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Combinatorial Chemistry in Higher School: Ten-Year Experience of Research, Educational, and Managerial Projects

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Abstract—Short overview is given of the author's group activities over the last decade in the research, educational and other projects related to combinatorial chemistry. The discovery of novel reactions and classes of heterocyclic scaffolds (oxazoles, indolizines, and imidazoles) led to new libraries, for which different types of biological activity (antimicrobial, adrenergic, anxiolytic, and anti-protozoal) was predicted and experimentally confirmed. Education of students at the Moscow State University with practical combinatorial chemistry course is reviewed, as well as other initiatives related to promotion of combinatorial chemistry in Russia.

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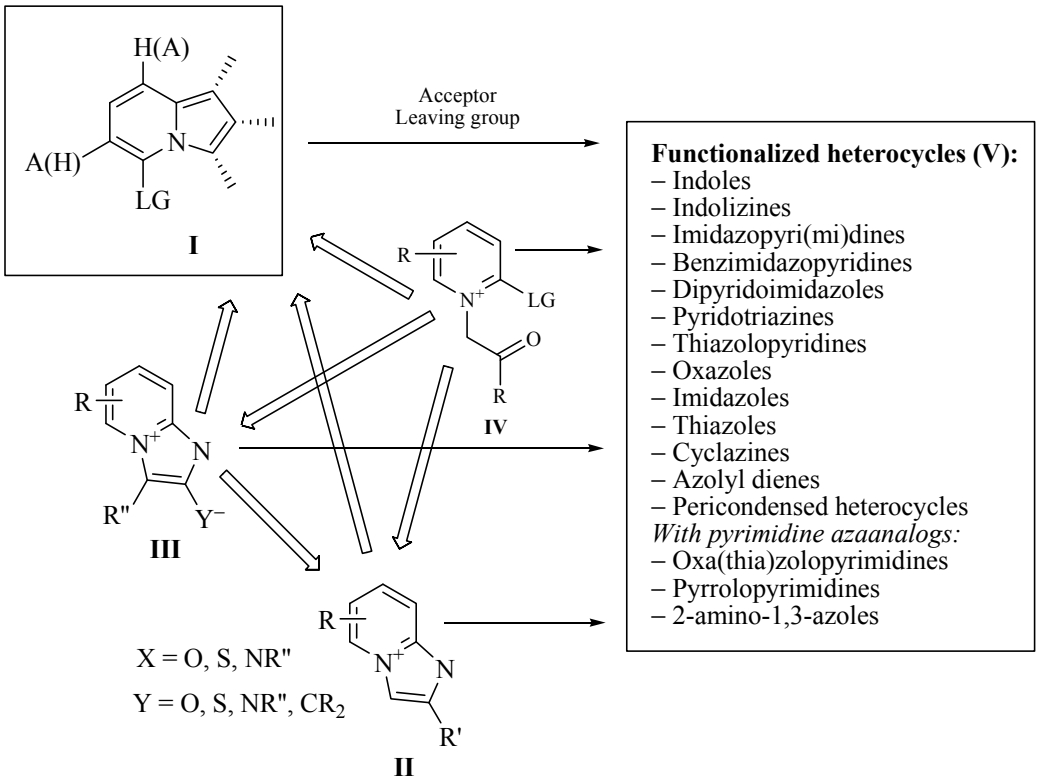
The progress of combinatorial chemistry in Russia is directly related to the problem of survival of domestic science (development of material basis, preservation of human resources), adaptation of basic science to practice, and search for optimum interaction between researchers and consumers of the final product. In Russia, no balance has yet been found in this field between university science and consumers' demand (state and private), unlike what is already true of foreign countries. This is just the reason why the available experience in combinatorial R&D is not only of historical interest, but also can form the basis for further development. The aim of the present publication is to give a brief review of research, applied, and educational and managerial projects associated with combinatorial chemistry and fulfilled over the past decade by our research group at the Chemical Department of the Moscow State University (MSU). In the first part we will dwell on the experience in the implementation of fairly abstract synthetic ideas into practical projects and in the second, approaches to teaching and promotion of combinatorial chemistry in Russia.

Certain Applied Aspects of Basic Heterocyclic Chemistry

Over a long time our research effort has been focused on bridged azolazines **I–III** (Scheme 1). The parent structure in this family is indolizine **I** which can be considered as a superposition of pyrrole and pyridine, two key archetypes of heterocyclic chemistry as a whole. Indolizines are isomeric and isostructural to indoles (certain некоторые indolizines can even be rearranged into indoles), which induced out interest in this subclass. In developing synthetic approaches to functionalized indolizines we discovered a number of new and quite unusual (structurally) types of cyclizations and rearrangements where the precursors of compounds **I** were cationoid **II** or mesoionic **III** azolopyridines, as well as pyridinium salts **IV**. Our long-standing research program [1] involved study of methods of synthesis and genetic interrelationships of compounds of classes **I–IV**, as well as use of these compounds as precursors of heterocyclic systems **V** [2–5]. Over the course of this research we synthesized hundreds of new compounds belonging to previously unknown subclasses of substituted heterocycles.

Obviously, this research is quite indirectly related to immediate problems of combinatorial chemistry. Radically new compound classes could at best enrich abundant combinatorial collections of "historical libraries," where a new structural type would contributed to the diversity of structural motifs. (In this case, a new compound will probably be demanded in the framework of a narrow-focus project, for example,

Scheme 1.



for testing on a concrete biological target). As a result, the very novelty of the structural type is depreciated. It is good if structures of a new subclass are structurally similar to already known drugs. This can give guidance to what kind of activity is purposeful to test for initially. And what to do then with absolutely new compounds?

One the few approaches able to at least roughly answer to this question, is the domestic program PASS [6, 7, 8]. A user enters the structural formula (standard mol/sdf file [9]) of one or many compounds, and the program predicts their possible biological activity spectrum. Once the developers of the PASS program failed to attend some scientific conference and asked the author of this paper to present their program instead of them [10]. As a result, we had to explore in detail the algorithm of this software, which can be briefly outlined as follows.

