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ANTITUMOR DRUGS BASED ON INDOLOCARBAZOL DERIVATIVES

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The aim of the work is to generalize the literature data on indolocarbazole derivatives with an antitumor activity.
Materials and methods. The objects of the study were the preparations based on indolocarbazole derivatives with the antitumor activity. To search for materials on the problem under study, the following search and information as well as library databases were used: Ebibrary, PubMed, CyberLeninka, ResearchGate, the State Register of Medicines, clinical trials registries clinline.ru and clinicaltrials.gov. The search for the following words / phrases was performed: indolocarbazoles, indolocarbazole derivatives, staurosporine, rebeccamycin, staurosporine derivatives. The search was conducted from January 11 until March 1, 2021. The compounds with a biological activity which were undergoing or had undergone preclinical and clinical trials, were taken into account. All the materials from 1977 to January 1, 2021, were taken into account.
Results. The materials obtained indicate that indolocarbazole derivatives are promising compounds for the creation of anticancer medicinal preparations due to their properties and peculiarities of the action mechanism. These drugs have a selective action due to the targeted interaction with specific molecular targets: kinases (especially protein kinase C and its isozymes), DNA and DNA topoisomerase. To date, many compounds from the class of indolocarbazoles have been synthesized and investigated. They have shown a high antitumor activity in the treatment of systemic and solid tumors. However, despite this, only one MP based on a staurosporine derivative, registered by the TN of Rydapt® (in the USA and EU countries) and Miticaid® (in the Russian Federation), is approved for use in the clinical practice.
Conclusion. Thus, the basic data from scientific publications on promising anticancer medicinal preparations based on compounds from the class of indolocarbazoles, have been summarized. The information is provided, in particular, on their molecular structure, the origin, classification, the main representatives of the class, which are at various stages of the research and are approved for use in the clinic.
Keywords: indolocarbazoles; indolocarbazole derivatives; antitumor agents; staurosporin derivatives; rebeccamycin derivatives
Abbreviations: P – pharmaceutical; MP – medicinal preparation; DF – dosage form; PKC – protein kinase C; DNA – deoxyribonucleic acid; TN – trade name

ПРОТИВООПУХОЛЕВЫЕ ПРЕПАРАТЫ НА ОСНОВЕ ПРОИЗВОДНЫХ ИНДОЛОКАРБАЗОЛА

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Цель. Обобщение литературных данных о производных индолокарбазола, обладающих противоопухолевой активностью.

Материалы и методы. Объектом изучения являлись препараты на основе производных индолокарбазола с противоопухолевой активностью. Для поиска материалов по исследуемой проблеме использовали следующие поисково-информационные и библиотечные базы данных: Ebibrary, PubMed, CyberLeninka, ResearchGate, а также Государственный реестр лекарственных средств, реестры клинических исследований clinline.ru и clinicaltrials.gov. Поиск проводился по следующим словам/словосочетаниям: индолокарбазолы (indolocarbazoles), производные индолокарбазолов (indolocarbazole derivatives), стауроспорин (staurosporine), ребеккамицин (rebeccamycin), производные стауроспорина (staurosporine derivatives), производные ребеккамицина (rebeccamycin derivatives). Поиск проводился с 11 января по 1 марта 2021 года; учитывались соединения с биологической активностью, проходящие или прошедшие доклинические и клинические испытания. Учитывались все материалы с 1977 года по 1 января 2021.

Результаты. Полученные материалы свидетельствуют о том, что производные индолокарбазола являются перспективными соединениями для создания противоопухолевых лекарственных препаратов благодаря их свойствам и особенностям механизма действия. Данные препараты обладают избирательностью действия, что обусловлено направленным взаимодействием с конкретными молекулярными мишенями: киназы (особенно протеинкиназа С и её изоферменты), ДНК и ДНК-топоизомеразы. К настоящему времени синтезировано и исследовано множество соединений из класса индолокарбазолов, показавших высокую противоопухолевую активность при терапии системных и солидных опухолей. Однако несмотря на это, только один лекарственный препарат на основе производного стауроспорина, зарегистрированный под ТН Rydapt® (в США и странах Евросоюза) и Митикайд® (в Российской Федерации), разрешен для применения в клинике.

Заключение. Таким образом проведено обобщение основных данных из научных публикаций, посвященным перспективным противоопухолевым препаратам на основе соединений из класса индолокарбазолов. В частности, приведены сведения об их молекулярном строении, происхождении, классификации, основных представителях класса, находящихся на различных стадиях исследований и разрешенных к применению в клинической практике.

