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SYNTHESIS OF NEW DERIVATIVES OF INDENOQUINOXALINECARBOXYLIC ACIDS WITH AMINES AND *IN SILICO* PREDICTION OF THEIR BIOLOGICAL ACTIVITY

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The corresponding amide derivatives of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid were synthesized in good yields by interaction with amines (N,N-dimethylpropane-1,3-diamine, novocaine, 2,6-dimethylpyrimidin-4-amine). The technique is simple and well reproducible. It provides preliminary activation of the carboxyl group by ethyl ester of monochlorocarbonic acid with its conversion to anhydride in chloroform in the presence of triethylamine. Anhydride gently reacts with amines under the same conditions without preliminary isolation to form the corresponding derivatives. Physicochemical and pharmacokinetic properties of the synthesized compounds were predicted using the ADMETlab 3.0 program. All tested compounds corresponded to Lipinsky's rule and can be classified as «drug-like». Pharmacokinetic parameters (clearance, half-life, ability to penetrate the blood-brain barrier and be absorbed in the intestine) indicated the possibility of their oral use. Computer screening using the PharmMapper database confirmed the ability of the synthesized compounds to bind to a number of biological targets involved in cell replication and division. This indicates their potential for intercalation into DNA for the treatment of viral infections and tumors and the prospects for their further studies using *in vitro* methods.

Keywords: synthesis, indenoquinoxalins, nitrogen heterocycles, biological activity, amines, DNA intercalators.

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Introduction

Quinoxalines and their derivatives are a class of nitrogen-containing heterocyclic structures of the benzodiazine family, which, due to their biological properties, find wide therapeutic application in medicine. Review articles analyzing research over the past two decades [1–3] on the routes of quinoxalines synthesis and their pharmacological activity indicate their antibacterial, antiviral, antimalarial, antifungal, antitumor, anticonvulsant, analgesic and other therapeutic effects. Indenoquinoxalines with a three-ring framework of benzene, pyridine and indene, attract special attention among the quinoxaline derivatives. They have a nearly flat structure [4] and are complementary in shape and charges to many biomolecules, which leads to their increased affinity for the latter when binding to them. Such interaction can affect the process of replication of the genetic material of certain viral proteins (protease, polymerase, topoisomerases, etc.), which results in their inhibition [5]. In addition, it is known that planar polycyclic compounds, which include indenoquinoxalines, are capable of being embedded between the nitrogenous bases of the DNA double helix, which leads to a slowdown or complete inhibition of the processes of transcription and replication of nucleic acids, and at the same time a slowdown or termination of reproduction. development of malignant tumors [6,7]. Targeted synthesis of DNA intercalators with antiviral properties based on indenoquinoxalines can solve both of the above problems at once and lead to the creation of drugs with a wide range of action - from influenza to tumors of various origins.

The aim of this work was the synthesis of new

compounds of the indenoquinoxaline series, condensation products of 11-oxoindeno [1,2-b]quinoxaline-6-carboxylic acid with amines of different structures, assessment of their pharmacological properties and ability to bind to biological targets by in silico methods.

Experimental

All reagents used were qualified «for synthesis» by Merck Millipore and used without additional purification. Control over the reaction and purity of the synthesized products was carried out using thin-layer chromatography on plates «Silufol» and «Silufol UV-254». The NMR spectra were recorded with Varian VXR-300 instruments (300 MHz for ^{1}H) in DMSO-d_6 solutions with TMS as an internal standard. Elemental analysis was performed on a PerkinElmer 2400 CHN. Mass spectra were recorded on a VG 70-70 EQ spectrometer. Ionization was carried out by a beam of Argon atoms with an energy of 10 kV (substances were dissolved in 3-nitrobenzyl alcohol). The melting points of compounds were measured in a sealed capillary. 11-Oxoindeno [1,2-b]quinoxaline-6-carboxylic acid was obtained by the method described elsewhere [8].

