concentration that reduced cell viability by 50 % [28].

Data analysis. The results were analyzed and illustrated using GraphPad Prism 6 software (GraphPad Software, USA). All data are presented as the mean (M) ± standard deviation (SD) of at least three independent experiments. A two-way ANOVA test (by Dunnett's test) and the column statistics of GraphPad Prism 6 software were used to analyze data. Statistical significance was identified at $P \leq 0.05$.

Results and Discussion

The cytotoxicity of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide was estimated towards the human myeloid leukemia HL-60 cells, human hepatocarcinoma HepG2 cells, human breast adenocarcinoma MCF-7 cells, human lung carcinoma A549 cells, human epidermoid cervix carcinoma KB3-1 cells, human embry-

onic kidney HEK293 cells, and murine fibroblast cell line NIH3T3 (Fig. 3 and 4). We have found that the HepG2 cells were the most sensitive to the effect of the thiadiazole derivative (IC_{50} = 9.4 μg/mL, Fig. 3, Table). The cells of HL-60 line were less sensitive to the effect of the compound (IC_{50} = 45.2 μg/mL). The substance shows low antitumor activity towards MCF-7 cells (IC_{50} = 97.6 μg/mL) and does not reach the IC_{50} value for A549 and KB3–1 cells at 100 μg/mL (Fig. 3, Table).

The *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide slightly inhibited the growth of the pseudonormal cells of HEK293 and NIH3T3 lines. The IC_{50} of this compound was 89.6 μg/mL for the HEK293 cells and did not reach the value of 100 μg/mL for the NIH3T3 cells (Fig. 4, Table). Noteworthy, the cytoto-