Ключевые слова: индолокарбазолы; производные индолокарбазолов; противоопухолевые агенты; производные стауроспорина; производные ребеккамицина

Список сокращений: ЛС – лекарственное средство; ЛП – лекарственный препарат; ЛФ – лекарственная форма; РКС – протеинкиназа С; ДНК – дезоксирибонуклеиновая кислота; ТН – торговое наименование

INTRODUCTION

Cancer is often referred to as “the pathology of the century” in the context of an endemic disease spreading throughout the world. Cancer has also been identified as “a true disease of modernity” (Roy Porter) or even “an important product of modernity” (Siddhartha Mukherjee). These two definitions are generally accepted and justified by a sharp increase in morbidity and mortality, which has been observed since the end of the 18th century [1]. In 2020, cancer continued to be one of the leading causes of death and an important obstacle to increasing life expectancy in all countries of the world. In 2019, The World Health Organization estimates cancer as the first or second leading cause of people’s deaths under 70 in 112 out of 183 countries, and is ranked as the third or fourth in 23 more countries [2].

Over the past two decades, cancer treatment with the use of pharmacological approaches has changed dramatically. Long years of fundamental and clinical research have led to the transition from classical anticancer therapy, characterized by a low selectivity of a drug action and accompanied by severe intoxication of the body, to more targeted antitumor “snipers” that effectively destroy populations of tumor cells with fewer side effects [3].

Among a wide range of anticancer drugs, compounds from the group of indolocarbazole derivatives are of particular interest. Indolocarbazoles are a unique class of indole alkaloids of a natural or synthetic kinds of origin, which have a number of therapeutic properties – antitumor, antibacterial, antiparasitic, antiviral, and an immunomodulatory activity [4–7].

The most significant biological profile of compounds from the group of indolocarbazole derivatives is their potential antitumor effect [8]. A distinctive feature of the action mechanism of these drugs is their ability to interact with several targets and induce various pathways of tumor cell death [9]. For them, such targets are DNA, topoisomerase and protein kinase C enzymes, which are responsible for regulating the main aspects of cell metabolism, including the progression of the cell cycle [10, 11].

Protein kinases C are a family of protein kinases, enzymes that phosphorylate proteins and thus participate in cell signaling cascades. The term “protein kinase C” refers to all described isoenzymes [12]. PKC inhibitors can reduce the expression of P-glycoprotein in tumor cells and thereby increase their sensitivity to chemotherapy [13]. PKC activation is also required for tumor angiogenesis [14].

Topoisomerases affect the topology of DNA and are able to relax their supercoiled molecules by introducing single- or double-stranded breaks followed by their DSB repair, as well as negative supercoils, or catenans. Inhibitors of these enzymes are widely used to suppress the activity of type I and / or type II tumor topoisomerases, blocking cells in the G2 phase and delaying their entry into mitosis [15].

Inhibitors of topoisomerases are ones of the most effective inducers of apoptosis, i. e., a programmed death of tumor cells [10]. In addition, a number of indolocarbazole derivatives with antiangiogenic activity have been

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synthesized. They are able to block vasculogenic mimicry in a tumor and restore the sensitivity of resistant cells to chemotherapeutic drugs [16, 17]. These features of the action mechanism determine a wide range of cytotoxic and antitumor activities of indolocarbazole derivatives.

THE AIM of the work is to generalize the literature data on indolocarbazole derivatives with an antitumor activity.

MATERIALS AND METHODS

The objects of the study were the preparations based on indolocarbazole derivatives with the antitumor activity. To search for materials on the problem under study, the following search and information as well as library databases were used: Ebibrary, PubMed, CyberLeninka, ResearchGate, the State Register of Medicines, clinical trials registries clinline.ru and clinicaltrials.gov. The search for the following words / phrases was performed: indolocarbazoles, indolocarbazole derivatives, staurosporine, rebeccamycin, staurosporine derivatives. The search was conducted from January 11 until March 1, 2021. The compounds with a biological activity that were undergoing or had undergone preclinical and clinical trials were taken into account. All the materials from 1977 until January 1, 2021, were taken into account.

The article is a review of the publications devoted to indolocarbazole derivatives, i.e., to the information on their structure, origin, classification, the main representatives of the class, which are at various stages of research and are approved for use in the clinic.

RESULTS AND DISCUSSION

General characteristics of indolocarbazole group compounds

The first indolocarbazoles were found out in streptomycetes and subsequently isolated from numerous representatives of flora and fauna. To date, this class of compounds has also been supplemented by a wide variety of synthetic compounds [18][1].

Indolocarbazoles are a class of heterocyclic compounds that include a planar ring consisting of indole and carbazole elements (Fig. 1, 2) [18]. Indole, carbazole and their derivatives are colorless solid crystalline substances that do not dissolve in water. Under standard conditions, the melting point of indole is 52°C, of carbazole, it is 247–248°C, and their boiling points are 253°C and 354–355°C, respectively[2,3]. The carbazole fragment serves as a ligand for many receptors and has the property of reverse coupling to enzymes, in particular, to DNA topoisomerase I [19], and the indole element is responsible for the interaction with DNA [20, 21].