Synthesis of compounds 1–3 (general method)

11-Oxoindeno[1,2-b]quinoxaline-6-carboxylic acid (1 g, 3.5 mmol) was dissolved in 30 mL of chloroform and cooled to 0^{0}C. Triethylamine (0.97 mL, 7 mmol) and ethyl monochlorocarbonate (0.34 mL, 3.5 mmol) were added to the cooled mixture. The mixture was stirred for approximately 1 h until the substances completely dissolved, then 3.5 mmol of the appropriate amine was added and stirred for 1 day at room temperature.

N-[3-(dimethylamino)propyl]-11-oxoindeno [2,1-b]quinoxaline-6-carboxamide (1)

N,N-dimethylpropane-1,3-diamine (0.36 g, 3.5 mmol) was used as an amine. After completion of the reaction, the mixture was filtered, the filtrate was extracted three times with water (50 ml), and the organic phase was evaporated to dryness. The residue was dissolved in 20 ml of a chloroform-acetone mixture (20:1) and applied to a silica gel column (size 25×3.5 cm). The eluate containing the product was evaporated to a volume of 15 ml and 40 ml of warm ethanol was added. After cooling, the precipitated product was filtered off, washed with ethanol (25 mL) and air-dried. Yield 1 g (79%), m.p. 207–210^{0}C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.51 (6H, s, CH_3); 1.97 (2H, m, CH_2), 2.82 (2H, m, CH_2), 3.57 (2H, m, CH_2); 7.77 (1H, t), 7.92 (3H, m), 8.23 (1H), d), 8.31 (1H, d), 8.43 (1H, d) (J=8 Hz, arom.); 9.73 (1H, m, NH). MS (EI), *m/z*: 360 $[M]^+$. Calculated $C_{21}H_{20}N_4O_2$: C 70.00, H 5.60, N 15.50. Found: C 70.1, H 5.66, N 15.59.

2-(Diethylamino)ethyl-4-[(11-oxoindeno [2,1-b]quinoxaline-6-carbonyl)amino]benzoate (2)

Novocaine (0.83 g, 3.5 mmol) was used as an amine. The precipitated product was filtered. It was recrystallized from water and then several times from isopropyl alcohol and dried in air. Yield 1.3 g (75%), m.p. 199–202^{0}C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 0.99 (6H, t, CH_3); 2.57 (4H, k, CH_2), 2.79 (2H, t, N–CH_2), 4.32 (2H, t, O–CH_3); 7.77 (2H, m), 7.91 (2H, d), 7.93 (1H, d), 7.99 (2H, m), 8.04 (2H, m), 8.39 (1H , d), 8.43 (1H, d) (J=8 Hz, arom.); 11.78 (1H, br. s, NH). MS (EI), *m/z*: 494 $[M]^+$. Calculated $C_{29}H_{26}N_4O_4$: C 70.40, H 5.30, N 11.30. Found: C 70.80, H 5.60, N 12.70.

N-(2,6-dimethylpyrimidin-4-yl)-11-oxoindeno [2,1-b]quinoxaline-6-carboxamide (3)

2,6-Dimethylpyrimidin-4-amine (0.83 g, 3.5 mmol) was used as an amine. Product *3* was solated and purified similarly to product *1*. Yield 0.93 g (70%), m.p.>300^{0}C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.41 (3H, s, CH_3); 2.54 (3H, s, CH_3), 7.73 (2H, m), 7.95 (1H, d), 8.06 (1H), t), 8.12 (1H, d), 8.25 (1H, d), 8.49 (1H, d) (J=8 Hz, arom.); 13.20 (1H, br. s, NH). MS (EI), *m/z*: 381 $[M]^+$. Calculated $C_{22}H_{15}N_5O_2$: C 69.30, H 4.00, N 18.40. Found: C 69.41, H 4.08, N 18.47.

