NEW MULTICOMPONENT SYNTHESIS OF COMPOUNDS WITH ANTICANCER PROPERTIES

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Abstract

Multicomponent reactions leading to the formation of compounds with potent anticancer properties has been investigated. Preliminary biological evaluation of the synthesized libraries identiefied of antiproliferative and apoptosis-inducing properties of new heterocyclic podophyllotoxin analogues.

Key words: Multicomponent synthesis, podophillotoxin, dihydropyridines, benzopyranes, pyranopyridones, pyridopyrazoles, pyranoqinolones, indenopyridines, apoptosis, scaffold, cytotoxity.

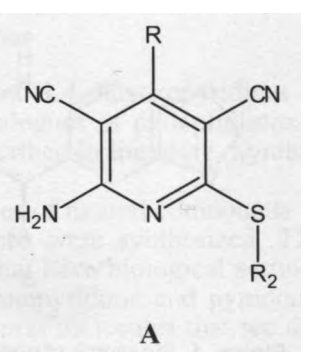
Scientific school of organic chemistry has more than 130 years history [1]. In the recent years we have been exploring novel approaches to heterocyclic compounds with potent biological activity. These investigations are the part of RF program aimed at developing heterocyclic system with agricultural and medicinal utility.

In this article we summarize the recent results in the common investigations of Department of Organic Chemistry Russian State Agrarian University-Moscow Timiryazev Agricultural Academy and Department of Chemistry, New Mexico Institute of Mining and Technology (professor A. Kornienko).

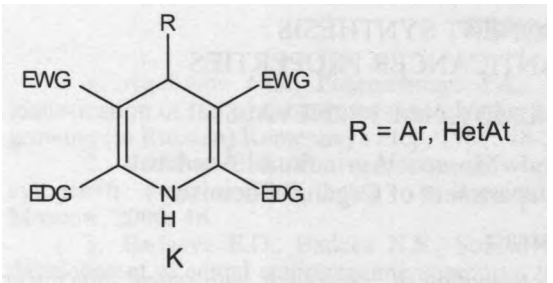
These investigations devote the most actual problem of modem medical chemistry - research of new effective anticancer compounds. Quick assembling of compounds to a complex molecule is an important aim of synthetic organic chemistry and one of the modem basic paradigms for searching for dmgs. One of the ways to solve this problem is performing one-pot multicomponent reactions (MCR) (or multicomponent syntheses) [2], especially to obtain heterocyclic drug-like libraries. Working out these methods is actual both academic and industrial problem. Solve last of them is dramatically important for green chemistry point of view [3, 4]. When MCR provides access to privileged medical scaffolds, their importance significally increase. Privileged medical scaffolds are compounds that possess wide spectrum of biological activity and are similar in the number of structural basis with natural biological active compounds.

Pyridines that contain fragment A are an example of a privileged medical scaffold. Usually these compounds are synthesized using aldehydes via 3-4 stages and the total yield is small (4-12 %).

There are more than 30 patents for various biological activities of this class of compounds. For example, pyridines A inhibit MAPK-activated PK-2 decreased TNFa production, it is important for treatment inflammation such as arthritis and rheumatism [5]. They also modulate androgen receptors [6]. Besides, that pyridines A are selective modulators of adenosine receptors with potential using for treatment Parkinson's disease, ischemia, asthma, epilepsy [7,8]. 1,4-Dihydropyridines, that contain fragment K are also privileged medical scaffolds and widely used for cardio-vascular diseases treatment, it is connected with its ability to blocked calcium canals [9].



A



Podophillotoxin 1 (fig.l), an antimitotic cyclolignan isolated from plants of the genus *Podophyllum*, attracted our attention because of its high cytotoxicity. Its semisintetic derivatives, etoposide 2 and teniposide, are currently used in clinic for the treatment of a variety of cancers. Due to the structural complexity of podophillotoxin 1, arising from the presence of four stereogenic carbons in ring C, most of the structure-activity relationship (SAR) studies have been performed by derivatization of the parent natural podophillotoxin [10, 11]. It was shown, that precence of the ring A is not critical for anticancer activity. There are few original syntheses of structural analogues of podophillotoxin in literature [10]. Japan scientists made an important contribution to the field by demonstrating that greatly simplified 4-aza-2,3-didehydropodophillotoxins 3 retain most of the cytotoxicity associated with the parent lignan [12,13]. Later Frenchscientists devised multicomponent synthesis of analogues 3[14].Recently Chinese scientists have proposed multicomponent synthesis of N-substituent dihydropyridine analogues of podophillotoxin 4 but information about their biological activity is absent [15]

