

DISCUSSION PAPERS, LECTURES, NEW TRENDS IN MEDICAL SCIENCE

CYTOTOXICITY OF A NEW CONDENSED BENZIMIDAZOLEDIONE DERIVATIVE AGAINST TUMOR AND NORMAL CELL LINES

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RESUME

Condensed benzimidazoledione derivatives with a nodal nitrogen atom can become the basis for the development of clinical therapeutic agents for the effective treatment of oncological diseases. This requires research that includes the synthesis and study of the antitumor activity of compounds of this group.

The aim. Search for new cytotoxic agents from a series of condensed benzimidazole diones with a nodal nitrogen atom.

Materials and methods. The cytotoxic profile of the synthesized compound was evaluated using an MTT test based on the reduction reaction of tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) by mitochondrial dehydrogenases of living cells to formazane crystals insoluble in water. The IC₅₀ values of the cytotoxic effect, which are concentrations of a compound leading to the death of 50 % of cells in a sample, were determined as indicators of effectiveness.

Result. The cytotoxicity of a new benzimidazole derivative, 7-bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione, was demonstrated against two tumor cell lines: lung adenocarcinoma (A549) and breast adenocarcinoma (MCF-7). In turn, for normal human embryonic kidney cells (Hek-293), this compound was approximately 2.5 times less toxic.

Conclusions. The results indicate that fused benzimidazole derivatives with a nodal nitrogen atom are a promising class of compounds for the development of new antitumor agents with selective toxicity.

Key words: fused benzimidazole dione, 7-bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione, cytotoxicity, proliferative activity of tumor cell lines, lung adenocarcinoma (A549), breast adenocarcinoma (MCF-7), human neuroblastoma (SH-SY5Y), human embryonic kidney cells (Hek-293)

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ЦИТОТОКСИЧНОСТЬ НОВОГО КОНДЕНСИРОВАННОГО ПРОИЗВОДНОГО БЕНЗИМИДАЗОЛДИОНА В ОТНОШЕНИИ ЛИНИЙ КЛЕТОК ОПУХОЛЕВОГО И НОРМАЛЬНОГО ПРОИСХОЖДЕНИЯ

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РЕЗЮМЕ

Обоснование. Конденсированные производные бензимидазолдиона с узловым атомом азота могут стать основой для разработки эффективных клинических терапевтических средств для лечения онкологических заболеваний. Для этого необходимо проведение исследований, включающих синтез и изучение противоопухолевой активности соединений данной группы.

Цель исследования. Поиск новых цитотоксических агентов из ряда конденсированных бензимидазолдионов с узловым атомом азота.

Методы. Цитотоксический профиль синтезированного соединения оценивали с использованием МТТ-теста, в основе которого лежит реакция восстановления соли тетразолия (3-(4,5-диметилтиазол-2-ил)-2,5-дифенил-тетразолиум бромид) митохондриальными дегидрогеназами живых клеток до нерастворимых в воде кристаллов формазана. В качестве показателей эффективности были определены величины IC₅₀ цитотоксического эффекта, представляющие собой концентрации соединения, приводящие к гибели 50 % клеток в пробе.

Результаты. Было продемонстрировано наличие цитотоксичности у нового производного бензимидазола – 7-бром-8-хлор-3,4-дигидро-1H-[1,4]оксазино[4,3-а]бензимидазол-6,9-диона в отношении клеток опухолевого происхождения: аденокарциномы легкого (A549) и аденокарциномы молочной железы (MCF-7). В свою очередь для нормальных клеток эмбриональной почки человека (Hek-293) данное соединение было примерно в 2,5 раза менее токсично.

Заключение. Полученные результаты показывают, что конденсированные производные бензимидазола с узловым атомом азота являются перспективным классом соединений для разработки новых противоопухолевых агентов с избирательной токсичностью.

