Синтез біологічно активних сполук

ФАРМАЦЕВТИЧНИЙ ЧАСОПИС

http://ojs.tdmu.edu.ua/index.php/pharm-chas

DOI https://doi.org/10.11603/2312-0967.2023.4.14290
УДК 547.789.1:615.012.1]073/.076

SYNTHESIS AND EVALUATION OF THE ANTICANCER ACTIVITY OF 2-AMINOISOINDOLE-THIZOLIDINONE HYBRIDS

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ІНФОРМАЦІЯ

Надійшла до редакції / Received: 02.10.2023
Після доопрацювання / Revised: 27.10.2023
Прийнято до друку / Accepted: 03.11.2023

Ключові слова:
organic synthesis;
heterocycles;
thiazolidinone;
isoindole;
anticancer activity.

АНОТАЦІЯ

The aim of the work. Synthesis 2-aminoisoindole thizolidinone derivatives via [2+3]-cyclocondensation reaction using different equivalents of electrophilic synthon $[C_2]^{2+}$ and the anticancer activity screening *in vitro* of synthesized molecules.
Materials and Methods. Organic synthesis, NMR spectroscopy, pharmacological screening *in vitro*.
Results and Discussion. The [2+3]-cyclocondensation reaction of 1-(1,3-dioxoisoindolin-2-yl)thiourea with chloroacetic acid, *N*-arylmaleimides and *β*-aroylacrylic acids in glacial acetic acid allowed to obtain 5-substituted 2-aminoisoindole thizolidinone hybrids. Synthesis of indole-containing 2-aminoisoindole thizolidinones was performed by the one-pot three-component synthetic protocol of 1-(1,3-dioxoisoindolin-2-yl)thiourea, appropriative isatin, and monochloroacetic acid. The anticancer activity of synthesized compounds was studied at a concentration of 10^{-5} M on a panel of sixty cancer cells according to the standard protocols of the National Cancer Institute (NCI, Bethesda, MD, USA) Developmental Therapeutic Program (DTP).
Conclusions. An efficient method for synthesis new isoindole-thiazolidinones was studied. Indole-containing 2-aminoisoindole thizolidinone derivative demonstrated a moderate level of anticancer activity with an impact on melanoma, renal, and breast cancer cell lines.

Introduction. Modern research in medicinal chemistry characterizes the thiazolidinone core as a powerful and synthetically available pharmacophore fragment in the search for new biologically active compounds [1,2]. One of the most popular synthetic approach to obtain 2 and 5-substituted thiazolidinone derivatives is the [2+3]-cyclocondensation reaction [3,4]. Diversity of *S,N*-binucleophiles such as mono- and disubstituted thioureas, thioamides, thiosemicarbazides, thiocarbohydrazides allows the formatting of 4-thiazolidone core with other pharmacologically attractive fragments in reaction conditions with different equivalents of electrophilic synthon $[C_2]^{2+}$ (*α*-halogen-containing carboxylic acids/esters, *N*-arylmaleimides, maleic anhydride, *β*-aroylacrylic acids, *α*-bromo-*γ*-butyrolactone, etc.) [5-7].

Recent research in the search for new biologically active molecules demonstrated that a combination of thiazolidinone fragment with different nitrogen-containing heterocyclic systems such as pyrrole, indole, pyrazole, triazole etc. is a promising way to identify anticancer molecules [1,2,8,9]. Isoindole derivatives are known as a azaheterocyclic multi-target antitumor agents with different molecular mechanisms of action (VEGFR-2, EGFR tyrosine kinase and HER2 inhibition) [10-13]. Despite the wide range of chemical and biological

studies of thiazolidinone and phtalimide derivatives, data on the synthesis and anticancer activity evaluation of isoindole-thizolidinone hybrids are limited [14-16].

Materials and Methods. Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer (PerkinElmer, Waltham, MA, USA) and were within ±0.4% of the theoretical values. All spectra were recorded at room temperature except where indicated otherwise and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are reported in Hz. LC-MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass backed TLC plates (Merck Kieselgel 60 F_{254}). Solvents and reagents that are commercially available were used without further purification. Starting compound **1.2** was prepared according to protocol described in [17].