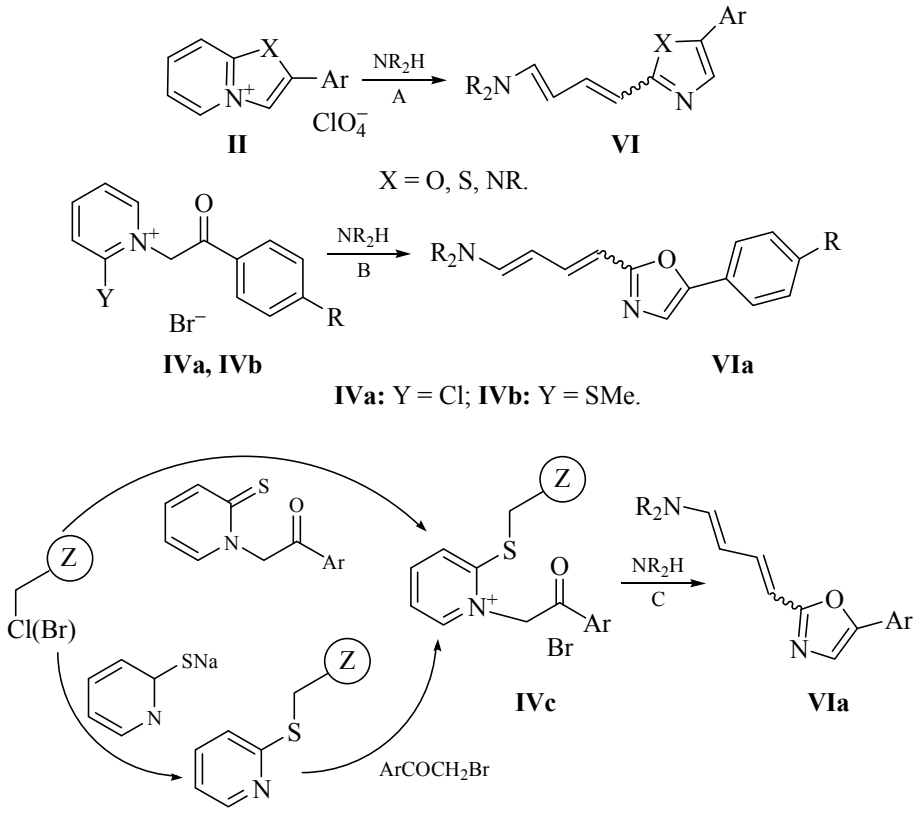
In the PASS program, thousands known drugs are already broken into small fragments; each fragment is assigned the same activity as in the whole molecule. If the same fragment is present in another drug (let it has a different structure but exhibits the same type of biological activity), the weight factor of this fragment increases. If such fragments are contained in an unknown structure, the program estimates the probability of one or another kind of activity. In our research, we could obtain strong evidence for the predictions of the PASS program by purposeful biological testing new families of compounds. Below we consider some samples for concrete classes of compounds.

Synthesis of Antimicrobial 1-Amino-4-(1,3-azol-2-yl)buta-1,3-dienes

About ten years ago we found that the pyridine ring of azolopyridinium salts **II** opens under the action of amines to form substituted dienes **VI** (Scheme 2A) [11, 12]. We considered family **VI** to hold great promise for synthesis of combinatorial libraries: The substituents (amine, aryl, and azole) and stereochemistry of the diene chain were readily varied, and the precursors of salts **II** were readily accessible compounds **IVa**.

At the same time, what kind of biological activity may be characteristic of such dienes was absolutely unclear, and we tried to predict it by means of the PASS program. The most probable was found to be the antimicrobial activity, and this prognosis was the same

Scheme 2.



for the whole family of azoles **VI**. Our experiments with gram-positive (*St. Aureus*) and gram-negative (*E. Coli*) microorganisms showed [10, 12], that, too, all compounds exhibited activity against both types of bacteria (Table 1).

Later we found that the same antimicrobial dienes of subclass **VIa** can be obtained in high yields in a shorter way: by quite an unusual transformation of 2-halopyridinium salts **IVa** (Scheme 2B, Y = Cl) [13–15]. The mechanism of this elegant one-pot trans-formation of pyridines into oxazoles appears to be tandem in nature (oxazole closing + pyridine destruction), and it provides a facile and efficient synthetic routes to a wide series of oxazoles **VIa**. It was established that salts **IVa** can be replaced bu their analogs **IVb** (Scheme 2B, Y = MeS) [16].

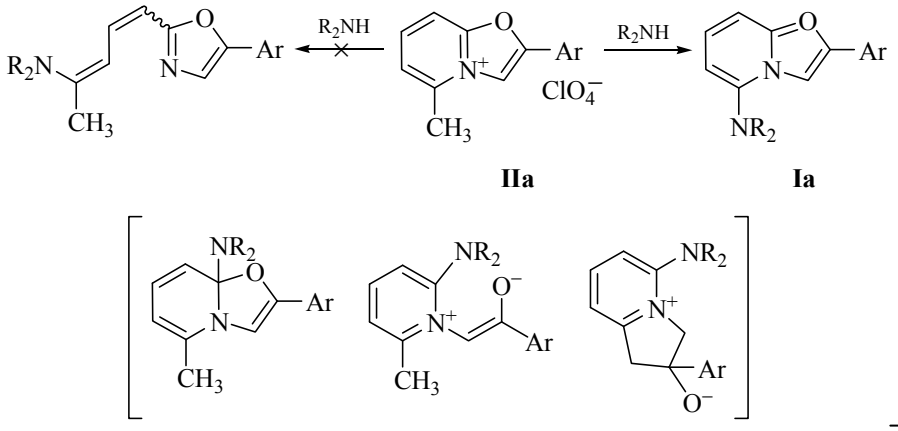
Such a replacement of function Y allowed us to realize a solid-phase modification of this reaction (Scheme 2C). As seen, the required pyridinium salt is "grown," though its sulfur atom, on a solid support Z. As phase Z we tried Merrifield resin and silica gel modified with a bromoalkyl residue. At the final stage the sulfur-containing linker disappears entirely from the final structure (remaining on the solid phase under the action of amine), while a pure oxazole **VIa** passes to solution [17, 18]. Our approach clearly demonstrates the logics in the answer on the question, what to do with new classes of compounds: first, to try to predict and search for their useful properties (Table 1) and second, to optimize the synthesis of libraries by searching for new liquid-phase reactions (Scheme 2B) and still more efficient solid-phase approaches (Scheme 2C).

Synthesis of 5-Aminoindolizines with Adrenergic Activity

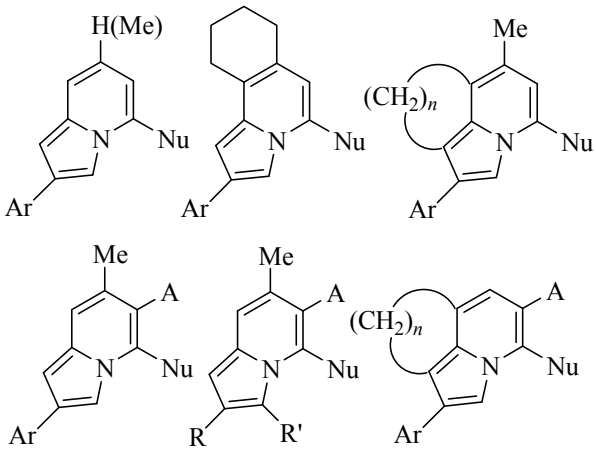
Exploring reactions of amines with homologs of oxazolopyridinium **IIa,** we unexpectedly obtained 5-aminoindolizines **Ia** instead of dienes (homologs of structures **VIa**) (Scheme 3) [11, 17].

The possible intermediates of this quite a rare example of the conversion of the oxazole ring into pyrrole are shown in the bottom part of Scheme 3. We showed [4, 5, 11, 19–26] that this reaction is general in nature; on can attach alicycles the pyridine fragment,

Scheme 3.



to introduce into it electron-acceptor groups, and substitute the six-membered fragment by pyrimidine and secondary amines by alcoholates. The examples of structural classes of the resulting products are shown below, and as the starting compounds for preparing salts **IIa** (and their analogs) we used readily accessible pyridin-2-ones and pyrimidinones.