Ключевые слова: конденсированный бензимидазолдион, 7-бром-8-хлор-3,4-дигидро-1H-[1,4]оксазино[4,3-а]бензимидазол-6,9-дион, цитотоксичность, пролиферативная активность клеточных линий опухолей, аденокарцинома легкого (A549), аденокарцинома молочной железы (MCF-7), нейробластома человека (SH-SY5Y), клетки эмбриональной почки человека (Hek-293)

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INTRODUCTION

Modern medicine offers numerous treatment options for different types of cancer, depending on the stage of the disease. Despite its limitations, chemotherapy remains a critical component of cancer treatment [1-3]. Its main advantages are its accessibility and effectiveness, due to the wide range of drugs available that not only treat cancer but also control the disease, preventing the spread of cancer cells and formation of metastases. Chemotherapy is based on the use of specialized drugs – cytostatic agents – that target tumor cells and prevent their growth and division. It is often used in conjunction with surgery and/or radiation therapy, but it can also be used as a stand-alone treatment for cancer. For many patients, chemotherapy plays a crucial role in the battle against cancer, increasing their chances of recovery.

To date, chemotherapy remains the only effective treatment option for many types of cancer [4]. For example, when surgery or radiotherapy are not an option due to extensive tumor spread or systemic involvement, or when there is a high risk of metastasis, chemotherapy is the first line of treatment. Chemotherapeutic agents have been an essential component of cancer treatment for several decades and continue to be the primary option for the management of advanced malignancies when surgery and/or radiotherapy are not feasible for various reasons [5-7].

A promising class of compounds that are already used as antitumor drugs or are under development are azaheterocyclic quinones, such as mitomycin C (a condensed polyfunctional indole-dione derivative) (**A**) [8] and its benzimidazole analogs (**B**) [9-12] (Fig. 1).

It has been reported that condensed alicyclic benzimidazolidiones (Fig. 1**B**) demonstrate more pronounced cytotoxic activity compared to the commercial drug mitomycin C (MMC) [13].

Previously, two new compounds with a similar structure were synthesized, namely, 7,8-dihalogenopyrido[1,2-a]benzimidazole-6,8-dione (**C**) and 7,8-dihalogeno-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole-6,8-dione (**D**) (Fig. 1), and studied their cytotoxicity against several tumor and normal cell lines which were then studied for their cytotoxicity against various tumor and normal cell lines [14]. These compounds demonstrated high cytotoxic effects against all cell lines examined. The cytotoxic

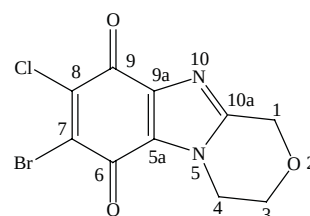
effect of the synthesized compounds was comparable to or exceeding those of the commercial antitumor drugs tamoxifen and mitomycin **C** by several-fold. Compound **D**, containing a saturated heterocycle, was more toxic to cancer cells but less toxic to normal cell lines than its unsaturated counterpart **C**.

THE AIM OF THE STUDY

To continue our previous work on the search for new cytotoxic agents among condensed benzimidazolidiones with a bridgehead nitrogen atom.

MATERIALS AND METHODS

Test compound: 7-Bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione.



The synthesis of this compound involved several steps (Fig. 2).

First, the heterocyclic core – 8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole (**2**) – was formed via reductive intramolecular cyclization of 4-(2-nitro-4-chlorophenyl)morpholine (**1**) using tin(II) chloride. This method is commonly used for the synthesis of similar structures, as it is the most efficient method [15, 16]. Subsequent functionalization of the condensed heterocycle **2** was achieved by bromination using N-bromosuccinimide in concentrated sulfuric acid, nitration of the dihalogen derivative **3** using a potassium nitrate – concentrated sulfuric acid mixture. The resulting 8-bromo-6-nitro-7-chloropyrido[1,2-a]benzimidazole (**4**) was reduced using titanium(III) chloride in an acidic aqueous-ethanol medium. Oxidation of the benzene ring in compound **5** was performed using a mixture of potassium nitrate and concentrated sulfuric acid.