For target compounds (**1.3**, **1.4**, **1.6**, **1.7**, **1.9**) the anticancer activity screening was accomplished according to the standard protocols of the National Cancer Institute (NCI, Bethesda, MD, USA) Developmental Therapeutic Program (DTP) [18-21]. The screening process included evaluation of antitumor activity at the concentration of 10^{-5} M against a panel of approximately sixty cancer cell lines representing different types of cancer (leukemia, melanoma, non-small cell lung cancer, colon, CNS, ovarian, renal, prostate, and breast cancers) and incubated fell within 48 hours. The endpoint was defined by sulforhodamine B. The results for investigated compounds were expressed as growth percentage (Growth percent, GP%) of cells relative to the growth of control cells without tested samples.

Results and Discussion. Phthalic anhydride **1.1** was used as a commercially available starting reagent to obtain 1-(1,3-dioxoisoindolin-2-yl)thiourea **1.2**. The [2+3]-cyclocondensation reaction of the above-mentioned *S,N*-binucleophile **1.2** with monochloroacetic acid and sodium acetate, leading to 2-((4-oxo-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-dione **1.3** using conventional thermal heating in acetic acid. 2-((4-Oxo-5-(2-oxoindolin-3-ylidene)-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-diones **1.4, 1.5** were obtained by interaction of 1-(1,3-dioxoisoindolin-2-yl)thiourea **1.2**, chloroacetic acid, appropriative isatin with catalytic amount of sodium acetate in the one-pot three-component protocol. The synthesis of compounds **1.6-1.8** was accomplished via a reaction of **1.2** and N-arylmaleimides in acetic acid. The same reaction conditions were used in the transformation of **1.2** and appropriative 4-oxo-4-phenylbut-2-enoic acid into 2-((4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-diones **1.9**, **1.10** (Figure 1).

The structure of target derivatives **1.3-1.10** was characterized by ^{1}H NMR and LC-MS spectra. Based on the ^{1}H NMR spectral analysis, a prototropic amino-imine tautomerism was established for the synthesized compounds, and the imino form can exist in the form of Z- and E-enantiomeric forms (Figure 2). Moreover, the

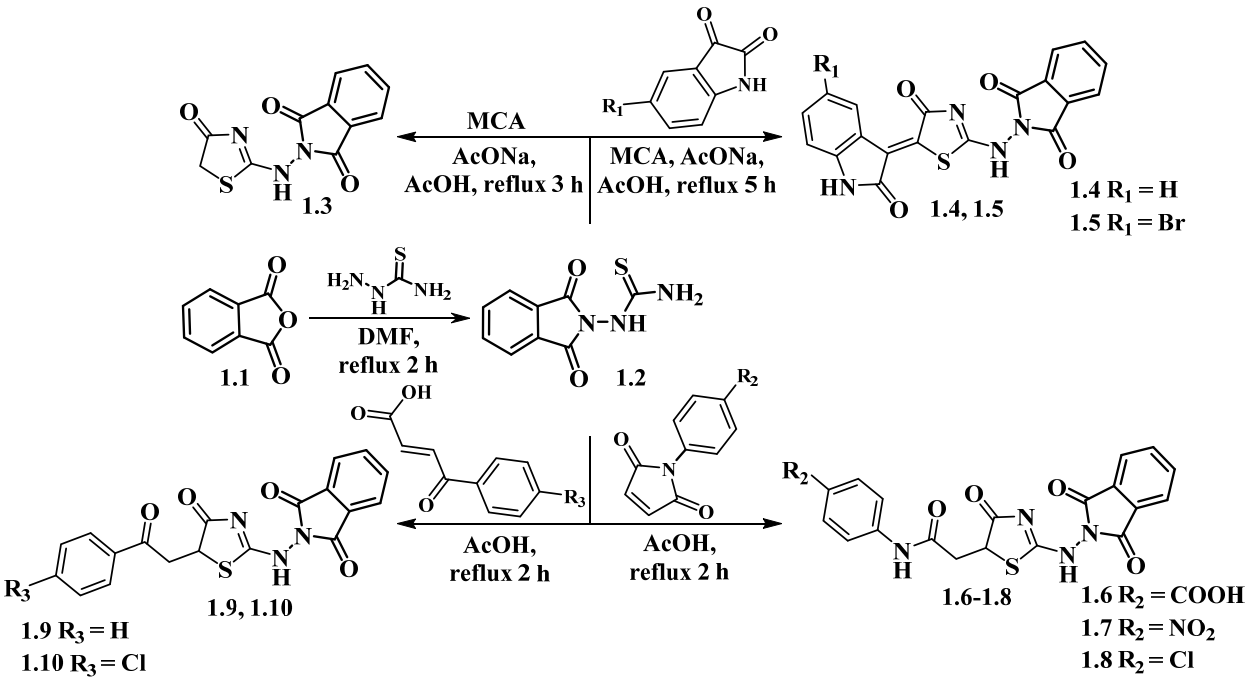

Fig. 1. Synthesis of 2-aminoisoindole thizolidinone derivatives.

