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BIOLOGICAL ACTIVITY OF ISOPROPYLAMINE ANTHRAQUINONE

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INFORMATION

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ABSTRACT

The aim of the work. To predict the drug-likeness and toxicity using modern web tools of the isopropylaminoanthraquinone compound, as well as to experimentally prove a possible mechanism of antitumor activity.
Materials and Methods. For the anthraquinone compound, an *in silico* drug-likeness and toxicity screening was performed using SwissADME and ProTox II online services. Prediction of the antitumor activity mechanism was analyzed using the US National Cancer Institute (NCI) PRISM service.
Results and Discussion. 1-Amino-4-(isopropylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid was synthesized by the reaction of nucleophilic substitution of bromamic acid with isopropylamine, which acted as a nucleoforming agent. The structure of the synthesized derivative (98% yield) was confirmed by ^{1}H, ^{13}C NMR, IR and LC-MS spectra. The studied anthraquinone compound showed satisfactory drug-like characteristics and a low toxicity profile.
Conclusions. The obtained results may become a platform for further structural optimization of the identified compound based on anthraquinone with an isopropylamine fragment in the development of modern anticancer drugs.

Introduction. Anthraquinones are a class of molecules that underlie several drugs and compounds with a broad spectrum of biological activities, namely laxative [1], anti-inflammatory [2], anticancer [3–5], antiviral [6], antimicrobial, antifungal [7] and neurotrophic [8]. The mechanism of their activity is determined by the electron-accepting properties of the anthraquinone system, which may form complexes with charge transfer with purine and pyrimidine bases of DNA [9]. Another property of the planar anthraquinone system is intercalation – the ability to be placed between pairs of DNA bases, reducing their degree of twisting and halting replication. Moreover, anthraquinones are well-known as inhibitors of tyrosinase [10], ecto-5'-nucleotidase [11], c-Met kinase [12], Caspase-3 and AKT activator [13], antagonist of platelet P2Y12 receptor [14], P2-receptor [15], antagonist and positive modulators of the P2X2 Receptor [16], activator of large conductance Ca^{2+}-activated K+ (BK) channels [17].

In recent years, 4-substituted anthraquinone derivatives have been actively studied as potential cytotoxic agents, firstly, due to their structural similarity to anthracyclines, mitoxantrone, and ametanthrone, and secondly, due to the presence of reactive centers for further functionalization to achieve this vector of biological activity [18–20]. It is worth noting that anthraquinone derivatives with an amino group in position 4 deserve special interest as potential cytotoxic agents. This is due to their ability to disintegrate with the release of a nitrogen molecule and the formation of a carbonium ion, which interacts with the nucleophilic DNA substrate and thus alkylates it. The formation of a covalent bond with nucleic bases changes the spatial structure of DNA, blocking the processes of transcription and replication [21]. Accordingly, the synthesis of new functionally substituted derivatives of 4-aminoanthraquinone as potential biologically active compounds is relevant in modern medicinal chemistry and the search for potential drug-like molecules.

Materials and Methods

2.1. General Information and Compound 2 Synthesis.

Melting points were measured in open capillary tubes on an IA 9200 Electrothermal melting point apparatus (Bibby Scientific Limited, Stone, UK) and are uncorrected. The elemental analyses (C, H, N) were performed using the FlashSmart CHNS/O analyzer (Thermo Scientific, Waltham, MA, USA) and were within ±0.4 % of the theoretical values. The 400 MHz-^{1}H and 100 MHz-^{13}C spectra were recorded on Varian Mercury 400 (400 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). Chemical shifts (δ) are quoted in ppm and coupling constants (J) are reported in Hz. LC–MS spectra were obtained on Ag-ilent 1260 Infinity II with single-quadrupole mass-selective detector Agilent 6125 (Agilent Technologies, Santa Clara, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (DC-Fertigfolien ALUGRAM Xtra SIL G/UV254, Germany) using eluents of different compositions. IR spectra were recorded on a spectrophotometer Specord M-80 (Carl Zeiss Industrielle Messtechnik GmbH, Jena, Germany) in KBr tablets. Solvents and reagents (Bromaminic acid sodium salt, CAS number: 6258-06-6; Isopropylamine, CAS number: 75-31-0) that are commercially available were used without further purification.

1-Amino-4-(isopropylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid (2).

A mixture of bromaminic acid (4.04 g, 0.01 mol) 1, isopropylamine (0.015 mol), and sodium carbonate (2.1 g) in water (50 mL) was heated to 70 °C. Then a suspension of $CuSO_4$ (0.5 g) and $FeSO_4$ (0.5 g) in water was added, the temperature of the reaction mixture was increased to 90–100 °C for 1 hour and kept at this temperature for 4 hours. The progress of the reaction and its completion were monitored by TLC until the disappearance of traces of starting compounds on the plate (eluent: *o*-xylene – acetone, 4:6). The reaction mixture was cooled to room temperature, acidified with concentrated HCl, and the precipitate that fell was filtered, washing with sodium chloride solution (20%, 60 ml). The crude blue product was dissolved in hot water (50 ml) and recrystallized from ethanol (Fig. 1).