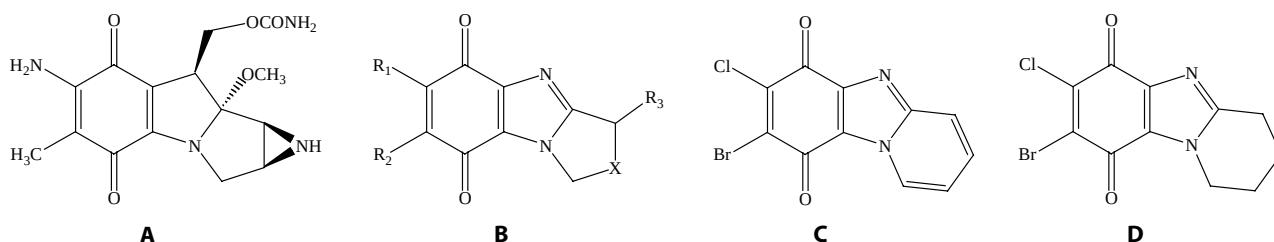
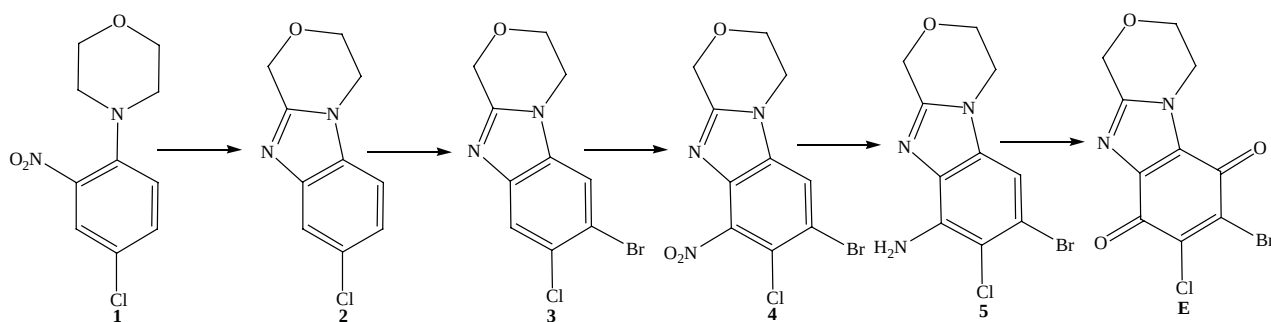


FIG. 1.

Structures of mitomycin C (**A**) and condensed benzimidazole diones (**B-D**) with antitumor activity


FIG. 2.

Scheme for the synthesis of 7-bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione (**E**)

The structure of all intermediates **2-5** and the final benzimidazoledione **E** was confirmed by a set of physicochemical analysis methods: IR and NMR spectroscopy, as well as high-resolution mass spectrometry. Figures 3 and 4 show the ^1H and ^{13}C NMR spectra of heterocyclic quinone **E**. Proton signal assignment was made based on ^1H - ^1H NOESY NMR spectroscopy.

The ^1H NMR spectrum (Fig. 3) shows three doublet signals from the six aliphatic protons $\text{H}^{1,1}$, $\text{H}^{3,3}$, and $\text{H}^{4,4}$ of the three methylene groups of the morpholine ring were recorded in the region of 4–5 ppm, while signals from the amino group protons at 5–6 ppm and aromatic protons at 6–9 ppm were absent. This indicates that the oxidation of the benzene ring in compound **5** (containing an amino group) was successfully oxidized to a benzoquinone ring, and the resulting benzimidazoledione contained no impurities. The proton material balance was maintained.

The presence of a $\text{C}=\text{O}$ group in compound **E** was confirmed by IR spectroscopy. The IR spectrum of this compound exhibited an absorption band at 1667 cm^{-1} characteristic of the carbonyl group of 1,4-benzoquinones [17], which was not present in the spectrum of the amino compound **5**.

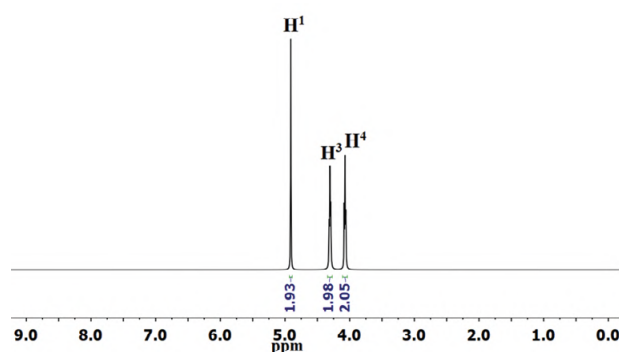
The carbon material balance was also maintained. The ^{13}C NMR spectrum (Fig. 4) revealed 7 signals corresponding to aromatic carbon atoms C^{5a} , C^6 , C^7 , C^8 , C^9 , C^{9a} , and C^{10a} at 130–174 ppm, as well as 3 signals corresponding to alkyl carbon atoms C^1 , C^3 , and C^4 within the range of 44 and 70 ppm.