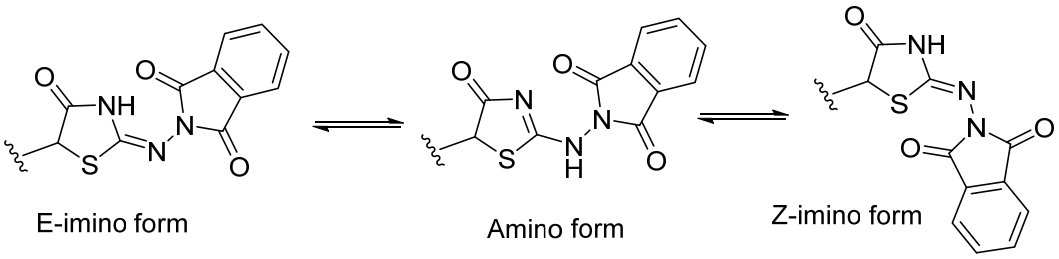

Fig. 2. Possible tautomeric forms for synthesized compounds.

chemical shifts of the imino form are located in the region of a weak magnetic field. The signal of the cyclic NH group appears in the form of a broad singlet at 11.28-12.63 ppm, and the similar exocyclic group in the form of a sharp singlet at 10.29-10.92 ppm. Signal doubling is characteristic for other substituents. The CH_2CH group, due to diastereotopic protons of the methylene fragment in the ^1H NMR spectrum, forms an ABX system with a set of two doublets, doublets and a multiplet, or due to the overlap of signals with the formation of three multiplets at 2.45-2.87, 2.97-3.88 and 4.00-4.77 ppm. It is worth noting that in the case of amides of 2-aryliminothiazolidin-4-one-5-acetic acids, no amino forms are identified, but only Z- and E-imino forms.

The screening results demonstrated in general a moderate level of anticancer activity of synthesized molecules (Table 1). Among studied compounds indole-containing 2-aminoisoindole thiazolidinone **1.4** showed the tumor lines' growth ranged from 70.17% to 123.12%, with an average growth value of 94.81%. Melanoma cancer line MALME-3M (growth percent 77.81 %), renal cancer line UO-31 (growth percent 70.17%), and breast cancer lines MCF7 (growth percent 73.57%), MDA-MB-231/ATCC (growth percent 77.88%) were the most sensitive to the activity of 5-ylidene derivative **1.4**.

Conclusions. In the present paper the [2+3]-cyclocondensation reaction of 1-(1,3-dioxoisoindolin-2-yl)thiourea with chloroacetic acid, *N*-arylmaleimides and β-aroylacrylic acids have been studied. Also, we reported an efficient one-pot three-component synthetic protocol for the heterocyclization of new indole-containing 2-aminoisoindole thizolidinone derivatives with satisfactory yield and high purity. The structure of the obtained compounds was confirmed by NMR spectroscopy and LC-MS spectrometry analysis. The in vitro screening of the anticancer activity allowed us to identify 2-((4-oxo-5-(2-oxoindolin-3-ylidene)-4,5-dihydrothiazol-2-yl)amino) isoindoline-1,3-dione, that demonstrated impact on melanoma, renal and breast cancer cell lines.

Experimental part

The general procedure for the synthesis of 2-((4-oxo-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-dione (1.3)

A mixture of 1-(1,3-dioxoisoindolin-2-yl)thiourea **1.2** (4.5 mmol), monochloroacetic acid (4.5 mmol), and sodium acetate (4.5 mmol) in the glacial acetic acid (10 mL) was heated under reflux for 3 h (monitored by TLC). After completion, the reaction mixture was cooled to room temperature. The formed yellow solid of **1.3** was

Table 1
Antitumor activity of synthesized compounds (10^{-5} M)