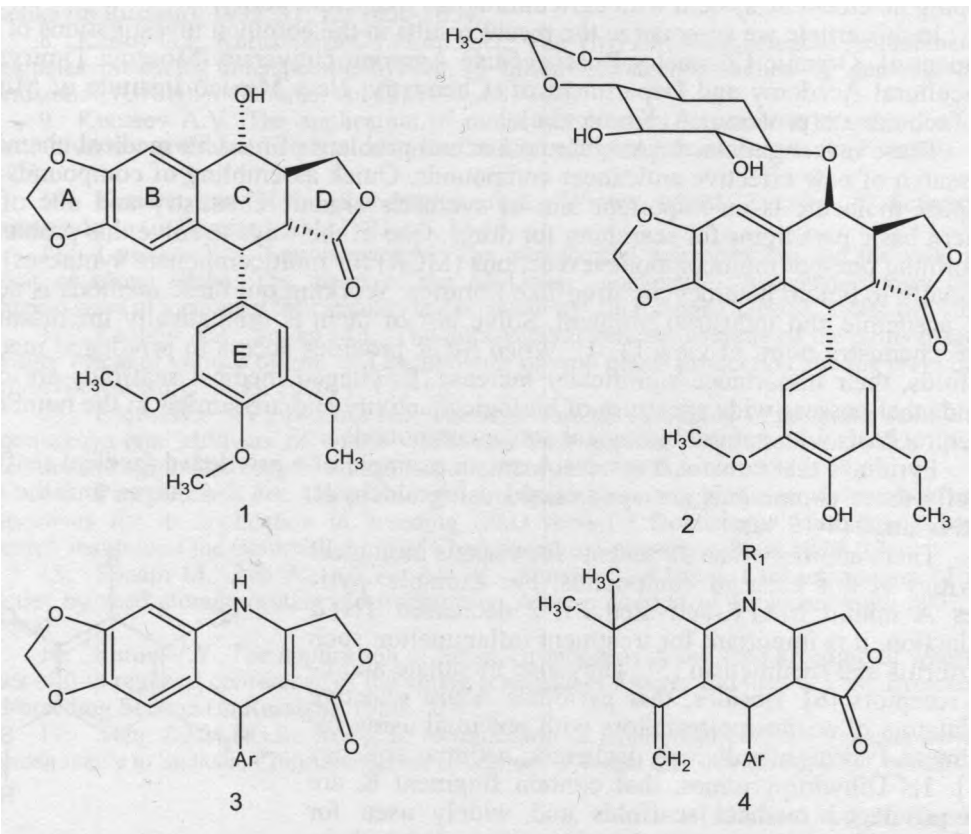


Figure. 1. Structures of podophillotoxin (1), etoposide (2) and 4-aza-2,3-didehydro analogues 3 and 4

Condensed pyranes and pyridones are one of the most important bioactive scaffold [16]. 4H-nafto[l,2-b]pyrane LY290181 (fig.2) which contains moiety of benzopyrane shows high cytotoxic activity [17]. Benzopyranes type S shows anticancer activity too [18, 19].

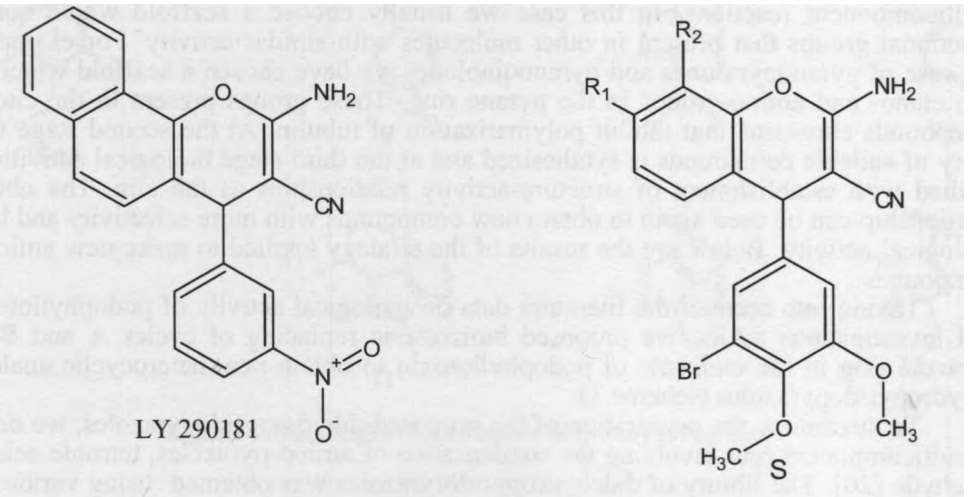


Figure. 2. Cytotoxic derivatives of pyranes

However, there is no information in literature about syntheses and biological activity of pyranopyridones tipe N (fig.3). There are only few examples of syntheses of naftoqinonopiranes P in literuture (fig.3) via two-staged reactions but information about their biological activity is absent.