The class of indolocarbazoles includes 5 subclasses of compounds differing in the structure of a planar aromatic ring. In this case, 5 isomers of the polycyclic system – indolo[2,3-a]carbazole (1), indolo[2,3-b]carbazole (2), indolo[2,3-c]carbazole (3), indolo[3,2-a]carbazole (4) and indolo[3,2-b]carbazole (5) (Fig. 3) [18] – are meant.

The most extensive, biologically significant and studied in detail is the subclass of 11,12-dihydroindolo[2,3-a] carbazole derivatives, including mainly compounds having indolo[2,3-a]pyrrolo[3,4-c]carbazole ring, in which 2 indole fragments are linked through a benzene ring with an amide or imide group. The indole moieties are linked through 1 or 2 bonds to the carbohydrate moiety. At the same time, this subclass also includes a small group of compounds that do not include an additional pyrrole ring in their composition [18].

Based on the number of glycosidic bonds that bind the carbohydrate moiety to the isoindole backbone, indolocarbazole derivatives can be divided into 2 subclasses – compounds of the staurosporin group (a) and rebeccamycin (c). In staurosporin and its derivatives, for example, K252a (b), glycoside is bound to 2 indole groups through nitrogen atoms, in contrast to the representatives of the rebeccamycin group, for example, cholyrin A (d), in which the carbohydrate residue is attached to only one indole. The staurosporin heterocycle is connected to the lactone ring, the rebeccamycin heterocycle – to the imide ring (Fig. 4) [25]. Both monosaccharides [23, 24] and disaccharides [25–28] can be included in the structure of indolocarbazoles as carbohydrate residues.

However, the literature also describes indolocarbazole derivatives with a different structure, for example, Go 6976 (Fig. 5) and AEB071 (sotrastaurin) (Fig. 6) – selective inhibitors of protein kinase C α, β1, δ, υ and ζ isozymes. Unlike staurosporine, Go 6976 is methyl- and cyanoalkyl-substituted non-glycoside indolocarbazole [29]; sotrastaurin contains a piperazine ring, in which the nitrogen atom in the ring carries an aryl group [30].

Various modifications of natural and synthetic derivatives of indolocarbazoles lead to changes in their physicochemical properties and biological activity. These factors are important for the development of potential antitumor agents. It is obvious that the antitumor effect of the target compound can be influenced by both substituents in the aglycone and the nature of the glycosidic residue, changing the pharmacodynamic and pharmacokinetic properties. [31].

Representatives of indolocarbazoles class

Staurosporin, the first of the discovered compounds of indolocarbazole derivatives, was isolated in 1977 at the Kitasato Institute (Japan) from the cultures of *Strep-*

[1] A few examples of indolocarbazoles found in the ClassyFire database. The Metabolomics Innovation Centre (TMIC) [Electronic resource]. Available from: http://classyfire.wishartlab.com/tax_nodes/C0001866

[2] PubChem Compound Summary for CID 798, Indole. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information [Electronic resource]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/6854

[3] PubChem Compound Summary for CID 6854, Carbazole. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information [Electronic resource]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/6854

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tomyces staurosporeus and *Streptomyces actuosus.* Staurosporin has antifungal and hypotensive effects, inhibits platelet aggregation, and is a potent inhibitor of various protein kinases. These factors lead to its use as an antitumor drug [32, 33].

In 1983, the parent of the second group of indolocarbazole derivatives, rebeccamycin (NSC 655649) (Bristol-Myers Co., USA) [34], which is structurally similar to staurosporin, but has a weaker inhibitory activity against protein kinases, was isolated from the strain of actinobacteria C-38383 [35]. The mechanism of the antitumor action of rebeccamycin is associated with the inhibition of topoisomerase I, which is due to its ability to interact with DNA [36].

In order to increase the solubility and the biological activity, the hydrophobic indolocarbazoles staurosporin and rebeccamycin underwent various modifications: a) the addition of substituents to the upper heterocycle, replacement of atoms in the upper heterocycle or removal of a heterocycle, b) modification of flat chromophore, c) modification of replacement or removal of the carbohydrate moiety [37–39].

Staurosporine derivatives

Midostaurine (CGP 41251, PKC 412, NVP-PKC412) (Fig. 7) is an N-benzoyl[4] derivative of staurosporin; it is a synthetic inhibitor of many kinases, including FLT3 and KIT, with antiangiogenic and antitumor activities [40]. It is approved by the FDA[5] and EMA[6] by the TN of Rydapt® (Novartis Pharmaceuticals, Switzerland)[7], in Russia this drug is registered by the TN of Miticaid® (LP-005927)[8]. This MP is a liquid capsule for the oral administration, each capsule contains 25 mg of midostaurin[9].