Compound	Mean Growth, %	Range of Growth, %	The Most Sensitive Cell Lines/Growth, %
1.3	100.00	86.53-117.39	CAKI-1 (Renal cancer) / 86.53 UO-31 (Renal cancer) / 87.67
1.4	94.81	70.17-123.12	MALME-3M (Melanoma) / 77.81 UO-31 (Renal cancer) / 70.17 MCF7 (Breast cancer) / 73.57 MDA-MB-231/ATCC (Breast cancer) / 77.88
1.6	100.67	87.88-112.04	UACC-62 (Melanoma) / 87.88 HL-60(TB) (Leukemia) / 89.64
1.7	106.29	90.52-130.49	MCF7 (Breast cancer) / 90.52
1.9	98.60	76.30-122.87	SNB-75 (CNS Cancer) / 76.30 HOP-92 (Non-Small Cell Lung Cancer) / 82.90

collected by filtration and recrystallized from a mixture of DMF–ethanol (1:2).

A yellow powder. Yield – 77 %. M. p. – 231–233°C (DMF:EtOH(1:2)). Anal. Calcd. for $C_{11}H_7N_3O_3S$, %: C 50.57; H 2.70; N 16.08. Found, %: C 50.65; H 2.67; N 16.14. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 4.09, 4.17 (2*br.s, 2H, CH_2), 7.82-7.94 (m, 4H, arom.), 12.30, 12.52 (br.s, s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 34.15, 123.31, 130.06, 134.78, 163.80, 164.07, 173.64. LC-MS (ESI), m/z, peak area: 262.0 $[M+H]^+$, 100.0 %.

The general procedure for the synthesis of 2-((4-oxo-5-(2-oxoindolin-3-ylidene)-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-diones (1.4, 1.5)

A mixture of 1-(1,3-dioxoisoindolin-2-yl)thiourea **1.2** (4.5 mmol), appropriate isatin (5.4 mmol), chloroacetic acid (4.5 mmol) was refluxed for 5 h with sodium acetate (9.0 mmol) in glacial acetic acid (10 mL) (monitored by TLC). The precipitated crystals were filtered off, washed with water and ethanol (5–10 mL), and recrystallized from a mixture of DMF–ethanol (1:2).

*2-((4-Oxo-5-(2-oxoindolin-3-ylidene)-4,5-dihydrothiazol-2-yl)amino) isoindoline-1,3-diones (**1.4**)*

A red powder. Yield – 69 %. M. p. – 224–226°C (DMF:EtOH(1:2)). Anal. Calcd. for $C_{19}H_{10}N_4O_4S$, %: C 58.46; H 2.58; N 14.35. Found, %: C 58.52; H 2.64; N 14.28. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.91 (d, *J* = 7.0 Hz, 1H, arom.), 6.97 (d, *J* = 7.0 Hz, 1H, arom.), 7.00-7.11 (m, 2H, arom.), 7.37 (br.s, 2H, arom.), 8.24 (d, *J* = 7.1 Hz, 1H, arom.), 8.83 (d, *J* = 7.1 Hz, 1H, arom.),10.89 (s, 1H, NH), 11.30 (s, 1H, NH). LC-MS (ESI), m/z, peak area: 388.0 $[M-H]^+$, 100.0 %.

*2-((5-(5-Bromo-2-oxoindolin-3-ylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-dione (**1.5**)*

A red powder. Yield – 72 %. M. p. – >350°C (DMF:EtOH(1:2)). Anal. Calcd. for $C_{19}H_9BrN_4O_4S$, %: C 48.63; H 1.93; N 11.94. Found, %: C 48.59; H 1.88; N 12.01. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.91 (d, *J* = 7.0 Hz, 1H, arom.), 6.97 (d, *J* = 7.0 Hz, 1H, arom.), 7.10-7.30 (m, 3H, arom.), 8.24 (d, *J* = 7.1 Hz, 1H, arom.), 8.78 (s, 1H, arom.), 10.92 (s, 1H, NH), 11.28 (s, 1H, NH). LC-MS (ESI), m/z, peak area: 468.0 $[M+H]^+$, 100.0 %.

The general procedure for the synthesis of 2-(2-((1,3-dioxoisoindolin-2-yl)amino)-4-oxo-4,5-dihydrothiazol-5-yl)-*N*-phenylacetamides (1.6-1.8)

A mixture of 1-(1,3-dioxoisoindolin-2-yl)thiourea **1.2** (4.5 mmol) and appropriate *N*-arylmaleimide (4.5 mmol) in glacial acetic acid (10 mL) was heated under reflux for 2 h. The process was monitored by TLC. After the synthesis was completed, the reaction mixture was cooled and the isolated solid products were filtered, washed with water and ethanol (5–10 mL), and recrystallized from appropriate solvent.

