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REVIEW

"... Not the pressure of demands or requirements of engineering make their stamp on the development of science as it is often stated but the science growing along its own logical way and the proper talents of its servants generously scatter the practical applications that strike the imagination of masses."

K.A. Timiryazev

Modern Trends of Organic Chemistry in Russian Universities

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Abstract—This review is devoted to the scientific achievements of the departments of organic chemistry in higher schools of Russia within the past decade.

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1. INTRODUCTION

This article is written by a large team of authors from many cities of Russia resulted from a Conference of the heads of departments of organic chemistry and related specialties. Just at this Conference we decided not only to establish mutual collaboration and reciprocal help but to write the history of our departments, namely, the history of the appearance and development of the organic chemistry in Russia [1] and to share the data on the scientific achievements within the last decade. The review covers just this issue.

We believe that the review would be useful and interesting for the readers since it sums up the results obtained by diverse scientific teams in definite chosen fields. Naturally such results are especially abundant in Moscow, Saint Petersburg, Kazan, Yekaterinburg, but no less interesting results shared authors working in Samara, Saratov, Omsk, Stavropol, and other places. Regretfully, due to various reasons independent of us we failed to include all the universities of Russia, and we apologize to the authors not included in the review. Yet we are going to build contacts with all our colleagues and within our possibilities give help to the groups which due to the great load of teaching process and of bureaucracy and because of financial difficulties in purchasing reagents and equipment are unable to carry out scientific research. I wish to thank everybody who replied and to wish them good luck.

Head of the department of organic chemistry at Lomonosov Moscow State University, Professor V. Nenaidenko

2. DEPARTMENT OF ORGANIC CHEMISTRY AT KAZAN FEDERAL UNIVERSITY

At the department of organic chemistry at Kazan Federal University 19 lecturers and 35 researchers are currently working, among them 3 Members of the Russian Academy of Sciences and 10 Doctors of Sciences, 65–70 students (specialists, bachelors, masters) and 28 postgraduate students specialize, six laboratories and scientific teams are operating.

Laboratory "Study of the structure of organic compounds" under the guidance of **Corresponding Member of the Russian Academy of Sciences I.S. Antipin** and **Academician A.I. Konovalov** performs since nineteen nineties investigations on the synthesis and supramolecular chemistry of macrocyclic compounds. These studies are carried out in cooperation with the laboratory "Calixarene chemistry" of the Arbuzov Institute of Organic and Physical Chemistry of the Kazan Scientific Center of the Russian Academy of Sciences. The early studies of this cycle were extensively presented in a number our reviews [3–5]. Within the publication [6] we discuss the results of the last decade.

In this time interval the interest of the Kazan school on supramolecular chemistry was focused on developing approaches based on controlled self-assembly of structural elements into ensembles with desired structure and functional characteristics in solution, on the phase boundary, and in the solid phase. This self-assembly is underlain by the synthesis of molecules capable due to the principles of molecular recognition and multicenter bonding to form supramolecular systems, materials, and devices. In this respect thiacalix[4]arenes are fairly promising (Fig. 2.1).

An important synthetic problem in the chemistry of thiacalix[4]arene is the development of approaches to the stereoselective functionalization of the lower rime of the macrocycle resulting in the formation of tetra-substituted derivatives with diverse spatial position of bonding centers required for the solution of specific problems of designing functional supramolecular systems. For instance, tetra-substituted derivatives in the *cone* conformation are efficient in the building discrete complexes and clusters, whereas the 1,3-*alternate* conformation is feasible for forming extended organometallic structures of various dimensionality (Scheme 2.1).

A common procedure for phenol groups functionalization is the macrocycle reaction with excess halo derivatives in dipolar aprotic solvents (mainly in acetone or acetonitrile) in the presence of alkali metals carbonates used as bases. In case of electrophilic reagents with *n*-donor groups the reaction proceeds stereoselectively and is governed by the template effect of the alkali metal cation in M_2CO_3. In the case of cations Na^+, K^+, Cs^+ the products are formed selectively in the conformations *cone*, *partial cone,* and 1,3-*alternate* respectively. Tetra-substituted derivatives prepared by etherification of the thiacalixarene platform catalyzed with a base are shown in Scheme 2.2 [7–25].

These derivatives are conformationally rigid and cannot change their stereoisomeric form in the course of further modification. They are promising precursors for the synthesis of amines, hydrazides, *N*-acylamides, and the other functional derivatives [26–36].

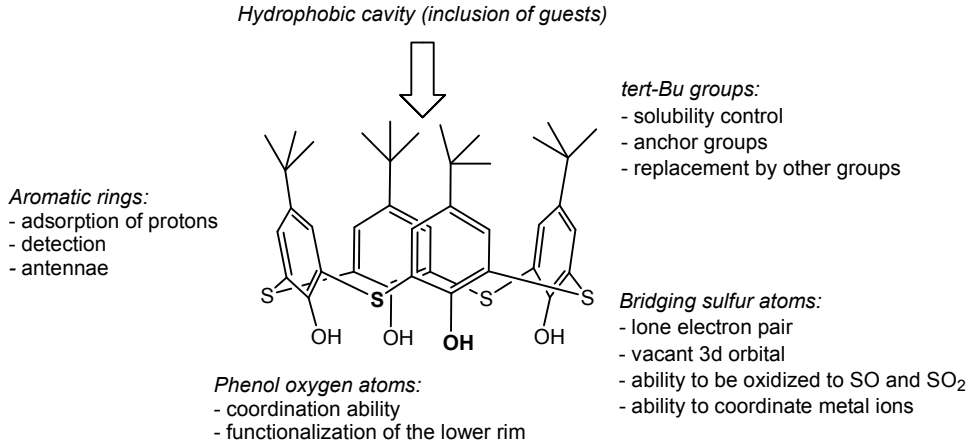


Fig. 2.1. Attractive features of thiacalixarene platform.

The replacement of the phenol oxygen atom for sulfur leads to a significant transformation of the complexing properties of the macrocycle caused by considerable changes in its size and by the presence of additional "soft" sulfur atoms. Proceeding from tetramercaptothiacalixarene (Scheme 2.3) in the stereoisomeric form 1,3-*alternate* made it possible to prepare carboxy, pyrazolyl derivatives with various number (2–4) of methylene units [20], cyanopropoxy-, cyanobenzyloxy- [37], as well as α,β,γ-pyridylmethoxy derivatives [38].

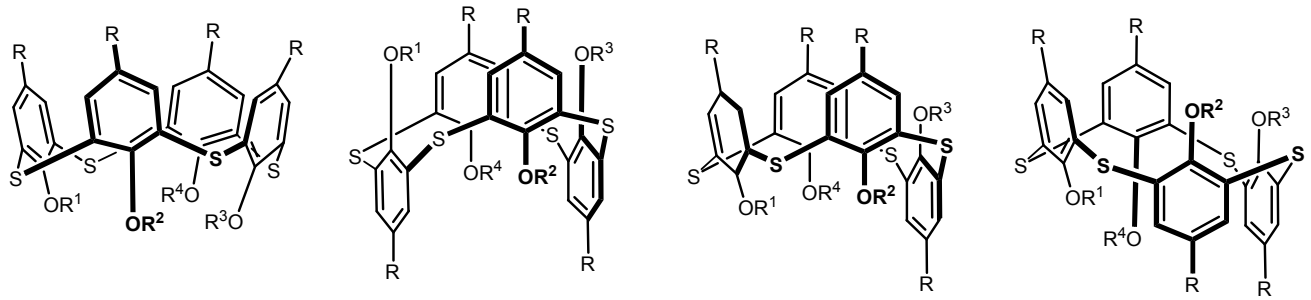
Bifunctional tetra-substituted thiacalix[4]arene derivatives in the 1,3-*alternate* conformation (Scheme 2.4), bearing two pairs of different substituents on the opposite sides of the macrocyclic platform are very interesting for the design of functional supramolecular architectures. These macrocycles allow the construction within a single nanomolecule of two spatially separated molecular regions with totally different properties, for instance, hydrophilic and hydrophobic, receptor and indicator, etc.

A significant contribution to the development of distal disubstituted thiacalixarenes *O*-derivatives, crucially important precursors for the production of bifunctional tetra-substituted derivatives (Scheme 2.4) was achieved by the team of **Professor S.E. Solovieva**.