High-resolution mass spectrometry was used to determine the molecular weight of compound **E**. The m/z $[\text{M}+\text{H}]^+$ value was 318.5311 Da, which agreed with the molecular formula of the synthesized compound $\text{C}_{10}\text{H}_6\text{BrClN}_2\text{O}_3$.

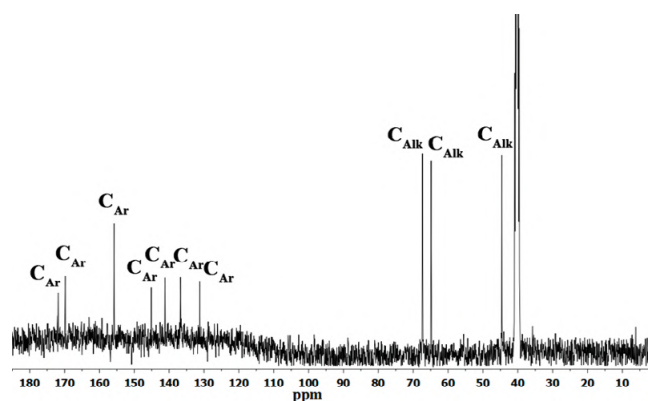
Cell lines and culture conditions

Human lung adenocarcinoma A549 cells, breast carcinoma MCF-7 cells, human neuroblastoma SH-SY5Y cells, and normal human embryonic kidney Hek-293 cells were obtained from the Institute of Cytology of the Russian Academy of Sciences, St. Petersburg, Russia. The cells were cultured in complete DMEM

supplemented with GlutaMAX, 10 % fetal bovine serum, and 1 % penicillin-streptomycin. The cells were incubated in a CO_2 incubator at 37°C (Binder CB150, USA), with a loosely closed lid, in an atmosphere of 5 % CO_2 and 98 % relative humidity for cell growth and proliferation.


FIG. 3.

^1H NMR spectra of 7-bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione (**E**) ($\text{DMSO}-d_6$)


FIG. 4.

^{13}C NMR spectra of 7-bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione (**E**) ($\text{DMSO}-d_6$)

Cytotoxicity assessment

The MTT assay was employed to determine the cytotoxicity of the synthesized compounds [18]. This technique is based on the conversion of tetrazolium salts (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into water-insoluble formazan crystals by mitochondrial dehydrogenases in living cells.

Exponentially growing cells were plated in 96-well plates (10,000 cells per well in 200 μ L). After 24 hours, test compounds dissolved in DMSO (concentrations ranging from 0.01 to 100 μ M) were added in triplicate (2 μ L per well). Control cells received 1 % DMSO.

Following 24- and 72-hour incubation with the compounds, MTT solution (5 mg/mL) was added to each well, and the plates were incubated at 37°C for 2 hours. The MTT reagent was then carefully removed and 200 μ L of DMSO added to dissolve any formazan crystals that had formed. Optical density was measured at 540 nm wavelength.

The IC_{50} values for the cytotoxic effect, which represent the compound concentrations leading to 50 % cell death in a sample, were used as efficacy endpoints in this study.

Statistical analysis

Statistical analysis was performed using descriptive and mathematical statistical methods, using the Statistica 10.0 (StatSoft Inc., USA) and GraphPad Prism 5.0 (GraphPad Software, USA) software packages. Quantitative data are presented as mean (Mean) and standard deviation (SD).

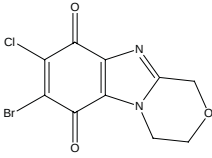
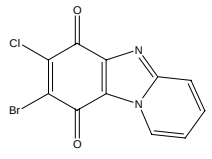
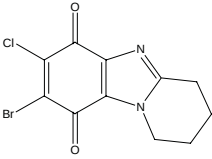
RESULTS AND DISCUSSION

The study employed a novel condensed benzimidazoledione **E**, which contains two halogen substituents. It is worth noting that polyhalogenated heterocyclic quinone derivatives may hold particular interest, as the presence of halogen atoms significantly enhances their biological activity [19]. The structural distinction of this compound compared to the previously studied benzimidazoledione **D** (Table 1) is the incorporation of an additional heteroatom (oxygen) into the heterocycle fused with the imidazole ring.