Results and discussion

A feature of a molecule capable of intercalation in DNA is the presence in its structure of a flat planar cycle, which causes its «embedding» into double-helical polynucleotides. At the same time, the structure and length of the linker fragment associated with the pharmacophore cycle plays a significant role and can significantly increase the affinity to DNA. For example, protonated tertiary amino groups, which are part of the linker fragment, provide additional interaction with the bottom of the minor groove due to negatively charged phosphate fragments that additionally stabilize intercalation [9].

The initial compound, 11-oxoindeno [1,2-b]quinoxaline-6-carboxylic acid, is very poorly soluble in water, which reduces its bioavailability; it also has a fairly high acidity. The DNA molecule is a polyanion, so to increase the affinity for binding a medicinal substance to it, it is desirable that the latter be well protonated and water-soluble. Such properties

can be provided to the carboxylic acid molecule by amino groups, which will be part of the corresponding amides when reacting with diamines. This approach was implemented in this work. The choice of amines is due to their different structures (aliphatic, aromatic, and heterocyclic), which will further affect their acid-base properties and solubility in an aqueous medium. In addition, novocaine is a well-known analgesic drug, and the pyrimidine cycle is part of many active pharmaceutical ingredients, which can significantly expand the range of therapeutic properties of the compounds obtained.

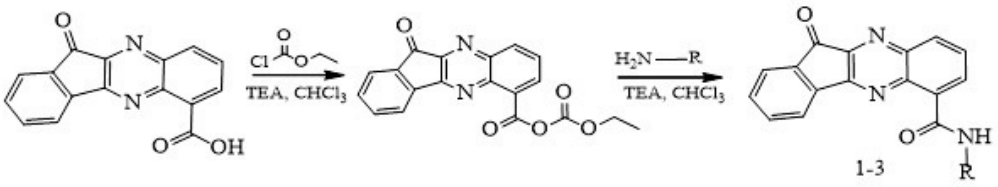
The formation of amide derivatives must be preceded by the stage of activation of the carboxyl group, which can be carried out in different ways. In our previous work [8], it was shown that the most effective method of activation in the preparation of amide derivatives of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid is its preliminary transformation into an anhydride group by reaction with ethyl ether of monochlorocarbonic acid. The mixed anhydride without preliminary separation reacts mildly with amines (N,N-dimethylpropane-1,3-diamine, novocaine, 2,6-dimethylpyrimidin-4-amine) at room temperature in the presence of triethylamine with the formation of target products 1–3 according to Scheme.

The synthesized products are yellow amorphous powders that are poorly soluble in most organic solvents, so their purification was carried out by the method of preparative column chromatography. The exception was compound 2, which was purified by recrystallization from water and then from isopropyl alcohol. The yields of final products after purification reached 70–79%, and the technique itself was well reproducible, which obviously indicates the effectiveness of this approach to the synthesis of indenoquinoxalinecarboxylic acid amides. The structure of compounds 1–3 was established using ^{1}H NMR spectroscopy and mass spectrometry, and the chemical composition was confirmed by elemental analysis.

By means of computer modeling using the ADMETlab 3.0 service [10], the synthesized compounds were evaluated for ADMET (adsorption, distribution, metabolism, excretion and toxicity). For comparison, we used Batracylin (8-aminoisoindolo [1,2-b]quinazolin-10(12H)-one; NSC320846), an anticancer drug currently undergoing phase 1 clinical trials (compound 4). The visualization of the results is presented in the form of «web» graphs (Figure), and the numerical values are given in Table 1.

The presented data prove that all compounds according to the parameters MW, log P, nHA, nHD, and nRot correspond to Lipinski's rule, and therefore can be classified as «drug-like» [11]. The physicochemical properties of the synthesized substances are included in the range of the lower (green zone) and upper (blue zone) limits of the graphs, that is, in the orange zone (Figure), which indicates their bioavailability and perspective as medicinal substances in the case of oral use.

