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DEVELOPMENT OF AN EFFECTIVE METHOD FOR SYNTHESIS OF NEW DERIVATIVES OF INDENOQUINOXALINE CARBOXYLIC ACIDS WITH ESTERS OF α-, β-AMINO ACIDS

11-Oxoindeno[1,2-b]quinoxaline-6-carboxylic acid was obtained by the cyclization reaction of 2,3-diaminobenzoic acid with ninhydrin. Five amide derivatives of indenoquinoxalinecarboxylic acid were first synthesized on its basis and with the use of esters of α- and β-amino acids. For the introduction of amino acid residues, three methods of preliminary activation of the carboxyl group were developed: with the help of dicyclohexylcarbodiimide, by converting it into an anhydride group, and into a mixed anhydride group with ethyl ester of monochlorocarbonic acid. The latter method showed significantly increased yields of target compounds and better reproducibility compared to the other two activation methods. The synthesized compounds were identified and characterized by the methods of chromatography-mass spectrometry and ^{1}H NMR spectroscopy. The pharmacological properties of the obtained compounds were predicted by computer modeling using the PharmMapper software. Analysis of the results showed that they may have the properties of DNA intercalators and be promising objects for high-throughput screening in the search for new effective antiviral and anticancer drugs.

Keywords: synthesis, indenoquinoxaline, amino acids, biological activity, DNA intercalator

Viral infections and oncological diseases remain one of the most widespread health care problems in the world, despite the great successes achieved by biomedical sciences [1]. Uncontrolled replication of genetic material is at the heart of the harmful effects of both viruses and oncological diseases on the body. Every virus, every cancer cell, regardless of their genome, necessarily goes through this stage. Considering that the replication of genetic material is of fundamental importance for the existence of all living organisms, it is reasonable to consider this process as a target for new potential antiviral and anticancer agents, and compounds that are able to effectively inhibit the replication process will be key objects in these studies. One of such compounds can be planar heterocyclic chromophores, which have the ability to be embedded between the nitrogenous bases of a double helix, that is, to perform the functions of DNA intercalators [2].

Indenoquinoxaline derivatives are important representatives of nitrogen-containing heterocycles, which in recent years have attracted considerable attention of researchers due to their high biological activity. They are able to suppress the reproduction of a wide range of infectious agents, as a result of which they exhibit antiviral, antibacterial and anti-inflammatory activity etc., which is explained by the mechanism of their intercalation in DNA [3–6]. In this regard, the synthesis of new compounds based on indenoquinoxaline, which could have similar properties, is expedient and relevant. The aim of this work is to find effective methods for the synthesis of new indenoquinoxaline carboxylic acid derivatives with amino acid ester residues to improve their bioavailability, with further study of the possibility of their intercalation into DNA.

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MATERIALS AND RESEARCH METHODS

All reagents used were qualified "for synthesis" by Merck Millipore. Control of reactions was carried out using thin-layer chromatography on Silufol and Silufol UV-254 plates. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solutions relative to TMS on a Bruker Avance 500 spectrometer (500 MHz). High resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. The melting points of compounds were measured in a sealed capillary. Computer modeling and calculation of pharmacological properties were carried out using the PharmMapper program [7–9].

11-Oxoindeno[1,2-b]quinoxaline-6-carboxylic acid (1)

The methodology given in [6] was used as a basis. A solution of 19,59 g (0,1 mol) of ninhydrin in 30 ml of glacial acetic acid was heated to 70 °C and, with constant stirring, added to a solution of 17,2 g (0,1 mol) of 2,3-diaminobenzoic acid heated to 70 °C in 35 ml of glacial acetic acid. The reaction mixture was stirred for 1 h, the precipitate that formed was filtered off, washed first with 50 ml of a mixture of acetic acid and water (1:1), then with 100 ml of hot (80 °C) water and dried in air, recrystallized from 200 ml of ethanol. Yield 19.3 g (70%), mp 320 °C. MS (TOF), *m/z*: 276 [M^+]. ^{1}H NMR spectrum δ, ppm, MHz: 7,76 t (1H), 7,93 m (3H), 8,12 d (1H), 8,25 d (1H), 8,35 d (1H) (J=8Hz, arom.); 13,75 br s (1H, COOH).