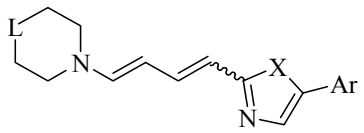
Nu = OAlk, NR_2; A = CN, $CONH_2$, COOR; n = 5–7.

Before our works indolizines with donor substituents were unknown. As in the previous example with dienes, the type of biological activity of these compounds was unobvious (even though structurally compounds **I** resembled their isostructural psychotropic indoles of the psilocin series). The PASS program predicted for indolizines **Ia** a high probability of binding with β2-adrenoreceptors. Based on this prognosis, we selected the most perspective 5-aminoindolizine structures and tested them for binding to rat brain synaptosomal membrane receptors [10, 18, 23], by comparing their ability to expel tritium-labeled reference compounds (Table 2).

The resulting data allow a conclusion that compound **I–III** deserve further study with the aim to reveal its adrenergic activity. At present antagonists of various subtypes of β-adrenoreceptors (practotol, atenolol, metoprolol, salbutamol, soterenol) are widely used in clinical practice for treating a number of cardiovascular and respiratory diseases, and the search for new biologically active still remains an urgent problem in pharmacology.

The synthesis of combinatorial libraries on the basis of indolizines **Ia** had an unexpected continuation. In In 2006 Tielmann and Hoenke [27], the chemists of the

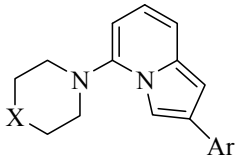
Table 1. Antibacterial activity of compounds **VI**



Ar = *p*-$NO_2C_6H_4$

Comp. no.	Substituent		Minimum bacteriostatic concentration (μg ml^{-1})	
	X	L	*St. aureus 6838 ATCC*	*E. coli 25922 ATCC*
6.1	O	CH_2	100	200
6.2	O	O	200	200
6.3	O	CH_2CH_2	200	200
6.4	NMe	CH_2	200	>200
6.5	S	CH_2	200	>200

Table 2. Biological activity of indolizines **Ia**



Ar = *p*-$NO_2C_6H_4$

Comp. no.	Substituent X	Concentration, μmol	Binding with receptors, % to control		
			D2-dopamine ^{3}H-spiperone[a]	M-muscarine ^{3}H-QNB[a]	b2-adrenoreceptors ^{3}H-propanolol[a]
Ia-1	O	100	71.4	152.2	97.0
		10	80.2	96.6	89.7
Ia-2	$(CH_2)_2$	100	40.7	106.7	84.8
		10	95.6	84.0	75.8
Ia-3	H, H	100	100.0	130.9	37.3
		10	95.6	100.4	47.5

[a] Control (100%).

pharmaceutical company Boehringer Ingelheim published a detailed research of our discovered recyclization of salts **IIa** into aminoindolizines. A vast library of such indolizines was used by Scheme 3 and tested for biological activity. In this work the synthesis technique was optimized (MW oven was used) and indolizines with an aryl residue different from *p*-nirophenyl were found to be unstable. The latter problem was a focus of Tielmann's methodical presentation (structures should not only be "beautiful;" the primary concern of combinatorial chemistry is stability of products) at one of European conferences [28]. We called attention of German researchers to an alternative way to stabilize compounds [26, 29, 30] by introducing an electron-acceptor residue A (Scheme 4), and this served for making close working contacts between our groups.

Synthesis of Imidazole Anxiolitics

In the research in the framework of an international INTAS project (no. 00-0711) in 2002–2003, the PASS program was used for biological activity predictions. Biologists of the Moscow Research Institute of Pharmacology tested potential anxiolitics synthesized by the chemists of Russia, Moldova, Belgium, Greece,

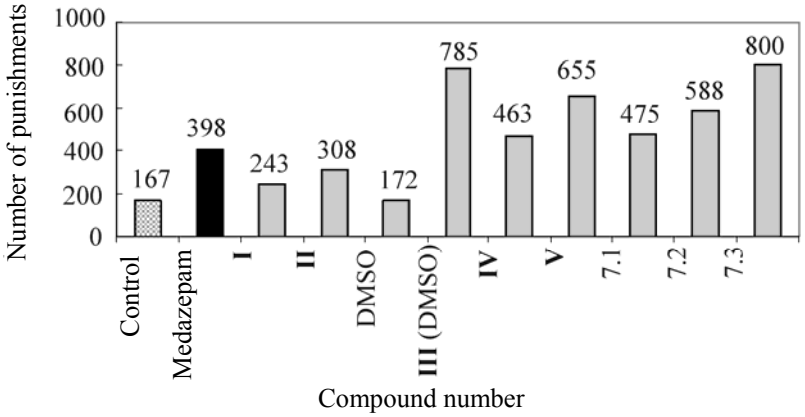
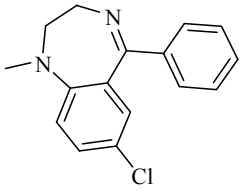
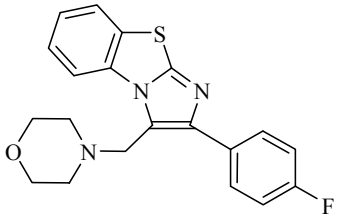
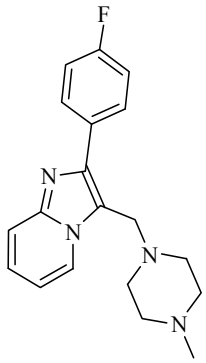
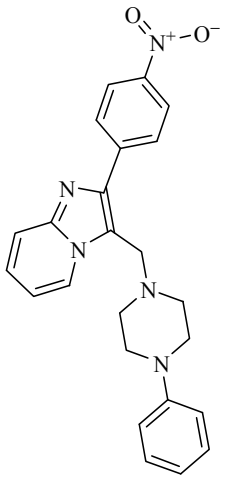


Fig. 1. Anxiolytic activity of condensed imidazoles.