Enzastaurine (LY-317615, LY317615) (Eli Lilly and Company, USA) (Fig. 8) is an acyclic bisindolylmaleimide derived from staurosporin that selectively inhibits protein kinase-β. The mechanism of the antitumor action of enzastaurin is due to several effects. First, the drug has anti-angiogenic properties associated with a decrease in the level of vascular endothelial growth factor. Second, enzastaurine directly induces the death of tumor cells by reducing the phosphorylation of protein kinase [41]. Numerous studies have been carried out in mono- and combined therapy of oncological diseases of various nosologies, for example, tumors of the nervous system [42–44], colon [45], lymphoma [46–49], Waldenstrom's myeloma and macroglobulinemia [50], non-small-cell lung cancer [51], prostate [52], ovaries [53], etc.

Sotrastaurine (AEB071) (Novartis Pharmaceuticals, Switzerland) is a selective inhibitor of PKC β [57], which prevents the activation of T cells, has a piperazine ring; therefore, this compound can be attributed to the class of organic compounds known as n-arylpiperazines (Fig. 6) [55]. The use of sotrastaurine in the treatment of diffuse large B-cell lymphoma, stomach cancer [56], ulveal melanoma [57], psoriasis [58], as well as in kidney transplantation, has been investigated [59, 60].

Lestaurtinib (A-154475, A-154475.0, CEP-701, KT-555, KT-5555, KT5555, SP-924, SP924, SPM-924) (Cephalon, Inc., USA) (Fig. 9)[10] has been studied in the treatment of infections of the central nervous system caused by free living amoebae [61], myeloid leukemia [62–64], polycythemia and essential thrombocythemia [65], myelofibrosis [66], prostate cancer [67, 68], neuroblastoma [69, 70] psoriasis [71].

Among the staurosporin derivatives, the antibiotic K-252a (Kyowa Hakko Kogyo Co., Ltd., Japan) (Fig. 10)[11], isolated from the culture of Nocardiopsis sp. K-252a, is a unique in its structure indolocarbazole glycoside, and exhibits a powerful neuroprotective antitumor activity. K-252a consists of K-252c and an extraordinary dihydrostreptose fragment linked together by two C-N bonds [72]. Its semi-synthetic derivative KT5720 inhibits cAMP-dependent protein kinase. The activity of KT5720 has been confirmed on granulosa cells of animal ovaries [73, 74].

A promising semi-synthetic staurosporine derivative is stauprimide (The Scripps Research Institute, USA), which inhibits the transcription of the MYC NME2 oncogene and also increases the efficiency of directed differentiation of embryonic stem cells [75, 76].

CEP-11981 (Cephalon, Inc., USA) (Fig. 11) is a targeted drug for oral administration, exhibiting a high inhibitory activity against several targets – receptors for vascular endothelial growth factor 1 and 2, tyrosine kinase 2, and a fibroblast growth factor-1, protooncogene c-SRC, and Aurora A. The studies of the pharmacological activity in animal and human tumor models have shown sustained dose-dependent antiangiogenic and antitumor effects. In addition, CEP-11981 has shown an excellent bioavailability, a metabolic stability, and other pharmacokinetic properties. Phase I clinical trials to evaluate the pharmacokinetics and pharmacodynamics of CEP-11981 in patients with advanced, recurrent / refractory solid tumors, have been completed [77, 78].

[4] PubChem. Compound Summary for CID 9829523, Midostaurin. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information [Electronic resource]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Midostaurin.

[5] Highlights of prescribing information. Rydapt. U.S. Food and Drug Administration [Electronic resource]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

[6] Rydapt. European Medicines Agency [Electronic resource]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rydapt

[7] RYDAPT® (midostaurin) Capsules. AML & ASM Treatment Novartis AG [Electronic resource]. Available from: https://www.rydapt.com.

[8] Instructions for the use of a medicinal product for medical application of Mitikaid®. State Registermedicines. Available from: http://grls.rosminzdrav.ru

[9] Highlights of prescribing information. Rydapt. U.S. Food and Drug Administration [Electronic resource]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf

[10] Lestaurtinib. DrugBank. Available from: https://www.drugbank.ca/drugs/DB06469

[11] PubChem. Compound Summary for CID 3035817, Antibiotic K 252a. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information [Электронный ресурс]. URL: https://pubchem.ncbi.nlm.nih.gov/compound/Antibiotic-K-252a

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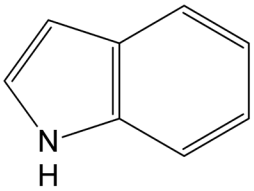