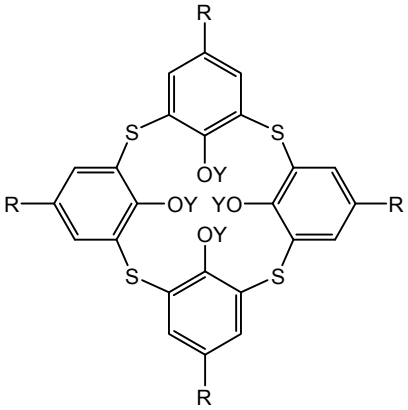
An original method of distal derivatives preparation was developed [39, 40] based on the stabilization of the partially substituted products owing to the formation of hydrogen bonds of the yet unsubstituted phenol hydroxy groups with the functional groups of substituents, in particular, with the phenacyl group whose carbonyl group is capable to participate in hydrogen bonds with phenol hydroxyls of the macrocycle (Scheme 2.5) [40, 41].

Two important characteristics of the distal derivatives of thiacalixarene were established for the first time which had a fundamental significance for further design of the polyfunctional macrocycles: the hydrolytic instability and ready transalkylation. Practically each *O*-functional group may be removed

Scheme 2.1.



Scheme 2.2.



R = *t*-Bu or H; Y = $(CH_2)_n$Br, *n* = 2–5; $(CH_2)_n$SH, *n* = 2–5; $(CH_2)_n$S-terPy, *n* = 2–5; $CH_2C(O)NEt_2$, $CH_2C(O)NEt_2$, $CH_2C(S)NEt_2$, $CH_2C(O)Ph$, $CH_2C(O)Ph$, N-propoxy-Phtalimide, $(CH_2)_3NH_2$, $NHC(O)NHPh$, $(CH_2)_3NH(NH_2)_2^+Cl^-$, $(CH_2)_3NHP(O)OEt_2$, $(CH_2)_3CN$, $(CH_2)_nC{=}CH$, *n* = 2–6; $CH_2Py(\alpha,\beta,\gamma)$, $(CH_2)_n$-Pyrazolyl, *n* = 2–4; $CH_2C_6H_4CN$.

from the macrocyclic platform by heating in DMF in the presence of a base (Na_2CO_3) or by boiling in toluene in the presence of primary amines [41] (Scheme 2.6).

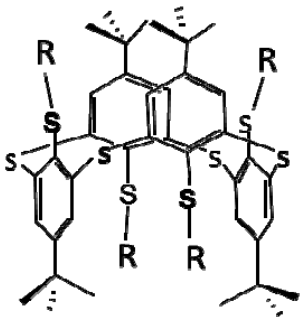
The cause of the acceleration of the hydrolysis of the Ar–O–C bond (Fig. 2.2) is the stabilization of the leaving anion group (*a*) due to the formation of two intramolecular hydrogen bonds between the oxyanion center and two adjacent phenol groups. In the case of classic calixarenes the distal derivatives are more stable against hydrolysis since only one hydroxy group takes part in the stabilization of the leaving group (*b*).

Spatially preorganized receptors (tectons) underlain by thiacalix[4]arenes and mercaptothiacalix[4]arenes (TCA and TMTCA) and metacyclophanes in 1,3-*alternate* stereoisomeric form containing functional groups with electron-donor atoms on the lower rim of the macrocycle (Scheme 2.7), were utilized in designing new coordination polymers. These studies were performed by S.E. Solovieva and A.S. Ovsyannikov in collaboration with the laboratory of molecular tectonics of University of Strasbourg (Professor M.W. Hosseini).

In the framework of these studies using the approach of the molecular tectonics a large series of coordination polymers was prepared characterized by diverse dimensionality (1D–3D) with cations Ag(I), Hg(II), Fe(II), Cu(II), Mn(II), Ni(II), Co(II), Zn(II). The regularities were established of the coordination site formation (supramolecular motif, dimensionality, porosity of the structure [17–21, 42–49].

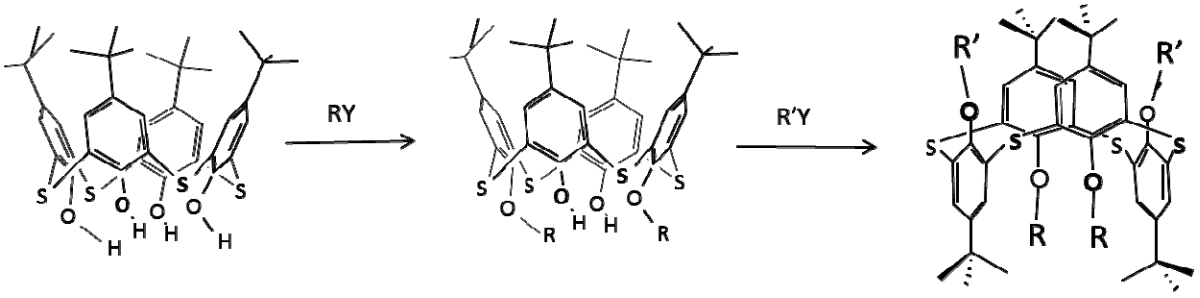
Supramolecular motifs at the formation of coordination polymers based on macrocycles in the 1,3-*alternate* stereoisomeric form with linear and square-

Scheme 2.3.

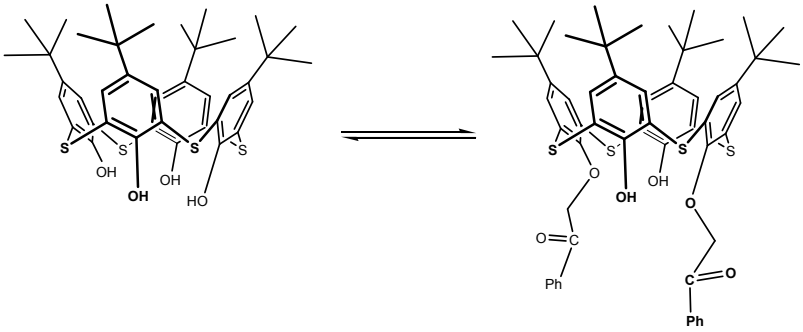


R = $(CH_2)_n$-Pyrazolyl, *n* = 2–4, $(CH_2)_3CN$, $CH_2C_6H_4CN$, $CH_2Py(\alpha,\beta,\gamma)$, CH_2-C_6H_4COOH (*m*- and *p*-isomers).

Scheme 2.4.



Scheme 2.5.



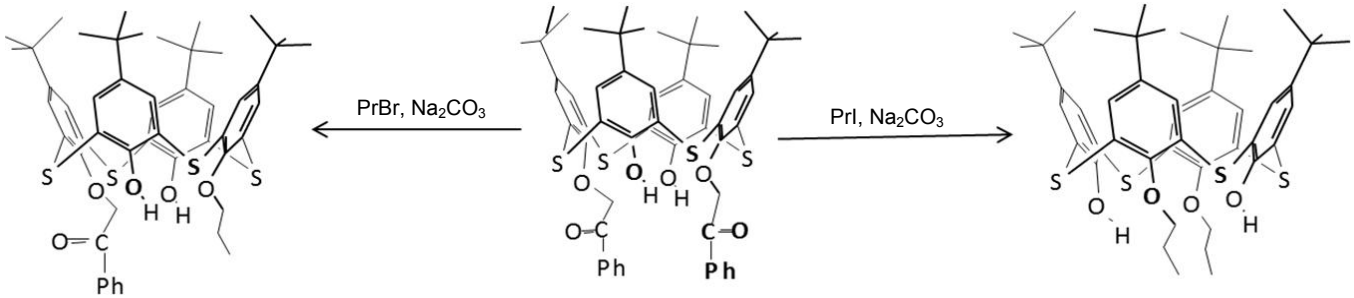
planar metal connectors are shown in Scheme 2.8. Cations with a flexible coordination sphere [Ag(I), Hg(II)] are the most efficient metal connectors for the preparation of coordination polymers. Coordination spheres of cations from the other *d*-elements [Co(II), Ni(II), Zn(II), Cu(II)] are less capable to adjust to the geometry of the organic tecton resuling in the involvement of solvent molecules in the coordination with the metal cations; solvent molecules, e.g., pyridine, play the role of additional ligands (Scheme 2.9) [48].