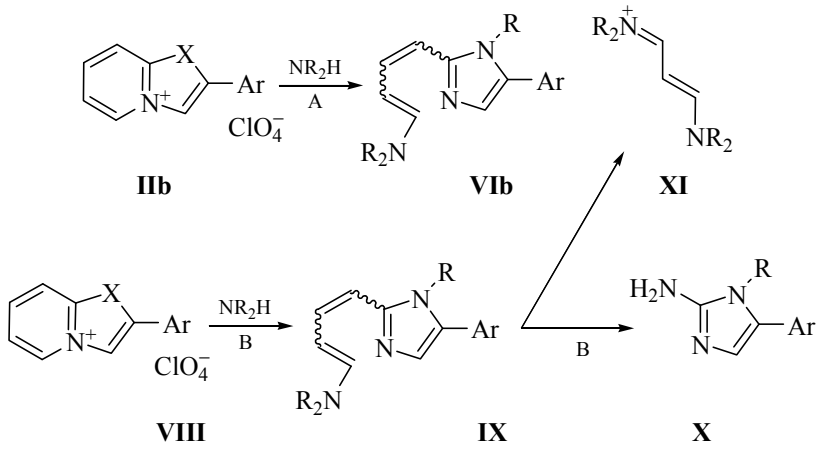
Table 3. Predicted structures of new anxiolytics and experimental evidence for biological activity

Compound	Structure	Prediction[a]			Dose, mg kg^{-1}	Varied parameter[b]
		Pa	Pi	Activity		
Control					0	167±32
Medazepam		0.891 0.783 0.734	0.006 0.002 0.005	Anxiolytic Benzodiazepine 1 agonist GABA receptor agonist	10.0	398±52
VII-1		0.694 0.688 0.354	0.010 0.005 0.007	Anxiolytic GABA A agonist Benzodiazepine agonist	10.0	475±59
VII-2		0.579 0.641 0.515 0.469 0.425	0.023 0.001 0.009 0.010 0.007	Anxiolytic Benzodiazepine omega agonist GABA A agonist 5 HT 2C agonist 5 HT 3 agonist	10.0	588±66
VII-3		0.655 0.670 0.424 0.415 0.368	0.014 0.001 0.018 0.007 0.045	Anxiolytic Benzodiazepine omega agonist GABA A receptor agonist 5 HT 3 agonist 5 HT 2C agonist	10.0	800±128

[a] PASS prediction as probabilities Pa (active) and Pi (inactive). [b] Number of attempts to quench thirst, irrespective of the attendant electric shock.

and Portugal. The synthetics were allowed to performed computer generation of any combinatorial libraries they were capable to synthesize. By means of the PASS program of 5500 virtual structures we chose ten the most promising ones which were first synthesized and then tested in animal experiments. Mice were exposed to a weak electric shock when attempted to quench thirst; after administration of a

Scheme 4.



potential drug, the fear of shock got weaker, and the frequency of shocks was to be increased.

As a perspective class we chose condensed imidazoles **VII**. The combinatorial library was synthesized as a training task [31]. As seen from Table 3 and Fig. 1, the compounds selected by the program not only exhibited the predicted activity, but also ranked above the standard anxiolitic medasepam. Note that the Moscow group obtained more active compounds than foreign partners (Fig. 1), which was mentioned in our joint publication [32]. Equally highly active were found to be certain representatives of a previously unknown class of imidazoles, which deserves special mentioning.

Biologically Active 2-Aminoimidazoles

Shortly after reporting the results on the synthesis of azolyldienes **VI** from azolopyridinium salts **II** (Scheme 2A) [12], we focused on the perspective to extend this type of transformation to other fused heterocycles. It was clear that by replacing the pyridine fragment in system **IIb** by the pyrimidine aza-analog **VIII** (cf. reactions A and B in Scheme 4) we would obtain, after six-membered ring opening, azadiene **IX** instead of diene **VIb**.

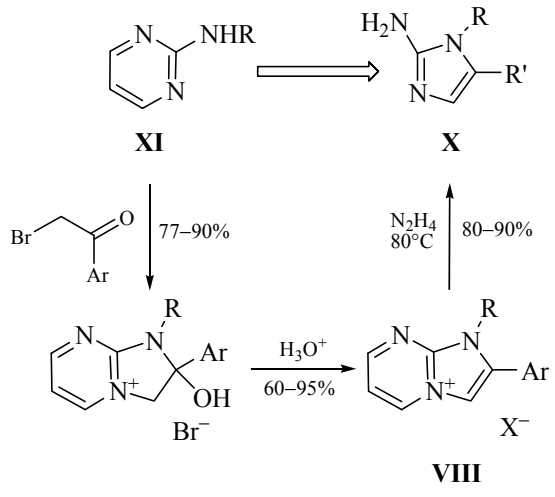
It was reasonable to expect that C=N bond cleavage in azadiene **IX** (Schiff base) would form imidazole **X** and fragment **XI**. 2-Aminoimidazoles **X,** while being structurally simple compounds, had scarcely been reported in the literature. That was roughly the logic of our project proposal in 1999, where we predicted this new reaction just "on the tip on the pen." However, it was not until 2001 that we could, by the trial-and-error method, chose an optimal strategy for the synthesis of imidazoles **X** from pyrimidines **XI** via condensed salts **VIII** (Scheme 5).

Table 4. Activity data of imidazols **X** against Leishmania major[a]

Substance	IC50 (mg ml^{-1})
Amphotericin B	0.19
10.1–10.3	0.78
10.4	3.13
10.5, 10.6	6.25
10.7–10.9	12.5
10.10–10.18	>25–>100

[a] The data were kindly provided by prof. K. Khan, HEJ Research Institute, Karachi.

Scheme 5.



Other strategies (for example, synthesis of salts **VIII** by alkylation) did not led to success, and the optimal agent for cleaving the pyrimidine ring proved to be hydrazine. Figure 2 shows the X-ray diffraction curves for one of the first aminoimidazoles (the graduation thesis of E. Belykh, 2001) [33].

We had long not made public the information on the discovered reaction, waiting for the results of biological tests (in the framework of the INTAS project) and going to patent the scheme of synthesis and activity of the obtained library. Unfortunately, our scheme was appropriated and publicized by third people, and our previously unknown compounds became components of commercial libraries. In this connection our project got disclosed, and the new patentable methodology formed the subject of open publications [33–35], presentations [36–39], and dissertations [24, 40]. Probably, the most important application of our reaction, according to our recent findings [41, 42], is the facile full synthesis of natural alkaloids of sea sponges having a 2-aminoimidazole motif in their structure and possessing anti-inflamematory activity. Our protocol involves as little as two–three stages, whereas previously the full synthesis of such natural substances involved 8–12 (!) stages.

The discovered reactions formed the basis of quite an interesting combinatorial project. According to the PASS prediction, amidazoles **X** might exhibit antiprotozoal activity and be effective against leishmaniasis (a tropical fever), an extremely heavy disease in Third World countries. The search for biological laboratories focused on tropical fevers led us to fruitful cooperation with the University of Karachi (Pakistan). Already first results showed (Table 4) that our imidazoles compare in the anti-leishmaniasis activity with the standard drug amphotericin (the disadvantage of the latter is its high toxicity). Searching for further funding for this project, we submitted a Russian–Pakistanian bilateral project proposal to the World Health Organization (WHO). Even though the WHO uses to fund early stages of search for drugs against tropical diseases, we were recommended to accumulate and extend evidence on the biological and ADME properties of our compounds. As a result, the whole project acquired a clear goal and quite obvious ways to reach this goal.