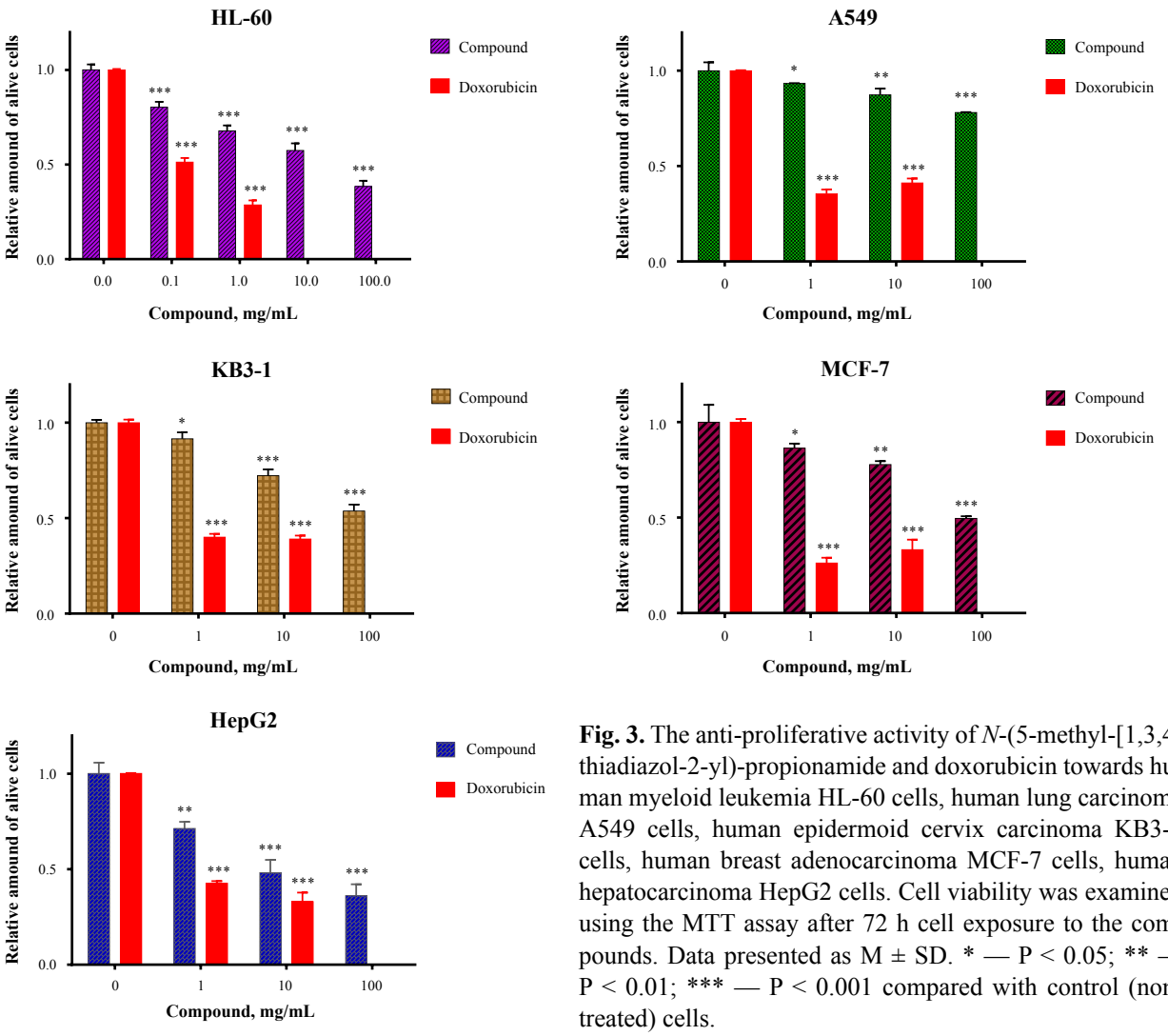

Fig. 3. The anti-proliferative activity of *N*-(5-methyl-[1,3,4] thiadiazol-2-yl)-propionamide and doxorubicin towards human myeloid leukemia HL-60 cells, human lung carcinoma A549 cells, human epidermoid cervix carcinoma KB3-1 cells, human breast adenocarcinoma MCF-7 cells, human hepatocarcinoma HepG2 cells. Cell viability was examined using the MTT assay after 72 h cell exposure to the compounds. Data presented as M ± SD. * — $P < 0.05$; ** — $P < 0.01$; *** — $P < 0.001$ compared with control (non-treated) cells.

Table. **Cytotoxicity indicator (IC50) of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide and doxorubicin at targeting human tumor and non-tumor cells**

Cells	IC_{50} (μg/mL) for *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide	IC_{50} (μg/mL) for doxorubicin
Tumor cells		
human lung carcinoma A549 cells	>100	0.92 ± 0.07
human myeloid leukemia HL-60 cells	45.20 ± 1.8	0.17 ± 0.03
human epidermoid cervix carcinoma KB3-1 cells	>100	0.75 ± 0.04
human hepatocarcinoma HepG2 cells	9.40 ± 0.48	0.82 ± 0.09
human breast adenocarcinoma MCF-7 cells	97.60 ± 0.72	0.78 ± 0.09
Non-tumor cells		
human embryonic kidney HEK293 cells	89.60 ± 0.90	0.63 ± 0.08
murine NIH3T3 fibroblasts	>100	0.90 ± 0.11

Comment: data presented as M ± SD

xicity of the doxorubicin was more prominent for the tumor and pseudonormal cells (Fig. 3, 4). Additional experiments are necessary in order to estimate more deeply the anticancer activity of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide.

The anticancer activity was reported for several derivatives of 1,3,4-thiadiazole. The 2-[5-(4-Substitutedphenyl)-[1,3,4]-thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid hydroxyamides inhibited the growth of HCT116 cells and reduced growth of tumors formed by Ehrlich ascites carcinoma (EAC) cells [29]. The biphenyl-disulfonamide derivative bearing 5-amino-1,3,4-thiadiazole-2-sulfonamide possessed the cytotoxicity towards the human