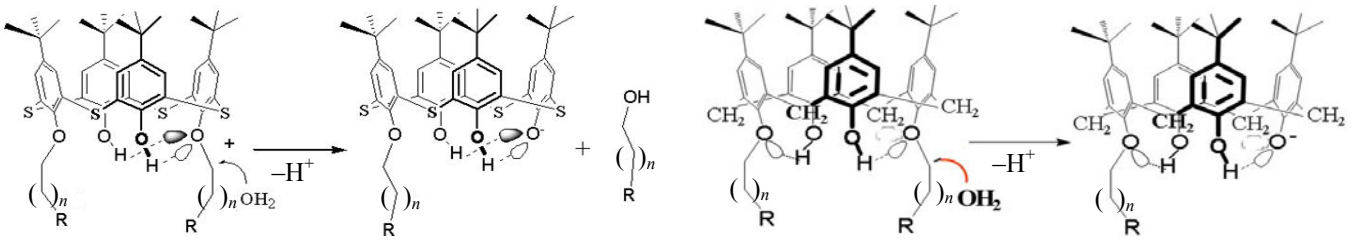
Tectons based on tetra-substituted functional derivatives of TCA and TMTCA depending on the spatial arrangement of the coordination sites are prone to the formation of either 3D and 2D coordination polymers if their geometry is the closest to tetrahedral, or 1D, when it is close to distorted rectangular.

The structure of the coordination polymer is considerably affected by the nature of the counterion, namely, the anion of the metal salt used in the synthesis of the metal-organic network. Anions either occupy the cavities between the chains of the coordination polymers or may themselves enter the coordination sphere of metal cations that as a rule leads to changing the supramolecular motif of the coordination polymer and results in complicating its structure. Here the governing role belongs to two factors: the coordinating ability and the size of the anion.

In Fig. 2.3 an example is presented of the influence of the coordination ability of anion on the structure of coordination polymers formed by macrocycle **1** [42]. In the case of the weakly coordinating tetrafluoroborate anion BF_4^- a nontubular 1D structure (*a*) is

Scheme 2.6.





a *b*

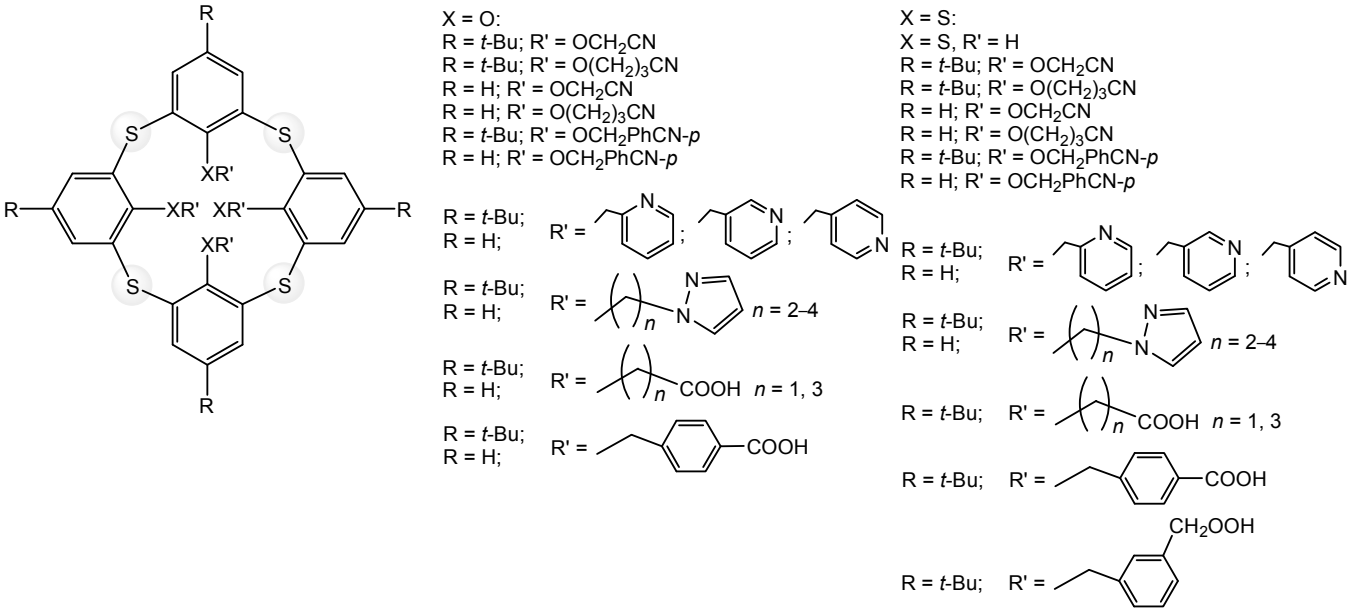
Fig. 2.2. Stabilization of leaving anion at the nucleophilic attack of distal disubstituted thiacalixarene (*a*) and calixarene (*b*).

formed where all the four coordination abilities of silver are functioning. The coordination site in this case is a slightly distorted tetrahedron. The situation significantly changes at the use of silver nitrate. The nitrate anion remains in the coordination sphere of silver cation and transforms the latter from the tetrahedral metal connector in a V-form one. As a result a tubular 1D structure (*b*) is formed. When the anion of large size cannot occupy the cavities between the chains of the coordination polymer, a cardinal restructuring occurs of the total crystal structure with the formation of porous material, e.g., in the case of macrocycle **1** with $AgSbF_6$.

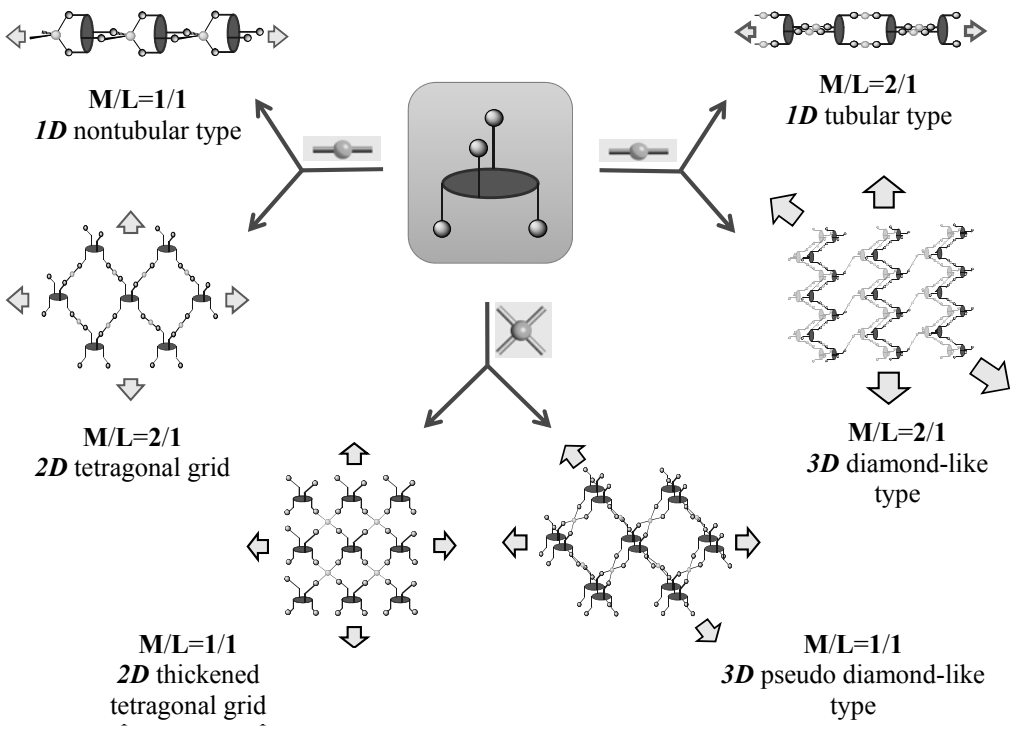
At the presence in solution of excess coordinating anion NO_3^- more complex 2D and 3D structures are formed with a larger content of metal ions. In particular, a unique 3D coordination network was obtained (Fig. 2.4, *d*) where the connectors were not single ions but nanosize clustars located 1.3 nm from each other (Fig. 2.4, *b*, *c*) containing ten siver ions bonded with each other with nitrate anions [21].