Note that the synthesis of imidazole libraries by Scheme 5 is fairly facile to accomplish, since the three its stages all form readily purified precipitates. In this

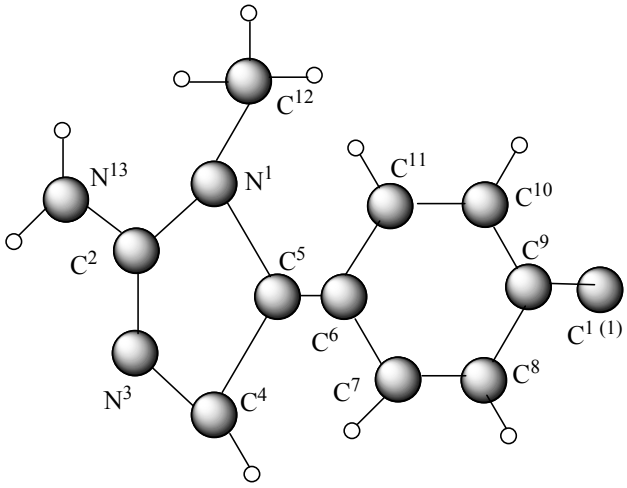


Fig. 2. X-ray diffraction structure of one of the first aminoimidazoles [33].

connection, the reaction was adapted for the SynCore apparatus as a training task for the special laboratory course in combinatorial chemistry at the MSU [31, 43–45]. Students and teachers prepared there a large library of imidazoles **X**. In the framework of the joint educational project with the Chemical Diversity Research Institute (CDRI, Khimki) we performed a demonstrative robotized screening of a series of imidazoles **X** and measured their primary properties of key importance for potential drugs (cytotoxicity, membrane transport ability, solubility, etc.). As seen from the example in Fig. 3, the general toxicity of these compounds is low.

Later the MSU could conclude contracts first with a small pharmaceutical company Pacific Pharma Technologies and then with a larger venture company Upstream Bioscience on the synthesis of big libraries of imidazoles **X** and their comprehensive screening. Initially, our compatriot Prof. A. Cherkasov performed *in vitro* experiments at specialized laboratories in Canada (Fig. 4) and later the African physician Prof. G. Olobo (University of Campala, Uganda) initiated *in vivo* experiments in "field" conditions. Even though the global financial crisis has made problematic finalization of the experiments planned for 2010, the available evidence instills cautious optimism [46].

Other Examples of Practical Application of New Reactions

The four above-considered examples illustrate an adaptation to applied tasks of a purely academic approach

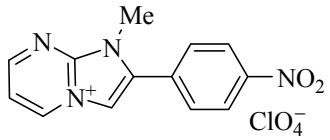
(design of previously unknown reactions and new families of compounds) to the design of useful properties. Therewith, the PASS program fulfilled its heuristic role. Now we would like mention in brief three more examples from our practice, in which the structural novelty of compound classes or uncommonness of observed transformations served as a basis for quite pragmatic applied projects directly related to combinatorial chemistry.

New Color Test for Amines

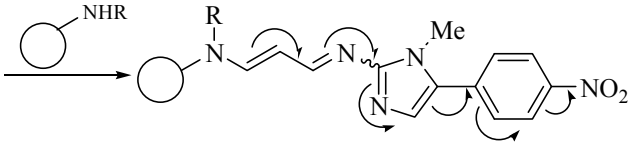
By reacting salts **II** and **IV** with amines (Scheme 2), we noted an intense violet color of dienes in those cases where the five-membered ring contained a *para*-nitrophenyl residue. Apparently, in the latter cases quite an extended conjugation chain arises: from the amino to nitro group via diene, azole, and phenyl ring. Still more intense (almost black) coloration under the action of amines was observed with imidazopyrimidinium salt **VIIIa** with the same *para*-nitrophenyl group, due to formation of analogous azadiene **IXa** (Scheme 6).

Practically, a new highly sensitive color test for secondary amines was discovered, which was superior by some parameters than the standard ninhydrin test (Kaiser test). This test was found to be the most valuable for solid-phase synthesis, since it allowed free

Scheme 6.



VIIIa



IXa

amino groups to be determined on the resin, even in the presence of thiols. We have patented this result together with researchers of the Catholic University of Leuven [47].

"*Inorganic*" *Bioactivity Component*

The second example illustrates the fact what an unexpected factor may affect biological activity in a series of one-type compounds. We found in our early work [48] that the reaction of 2-chloropyridinium salts **IVa** with potassium thiocyanate proceeds with a smooth closure of the thiazole ring to form condensed

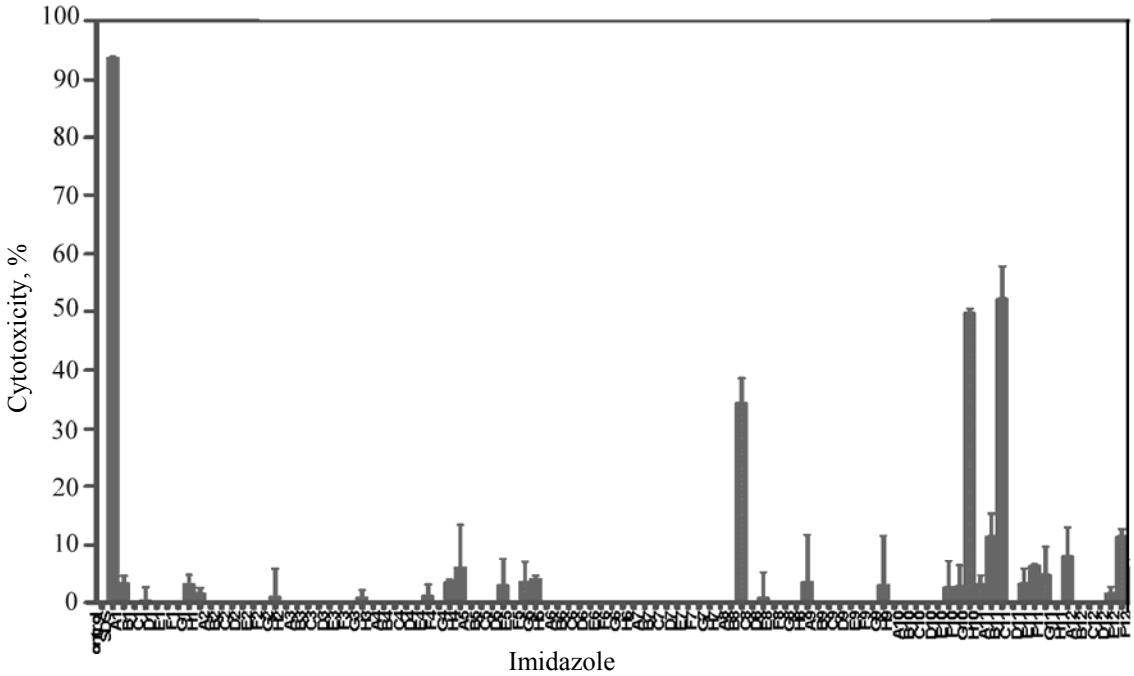


Fig. 3. Cytotoxicity testing of the imidazoles 10 library on HEK 293 cell culture. The data were kindly provided by the CDRI, Khimki.