General method of synthesis of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid derivatives with amino acid esters.

30 ml of chloroform was added to 1 g (0,0035 mol) of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid (1) and cooled to 0 °C. 0,97 ml (0,07 mol) of triethylamine and 0,34 ml (0,0035 mol) of monochlorocarbonic acid ethyl ester were added to the cooled mixture. The mixture was stirred for approximately 1 hour until the substance completely dissolved, then 0,0035 mol of amino acid ester hydrochloride was added and stirred for 1 day at room temperature.

Ethyl 2-[(11-oxoindeno[1,2-b]quinoxaline-6-carbonyl)amino]acetate (2).

It was synthesized from 1 g (0,0035 mol) of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid (1) and 0,49 g (0,0035 mol) of glycine ethyl ester hydrochloride. After completion of the reaction, the mixture was filtered, the filtrate was extracted with water (3 times 50 ml each), the organic phase was evaporated to a dry residue. The residue was dissolved in 20 ml of a mixture of chloroform-acetone, 20:1 and introduced into a column with silica gel (25x3,5 cm), eluent chloroform-acetone, 20:1. 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 0,76 g (60%), mp 247–249 °C. MS (TOF), *m/z*: 361 [M+]. ^{1}H NMR spectrum δ, ppm, MHz: 1,4 t (3H, CH_3); 4,4 m (4H, CH_2); 7,68 t (1H), 7.87 q (2H), 7,97 d (1H), 8,40 d (1H), 8,51 d (1H), 8,91 d (1H) (J= 8 Hz, aroma); 11,17 br s (1H, NH).

Methyl 2-[(11-oxoindeno[1,2-b]quinoxaline-6-carbonyl)amino]acetate (3).

It was synthesized similarly to (2) from 1 g (0,0035 mol) of 11-oxoindeno[1,2-b] quinoxaline-6-carboxylic acid (1) and 0,44 g (0,0035 mol) of glycine methyl ester hydrochloride. The yield is 0,57 g (47%), mp 222–224 °C; MS (TOF), *m/z*: 347 [M^+]. ^{1}H NMR spectrum δ, ppm, MHz: 3,77 s (3H, CH_3); 4,39 d (2H, CH_2); 7,78 t (1H), 7,95 m (3H), 8,38 d (1H), 8,44 d (1H), 8,64 d (1H) (J=8Hz, arom.); 10,64 br s (1H, NH).

Methyl 3-[(11-oxoindeno[1,2-b]quinoxaline-6-carbonyl)amino]propanoate (4).

It was synthesized similarly to (2) from 1 g (0,0035 mol) of 11-oxoindeno[1,2-b] quinoxaline-6-carboxylic acid (1) and 0,49 g (0,0035 mol) of β-alanine methyl ester hydrochloride. Chloroform was used as eluent. The yield is 0,53 g (42%), mp 160–162 °C; MS (TOF), *m/z*: 361 [M^+]. ^{1}H NMR spectrum δ, ppm, MHz: 3,33 s (3H, CH_3); 2,75 t, 3,75 m (4H, CH_2); 7,76 t (1H), 8,24 m (3H), 8,32 t (2H), 8,55 d (1H) (J=8Hz, arom.); 10,17 br s (1H, NH).

Ethyl 2-[[2-[(11-oxoindeno[2,1-b]quinoxaline-6-carbonyl)amino]acetyl]amino]-acetate (5).

It was synthesized similarly to (2) from 1 g (0,0035 mol) of 11-oxoindeno[1,2-b] quinoxaline-6-carboxylic acid (1) and 0,69 g (0,0035 mol) of diglycine ethyl ester hydrochloride. The product fell out of the reaction mass, it was filtered, dissolved in 1 L of boiling chloroform, passed through a layer of Al_2O_3 (2 cm). 500 ml of chloroform was distilled off, 300 ml of hot ethanol was added, and the solvent was distilled off to a volume of 40 ml. The precipitated product was filtered, washed with ethanol (40 mL) and air-dried. The yield is 0,8 g (55%), mp 264–266 °C. MS (TOF), *m/z*: 418 [M^+]. ^{1}H NMR spectrum δ, ppm, MHz: 1,21 t, 4,13 k (5H, CH_3-CH_2); 4,01 d, 4,26 d (4H, CH_2-N); 7,95 br s (1H, NH); 7,75 t (1H), 7,9 m (2H), 8,33 d (1H), 8,51 d (1H), 8,63 d (1H), 8,71 d (1H) (J= 8Hz, aroma); 10,89 br s (1H, NH).