When evaluating the cytotoxic activity of compound **E** (Table 1) against tumor-derived cells – lung

TABLE 1

IC_{50} VALUES (μ M) OF THE CYTOTOXIC EFFECT OF BENZIMIDAZOLEDIONE SERIES COMPOUNDS

No.	Compound	A549	MCF-7	SH-SY5Y	Hek-293
1	 (E)	11.86 $\pm$ 0.19	8.90 $\pm$ 0.19	10.75 $\pm$ 0.93	25.38 $\pm$ 0.02
2	 (C)	12.38 $\pm$ 0.21	9.02 $\pm$ 0.17	9.76 $\pm$ 0.47	16.78 $\pm$ 0.39
3	 (D)	7.81 $\pm$ 0.64	8.35 $\pm$ 0.32	9.49 $\pm$ 0.80	16.01 $\pm$ 0.18
4	Mitomycin C	18.09 $\pm$ 1.80	20.37 $\pm$ 1.74	7.04 $\pm$ 0.02	6.59 $\pm$ 1.46

adenocarcinoma (**A549**), breast adenocarcinoma (**MCF-7**), human neuroblastoma (**SH-SY5Y**) – and normal-derived cells – human embryonic kidney (**Hek-293**), it was observed that this compound exhibited pronounced cytotoxicity specifically against tumor-derived cell cultures (Table 1). For comparison, the cytotoxicity of two previously characterized compounds with similar structural features, **C** and **D**, is also presented in the table.

Comparing the activity of the novel heterocyclic quinone **E** with the cytotoxicity of the commercial antitumor drug mitomycin C, this compound was more effective than the reference molecule against the A549 and MCF-7 cell lines. However, mitomycin C exhibited greater cytotoxicity against SH-SY5Y cells. Notably, this compound also retains the ability to have a less pronounced toxic effect on normal cells, similar to the previously synthesized benzimidazolediones **C** and **D**, which contain a pyridine or piperidine ring, respectively. At the same time, the IC_{50} values for synthesized benzoquinone **E** are significantly lower than those for previously obtained compounds. This clearly indicates the potential of condensed benzimidazoledione derivatives as cytotoxic agents with a selective mechanism of action specific to tumor-derived cells.

Furthermore, to determine the potential antiproliferative properties of the novel heterocyclic quinone **E**, we conducted studies to measure IC_{50} values for various time points of exposure to this compound in tumor-derived cells. Specifically, we extended the exposure time from 24 hours to 72 hours, corresponding to the duration of multiple cell cycles.

After 72 hours of incubation, it was found that tumor-derived cells exhibited 50 % mortality at lower concentrations of benzimidazoledione **E** (IC_{50} values: for **A549** – $6.34 \pm 0.43 \mu\text{M}$, for **MCF-7** – $6.70 \pm 0.06 \mu\text{M}$, and for **SH-SY5Y** – $5.98 \pm 0.24 \mu\text{M}$) compared to shorter 24-hour exposures. For example, for the lung adenocarcinoma cell line, the IC_{50} decreased almost twofold after 72-hour exposure to benzoquinone **E** compared to 24-hour treatment.

Therefore, the findings obtained allow us to infer that the novel benzimidazoledione **E** not only exerts a potent cytotoxic effect, leading to the rapid death of tumor cells, but also effectively inhibits their proliferative capacity. This suggests the potential of utilizing this compound as the basis for developing therapeutic agents that can influence the proliferative potential of cancer cells.

CONCLUSION

The new condensed benzimidazoledione derivative, 7-bromo-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione (**E**), exhibited stronger cytotoxicity compared to the commercial antitumor drug mitomycin C against tumor-derived cell lines – lung adenocarcinoma (**A549**) and breast adenocarcinoma (**MCF-7**). Moreover, this compound was significantly

less toxic to normal cells. These data, along with previously obtained results on the cytotoxic profile of structurally related compounds, suggests that condensed benzimidazoledione derivatives are promising candidates for the development of novel selective chemotherapeutic agents.

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Conflicts of interest

The authors declare no conflicts of interest.

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