Evaluation of the pharmacokinetic characteristics (Table 2) of the obtained compounds showed that substances 2 and 3 are able to penetrate the blood-



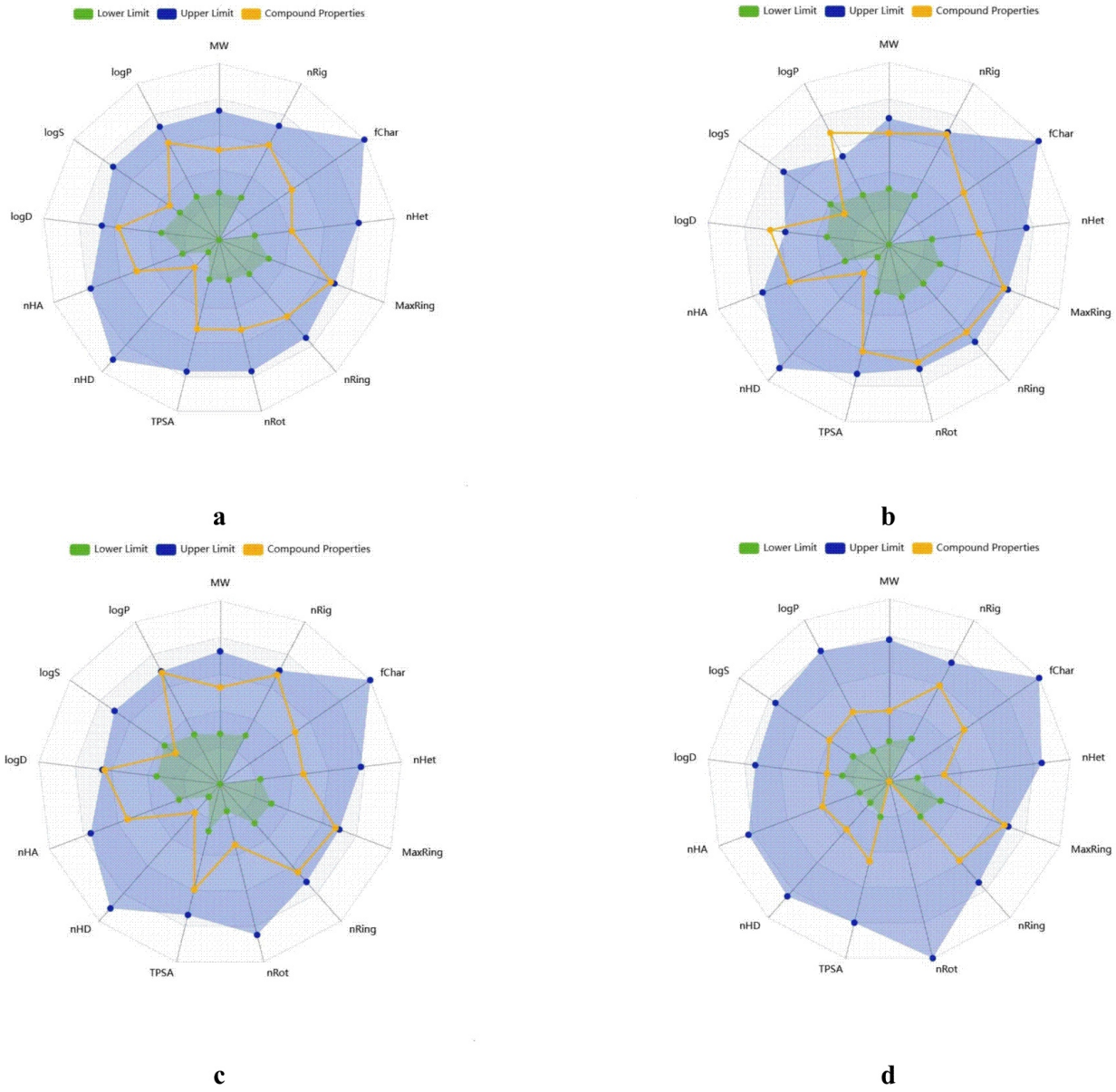
Scheme. R: 1 – $-(CH_2)_3-N(CH_3)_2$ (79%), 2 – $-C_6H_4-COO-(CH_2)_2-N(C_2H_5)_2$ (75%), 3 – 4(2,6-Me_2)Pyr (70%), Pyr – pyrimidine