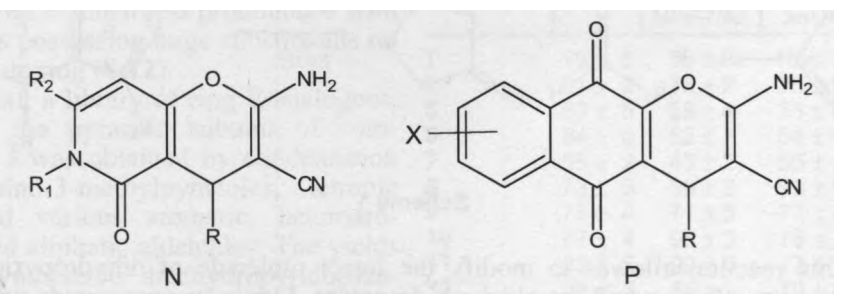


Figure 3. Potential cytotoxic pyranopyridones

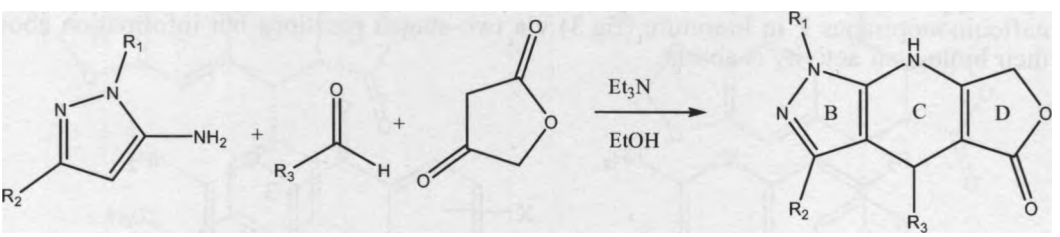
Thus, the information in literature about pyridines A and 1,4-dihydropyridines K showing cytotoxicity is not found. Furthermore, synthetic analogues of podophillotoxin with ring A and B replaced by heterocyclic moiety are not described in literature. Synthesis of heterocyclic pyranes type N and P is interesting too.

We use the next strategy to solve this problem. Analogues of natural compounds to found new medical preparations via multicomponent reactions were synthesized. The main point of the approach is selection of natural molecules that have biological activity as the aim. Podophillotoxin, cytotoxic alkaloids contain pyranopyridone and pyranoqinolone moiety, kamptomicine and others are examples of natural molecules that we de-

scribe in this publication. At the first stage based upon literature data on structure-activity relationship (SARs), the fragment which is responsible for the basic biological properties (privileged medical scaffold) is picked out of the molecules of these compounds and multicomponent methods of synthesis are proposed. It is often possible to pick out the structure of some similar scaffolds and each of them can be synthesized by multicomponent reactions. In this case we usually choose a scaffold which contains functional groups that present in other molecules with similar activity. For example, in the case of pyranopyridones and pyranoqinolones we have chosen a scaffold which contain ciano- and amino-groups in the pyrane ring. These groups present in the citotoxic compounds chromens that inhibit polymerization of tubulin. At the second stage the library of suitable compounds is synthesized and at the third stage biological activities are studied with establishment of structure-activity relationships as the aim. The obtained relationship can be used again to obtain new compounds with more selectivity and higher biological activity. Below are the results of the strategy applied to make new anticancer compounds.

Taking into account the literature data on biological activity of podophyllotoxin 1 and investigations SARs, we proposed bioizosteric replacing of cycles A and B with pyrazole ring in the molecule of podophyllotoxin to obtain new heterocyclic analogues dihydropyridopyrazoles (scheme 1).

To streamline the preparation of the proposed dihydropyridopyrazoles, we devised a multicomponent rout involving the condensation of amino-pyrazoles, tetronic acid, and aldehyde [20]. The library of didehydropyridoryrazoles was obtained using various substituents in the molecules aminopyrazole and aldehyde. Didehydropyridoryrazoles are heterocyclic analogues of podophillotoxin 1.