In the laboratory "Study of the structure of organic compounds" the main issue in the investigations of the scientific team of **Assistant-Professor V.A. Burilov** is the directed synthesis of macrocyclic amphiphilic compounds on the platform of *p*-*tert*-butylthiacalix[4]-arene able to act as "smart" surfactants capable both of self-association and bonding to the other molecules. For instance, one among the key targets was the development of a unique synthetic protocol for the synthesis of a wide series of the amphiphilic thiacalix[4]arenes derivatives in the 1,3-*alternate* stereoisomeric form where would be attained the spatial separation of the lipophilic and hydrophilic parts of the molecule. To attain this target one of the tasks to be achieved was the synthesis of bifunctional tetra-substituted derivatives of thiacalix[4]arenes in the 1,3-*alternate* stereoisomer form containing diverse type substituents located

Scheme 2.7.



Scheme 2.8.



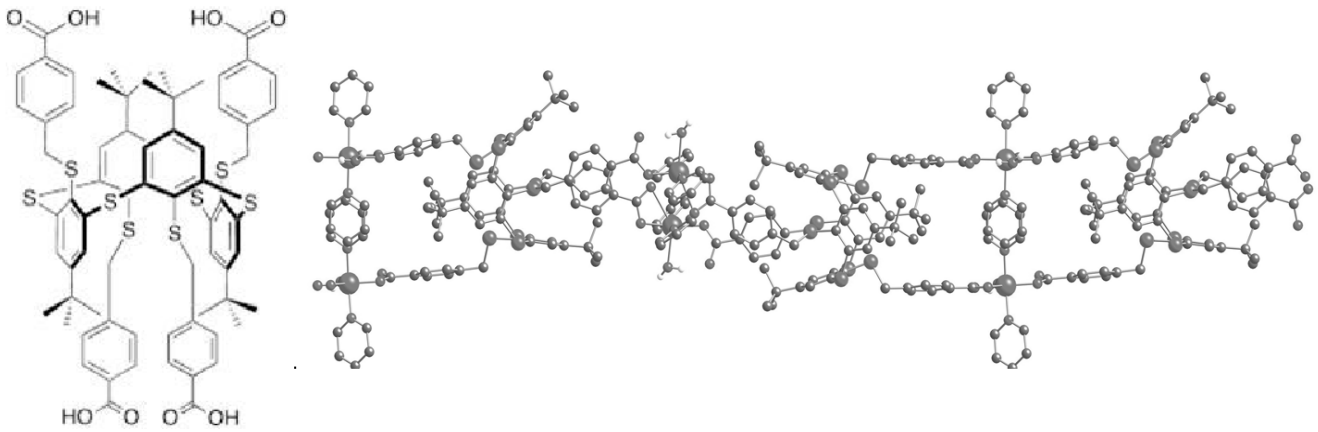
on the different sides of the macrocyclic cavity (Scheme 2.4).

The synthesis of such bifunctional derivatives was suggested to be performed by successive alkylation of macrocycles by Mitsunobu reaction that provided a possibility to prepare selectively distally substituted products in high yields with subsequent production of tetra-substituted compounds using Mitsunobu reaction. Applying this approach (Scheme 2.10) made it possible to produce a series of compounds containing lipophilic alkyl fragments as well as azidopropylene fragments ensuring further introduction in the macrocycle of polar groups by copper-catalyzed reaction of azide-alkyne cycloaddition (CuAAC) [50, 51].

For the same purposes Williamson alkylation reaction also may be utilized. For instance, the macrocycle alkylation in the presence of cesium hydroxide at microwave heating (Scheme 2.11) furnished a series of compounds containing lipophilic fragments as well as propargyl groups [52].

The obtained macrocycles with azide or alkynyl functional groups were modified with diverse groups using the CuAAC reaction (Scheme 2.12) [53–55].

Scheme 2.9.



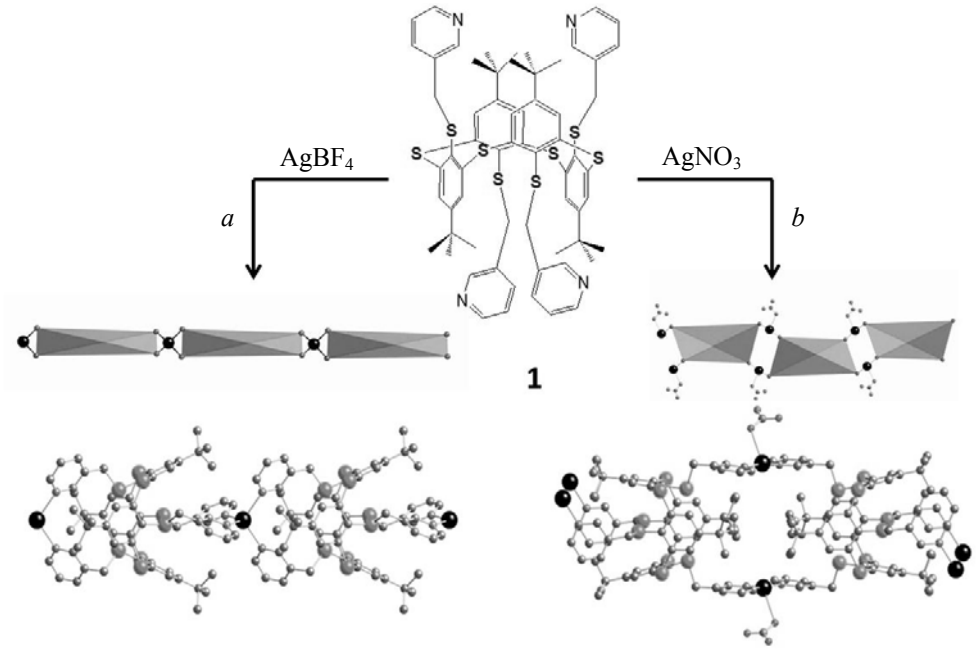


Fig. 2.3. Effect of anion on the structure of the coordination polymer with macrocycle **1**.

The macrocycles containing terminal triple bonds were also modified with the use of CuAAC reaction. A curious feature of the process was observed: from the initial thiacalix[4]arenes derivatives present as a mixture of stereoisomeric forms 1,3-*alternate-partial cone*, 2 : 1, the CuAAC reaction afforded products of exclusively 1,3-*alternate* stereoisomeric form [50] (Scheme 2.13).

We synthesized for the first time thiacalix[4]arenes derivatives in the 1,3-*alternate* stereoisomeric form possessing diacetylene substituents capable of photopoly-

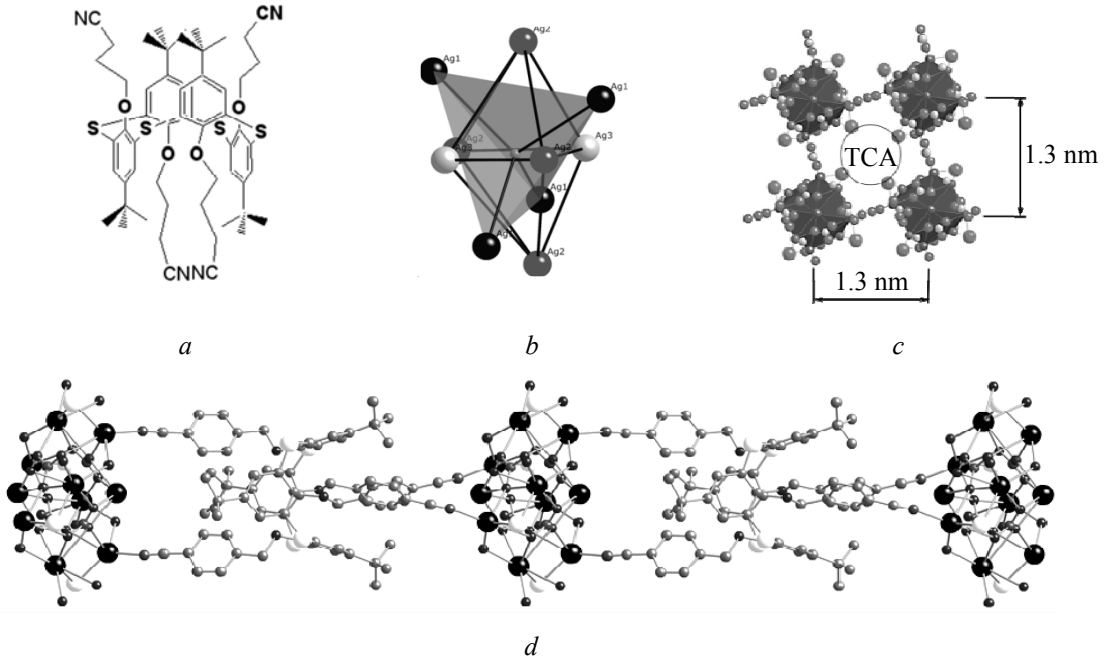


Fig. 2.4. Formation of 3D metal-organic network: tecton structure (*a*); structure of decanuclear cluster of silver cations (*b*); fragment of spatial arrangement of decanuclear clusters (*c*); part of the structure of 3D metal-organic network (*d*).

merization on the one side of the macrocyclic plane and azide fragments on the other side, the latter being precursors of subsequent CuAAC reactions [56]. These diacetylene derivatives are fairly promising molecules from the viewpoint of preparation of polyacetylene-containing materials capable of changing their optical characteristics under the action of various substrates and environmental conditions. The obtained macrocycles were modified by both non-catalyzed and copper-catalyzed reaction of azide-alkyne cycloaddition (Scheme 2.14).