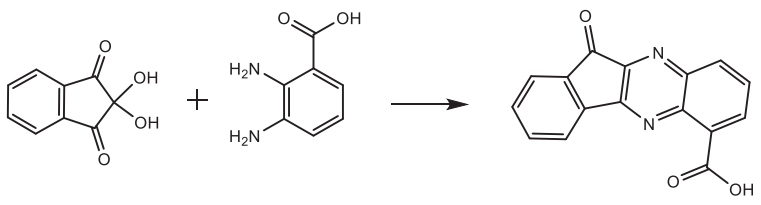
Methyl 2-[(11-oxoindeno[1,2-b]quinoxaline-6-carbonyl)amino]-3-phenylpropanoate (6).

It was synthesized similarly to (2) from 1 g (0,0035 mol) of 11-oxoindeno[1,2-b] quinoxaline-6-carboxylic acid (1) and 0,75 g (0,0035 mol) of β-phenyl methyl ester hydrochloride α-alanine. A benzene-acetone mixture (20:1) was used as eluent. The eluate was evaporated to 10 ml and 30 ml of a warm methanol-water mixture (9:1) was added. The precipitated product was filtered off, washed with aqueous methanol and dried in air. The yield is 0.61 g (40%), mp 142–145 °C. MS (TOF), *m/z*: 437 [M^+]. ^{1}H NMR spectrum δ, ppm, MHz: 3,28 d (2H, Ar-CH_2); 3,73 s (3H, CH_3); 5,11 m (1H, CH); 7,28 m (5H), 7,69 d (1H), 7,73 t (1H), 7,84 t (1H), 7,91 d (1H), 7,97 t (1H), 8,35 d (1H), 8,61 d (1H) (J=8Hz, arom.); 10,29 br s (1H, NH).

RESULTS AND DISCUSSION

11-Oxoindeno[1,2-b]quinoxaline-6-carboxylic acid (1) was synthesized by the cyclocondensation reaction of ninhydrin with 2,3-diaminobenzoic acid, according to the method given in [6] (Scheme 1):

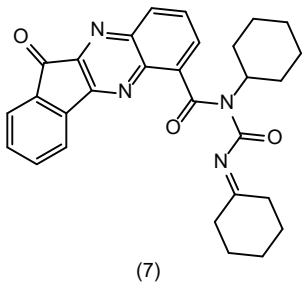
Scheme 1



(1)

It follows from theoretical ideas that two isomers can be formed as a result of condensation, which differ in the position of the carboxyl group: 11-oxoindeno[1,2-b] quinoxaline-6-carboxylic acid (1) or 11-oxoindeno[1,2-b] quinoxaline-9-carboxylic acid. However, in practice, the formation of only one compound was observed, which was confirmed by the methods of chromatography-mass spectrometry and ^{1}H NMR spectroscopy. In work [6], the compound 6-chloro-11H-indeno[1,2-b]quinoxalin-11-one was synthesized by a similar method – condensation of 1,2-diamino-3-chlorobenzene with ninhydrin. Using X-ray structural analysis, the authors proved that only one isomer is formed as a result of the reaction – a 6-substituted compound. The explanation for this factor is not provided, although it is worth noting that the formation of the isomer in the 6-position is facilitated by a steric factor: the more distant location of the carboxyl group (or the chlorine atom) from the carbonyl group in the indene ring, which minimizes the repulsion between them. Based on these considerations and the results obtained by the authors of [7], the formation of an isomer with a carboxyl group in position 6 should also be expected in our case with high probability.