Scheme 1

This reaction allowes to modify the intact molecule of dihydropyridoryrazole both in the pyrazole ring and the aldehyde fragment. Synthesis compounds with various pyrazole rings B and invariable 3,4,5-threemethoxyphenile ring E were the first target of these investigations (fig. 4).

Analogues 8-13 were evaluated for antiproliferative activity against three cancer cell lines HeLa, MCF-7/AZ and Jurkat. The corresponding cell were treated with the test compounds at final concentrations of 5 and 50 μM. Cell viability was assessed using MTT method.

The yield and citotoxicity (5 μM) data, including podophillotoxyn 1, etoposid 2, are shown in tab. 1. In addition, the same compounds were tested for their ability to induce apoptosis in Jurkat cell in a flow cytometric Annexin-V/propidium iodide assay at final concentrations of 5 μM. Percentages of apoptotic cells after 48 h treatment are shown in the tab. 1.

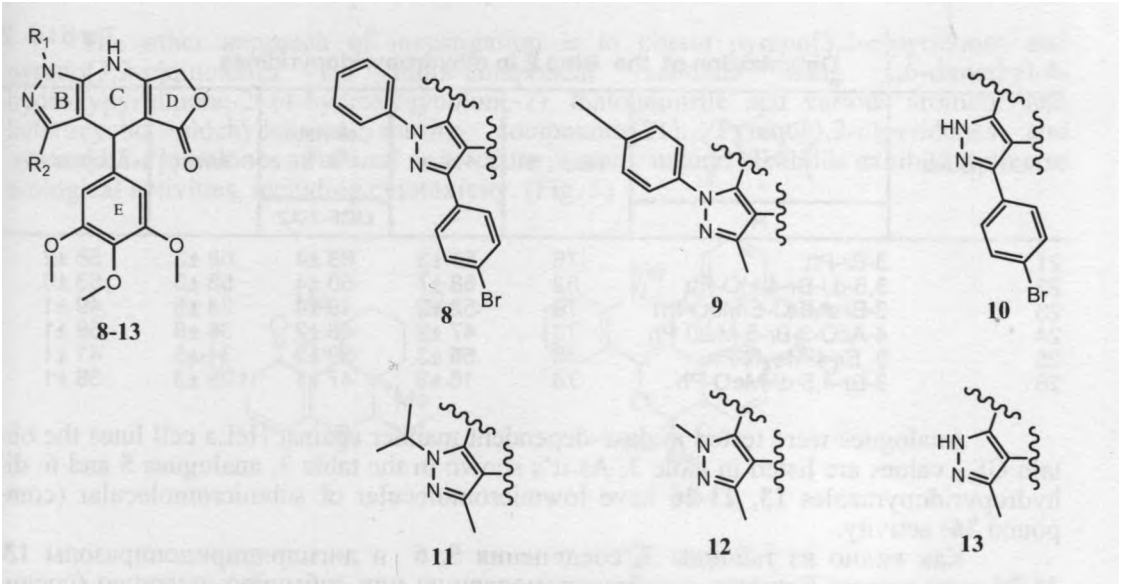


Figure 4. Modifications of structure dihydropyridopyrazole

As it's shown in the table 1 methylendioxyphenil ring can be replaced by pyrazole fragment. Among the pyrazole analogues that contains 3-methyl-1H-pyrazole moiety, compound 13 shows very similar potencies. The growth inhibitory activity is much less pronounced with analogues possessing large substituents on the pirazole ring (8-12).

Next, a library of ring E analogues, base on the pyrazole subunit of compounds 13 was obtained by condensation of 5-amino-3-methylpyrazoles, tetronic acid, and various aromatic, heteroaromatic, and aliphatic aldehydes. The yields of the synthesized didehydropyridopyrazoles, their antiproliferative potencies against the same three cell lines, and percent of apoptosis induction of Jurkat cell are given in table 2. It is shown that all of the other most potent analogues, namely 21-26, have a bromine substituent at the meta position of the aromatic ring E. *m*-Cl 27, 28, *m*-F 29 substituents, or orto-30 and para-31 positioning of the bromine do not produce an effect similar to the meta bromo substituent. Aliphatic 32, 33 and heterocyclic 34-40 analogues are much less potent or inactive. In general, percent of apoptosis induction in Jurkat cell parallels the antiproliferative potency of the analogues being highest (50-58 %) with the meta bromo analogues 21-26.