The synthesized macrocycles containing polar carboxy head groups are capable to be built in the vesicles of DPPC phospholipide (Dipalmitoylphosphatidylcholine). These calixarene-modified vesicles decorated with Tb(III) ions exhibited highly intensive "green" luminescence quenched in the presence of pyridoxine even at the substrate concentration 7 μmol L^{-1} [51].

By utilizing thiacalix[4]arene ammonium triazole derivatives with anionic dye Eosin H nanoparticles were obtained of the size 120–130 nm that exhibited an exclusive selectivity of bonding with respect to alkyl sulfate surfactants sodium dodecyl and laureth sulfates. The luminescent response of the system based on the separation of the free dye molecule is observed at the surfactant concentration 3.5 μmol L^{-1} [53] (Scheme 2.15).

Amphiphilic calixarenes containing six amino groups as polar fragments are capable to interact with calf thymus DNA through the formation of nanoaggregates of the size ~50–100 nm that results up to 5 times compactization of the calf thymus DNA. It is very promising for the development of non-viral transfection agents [55].

Polyacetylene particles were prepared containing in the composition carboxy or amino calixarenes derivatives and 10,12-pentacosadiynoic acid as a basic component. Photopolymerized vesicles containing the tetracarboxylate calixarene exhibit a selective colorimetric response concerning lanthanide cations Gd(III), Tb(III) and Dy(III), but the other cations do not cause a color change in these vesicles [56]. The lowest limit of lanthanide ions detection is 10 μmol (Scheme 2.16).

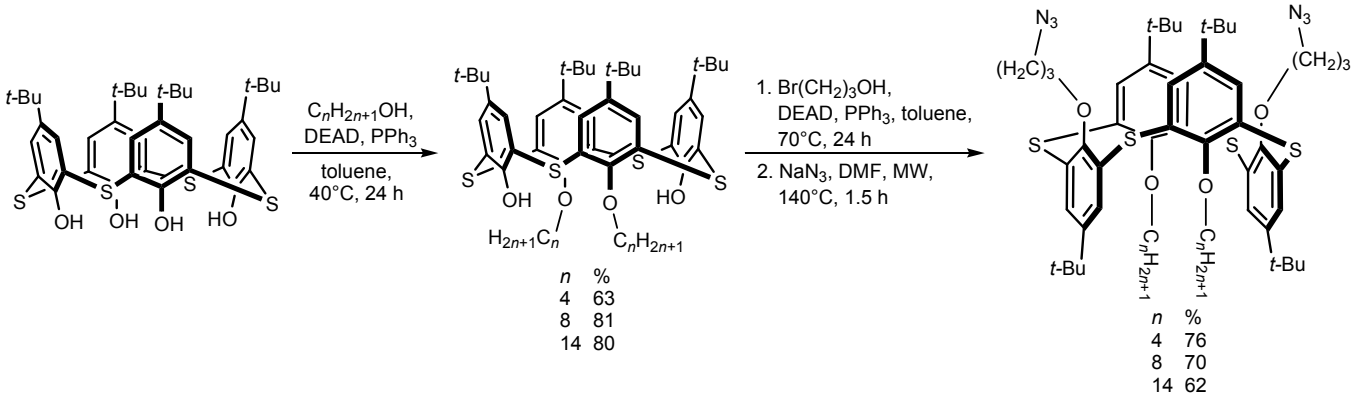
The group of **Professor I.I. Stoikov** performs research on modeling and development of approaches to the synthesis of receptors and nanosized structures proceeding from (thia)calix[4]arene [57–65], pillar[5]-arene [66–73], as well as nanosized silicon dioxide particles [74–76], capable of molecular recognition of biologically important substrates.

Using Kabachnic–Fields reaction appropriate macrocyclic amines were transformed in (thia)calix[4]-arene substituted at the lower rim with α-aminophosphonate fragments [25, 61] (Scheme 2.17). The macrocyclic α-aminophosphonates are able to extract selectively some acids from multicomponent mixtures.

The preparation of new ammonium derivatives from *p-tert*-butyl-thiacalix[4]arenes tetra-substituted at the lower rim permits the statement on the creation of new ionic liquids possessing receptor properties [62]. The formation of supramolecular associates was shown from the synthesized macrocyclic compounds with fluorescein, amino acids, bovine serum albumin, and DNA from salmon testes [63–65] (Scheme 2.18).

A series of hybrid organic-inorganic submicro- and nanoparticles of silicon dioxide was synthesized

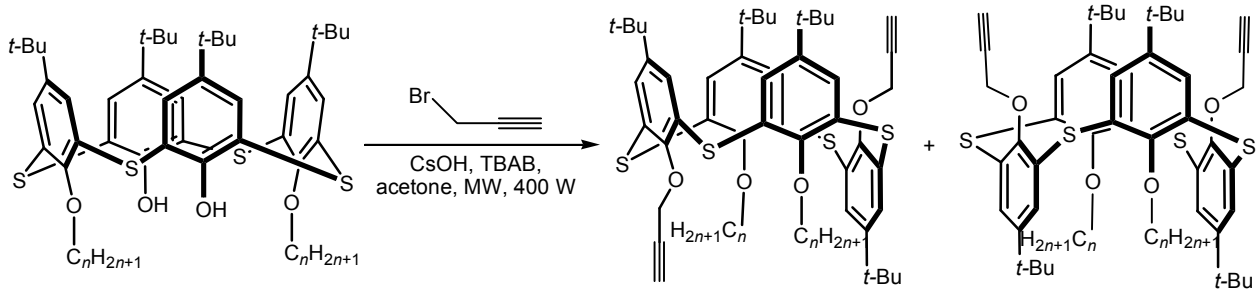
Scheme 2.10.



n	%
4	63
8	81
14	80

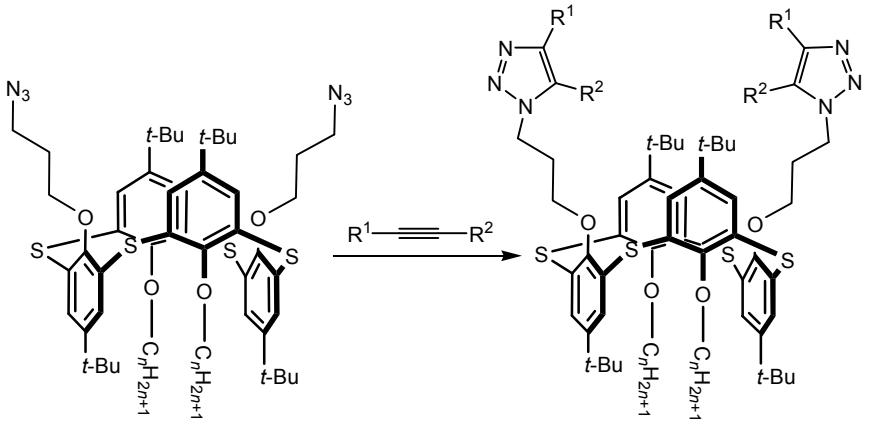
n	%
4	76
8	70
14	62

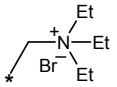
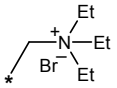
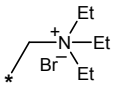
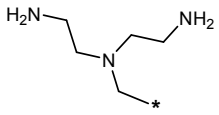
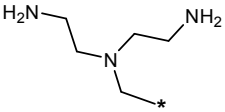
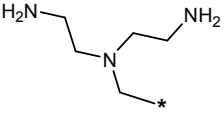
Scheme 2.11.



n = 4 79%
n = 8 83%
n = 14 86%

Scheme 2.12.