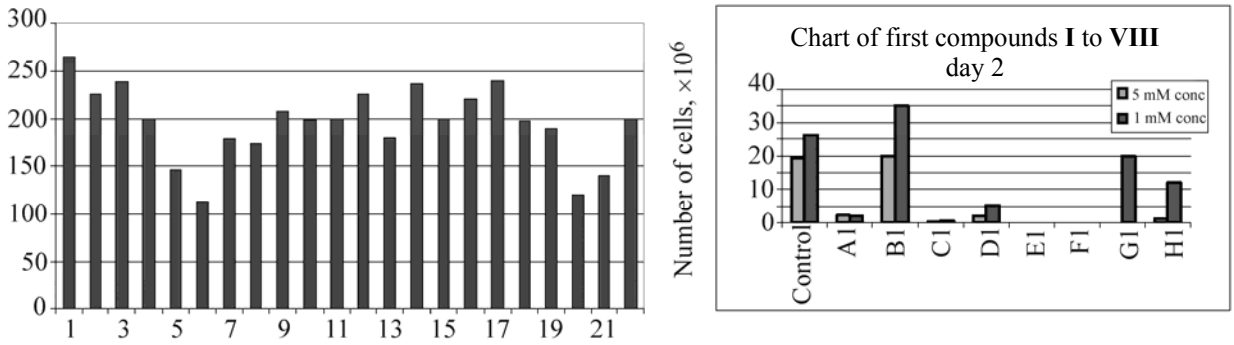
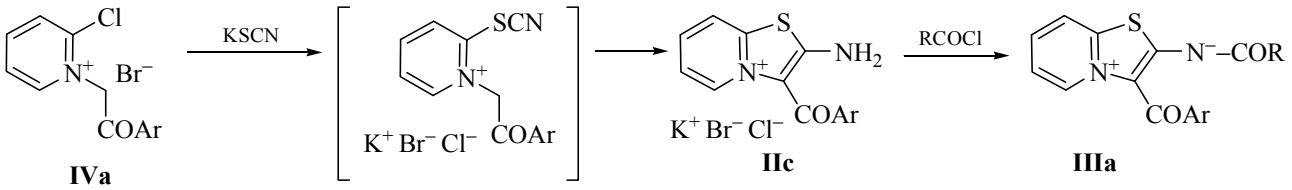


Fig. 4. Death of Leishmania major cells under the action of compounds **X**. (Right) The number of parasite cells remaining by the 2nd day for the selection of the first 8 compounds. The data are kindly provided by Prof. A. Cherkasov, University of British Columbia (Canada).

ionic systems **IIc** (Scheme 7). The structural novelty of the reaction consisted in that, usually, all the three atoms of thiocyanates (S–C–N) are involved in thiazole ring formation, whereas in our discovered reaction the thiocyanate nitrogen was not incorporated into the new thiazole ring.

Scheme 7.

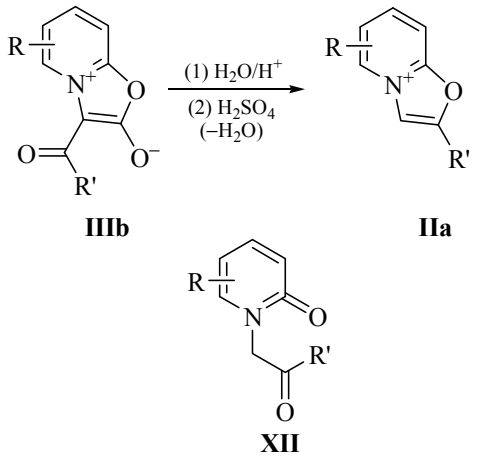


Salts **IIc** showed activity in certain agrochemical tests. This activity varied incomprehensibly and quite dramatically: from necrosis of seeds to enhancement of their germinating ability. In our bilateral project with the Japanese agrochemical concern Nippon Soda we undertook a more detailed study of structure–activity correlations. It was found [49] that the nature of the aryl group (seemingly the only varied residue) is almost insignificant, and the key role here, incredible as it may seem, belongs to the nature of the inorganic counterion in the obtained salts. To find out what proportion between chloride, bromide, and thiocyanate in salts **IIc** affect bioactivity, we applied anionic chromatography, a technique typical of analysis of mineral substances.

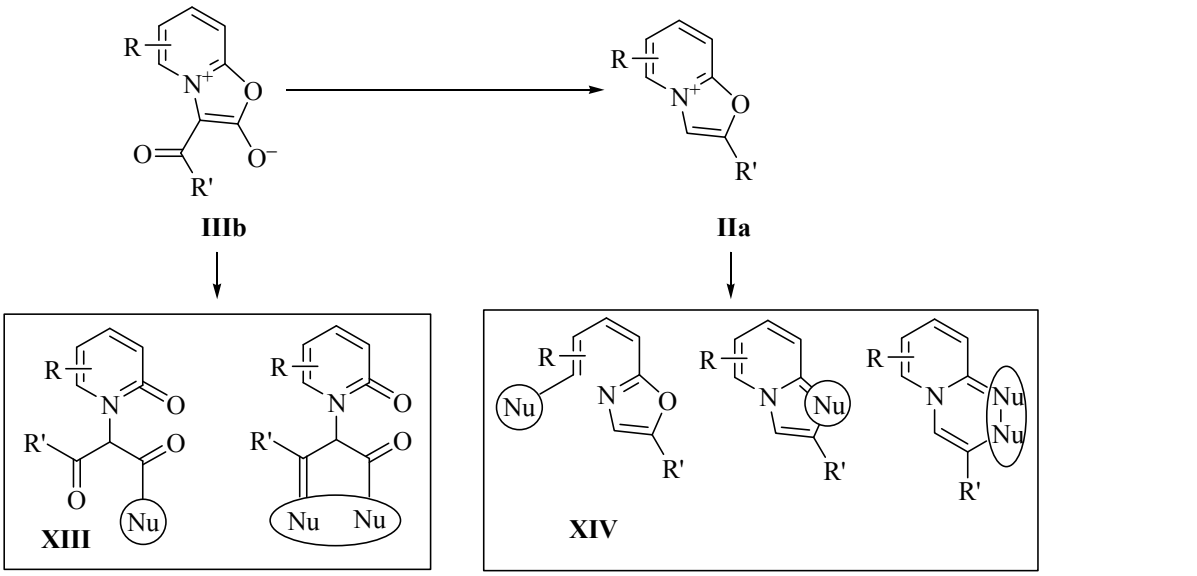
Principle of "Supereconomic" Reagents in Combinatorics

The third example relates to new perspectives of practical use of structurally unusual compounds: mesoionic compounds. We have long studied the chemistry of the entire class of mesoionic systems of the general formula **III** (Scheme 1) under financial support of the Russian Foundation for Basic Research. (thus, salts **IIc** in Scheme 7 were prepared as precursors of extremely stable mesoionic imidates **IIIa**). During research into the chemistry of mesoionic oxazoles **IIIb** (bicyclic munchnones), we noted not only the facility of their hydrolytic cleavage into pyridones **XII**, but also its associated possibility of simultaneous recyclization of neutral systems **IIIb** into salts **IIa** (Scheme 8) [4, 50–52].

Scheme 8.



Scheme 9.