Blue crystals, yield: 98 %, Rf = 0.81 (ethyl acetate/benzene: 1/2), mp 262–264 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 1.10–1.20 m (6H, CH_3),

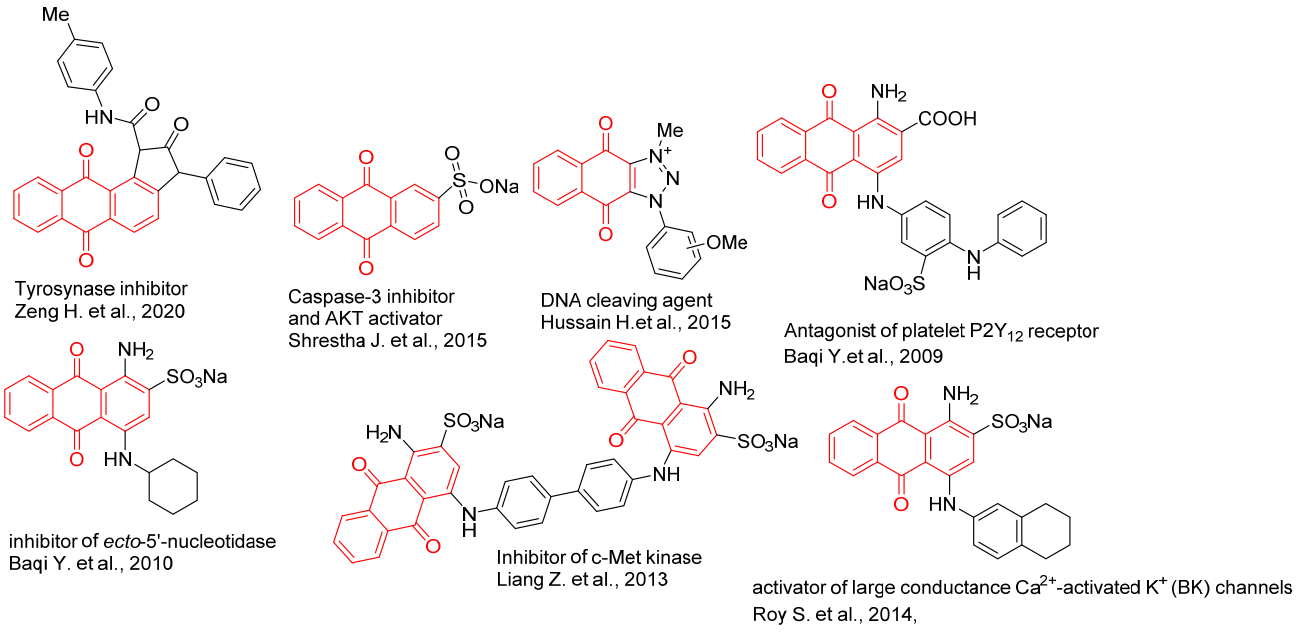

Fig. 1. Structures of biologically active anthraquinones.

3.90–3.95 m (1H, CH), 7.80 t (3H, arom.), 8.20 d (2H, arom.), 10.80 s (1H, NH). ^{13}C NMR (126 MHz, DMSO-d6, δ): 45.2, 60.2, 109.3, 109,6, 121.6, 126.1, 126.3, 132.6, 133.0, 134.4, 143.5, 143.7, 145.8. IR (KBr, cm^{-1}): 1460 (CH), 1500 (NH), 1630 (C=O), 2920 (CH_3). LC-MS, (m/z) [$C_{17}H_{16}N_2O_5S + H^+$] = 361.2.

2.2. Cell lines.

Cell lines K562, HaCaT, Balb-3T3, U937, HT1080, HT-29, Skov-3, HCT-116 were kindly provided by the Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine (Kyiv, Ukraine). Cells were cultivated in Dulbecco's Modified Eagle Medium (DMEM, Biowest, Nuaillé, France) or RPMI-1640 medium (Biowest, France), containing 10% of fetal bovine serum (FBS, Biowest, Nuaillé, France) according to the recommendations of American Type Culture Collection (ATCC), under the incubation condition of 5 % CO_2 humidity at 37 °C.