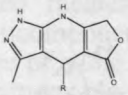
Table 1

Optimization of the Pyrazole Moiety of Dihydropyridopyrazole Structure

Compound	HeLa	% cell viability		% apoptosis
		MCF-7/AZ	Jurkat	Jurkat
1	19 + 5	55 ±3	18 ± 5	54 ±2
2	91 ± 2	76 ±2	75 ±5	4 ± 3
5	53 ± 5	58 ±4	35 ±6	49 ±4
6	54 ± 6	52 ±3	54 ± 1	55 ±4
7	55 ± 2	43 ±2	55 ±4	55 ± 4
8	73 ± 5	90 ±3	99 ±1	2 ± 1
9	77 ± 4	71 ±5	77 ±2	23 ± 1
10	67 ± 4	98 ±3	78 ±7	5 ± 1
11	83 ± 5	99 ±0	77 ±9	4 ± 0
12	55 ± 3	98 ±1	79 ±4	5 ± 1
13	50 ± 2	58 ±5	47 ±3	55 ±4
2 at 50 **pM**	15 ± 3	57 ±4	50 ±2	61 ±6

Table 2

Optimization of the Ring E in dihydropyridopyridines

Compound	 R	Yield , %	HeLa	Cell viability,% MCF-7/AZ	Jurkat	Apoptosis,%
21	3-Br-Ph	76	51 ±3	63 ±4	68 ±3	58 ±2
22	3,5-dJ-Br-4-HO-Ph	52	58 ±7	60 ±4	58 ±3	53 ±0
23	3-Br-4-EtO-5-MeO-Ph	76	52 ±2	49 ±4	28 ±5	49 ±1
24	4-AcO-3-Br-5-MeO-Ph	73	47 ±2	46 ±2	36 ±6	58 ±1
25	3_Br-4-Me_2N-Ph	75	55 ±3	59 ±3	34 ±5	41 ±1
26	3-Br-4,5-d/-MeO-Ph	78	16 ±3	47 ±1	29 ±3	56 ±1

Analogues were tested in dose-dependent manner against HeLa cell lines the obtain GI_{50} values are listed in table 3. As it's shown in the table 3, analogues 5 and 6, dihydropyridopyrazoles 13, 21-26 have lowmicromolecular or submicromolecular (compound 26) activity.

Как видно из таблицы 3, соединения 5, 6 и дигидропиридопиразолы 13, 21-26 показывают близкую низкомикромолярную или субмикромолярную (соединение 26)активности.

Table 3

GI_{50} of dihydropyridopyrazole

GI_{50} (μM)		GI_{50} (μ M)		GI_{50} (μM)	
Compound	HeLa	compound	HeLa	compound	HeLa
1	0.02	**13**	5 ± 1	**24**	4 ± 1
2	8 ± 2	**21**	5 ± 1	**25**	6 ± 1
5	6 ± 1	**22**	8 ± 2	**26**	0.75 ± 0.1
6	6 ± 1	**23**	5 ± 1	**27**	10 ± 2

Caspases are a family of proteolytic enzymes, which are normally present inside the cells as zymogens, that upon activation during the apoptotic process cleave many protein substrates resulting in irreversible cell death. Indeed, analogues 13 and 21-27 used at 5 μM concentrations elicited 3 to 4.5 fokd increase in caspase-3 activity.

Apoptosis was further characterized by the Western blot analysis. Cleavage of the procaspase-3 to produce the active enzyme was observed in Jurkat cells in time-dependent manner after treating the cells analogue 13. Because endonuclease-mediated cleavage of nuclear DNA fragments (180-200 base pair long) is a hallmark of apoptosis in many cell types, DNA-laddering assay was performed.

After treating the Jurkat cells analogue 13 cleavage of the nuclear DNA was produce the same as etoposide 2.

As well known, the normal nucleated white blood cells are a common target of many cancer chemotherapeutic agents leading to serious side effects. That's why dihydropyridopyrazole analogues were tested for their ability to induce apoptosis in human primary lymphocytes. Human lymphocytes were purified from whole blood obtained from healthy volunteers and treated with analogues 13, 21-26 to assess the extent of apoptosis induction with flow cytometric Annexin-V/propidium iodide assay. It was found that none of these compounds show any apoptosis induction in human noncancerous lymphocytes after 24h of treatment.