Figure 1 – Structural formula of indole

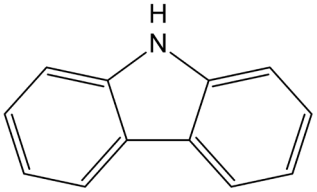


Figure 2 – Structural formula of carbazole

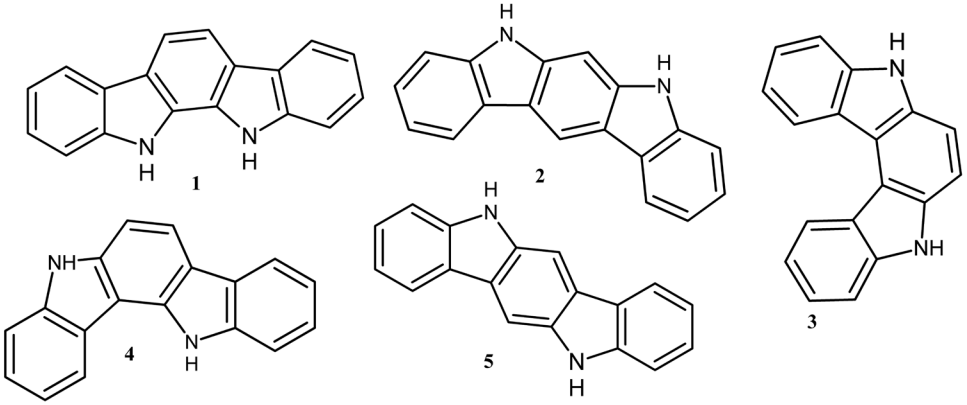
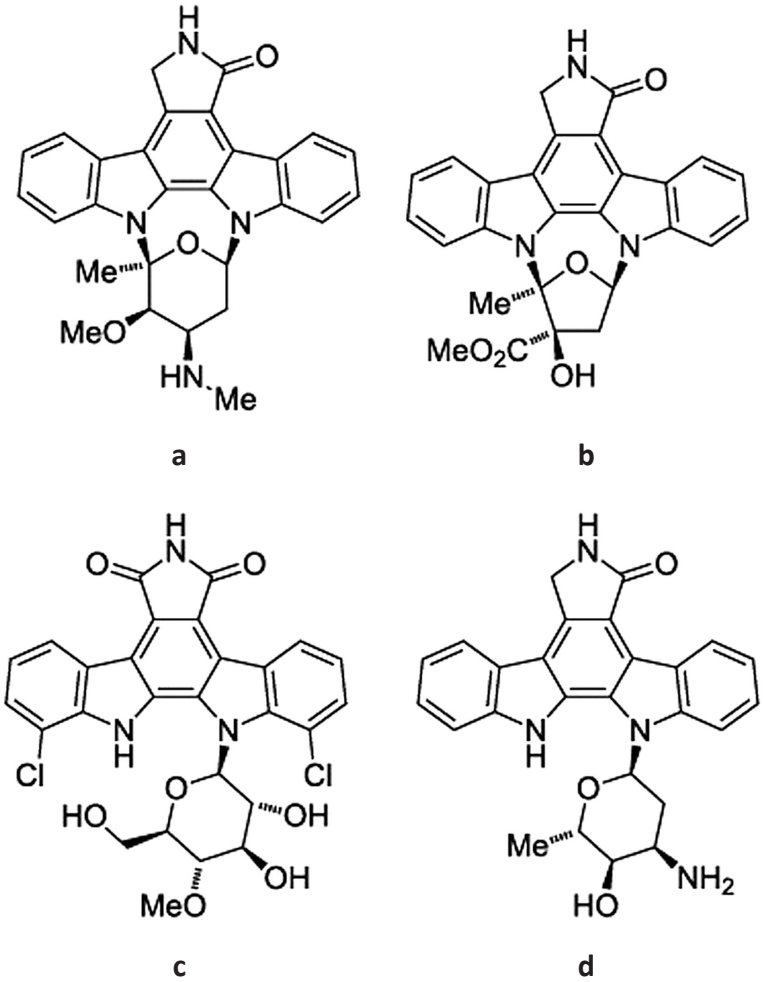


Figure 3 – Structural formulas of indolocarbazole isomers



a **b** **c** **d**

Figure 4 – Structural formulas of indolocarbazole derivatives

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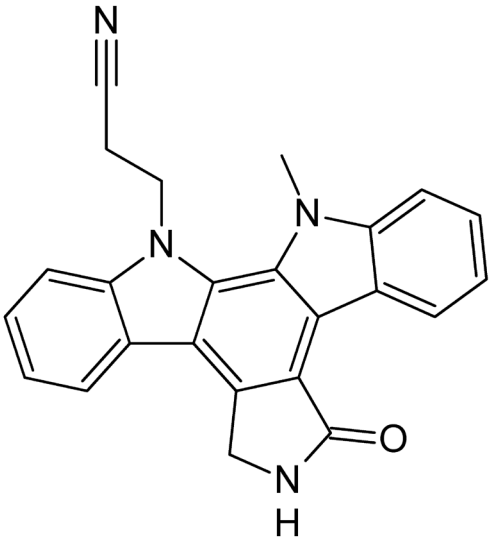