It had long been not quite obvious for us what benefits can be gained by pharmaceutical industry from the transformation of one labile system into another (**IIIb** into **IIa** in Scheme 8). This had been the case until Bayer announced its memorable Synthon project [53]. The goal of this project was to create the world's largest bank of rare reagents, so-called synthons. We turned attention of Bayer's chemists to the fact that the transformation in Scheme **VIII** is the most economic, since it represents a rare example of this a synthon-to-synthon transformation. Actually, munchnones **IIIb** can be reacted with various nucleophiles (and binucleophiles) to obtain large collections of compounds **XIII** (Scheme 9). If these synthons and products are no longer interesting, old synthons (**IIIb**) can be easily converted into new ones (**IIa**) and obtain new-type libraries **XIV**, using the same nucleophiles. The "Synthon-from-Synthon" Project formed the basis of a long-year cooperation between the MSU and Bayer and was continued until radical reorganization of the company. To our knowledge, one of compounds **XIII** exhibited well-pronounced anticancer properties.

As seen, certain synthetic ideas which, at first glance, seemed to be quite far from the practice of combinatorial chemistry, could be materialized in concrete libraries of biologically active compounds. Concluding the brief review of these projects, we would like to mention some other experimental findings (Scheme 10) which are direct candidates of combinatorial chemistry applications.

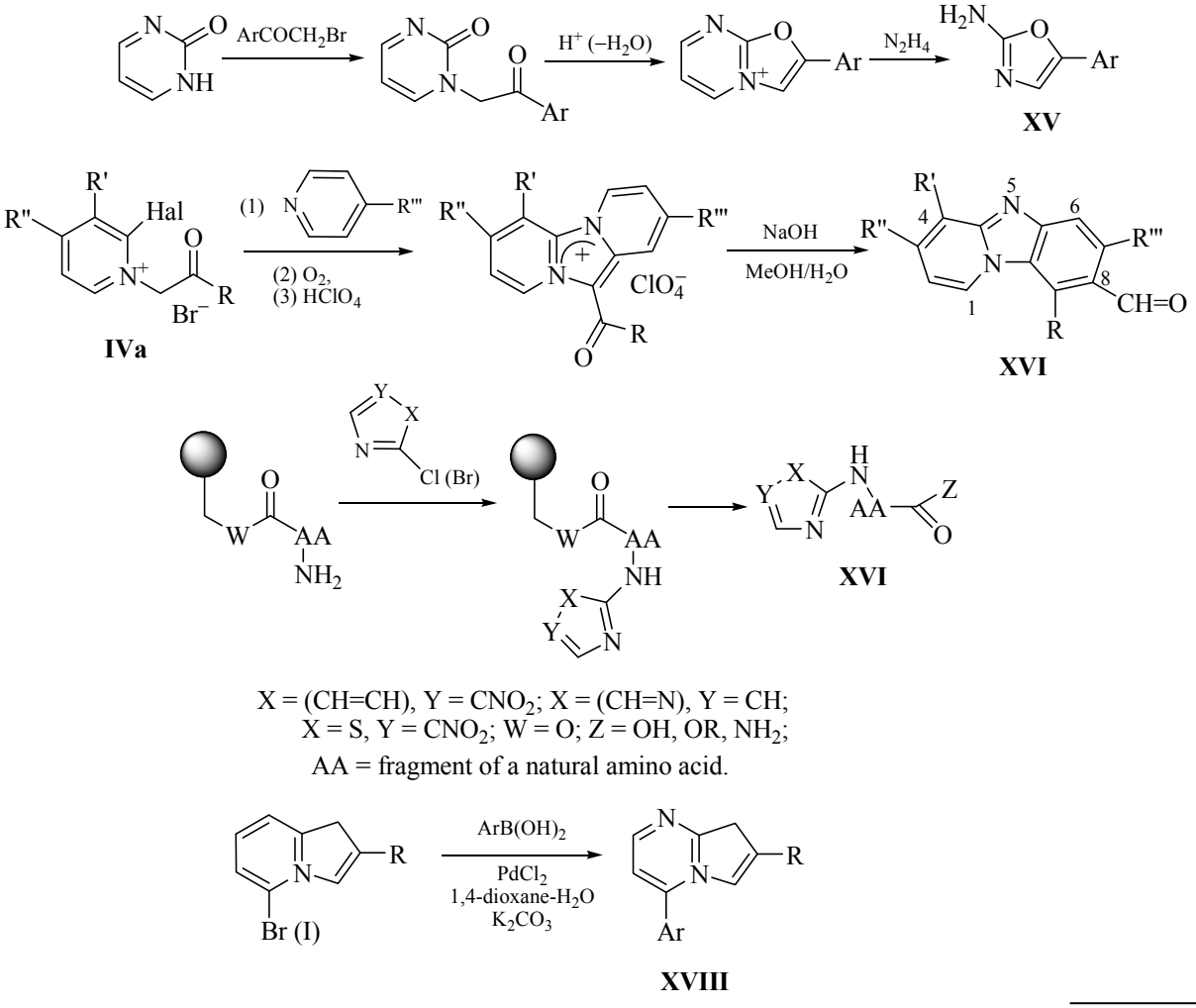
First, this is an interesting and a previously hardly accessible class of useful reagents, substituted 2-aminooxazoles **XV** which were suggested to be prepared from the cheap pyrimidone by a scheme analogous to Scheme 5 [54]. Second, this is a family of pyrido[1,2-*a*]benzimidazole aldehydes **XVI** which can be easily prepared from salts **IVa** by successive action of pyridine and alkali [52]. This tricyclic system is a typical example of a pharmacophore skeleton: Even its simplest parent structure is analgesic, and no universal convenient synthetic approach to functional derivatives of such scaffold is still known.

The third family is potential antidiabetic preparations on the basis of non-natural heterocyclic amino acids **XVII** [57]. Finally, one of the recent results is provided by the parallel liquid-phase synthesis of the library of 5-arylindolizines **XVIII** [58, 59] and aza-analogs [60] by the cross-coupling reaction. These indolizines are quite an interesting type of indicators: They exhibit a strong fluorescence with a high quantum yield, and, therewith, change the radiation color on protonation (due to a radical rearrangement of their π system).

Special Student Labaratory of Combinatorial Chemistry at the MSU

In 2001, the author of the present paper organized at the Chemical Department of the MSU the first Russian special student laboratory of combinatorial chemistry. By late 1990s, a number of chemical

Scheme 10.



X = (CH=CH), Y = CNO_2; X = (CH=N), Y = CH;
X = S, Y = CNO_2; W = O; Z = OH, OR, NH_2;
AA = fragment of a natural amino acid.

companies specializing in combinatorial chemistry have already appeared, and, therefore, students possessing basic skills in parallel synthesis have been well in-demand. Even though no background experience had been available, we could successfully develop three types of training tasks corresponding to three methodical aspects of combinatorial synthesis: (1) computer design of libraries; (2) solid-phase synthesis; and (3) parallel liquid-phase reactions. Trainings are usually conducted in autumn semester for 5th-year students (specialization "Organic Chemistry") during their prethesis practice. Let us dwell briefly on each type of tasks.