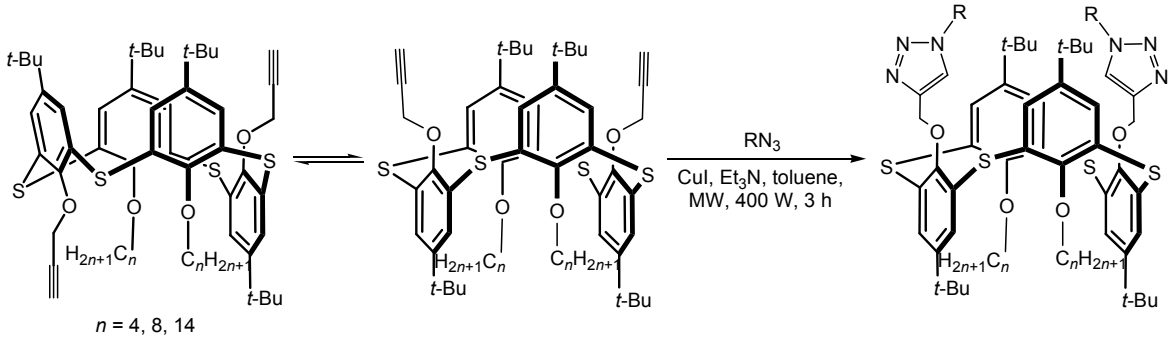


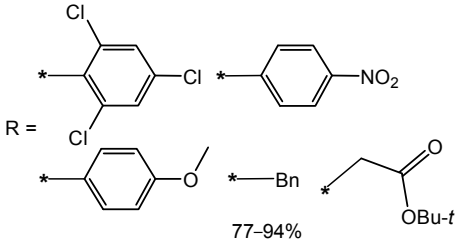
n	R^1	R^2	%
4	COOH	COOH	74
8	COOH	COOH	70
14	COOH	COOH	61
4		H	75
8		H	84
14		H	81
4		H	95
8		H	94
14		H	90

containing proton-donor/proton-acceptor fragments and thiacalix[4]arene derivatives in various configurations [74–76] (Scheme 2.19). Organosilicon hybrid particles showed a selective adsorption depending on the nature of the particles: Hydrophilic unmodified particles adsorbed on the surface substrates with pronounced acid properties by hydrogen bonding, whereas silicon dioxide modified with macrocyclic hydrophobic compounds bound guest molecules of similar nature mainly by stacking procedure [76].

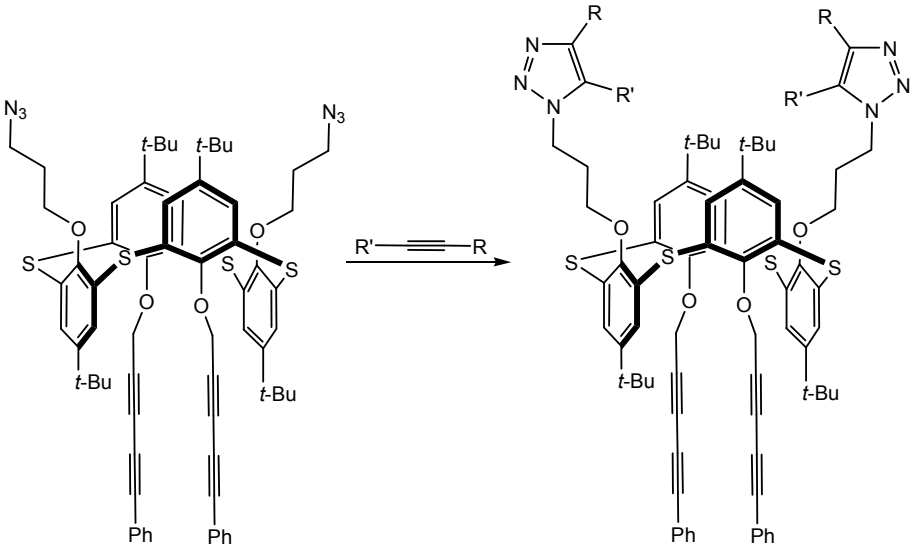
The method of induced asymmetric synthesis was used for the preparation of deca-substituted pillar[5]-arenes containing (*R*)-(+)-1-phenylethane-1-acetamide or (*S*)-(–)-1-phenylethane-1-acetamide fragments (Scheme 2.20) [72]. The spectroscopy of circular dichroism revealed the stereoselectivity of the formation of two stereoisomer pairs *p*SR/*p*RR and *p*RS/*p*SS of the deca-substituted pillar[5]arenes. The synthesized pillar[5]arenes form in trichloromethane spheric chiral nanosized aggregates (46–89 nm).

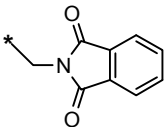
Scheme 2.13.



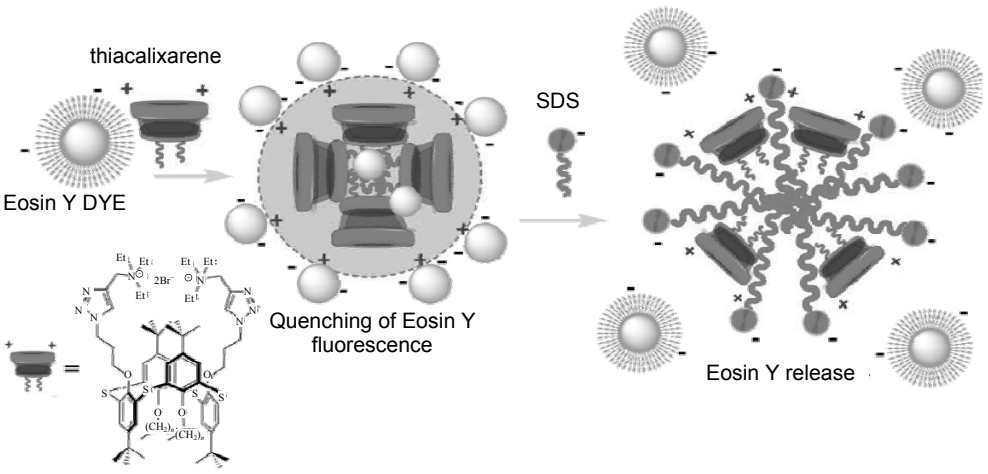


Scheme 2.14.

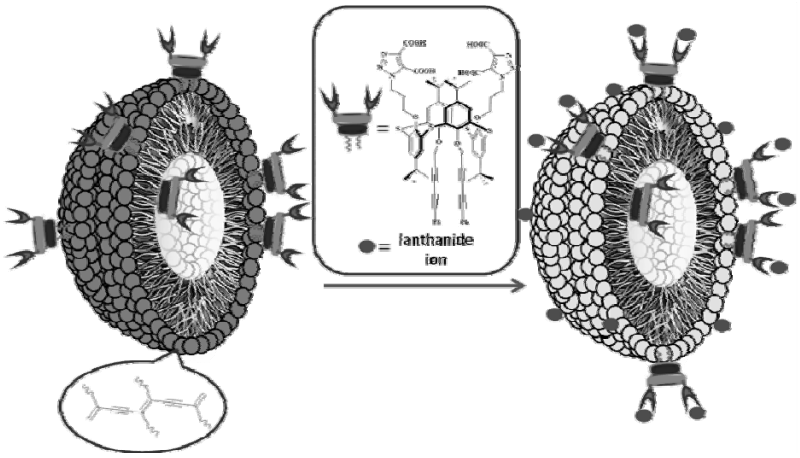


R	R'	Yield, %
CH_2Ph	H	85
	H	70
CH_2NH_2	H	75
COOH	COOH	75

Scheme 2.15.