Figure 5 – Structural formula of Go 6976

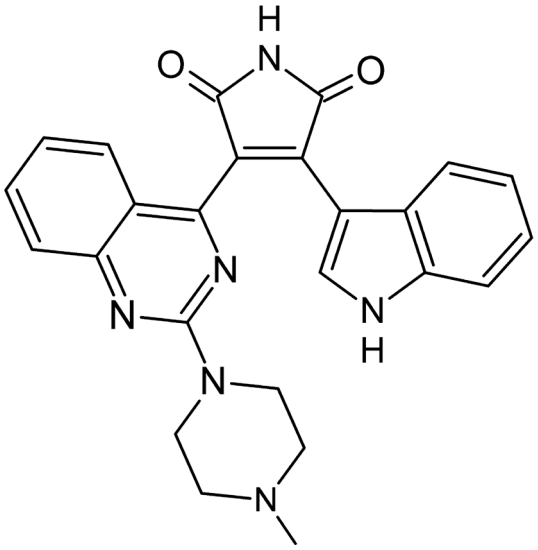

Figure 6 – Structural formula of sotrastaurine

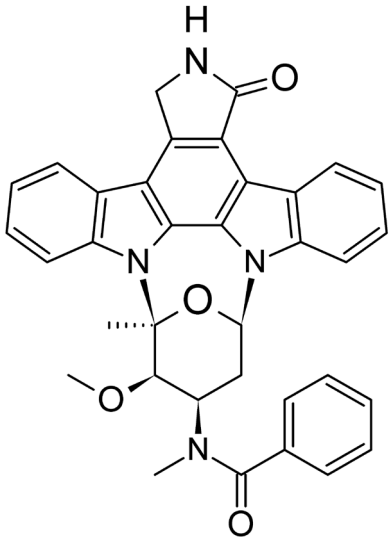

Figure 7 – Structural formula of midostaurine

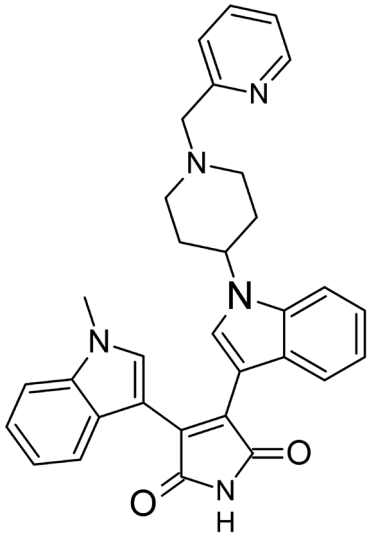

Figure 8 – Structural formula of enzastaurin

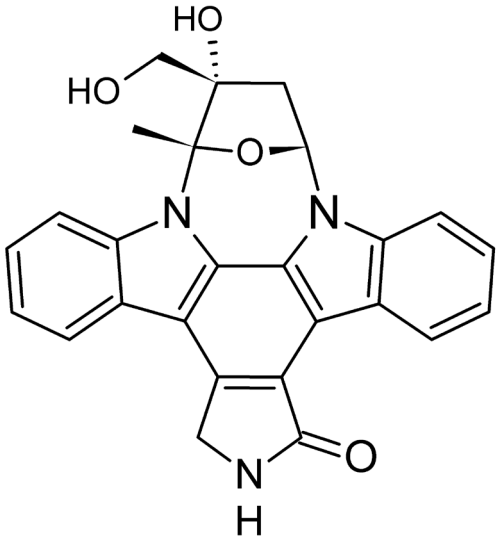

Figure 9 – Structural formula of Lestaurtinib

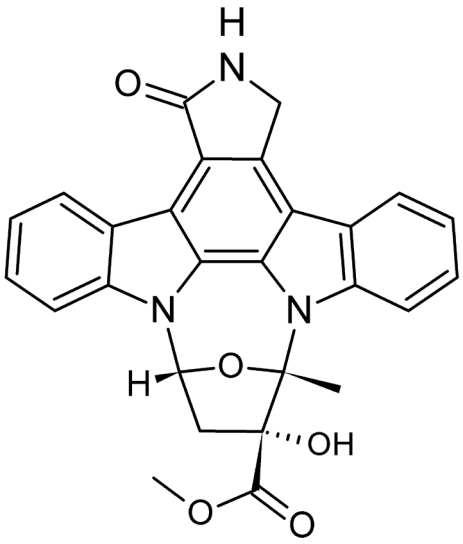

Figure 10 – Structural formula of K-252a

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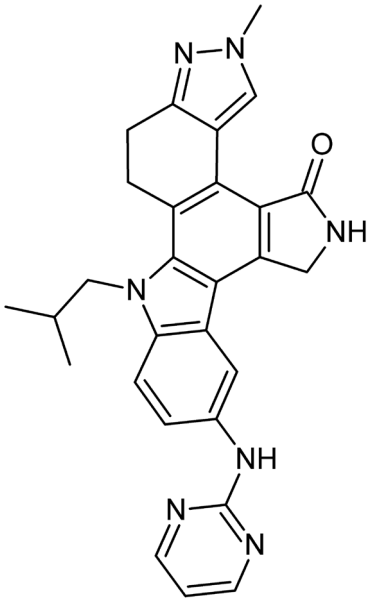