2.3. MTT assay for measuring cells viability.

For the assay, either 4.000 adherent cells or 15.000 suspension cells per well were plated in 96-well plates with 100 µL of either DMEM or RPMI-1640 media, enriched with 10 % heat-inactivated fetal bovine serum. The cells were cultured for 72 h at 37 °C in a CO_2-incubator and treated with the compound at concentrations of 1, 10, and 50 µM. Post incubation, the media was substituted with MTT reagent (5 mg/mL) and further incubated for 4 hours. The formed formazan crystals were solubilized in dimethylsulfoxide, and the absorbance was read using a BioTek ELx800 Absorbance Reader (BioTek Instruments Inc., Winooski, VT, USA). The IC_{50} values were determined through nonlinear regression analysis using GraphPad Prism 8 software version 8.0.1 (GraphPad Software, San Diego, CA, USA). Data were presented as the mean (M) ± standard deviation (SD) from three replicates [25].

Results and Discussion

3.1. Synthesis of title compound.

Compound 2 was synthesized via the nucleophilic substitution reaction of broma-minic acid 1 with isopropylamine as the nucleophilic agent (Fig. 2). It should be noted that in this reaction, a bifunctional catalyst consisting of divalent ferric salts and copper is used in an aqueous medium.

The identity and purity of the obtained anthraquinone-containing isopropylamine derivative was confirmed by the analysis of ^{1}H, ^{13}C NMR and LC-MS spectral data. Signals for the methyl groups of isopropylamine in compound 2 appear as a multiplet at 2.22-2.27 ppm. The enone fragment of 1-amino-4-(isopropylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid appears as two doublets at 8.17 and 8.22 ppm, the first with the spin constant spin-spin coupling of 16.1 Hz, which indicates the presence of a hydrogen bond in these protons. In addition, in the ^{13}C NMR spectrum of compound 2, signals of carbon atoms within carbonyl (C=O) groups were observed at 184.1 and 182.0 ppm. The peak of the molecular ion, which was observed at the value of m/z 361.0 $[M+H]^+$ in the mode of positive ionization in the mass spectrum, confirmed the formation of Compound 2.

3.2. Molecular and pharmacokinetic properties.

ADME prediction for the Compound 2 was conducted using the SwissAdme online server [22]. The results suggest favorable gastrointestinal absorption but indicate a lack of ability to penetrate the blood-brain barrier. The predicted lipophilicity, represented by log Po/w, indicates promising permeability across cell membranes and oral absorption for the studied derivative. Importantly, the compound is not anticipated to act as a substrate for P-glycoprotein. Its negative skin permeability suggests limited penetration through the skin's cellular barrier. SwissAdme also predicts potential pharmacokinetic interactions with specific cytochrome P450 enzymes, notably CYP2C9 and CYP3A4. Despite these findings, the collective predictive data support Compound 2 as a promising candidate for further detailed investigations (Table).

Continuing our in silico studies, we employed similarity score measures using SwissSimilarity, which offers various two-dimensional screening methods with FP2 topological chemical fingerprints utilizing data from the Ligand Expo database to identify similar drug candidates or known bioactive molecules across all libraries of small molecules [23]. The similarity score ranges from 0 for entirely different molecules to 1 for identical compounds. Consequently, path-based (linear) molecular

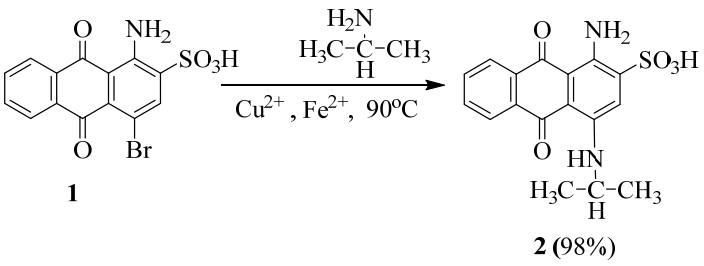

Fig. 2. Synthesis of anthraquinone-containing isopropylamine derivative. Reagents and conditions: bromaminic acid 1 (0.01 mol), isopropylamine (0.015 mol), $CuSO_4$ (0.5 g), $FeSO_4$ (0.5 g), Na_2CO_3 (2.1 g), reflux, 2 h, 88–98 %.

Table
Physicochemical and pharmacokinetics properties of Compound 2

	Physicochemical properties	
1	Molecular weight	360.38
2	Num. heavy atoms	25
3	Num. arom. heavy atoms	12
4	Num. rotatable bonds	3
5	Num. H-bond acceptors	5
6	Num. H-bond donors	3
7	Molar Refractivity	92.93
8	TPSA Å²	134.94
9	Consensus log Po/w	1.89
10	Lipinski᾽Rule	Yes
	Pharmacokinetics	
11	GI absorption	High
12	BBB permeant	No
13	P-gp substrate	No
14	CYP1A2 inhibitor	No
15	CYP2C19 inhibitor	No
16	CYP2C9 inhibitor	Yes
17	CYP2D6 inhibitor	No
18	CYP3A4 inhibitor	Yes
19	Log Kp (SP) (cm/s) (skin permeation)	-6.50
20	Bioavailability Score	0.56

fingerprint analysis from the DrugBank database identified four compounds with similarity scores ranging from 0.852 to 0.729 (Figure S1, Supplementary Materials).