The other approach of investigation is to obtain pyrano[3,2-c]pyridones and pyrano[3,2-c]qinolones via multi-component reactions using 1,6-dimethyl-4-hydroxypyridinone-2 (4-hydroxyqynolone-2), malononitrile and various aromatic and heterocyclic aldehydes as starting compounds[21], Pyrano[3,2-c]pyridones and pyrano[3,2-c]qinolones structural unit occurs in many natural alkaloids exhibiting diverse biological activities, including cytotoxicity. (Fig. 5)

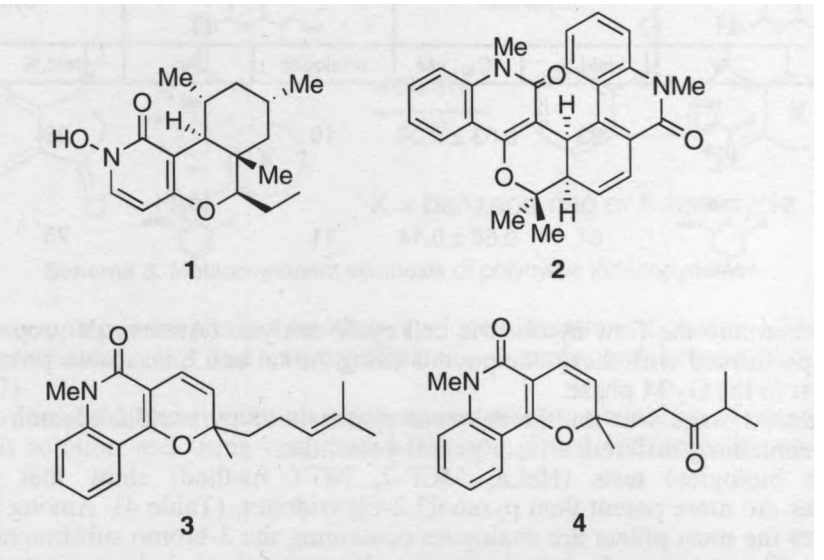
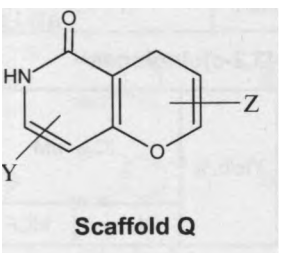
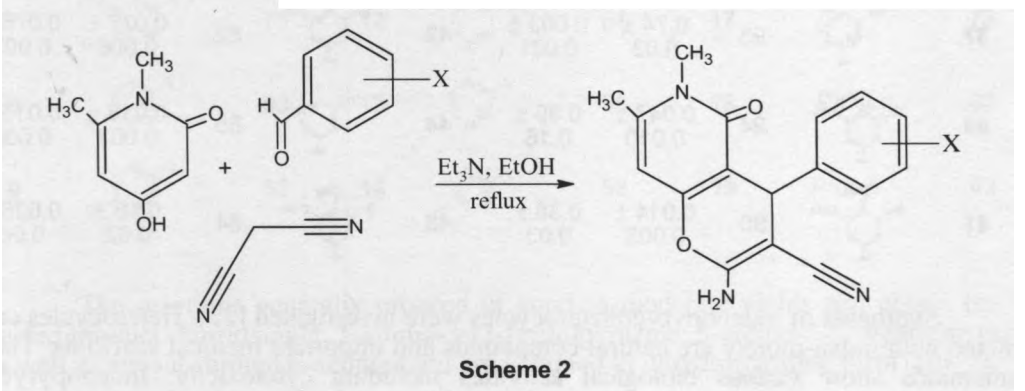


Figure 5. Structure of antycancer pyrano[3,2-c]pyridine- and pyrano[3,2-c]qinolone-conteining alkaloids 1-4



Somewhat suɒrisingly, the biology of compounds containing scaffold Q has not been thoroughly investigated with the exception of antibacterial properties associated with some of these compounds (see [21] and quoted literature).

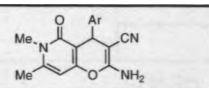
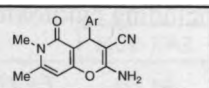
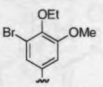
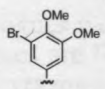
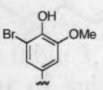
At the first stage the following reaction of 1,6-dimethyl-4-hydroxypyridone-2 with malononitrile and various aromatic aldehydes was performed to obtain pyrano[3,2-c]pyridones (scheme 2).



The biological tests (HeLa, MTT method) show that most potent submikromolar and lowmikromolar analogues have a 3-bromo substituent in the aromatic ring (Table 4).