*4-(2-(2-((1,3-Dioxoisoindolin-2-yl)amino)-4-oxo-4,5-dihydrothiazol-5-yl) acetamido)benzoic acid (**1.6**)*

A white powder. Yield – 67 %. M. p. – 223–225°C (DMF:EtOH(1:2)). Anal. Calcd. for $C_{20}H_{14}N_4O_6S$, %: C 54.79; H 3.22; N 12.78. Found, %: C 54.72; H 3.25; N 12.74. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.71 + 2.87 (m, 1H, CH_2), 3.01 (dd, 1H, *J* = 17.1, 10.2 Hz, CH_2), 3.29 (m, 1H, CH_2), 4.67+4.82 (dd, 1H, *J* = 10.2, 3.7 Hz, CH), 7.61 (d, 2H, *J* = 8.4 Hz, arom.), 7.68 (d, 1H, *J* = 8.4 Hz, arom.), 7.81 (m, 8H, arom.), 7.91 (m, 1H, arom.), 10.46 (s, 1H, NH), 12.27 + 12.63 (s, 1H, NH). LC-MS (ESI), m/z, peak area: 439.0 $[M+H]^+$, 100.0 %.

*2-(2-((1,3-Dioxoisoindolin-2-yl)amino)-4-oxo-4,5-dihydrothiazol-5-yl)-N-(4-nitrophenyl)acetamide (**1.7**)*

A yellow powder. Yield – 78 %. M. p. – 203–205°C (EtOH). Anal. Calcd. for $C_{19}H_{13}N_5O_6S$, %: C 51.94; H 2.98; N 15.94. Found, %: C 52.01; H 2.93; N 15.89. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.45 + 2.51 (m, 1H, CH_2), 3.06 (dd, 1H, *J* = 17.6, 10.0 Hz, CH_2), 3.30 (m, 1H, CH_2), 4.68+4.77 (m, 1H, CH), 7.74 (m, 2H, arom.), 7.81 (m, 6H, arom.), 10.76 (s, 1H, NH), 12.38 + 12.55 (s, 1H, NH). LC-MS (ESI), m/z, peak area: 440.0 $[M+H]^+$, 100.0 %.

*N-(4-Chlorophenyl)-2-(2-((1,3-dioxoisoindolin-2-yl) amino)-4-oxo-4,5-dihydrothiazol-5-yl)acetamide (**1.8**)*

A brown powder. Yield – 81 %. M. p. – 108–110°C (DMF:EtOH(1:2)). Anal. Calcd. for $C_{19}H_{13}N_5O_6S$, %: C 53.21; H 3.06; N 13.06. Found, %: C 53.15; H 3.13; N 13.01. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.71 + 2.87 (m, 1H, CH_2), 2.97 (dd, 1H, *J* = 17.0, 10.3 Hz, CH_2), 3.24 (m, 1H, CH_2), 4.37 (m, 1H, CH) 4.66 (dd, 1H,*J* = 10.3, 3.6 Hz, CH), 7.19 (d, 2H, *J* = 7.6 Hz, arom.), 7.33 (m, 3H, arom.), 7.55 (m, 3H, arom.), 7.85 (m, 3H, arom.), 7.93 (m, 2H, arom.), 8.03 (m, 3H, arom.), 10.29 (s, 1H, NH), 12.53 + 12.26 (s, 1H, NH). LC-MS (ESI), m/z, peak area: 427.0/429.0 $[M+H]^+$, 100.0 %.

The general procedure for the synthesis of 2-((4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothiazol-2-yl)amino)isoindoline-1,3-diones (1.9, 1.10)

A mixture of 1-(1,3-dioxoisoindolin-2-yl)thiourea **1.2** (4.5 mmol), appropriate *β*-aroylacrylic acide (5.4 mmol) was refluxed for 2 h in glacial acetic acid (10 mL) (monitored by TLC). The obtained precipitate was filtered off, washed with water and ethanol (5–10 mL), and recrystallized from ethanol.