Figure 11 – Structural formula of CEP-11981

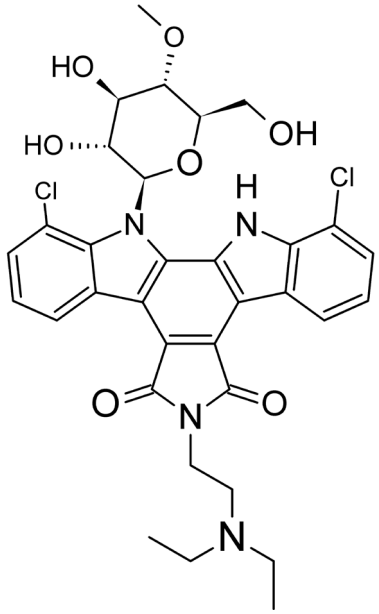

Figure 12 – Structural formula of becatecarin

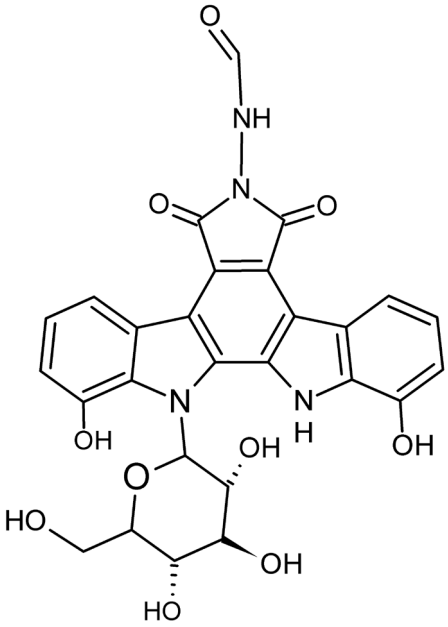

Figure 13 – Structural formula of NB-506

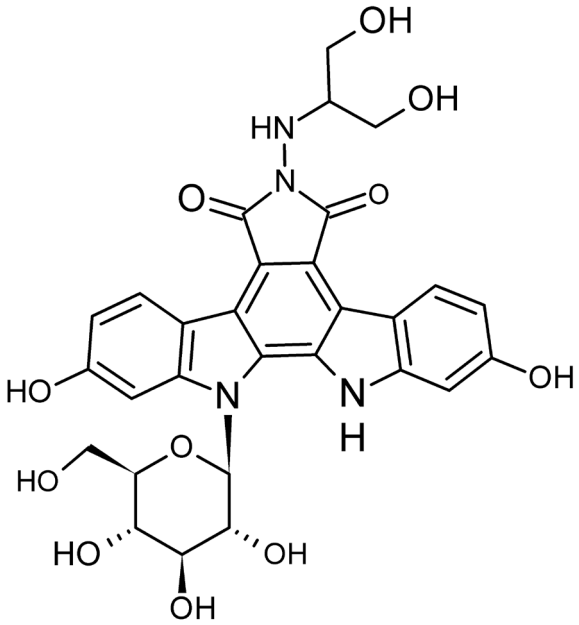

Figure 14 – Structural formula of edothecarin

Go 6976 (Godecke AG, Germany) (Fig. 5) is an indolocarbazole derivative containing a propane nitrile radical instead of a glycosidic residue[12]. Go 6976 is a selective inhibitor of PKC α and β, it moderately inhibits the activation of protein kinase regulated by extracellular signals [79]. In addition, this indolocarbazole is a potential anticancer drug due to its ability to stimulate the formation of cellular compounds (the formation of an increased number of desmosomes and adhesions), to suppress migration and invasion of tumor cells [80].

In the literature, there are also data on many other compounds of staurosporin derivatives: ZHD-0501 [81]; BMY-41950 (RK 1409) [82]; UCN-01 and UCN-02 [83]; CEP-7055 and CEP-5214 [84]; CEP-701; CEP-2563 and CEP-751 (KT-6587) [85]; KT5926 [86]; Ro 318220 and GF 109203X [87]; CEP-1347[13], and others.

Among the domestic compounds of staurosporine derivatives, the most famous are the N-glycosides of

[12] PubChem Compound Summary for CID 3501, Go-6976. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information [Electronic resource]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Go-6976

[13] CEP-1347. DrugBank [Electronic resource]. Available from: https://go.drugbank.com/drugs/DB05403

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indolo [2,3-a] pyrrolo [3,4-c] carbazole-5,7-diones of indolocarbazoles: LHS-976, LHS-983, LHS-985, LHS-999, LHS-1006, LHS-1007, LHS-1040, LHS-1054, LHS-1098, LHS-1208, LHS-1269, etc. [88-93]. Today, compounds LHS-1208 and LHS-1269 are the most studied among them as antitumor agents.