Table 4

Synthetic yields and cytotoxicity of most active pyrano-[3,2-c]- pyridones

		Synthesis				Synthesis	
analoges	Ar	yield,%	IC_{50}, μM	analoges	Ar	yield,%	IC_{50}, μM
8		83	0.33 ± 0.06	**10**		88	1.1 ± 0.8
9		87	0.58 ± 0.14	**11**		75	2.7 ± 1.1

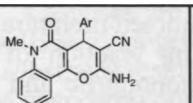
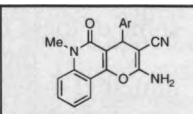
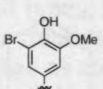
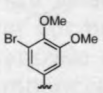
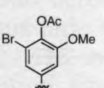
Furthermore the flow cytometric cell cycle analysis (Annexin-V/propidium iodide method), performed with these compounds using Jurkat cell line, shows pronounced cell cycle arrest in the G_2/M phase.

The next stage was multicomponent synthesis of pyrano[3,2-c]qinolone analoges (table 5) containing different aril- or getaril-substitute.

The biological tests (HeLa, MCF-7, MTT method) show that pyrano[3,2-c]qinolones are more potent than pyrano[3,2-c]pyridones. (Table 4). Among pyrano[3,2-c]qinolones the most potent are analogues containing the 3-bromo substituent in the aromatic ring. This compounds show lownanomolar cytotoxicity, induce apoptosis in cancer cells and destroy nuclear DNA (DNA laddering method). Furthermore, pyrano[3,2-c]qinolones show inhibition of tubulin polymerization *in vitro*.

Table 5

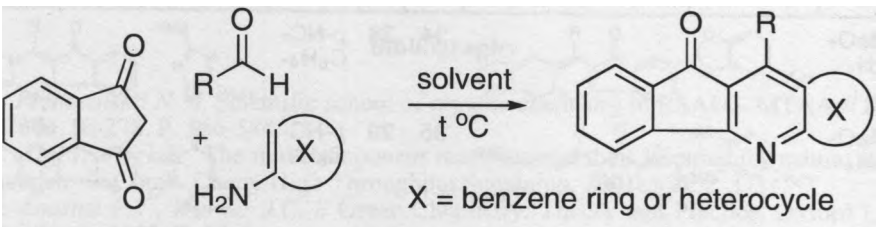
Synthetic yields and cytotoxicity of most active pyrano-[3,2-c]qinolones

		Yield,%	IC_{50}, μM				Yield,%	IC_{50}, μM	
analogues	Ar		HeLa	MCF7	analogues	Ar		HeLa	MCF7
37		93	0.74 ± 0.03	0.003 ± 0.001	**42**		82	0.077 ± 0.006	0.075 ± 0.007
40		94	0.047 ± 0.010	0.39 ± 0.16	**44**		85	0.013 ± 0.003	0.015 ± 0.008
41		95	0.014 ± 0.003	0.38 ± 0.03	**45**		84	0.18 ± 0.02	0.025 ± 0.06

Syntheses of indenopyrydoheterocycles were investigated [22]. Heterocycles conjuncted with indan-moiety are natural compounds and important medical scaffolds. These compounds show various biological activities including cytotoxicity. Indenopyrydon

NSC 314622 is a structural derivative of nature alkaloid camptotecine, it has planar polycyclic structure, intercalates to complex DNA - topoisomerase I, stops mitosis with the following induction of apoptosis[22].

As a part of the program aimed at developing multi-component synthetic routes to heterocyclic scaffold with medical utility, we have been exploring novel approaches to indenoheterocycles, that are analogues of camptothecin and NSC 314622 (Scheme 3).



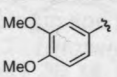
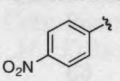
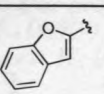
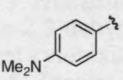
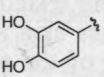
Scheme 3. Multicomponent synthesis of polycyclic indenopyridines

A three-component process involves cyclocondensation of indane-l,3-dione, anilines or aminoheterocycles and various aliphatic, aromatic and heterocyclic aldehydes (tab.6 and 7).

We found that most optimum reaction conditions are bubbling of oxygen through the reaction solution and using acetic acid-ethylene glycol (2:1) mixture as solvent at 120 °C.