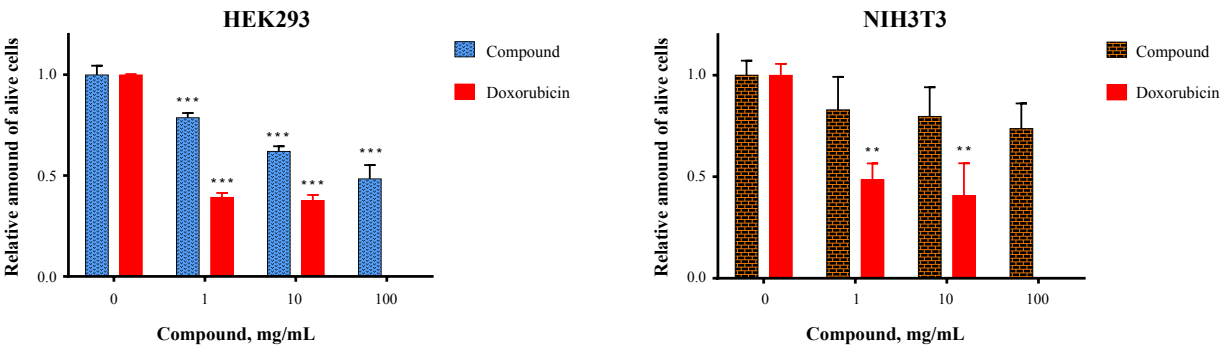

Fig. 4. The anti-proliferative activity of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide and doxorubicin towards non-tumor cells (human embryonic kidney HEK293 cells and murine NIH3T3 fibroblasts). The cell viability was examined using the MTT assay after 72 h of exposure to the compounds. Data presented as M ± SD. ** — $P < 0.01$; *** — $P < 0.001$ compared with control (non-treated) cells.

colon carcinoma HCT116 cells with the GI_{50} value of 3.8 μg/mL and lesser cytotoxicity towards the non-small cell lung cancer H460 and breast carcinoma MCF7 cells [30]. N-(5-Nitrothiazol-2-yl)-2-((5-((4-(trifluoromethyl) phenyl)amino)-1,3,4-thiadiazol-2- yl)thio)acetamide inhibited the viability of the human leukemia K562, MT-2, Jurkat and cervical carcinoma HeLa cells with the IC_{50} values of 33.0, 166.8, 17.9 and 12.4 μM, respectively [31]. Altogether it indicated that 1,3,4-thiadiazol core could be a potential scaffold to develop anticancer drugs. Further in-depth analyses are needed to determine the compounds' selectivity, their mechanisms of action and possible side effects.

Conclusion

The synthesized thiadiazole derivative *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide demonstrated the growth of its inhibitory action towards the tumor cells of HepG2 (liver), HL-60 (leukemia), and MCF-7 (breast) lines with the IC_{50} values in the range of 9.4–97.6 μg/mL. The human hepatocellular carcinoma HepG2 cells were the most sensitive to the effect of the studied compound with the IC_{50} value of 9.4 μg/mL. The anti-proliferative activity of *N*-(5-methyl-[1,3,4]thiadiazol-2-yl)-propionamide dropped in the order: hepatocarcinoma > leukemia > breast carcinoma cells. The derivative slightly inhibited the growth of non-tumor cells of the HEK293 and NIH3T3 lines.

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Антинеопластична дія *in vitro* *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінаміду щодо пухлинних клітин

Н. С. Фінюк, І. В. Драпак, Б. С. Зіменковський, Р. С. Стойка

Мета. Вивчити антинеопластичну дію *in vitro* нового гетероциклічного похідного *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінаміду. **Методи.** Культура клітин; МТТ тест. **Результати.** Нами синтезовано похідне *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінамід, який володіє діуретичною, кардіопротекторною і протизапальною дією. У роботі досліджено вплив сполуки на життєздатність пухлинних клітин різного тканинного генезу: печінки (HepG2), молочної залози (MCF-7), легені (A549), шийки матки (KB3-1), лейкозу (HL-60), а також непухлинних клітин (HEK293 і NIH3T3). Показник цитотоксичності сполуки варіював в межах 9,4–97,6 мкг/мл. Клітини HepG2 гепатокарциноми людини були найбільш чутливі до дії похідного *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінаміду з IC_{50} = = 9,4 мкг/мл. Досліджувана сполука мала незначну токсичність щодо непухлинних клітин ліній HEK293 і NIH3T3. **Висновки.** Антипроліферативна дія *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінаміду щодо пухлинних клітин зменшувалася у наступному порядку: гепатокарцинома > лейкоз > карцинома молочної залози. Отже, нам вдалося синтезувати *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінамід, який одночасно має діуретичну, кардіопротекторну, протизапальну та протипухлинну дії. Дані характеристики роблять досліджувану сполуку потенційним протипухлинним чинником.

Ключові слова: *N*-(5-метил-[1,3,4] тіадіазол-2-іл)-пропінамід, цитотоксичність *in vitro*, протипухлинна активність.

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