An indolocarbazole derivative **LHS-1208** exhibits a strong inhibitory activity against kinases[14] – cyclin-dependent kinase, protein kinase C and tyrosine kinase; the second target is DNA and the DNA topoisomerase complex. To date, preclinical trials of an injectable dosage form LHS-1208 containing dimethyl sulfoxide and a solubilizer Kollidon 17PF as a co-solvent of the hydrophobic active substance, have been completed [94]. For this compound, a liposome-based DF was also developed in the form of a lyophilisate for the preparation of an injection emulsion [95].

LHS-1269 is an indolocarbazole derivative with a carbohydrate residue xylose, which has cytotoxic and antiangiogenic effects and has shown a high antitumor activity against a number of transplanted ascites and solid tumor models [96, 97]. To date, a composition and technology for producing an injectable liposomal dosage form have been developed for LHS-1269 [98].

Rebeccamycin derivatives

On the basis of rebeccamycin, a glycosyl-dichloroindolocarbazole analogue with the improved water solubility denoted as becatecarin (BMS-181176, BMY-27557, NSC-655649, XL 119, XL-119, XL119) (National Cancer Institute, USA) (Fig. 12)[15] was obtained [99]. Becatecarin is an antitumor antibiotic with an inhibitory activity against topoisomerase I and topoisomerase II, as well as the ability to intercalate DNA [100, 104]. It has been studied in the treatment of lung cancer [101, 104], blood cancer [102], tumors of the nervous system [99] and solid tumors [103].

NB-506 (Banyu Co., Japan) (Fig. 13) is a glycoside derivative of rebeccamycin, the antitumor activity of which is due to its ability to interact with DNA and inhibit topoisomerase I. The glucose residue attached to the planar chromophore of indolocarbazole, plays a significant role in the interaction of drugs with nucleic acids; it promotes the stabilization of covalent complexes of topoisomerase I – DNA [105]. It has been reported that NB-506 is in clinical trials [106].

Edothecarin (J-107088, J-107088, PF-804950, PHA-782615) (Banyu Co., Japan) (Fig. 14) is a NB-506 derivative with a broad spectrum of antitumor activity, it is a topoisomerase I inhibitor that induces cleavage of single-stranded DNA more effectively than original indolocarbazole or camptothecin. In contrast to other inhibitors of topoisomerase I, the antitumor activity is less dependent on the cell cycle. Despite the fact that J-107088 has a structure similar to staurosporin, this drug does not possess the properties of a protein kinase inhibitor [107]. It has been actively studied in mono- and combined therapy of oncological diseases [108–115].

It was also found out that when grown in a specific medium containing 0.05% potassium bromide, *Saccharothrix aerocolonigenes* ATCC 39243 produces a rebeccamycin analog which has been indicated as brombeccamycin. It has the same structure as rebeccamycin, except the replacement of two chlorine atoms with bromine atoms in the molecule. The authors of the study suggest that the compound has an activity against mouse P-388 leukemia [116].

Rebeccamycin-based compounds have also been obtained. They are: BMS-250749, BMS-210287, BMS-251873, SA315F, AT2433-A1, AT2433-A2, AT2433-B1, AT2433-B2, etc. [117].

CONCLUSION

An important issue in medical science is the creation of new MPs for the treatment of cancer. Indolocarbazole derivatives are a promising class of anticancer drugs characterized by a directed mechanism of the action on targets such as kinases (especially PKC and its isozymes), DNA and DNA topoisomerases I and II. These compounds, along with the antitumor effect, have a wide spectrum of a biological activity, which also makes it possible to use them in the therapy of other nosologies, including transplantology.

To date, a fairly large number of compounds that are at various stages of preclinical and clinical studies, have been synthesized. They belong to two subclasses – derivatives of staurosporin and rebeccamycin.

However, for clinical practice, only one drug based on a staurosporine derivative, midostaurine, registered abroad by the TN of Rydapt® (in the Russian Federation its TN is Miticaid) has been approved for use. Therefore, to expand the arsenal of targeted anticancer drugs, it is necessary to study the known synthesized indolocarbazole derivatives, as well as to search for new compounds with improved characteristics, further.

[14] Isoenmers are not specified.

[15] PubChem Compound Summary for CID 101524, Becatecarin. PubChem. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information [Электронный ресурс] Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Becatecarin

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Alexander P. Kolpaksidi – searching for materials, writing, planning and editing the review;
Maria V. Dmitrieva – searching for materials, planning and editing the review;
Ilya V. Yarosh – searching for materials; Ivan I. Krasnyuk – planning and searching for materials.

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