To improve the bioavailability of indenoquinoxaline acid, it is advisable to combine it with organic substances that are related to biological objects - amino acids. Therefore, the next stage of the work was the synthesis of indenoquinoxaline acid derivatives containing amino acid residues. For this, methyl and/or ethyl esters of glycine, β-alanine, diglycine and β-phenyl-α-alanine were used.



(7)

The classic method of obtaining an amide bond is the combination of a carboxyl and an amino group. In the case of amino acids, dicyclohexylcarbodiimide is used to activate the -COOH group. However, the main (>90%) product of this reaction turned out to be the corresponding acetylurea (compound (7), and the desired products were isolated with very low yields - 5-10%.

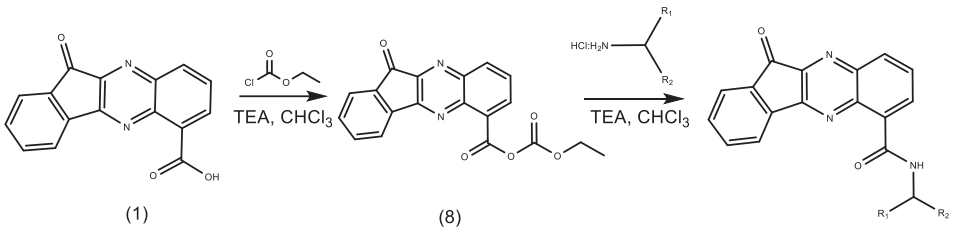
At the next stage, an attempt was made to activate the carboxyl group of indenoquinoxalic acid by converting it into chloride anhydride. Acylation of amino acid esters with indenoquinoxalinecarboxylic acid chloride (1) also turned out to be ineffective, because it practically did not lead to the formation of target products. Numerous attempts to add a tertiary amine to a mixture of amino acid hydrochloride and indenoquinoxaline carboxylic acid chloride led to tarnishing of the reaction mass, which is probably associated with the destruction of the heterocyclic system.

Later, the activation of the carboxyl group was carried out by treating indenoquinoxaline carboxylic acid with monochlorocarbonic acid ethyl ester, resulting in a mixed anhydride. It mildly reacted at room temperature in the presence of triethylamine with free bases of amino acid esters to form the desired products (2)-(6) (Scheme 2).

All synthesized compounds are yellow crystalline powders that are poorly soluble (except for compound 6) in most organic solvents. Their purification was carried out by the method of preparative column chromatography. The exception was compound (5), which was purified by recrystallization from a mixture of chloroform and ethanol (1:5). The yields of final products after purification reached 40-60%, and the technique itself

was well reproducible, which obviously indicates the effectiveness of this approach to the synthesis of indenoquinoxaline carboxylic acids, which contain residues of esters of the corresponding amino acids.

Scheme 2



(1) (8)

2 - R_1=-H, R_2=-COO-C_2H_5 (60%)
3 - R_1=-H, R_2=-COO-CH_3 (47%)
4 - R_1=-H, R_2=-CH_2-COO-CH_3 (42%)
5 - R_1=-H, R_2=-CO-NH-CH_2-COO-CH_3 (55%)
6 - R_1=Ph-CH_2, R_2=-COO-CH_2-CH_3 (40%)

All synthesized substances were analyzed for the possibility of binding to potential targets using the PharmMapper database [7-9] – 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. The table shows the best binding targets by normalized match score (Z_{ab}). This measure 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 formula:

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

where F_{ab} is the initial assessment of the suitability of ligand “a” to the pharmacophore target “b”; F_a - the average value of the indicators of the compatibility of ligand “a” to all targets; SD_{Fa} - standard deviation of F_{ab} distribution.

The analysis of the synthesized substances showed that the specified compounds can bind to a large 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.