*2-((4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothiazol-2-yl)amino) isoindoline-1,3-diones (**1.9**)*

A yellow powder. Yield – 76 %. M. p. – 186–188°C (EtOH). Anal. Calcd. for $C_{19}H_{13}N_3O_4S$, %: C 60.15; H 3.45; N 11.08. Found, %: C 60.09; H 3.51; N 11.03. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.55 + 2.67 (m, 1H, CH_2), 3.73 + 3.79 (m, 1H, CH_2), 4.00 + 4.05 (m, 1H, CH), 7.55 (m, 3H, arom.), 7.65 (t, 2H, *J* = 7.6 Hz, arom.), 7.88 (m, 6H, arom.), 7.96 (m, 6H, arom.), 8.04 (d, 1H, *J* = 7.6 Hz, arom.), 12.31 + 12.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm 41.0, 49.4, 123.2, 128.0, 128.7, 130.0, 133.8, 134.7, 135.3, 158.5, 163.7, 196.9. LC-MS (ESI), m/z, peak area: 380.0 $[M+H]^+$, 100.0 %.

*2-((5-(2-(4-chlorophenyl)-2-oxoethyl)-4-oxo-4,5-dihydrothiazol-2-yl)amino) isoindoline-1,3-dione (**1.10**)*

A yellow powder. Yield – 68 %. M. p. – 205–207°C (EtOH). Anal. Calcd. for $C_{19}H_{13}N_3O_4S$, %: C 55.15; H 2.92; N 10.15. Found, %: C 55.21; H 2.98; N 10.08. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.72 + 2.78 (m, 1H, CH_2), 3.81 + 3.88 (dd, 1H, J = 9.9, 19.2 Hz, CH_2), 4.01 + 4.09 (dd, 1H, J = 3.3, 19.2 Hz, CH), 7.60 (m, 3H, arom.), 7.84 (m, 3H, arom.), 7.86 (m, 6H, arom.), 7.94 (m, 4H, arom.), 8.04 (d, 2H, J = 8.4 Hz, arom.),12.31 + 12.59 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm 41.0, 49.1, 123.1, 128.0, 128.4, 130.1, 133.4, 134.3, 135.2, 158.1, 163.3, 196.2. LC-MS (ESI), m/z, peak area: 412.0/414.0 $[M+H]^+$, 100.0 %.

Funding. The research leading to these results has received funding from the Ministry of Health of Ukraine, under the project number 0121U100690, and the National Research Foundation of Ukraine, under the project number: 2020.02/0035.

Acknowledgments. The authors would like to thank all the brave defenders of Ukraine who made the finalization of this article possible.

Conflicts of interest. The authors declare no conflict of interest.

Конфлікт інтересів: відсутній.

СИНТЕЗ ТА ОЦІНКА ПРОТИПУХЛИННОЇ АКТИВНОСТІ 2-АМІНОІЗОІНДОЛ ТІАЗОЛІДИНОВИХ ГІБРИДІВ

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Мета роботи. Синтез похідних 2-аміноізоіндол тіазолідинону шляхом реакції [2+3]-циклоконденсації шляхом використання різноманітних еквівалентів діелектрофільного синтону $[C_2]^{2+}$ та скринінг протипухлинної активності синтезованих сполук *in vitro*.

Матеріали і методи. Органічний синтез, ЯМР спектроскопія, фармакологічний скринінг *in vitro*.

Результати й обговорення. Шляхом реакції [2+3]-циклоконденсації 1-(1,3-діоксоізоіндолін-2-іл)тіосечовини з монохлороцтвою кислотою, *N*-арилмалеімідами і *β*-ароїлакриловими кислотами в середовищі льодяної оцтової кислоти було одержано 5-заміщені 2-аміноізоіндол тіазолідинонові гібриди. Синтез індолвмісних 2-аміноізоіндол тіазолідинонів було здійснено одностадійною трикомпонентною реакцією of 1-(1,3-діоксоізоіндолін-2-іл)тіосечовини, відповідного ізатину та монохлороцтової кислоти. Протиракова активність синтезованих сполук була вивчена в концентрації 10^{-5} М на панелі з 60 ракових клітин відповідно до стандартних протоколів Національного Інститут Раку (NCI, Bethesda, MD, USA) Developmental Therapeutic Program (DTP).

Висновки. Досліджено ефективний метод синтезу нових ізоіндолтіазолідинонів. Індолвмісний 2-аміноізоіндолтизолідинон, продемонстрував помірний рівень протипухлинної активності з впливом на клітинні лінії меланоми, раку нирок і молочної залози.

Ключові слова: органічний синтез; гетероцикли; тіазолідинон; ізоіндол; протиракова активність.

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