Table 1

Physicochemical parameters of compounds 1–4*

Compound	MW	log P	nHA	nHD	TPSA	nRot	log D
normative indicators	<500	<5	<10	<5	<140	<11	<3
1	360.16	2.311	6.0	1.0	75.19	6.0	2.436
2	494.20	4.821	8.0	1.0	101.49	10.0	3.724
3	381.12	2.935	7.0	1.0	97.73	3.0	2.923
4	249.09	1.159	4.0	2.0	58.69	0.0	1.349

Note: * – MW is the molecular weight; log P is the logarithm of the n-octanol/water distribution coefficient at pH 7.4; log D is the logarithm of the *n*-octanol/water distribution coefficient; nHA and nHD are the numbers of hydrogen bond acceptors and donors, respectively; nRot is the number of rotatable bonds; and TPSA is the topological polar surface area.



Graphic representation of the analysis of the physical and chemical properties of the synthesized compounds: a – Compound 1; b – Compound 2; c – Compound 3; and d – Compound 4

Table 2

Pharmacokinetic parameters of compounds 1–4

Compound	HIA*	BBB*	CL, ml/min/kg	$T_{1/2}$, h
Normative indicators	HIA+ HIA–	BBB+ BBB–	high (>15) moderate (5–15) low (<5)	ultra-short (<1) intermediate short (1–4) long (>4)
1	+(0)	–(0.866)	7.834	3.108
2	+(0.006)	+(0)	3.092	0.978
3	+(0.003)	+(0.011)	0.818	1.356
4	+(0.005)	–(0.905)	3.477	1.867

Note: * – The output value is the probability of being BBB+, HIA+.

brain barrier (BBB) and be absorbed in the human intestine (HIA). Low clearance (CL) values were obtained for compounds 2 and 3, while for compound 1 it has a moderate value. According to the half-life ($T_{1/2}$), substances 2 and 3 belong to drugs with a short half-life, and in the case of compound 1, it is extremely short.

Data on predicted toxicity are shown in Table 3. Parameters such as DILI (Drug Induced Liver Injury), AMES (mutagenic potential), genotoxicity and CARC (carcinogenic potential) were considered.

Table 3

Toxicity parameters for compounds 1–4

Compound	DILI	AMES	Genotoxicity	CARC
Normative indicators	0–0.7			
1	0.966	0.925	0.894	0.706
2	0.995	0.921	0.999	0.522
3	0.998	0.850	0.861	0.703
4	0.973	0.824	1.000	0.631

In silico prediction showed that all synthesized substances exhibit high toxicity. It should be noted that high values of genotoxicity and mutagenicity are characteristic of DNA intercalators and indirectly confirm the ability of compounds to bind to DNA. The negative factor of high toxicity of substances can cause a positive effect in the case of its use for the treatment of tumors. This fact is confirmed by the high values of the corresponding indicators for the drug batracillin (compound 4), which is positioned as an antitumor drug, an active inhibitor of DNA topoisomerase I and II type [12].

All synthesized substances were analyzed *in silico* for the possibility of binding to potential biological targets by means of screening using the PharmMapper database [13], an integrated web server of pharmacophores, which is based on reverse molecular docking for the identification of potential targets of small molecules. Those involved in cell replication and division were primarily chosen as potential targets. The program has identified about 50 potential targets for binding. Table 4 presents the best binding targets by normalized match score (Z_{ab}). This metric (which has a maximum of 1) combines the fit score and its eigenvector in the score matrix and normalizes them to a vector with a mean of zero and a standard deviation of one. Its calculation is carried out according to the following formula:

$$Z_{ab} = \frac{F_{ab} - F_a}{SD_{Fa}},$$

where F_{ab} is the initial assessment of the compatibility of the compound «a» with the pharmacophore target «b»; F_a is the average value of indicators of compliance of compound «a» to all targets; and SD_{Fa} is the standard deviation of F_{ab} distribution.