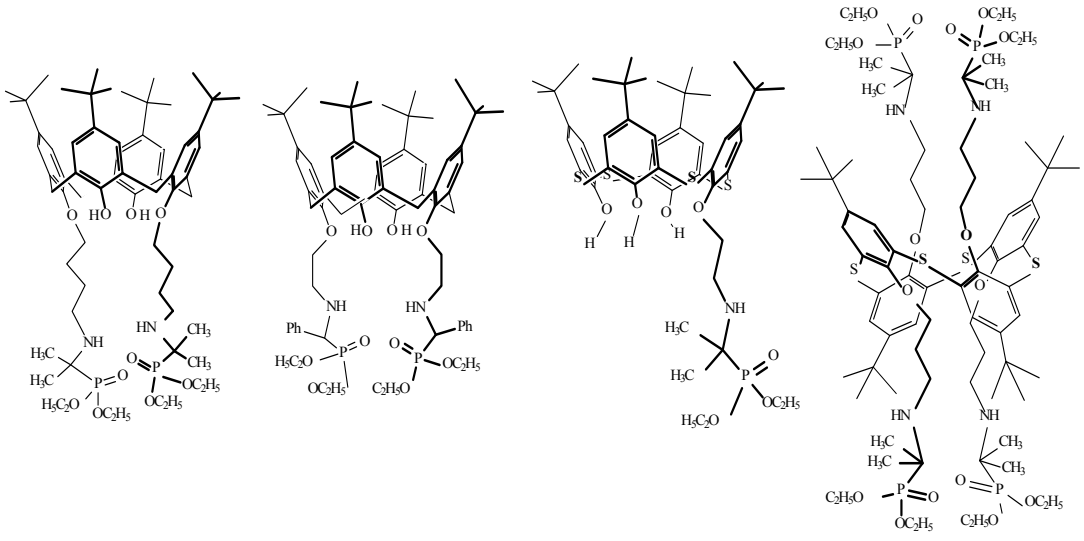
Scheme 2.16.



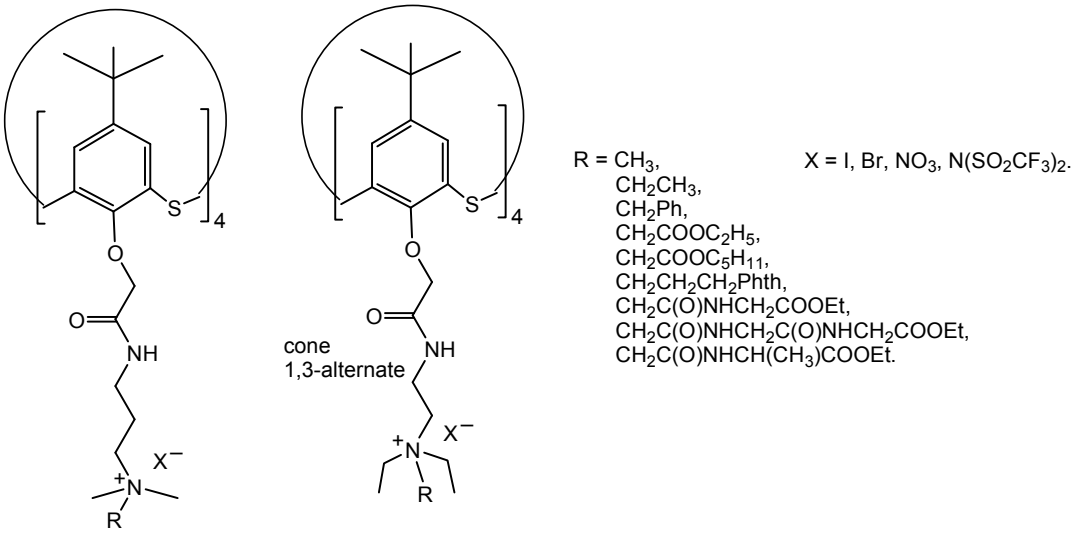
Under the guidance of **Assistant-Professor A.R. Kurbangalieva** and **Doctor Katsunori Tanaka** in the Russian-Japanese KFU – RIKEN "Laboratory of bifunctional chemistry" (founded in June 2014) the development is carried out of homo and hetero glycoconjugates (molecular receptors) for selective recognition and visualization of target tumor cells and tissues in living bodies [77–82]. For the first time heterogeneous structurally organized *N*-glycoalbumins were synthesized with a fixed ratio of two different glycans and their definite reciprocal position (Scheme 2.21). This was achieved with the help of new precursor based on azide. In its molecule first two different asparagine-bound glycans (*N*-glycans) were introduced. The subsequent conjugation of the obtained heterogeneous glycanazides with the fluorescently labeled albumin using the procedure of two successive click reactions allowed the control of the reciprocal spatial location of different glycans on the albumin surface [78, 79].

Visualization *in vivo* and the study of the biodistribution of the prepared glycoclusters in the bodies of model mice by the method of noninvasive fluorescent microscopy showed that various glycoconjugates accumulate selectively in definite organs or come out of the organism by diverse ways. The structure of the glycan fragment, the number of glycans on albumin, and their spatial distribution in the composition of the heterogeneous glycocluster play an important role both in the kinetics of the biodistribution and in the specificity

Scheme 2.17.



Scheme 2.18.

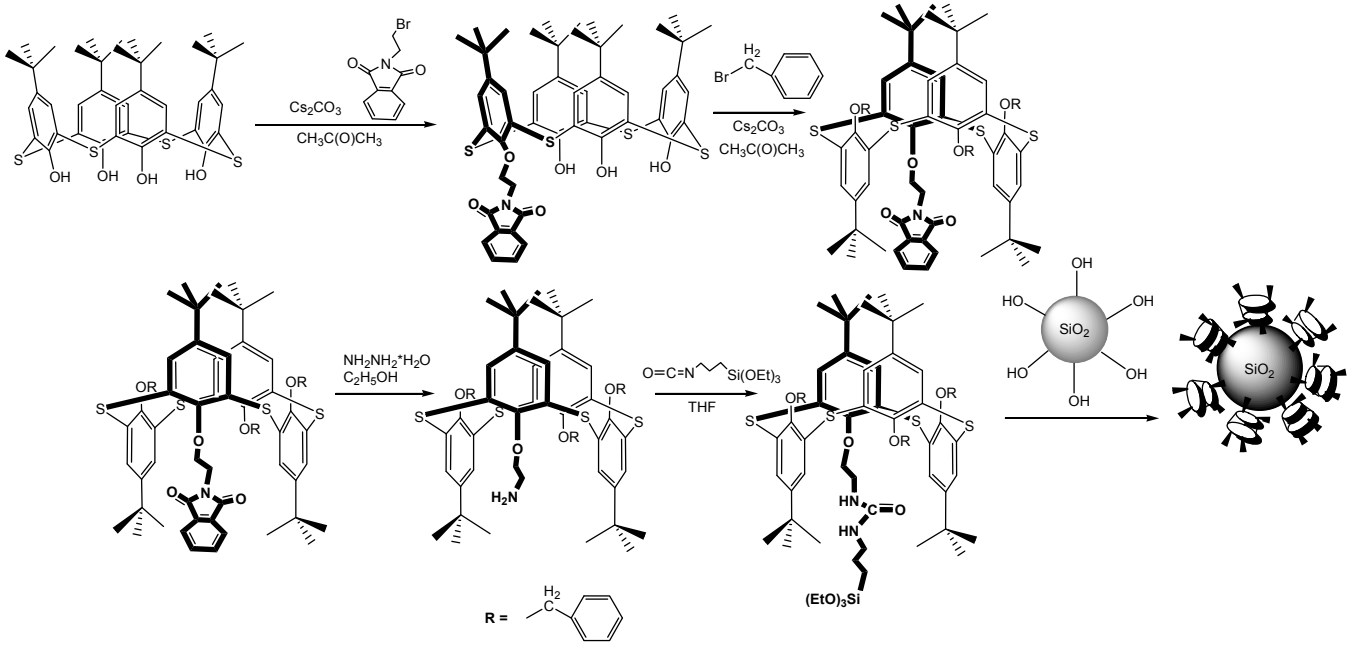


of clusters accumulation in various organs *in vivo* [78].