T a b l e 6

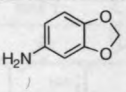
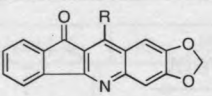
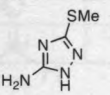
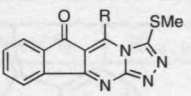
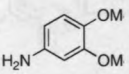
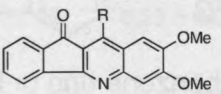
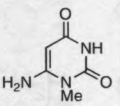
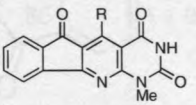
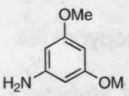
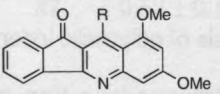
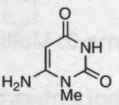
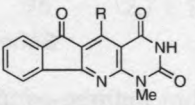
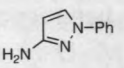
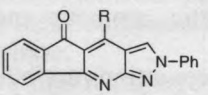
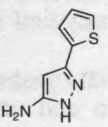
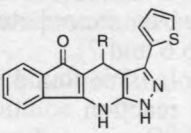
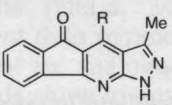
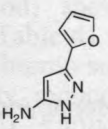
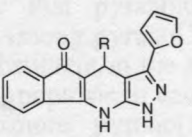
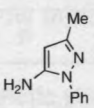
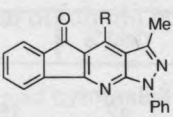
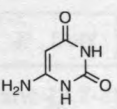
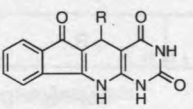
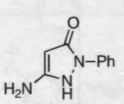
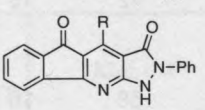
Indenopyridines (X=5-amino-1,2-dihydropyrazole-3-one)

	R	Yield , %		R	Yield,%		R	Yield, %
5		63	**10**		42	**15**		46
6		67	**11**		68	**16**		55
7		70	**12**		61	**17**		73
8		80	**13**		55	**18**	Ethyl	33
9		52	**14**		53	**19**	Propyl	43

The reactions generally proceed in good to moderate yields and obtain the expected product. Surprisingly, 5-amino-3-(2-fyrile)pyrazole, 5-amino-3-(2-tienile)pyrazole as well as not substituted 6-aminouracil are obtained in dihydropyridine form (tab. 7).

Table 7

Indenopyridines 21-33

	R		Structure	Yield ,%		R		Structure	Yield ,%
21	*p*-MeO-C_6H_4-			34	**28**	*p*-NC-C_6H_4-			48
22	*p*-MeO-C_6H_4-			35	**29**	*p*-NC-C_6H_4-			51
23	*p*-MeO-C_6H_4-			30	**30**	*p*-MeO-C_6H_4-			56
24	*p*-MeO-C_6H_4-			41	**31**	*p*-NC-C_6H_4-			65
25	*p*-MeO-C_6H_4-			30	**32**	*p*-NC-C_6H_4-			61
26	*p*-MeO-C_6H_4-			72	**33**	*p*-MeO-C_6H_4-			72
27	*p*-MeO-C_6H_4-			63					

Using the Annexin-V/propidium iodide assay the compounds were tested for their cell-killing and apoptosis inducing properties against the Jurkat cell lines as a model for human T-cell leukemia. The cells were treated with DMSO solutions of the respective compounds at 25 (iM. All compounds exhibit small levels of cytotoxicity and apoptosis induction, with the exception of 6-aminouracil analogue, it was found that this compound is more active than etoposide.

Conclusions

We have used multi-component reactions to obtain the privileged medical scaffold on the basis of derivatives of pyrrolidine [23], dihydropyridine [24], benzopyranopyridine [25]. It was shownthat these compounds remain cytotoxic and induce apoptosis in cancer cells, at the same time aren't toxic for lymphocyte of human. We simplified the structure of cytotoxic alkaloids contained pyranopyridone or pyranoqinolone moiety, using multicomponent method of synthesis. Due to this method the library of pyranopyridones

and pyranoqinolones was obtained. The biological tests show that these compounds show lownanomolar cytotoxicity, induce apoptosis, pronounce cell cycle arrest in the G2/M phase and show inhibition of tubulin polymerization in vitro [26]. The high active compounds were synthesized, that can be the basis for new anticancer preparations.

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SUMMARY

Podophillotoxin has been extensively used as a lead agent in the development of new anticancer drugs. Libraries of structurally simple analogues of Podophillotoxin - dihydropyridopyrazoles, pyranopyridones, pyranochinolones, indenopyridines - are prepared by a straightforward multicomponent synthesis and demonstraited to display antiprolifarative properties in a number of human cancer cell lines.