The analysis of the synthesized substances showed that the specified compounds can bind to a significant number of potential biological targets, which are primarily involved in the replication and division of cells with a fairly large normalized index of correspondence, and therefore, with a high degree of probability, can be DNA intercalators.

Conclusions

A number of its amide derivatives were synthesized on the basis of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid and amines of various structures. The obtained compounds were analyzed for physicochemical and pharmacokinetic parameters using the ADMETlab 3.0 program. It was shown that they can potentially be classified as «drug-like». Screening for pharmacological properties by the PharmMapper web server confirmed with a high degree of probability their ability to bind to a number of biological targets involved in cell replication and division. Thus, it was shown *in silico* that the

Table 4

The value of the initial score (F_{ab}) and the normalized indicator (Z_{ab}) of compounds 1–3 in relation to some pharmacophore targets

Synthesized compounds	Biological target	F_{ab}	Z_{ab}
1	Interferon-induced, double-stranded RNA-activated protein kinase	2.495	0.8317
	RNA ligase	2.402	0,8007
	Protein kinase of cell division	2.397	0.7990
2	Tyrosine-protein kinase receptor erbB-2	2.878	0.7195
	Transcription regulator, family IclR	2.831	0.7078
3	Transcription regulator, family IclR	2.968	0,7420
	DNA topoisomerase (II type)	2.962	0.7406
	Tyrosine protein kinase	2.957	0.7391

synthesized amides of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid can be high-affinity DNA ligands, which allows considering them as potential anti-infective and anti-tumor agents for further investigation *in vitro*.

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СИНТЕЗ НОВИХ ПОХІДНИХ ІНДЕНОХІНОКСАЛІНКАРБОНОВИХ КИСЛОТ З АМІНАМИ ТА ПРОГНОЗУВАННЯ ЇХ БІОЛОГІЧНОЇ АКТИВНОСТІ *IN SILICO*

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Відповідні амідні похідні 11-оксоіндено[1,2-b]хіноксалін-6-карбонової кислоти були синтезовані з добрими виходами при взаємодії з амінами (N,N-диметилпропан-1,3-діаміном, новокаїном, 2,6-диметилпіримідин-4-аміном). Методика синтезу є простою і результати добре відтворюються. Методика синтезу передбачає попередню активацію карбоксильної групи етиловим естером монохлорвугільної кислоти з перетворенням її на ангідрид у хлороформі за присутності триетиламіну. Ангідрид за тих же умов без попереднього виділення м'яко реагує з амінами з утворенням відповідних похідних. Фізико-хімічні та фармакокінетичні властивості одержаних сполук передбачені за допомогою програми ADMETlab 3.0. Усі протестовані сполуки відповідають правилу Липинського і можуть бути віднесені до «drug-like». Фармакокінетичні показники (кліренс, період напіввиведення, здатність проникати через гематоенцефалічний бар'єр та абсорбуватися у кишечнику людини) вказують на можливість їх перорального застосування. Комп'ютерний скринінг із застосуванням бази даних PharmMapper підтвердив можливість одержаних сполук зв'язуватись з рядом біологічних мішеней, що беруть участь у реплікації та поділі клітин. Це вказує на їх потенційні можливості до інтеркаляції в ДНК для лікування вірусних інфекцій та пухлин і перспективність їх подальших досліджень методами *in vitro*.

Ключові слова: синтез, інденохіноксаліни, азотвмісні гетероцикли, біологічна активність, аміни, інтеркалятори ДНК.

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Keywords: synthesis; indenoquinoxalins; nitrogen heterocycles; biological activity; amines; DNA intercalators.

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