Thus, for the first time, amide derivatives with esters of amino acids: glycine, β-alanine, diglycine and β-phenyl-α-alanine were obtained and identified on the basis of 11-oxoindeno[1,2-b]quinoxaline-6-carboxylic acid. Production of amide derivatives was carried out through the stage of activation of the carboxyl group in three ways: using dicyclohexylcarbodiimide; due to its preliminary transformation into chloride anhydride, as well as into a mixed anhydride with ethyl ester of monochlorocarbonic

Table 1

The value of the original score (F_{ab}) and the normalized indicator (Z_{ab}) of the correspondence of indenoquinoxaline-6-carboxylic acid amides (2)-(6) with amino acid esters to some pharmacophore targets

Synthesized compounds	Biological target	F_{ab}	Z_{ab}
2	Transcription regulator, IclR family	3,02	0,76
	Protein 1C40, which controls cell division	3,82	0,64
3	Receptor tyrosine protein kinase	3,00	0,75
	A component of DNA polymerase processivity	2,94	0,73
	RNA-binding protein	2,93	0,73
4	RNA-binding protein	2,98	0,74
	Tyrosine protein kinase	2,97	0,74
5	Protein 1C40, which controls cell division	3,95	0,66
6	The main DNA-binding protein	3,63	0,73
	Tyrosyl-tRNA synthetase	3,00	0,75

acid. The last method turned out to be the most effective. It reproduces well and allows obtaining the target products in acceptable yields. Computer modeling of the biological activity of the synthesized compounds showed their ability to bind biological targets involved in cell replication and division, which indicates their potential use as DNA intercalators for the creation of antiviral and anticancer agents.

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РОЗРОБКА ЕФЕКТИВНОГО МЕТОДУ СИНТЕЗУ НОВИХ ПОХІДНИХ ІНДЕНОКСАЛІНКАРБОНОВИХ КИСЛОТ З ЕСТЕРАМИ α-, β-АМІНОКИСЛОТ

Реакцією циклізації 2,3-діамінобензойної кислоти з нінгідрином було отримано і охарактеризовано 11-оксоіндено[1,2-b]хіноксалін-6-карбонову кислоту. На її основі із застосуванням метилового та/або етилового естерів гліцину, β-аланіну, дигліцину та β-феніл-α-аланіну вперше було синтезовано п'ять амідних похідних інденохіноксалінкарбонової кислоти: етил 2-[(11-оксоіндено[1,2-b]хіноксалін-6-карбоніл)аміно]ацетат; метил 2-[(11-оксоіндено[1,2-b]хіноксалін-6-карбоніл)аміно] ацетат; метил 3-[(11-оксоіндено[1,2-b]хіноксалін-6-карбоніл)аміно] пропаноат; етил 2-[[2-[(11-оксоіндено[2,1-b]хіноксалін-6-карбоніл)аміно]ацетил]аміно] ацетат; метил 2-[(11-оксоіндено[1,2-b]хіноксалін-6-карбоніл)аміно]-3-фенілпропаноат. Синтезовані сполуки ідентифіковано та охарактеризовано методами хроматомас-спектрометрії та ^{1}H ЯМР-спектроскопії.

Для введення амінокислотних залишків було опрацьовано три способи попередньої активації карбоксильної групи. Перший – за допомогою дициклогексилкарбодііміду. Показано, що в цьому випадку основним (>90%) продуктом даної реакції виявилась відповідна ацетилсечовина. Другий спосіб полягав у переведенні карбоксильної групи у хлорангідридну ацилюванням естерів амінокислот хлорангідридом інденохіноксалінкарбонової кислоти. Цей спосіб теж виявився неефективним, оскільки не приводив до утворення бажаних продуктів внаслідок руйнування гетероциклічної системи. Третім способом було переведено карбоксильну групу у змішаноангідридну із застосуванням етилового естеру монохлорвугільної кислоти. Останній метод виявив значне збільшення виходів цільових сполук та кращу відтворюваність порівняно з іншими двома методами активації, тому може вважатися найбільш ефективним для синтезу зазначених речовин.

Шляхом комп'ютерного моделювання із застосуванням програмного забезпечення PharmMapper для отриманих сполук було спрогнозовано фармакологічні властивості. Аналіз результатів показав, що вони можуть мати властивості інтеркаляторів ДНК та бути перспективними об'єктами для високопродуктивного скринінгу у пошуку нових ефективних антивірусних та протиракових препаратів.

Ключові слова: синтез, інденохіноліни, амінокислоти, біологічна активність, ДНК інтеркалятори.

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