Given our prior findings, we were particularly interested in exploring the potential targets of 1-amino-4-(isopropylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid. SwissTargetPrediction is an online tool specialized in target prediction based on structural similarities between investigational compounds and well-established ligands [24]. Ectonucleoside triphosphate diphosphohydrolase 1 (UniprotID: P49961, CHEMBL5722), Hepatocyte growth factor (UniprotID: P14210, CHEMBL5479), and CDGSH iron-sulfur domain-containing protein 1 (UniprotID: Q9NZ45, CHEMBL1795168) emerged as the top predicted targets due to the similarity of the tested compound (Figure S2, Supplementary Materials).

3.3. Cytotoxic activity in vitro of Compound 2.

The Compound 2 was assessed for its cytotoxic activity on several pseudo-normal and tumor cell lines. The pseudo-normal cell lines included mouse embryonic fibroblasts (BALB-3T3) and human keratinocytes (HaCaT), while tumor cell lines were represented by colon (HCT-116, HT-29), leukemia (K562, U-937), ovarian (Skov-3), and fibrosarcoma (HT-1080). It was found that the compound 2 did not impact significantly the viability of any of studied cell lines, with an IC_{50} exceeding 50 μM (Fig. 3). At a concentration of 10 μM, it modestly suppressed the growth of BALB-3T3, HaCaT, K562, HCT-116, HT-29, and Skov-3 cells.

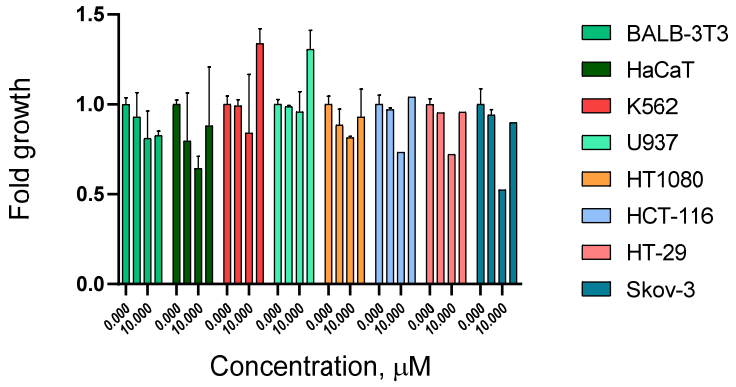

Fig. 3. Effect of compound 2 on the viability of pseudonormal and tumor cell lines after 72 h of treatment.

Conclusions. The synthesis of 1-amino-4-(isopropylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid from bromaminic acid with isopropylamine via the nucleophilic substitution reaction. The target compound revealed satisfactory drug-like parameters according to the SwissAdme prediction and possessed moderate cytotoxic activity on BALB-3T3, HaCaT, K562, HCT-116, HT-29, and Skov-3 cell lines.

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Conflicts of interest: authors have no conflict of interest to declare.

Конфлікт інтересів: відсутній.

БІОЛОГІЧНА АКТИВНІСТЬ ІЗОПРОПІЛАМІНОАНТРАХІНОНУ

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Мета роботи. Здійснити прогнозування лікоподібності та токсичності з використанням сучасних веб-інструментів сполуки ізопропіламіноантрахінону, а також експериментально довести можливий механізм реалізації протипухлинної активності.
Матеріали і методи. Для сполуки антрахінону проведено *in silico* скринінг лікоподібності та токсичності з використанням онлайн-сервісів SwissADME та ProTox II. А для прогнозування механізму реалізації протипухлинної активності було виконано аналіз за допомогою сервісу PRISM Національного інституту раку США (NCI).
Результати й обговорення. 1-аміно-4-(ізопропіламіно)-9,10-діоксо-9,10-дигідроантрацен-2-сульфокислоту було синтезовано за допомогою реакції нуклеофільного заміщення бромамінової кислоти ізопропіламіном, який виступав як нуклеофуючий агент. Структуру синтезованого похідного (з виходом 98 %) підтвердили спектри ^{1}H, ^{13}C NMR, IR і LC-MS. Досліджувана сполука антрахінону в результаті проведених досліджень проявила задовільні лікоподібні характеристики та низький профіль токсичності.
Висновки. Результати, отримані в процесі досліджень, можуть стати платформою для подальшої структурної оптимізації ідентифікованої сполуки на основі антрахінону з фрагментом ізопропіламіну в розробці сучасних протипухлинних лікарських засобів.

Ключові слова: антрахінони; синтез; цитотоксичність; SwissAdme.

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