Design of Virtual Libraries

Two or three seminar lessons (for a group of 20–25 students) are needed. Three or four PCs, accessible ISIS Base program, as well as library generation program are used. (The latter program was developed by PhD A.V. Efimov and is in free access in [61].) One lesson is devoted to the description of the possibilities of ISIS Base, training in working practices with ISIS Draw, and description of chemical structure formats (mol and sdf files). As an example, the simplest database of several structures is created, and explanations on how to make structure search queries, as well as on how to export and import sdf files are given. Then two types of conventional reagents between which a reaction will be performed (for example, 3 amines and 3 aldehydes for reductive amination) are entered into the united base, and atoms to be "stuck together" are marked by means of the ISIS program. Search queries are used to export from the base two sets of reagent structures (sdf files A and B). At the final stage, the generator "multiplies" reagent files A and B, and the resulting new structural database

is looked though visually (to exclude input errors). At the next (grading) lesson the students are able to fulfill the entire sequence in themselves. As an additional training tool, comparison of the obtained virtual product structures by various parameters, for example, check for compliance of Lipinski's rule, can be suggested. The library generation task becomes especially illustrative, when already four files have to be "stuck together," for example, four types of reagents in the multicomponent Ugi reaction.

Solid-Phase Synthesis

Training can employ any of the four our developed procedures [44, 57]. Having compared different techniques of working with polymer supports: with standard vials, lanterns, filter tubes (Billboard kit), or "tea bags," we chose the latter one. The necessary condition for successful completion of the training course was to determine the yield of the product and analyze its spectra (NMR and GC–MS data).

Liquid-Phase Parallel Synthesis

Two well-developed tasks can be used for training [31, 45].

Initially we experimented much with reductive amination [31], but eventually it was rejected because of inconveniences associated with multiple evaporations of solutions. We decided that "liquid-phase" tasks are illustrative exclusively with reactions resulting in precipitate formation. Note that here, too, special equipment (let it be very simple) for parallel separation of precipitates is required. The best training task, in our opinion, is the Ugi reaction [45], where both expensive equipment (for example, SynCore) and a simple centrifuge can be used to separate precipitates from solutions.

Already over many years, the trainings are completed with fam visits to commercial research laboratories equipped with modern instrumentation for combinatorial synthesis and robotized library screening. Earlier such welcome days were usually held by Moscow laboratories of the ChemBridge company. Beginning with 2005, our students are hosted by the CDI. In the framework of one of such visits, CDI staff members performed fast bioscreening of the compound library prepared by students in their training (see Fig. 3). Probably, this fact provides one of the best examples of a fruitful symbiosis of goals and potentials of a university and production company.

Scientific Conferences and Symposia

Late 1990s was a very difficult time for domestic science. The general funding curtailment, loss of researchers, and slump of interest in basic research affected dramatically scientific contacts. Thus, over that period in Russia almost no scientific conferences were held in the field of organic chemistry. At the same time, combinatorial chemistry experienced a real boom in that period: Qualified synthetic chemists initiated successful collaboration with foreign pharmaceutical companies, contractual synthesis of libraries and reagents was in blossom, and first private laboratories were vigorously developed. Having found ourselves in the epicenter of these events and trying to coordinate our research, commercial, and educational project, we could agree with a number commercial companies on joint organization and holding of scientific symposia on issues associated with combinatorial organic synthesis. The results of these activities, i.e. events organized under the (co)chairmanship of the author, are listed in Table 5.

In different times, our partners were ChemBridge, Bayer, ChemDiv, and other companies. The university formed the scientific program and invited prominent lectors (foreign inclusive), and the business partners provided grants for lectors and young researchers and paid most organizational expenses. Attractive role was also played by the choice of the place for conferences (not infrequently, Golden Ring towns). The table shows how frequently the scientific meetings were held.

Just then Euroasian Conferences on Heterocyclic Chemistry were initiated, which were first held in Russia but very soon outstepped its borders and became regular international scientific events (Thessaloniki-2006, Kuwait-2008, Alicante-2010) [62, 63]. One of our partners in that period, ChemBridge Corporation, could quite professionally transform their experience in organizing Russian meetings and became an organizer of international conferences in combinatorial and medicinal chemistry ASCMC/ASMC in Moscow (2004), St. Petersburg (2007), and Kiev (2009). The "Economy of Organic Synthesis" Conference (Moscow, 2002) resulted in the appearance of the first domestic depot of imported chemical reagents Acrus. In organizing the "UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology" Symposium (Moscow, 2004) we could attract money of the UN Special Commission on Combinatorial Chemistry (ICS UNIDO), invite as

Table 5. Scientific conferences on organic and combinatorial chemistry

Date	Name	Place	Organizers
1999, March	Organic Synthesis and Combinatorial Chemistry	Zvenigorod	MSU, ChemBridge
2000, April	Organic Chemistry in XX Century	Zvenigorod	MSU, ChemBridge
2000, September	Heterocycles in Organic and Combinatorial Chemistry (1st Eurasian Conference)	Suzdal	MSU, Bayer
2000, September	1st Russian Conference on the Chemistry of Heterocycles on the Memory of A. N. Cost	Suzdal	MSU, ChemDiv
2001, March	Strategy and tactics of Organic Synthesis	Yaroslavl	MSU, ChemBridge
2001, October	Modern Technologies of Combinatorial Chemistry	Moscow	MSU
2002, February	Economy of Organic Synthesis	Moscow	MSU, NPC
2002, September	Heterocycles in Organic and Combinatorial Chemistry (2nd Eurasian Conference)	Great Novgorod	MSU, Bayer
2002, November	Combinatorial Chemistry and Drug Birth	Moscow, IOC RAS	MSU, InterCare
2003, July	Organic Chemistry – Decay or Revival?	Uglich—Moscow (motor ship)	MSU, ChemBridge
2004, May	UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology	Moscow	MSU, UNIDO
2004, September	Heterocycles in Organic and Combinatorial Chemistry (3rd Eurasian Conference)	Novosibirsk	MSU, Novosibirsk State University

lectors the best foreign specialists, and hold, in our training laboratory at the MSU, a practical training on combinatorial chemistry for Deans of the Chemical Departments of almost all Russian universities.

Over the past five years, the situation with regular scientific conferences and schools (especially, in medicinal chemistry and organic synthesis) has evidently improved. At the same time, the financial crisis forced many pharmaceutical companies to cut down their expenses for combinatorial projects, which resulted in a fall of the general interest in this field among synthetic chemists. It is noteworthy that the domestic pharmaceutical industry is developing in a specific way, and combinatorial chemistry in Russia is not excluded to experience the blossoming period in future. As positive long-standing trends we can mention, for example, the Program of Revival of Domestic Pharmaceutical Industry until 2020 (Pharma-2020 Project), which includes, as an essential constituent part at the early stage, development of projects in combinatorial chemistry [64]. Other positive tendencies include the growing interest of State Corporations in the problems of search for new biologically active compounds and its associated infrastructure. The main guarantee for successful future projects in combinatorial chemistry is, in our opinion, qualified research staff which has not only been lost over the past decade, but, by contrast, gained quite a qualified training.

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