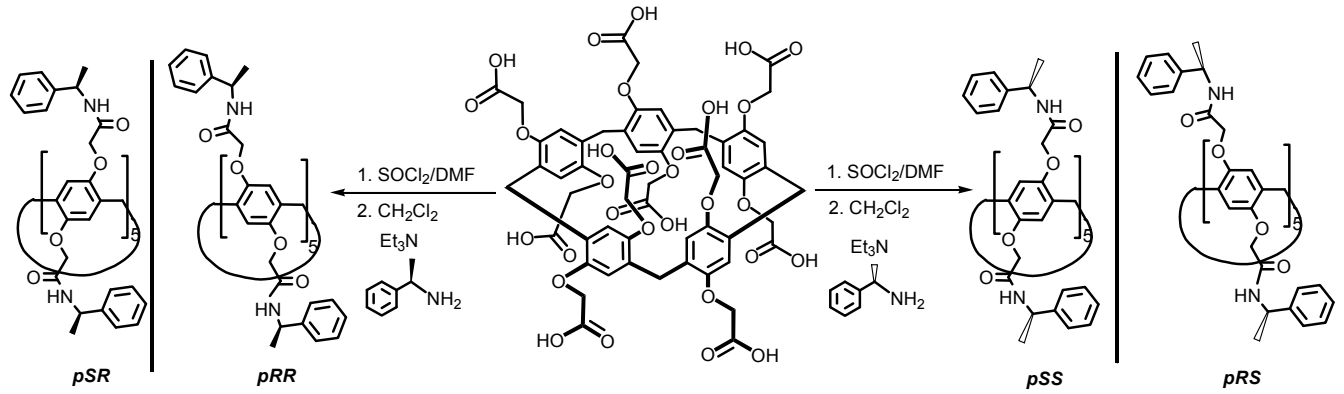
The observed selective and fast accumulation of *N*-glycoconjugates in certain tissues and organs may by utilized for making diagnostic agents and qualitatively new systems for the targeted delivery of drugs. A catalyst was obtained based on gold(III) and *N*-glycol-albumin that might be selectively transported in a definite organ of the living body [83]. The subsequent introduction of fluorescently labeled propargyl ether reacting with the amino groups of the protein molecules made it possible to perform conjugation in liver or intestines. Thus the targeted delivery of a catalytic complex based on glycoalbumin allowed the performance of various reactions selectively in the target organ.

New method was developed for detection and visualization of acrolein [84, 85]. The procedure consists in a non-catalyzed click reaction with acrolein of phenylazide or fluorescent phenylazide containing a tetramethylrhodamine (TAMRA) fragment

Scheme 2.19.



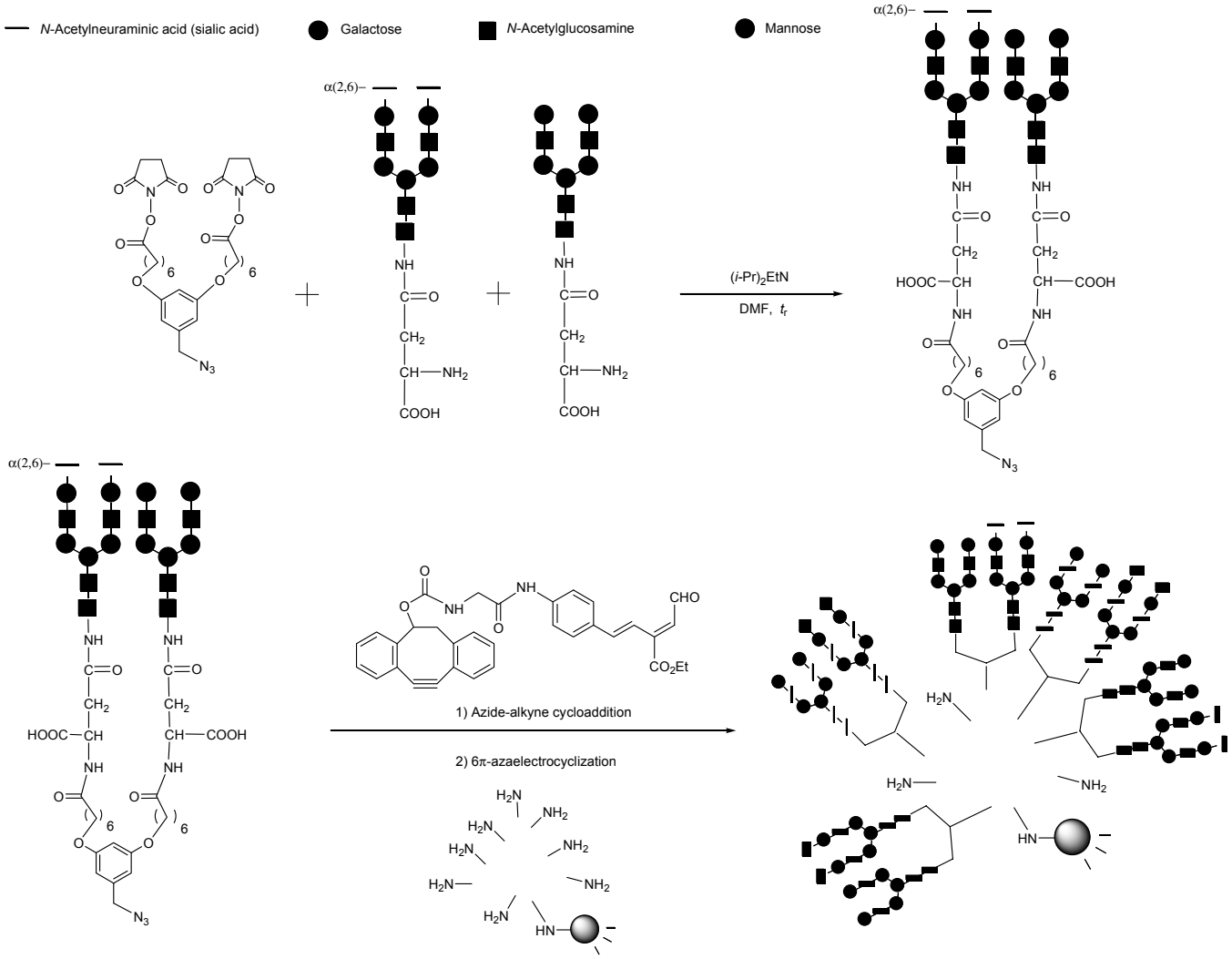
Scheme 2.20



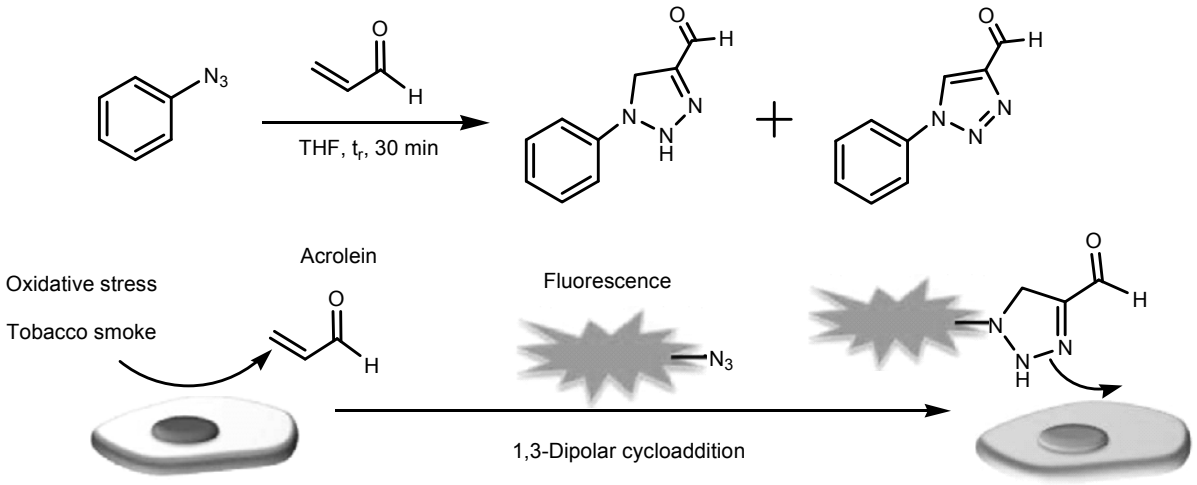
(Scheme 2.22). The developed approach is promising for detection of acrolein in living systems that is important both for the study of oxidative stress and for the understanding the causes of arising and developing various diseases on the molecular level.

The synthesis of new compounds and study of their biological activity is carried out by two research teams of the Department: those of **Assistant-Professor A.R. Kurbangalieva**, **Professor G.A. Chmutova**, and **Assistant-Professor A.V. Nemtarev**. The scientific

Scheme 2.21.



Scheme 2.22.



group of A.R. Kurbangalieva and G.A. Chmutova develops preparative synthetic methods, studies the structure and properties of new chemically and biologically active derivatives of five-membered heterocycles of the series of 2(5)-furanone and 3-pyrrolin-2-one. The attention is focused on the search for chemo-, regio-, and stereoselective reactions of thiylation, amination, oxidation, and cyclization of diverse 2(5*H*)-furanone derivatives [86–91] (Scheme 2.23). First specimens were synthesized of macroheterocyclic compounds of various composition and structure bearing an unsaturated γ-lactone fragment [92].

The testing the biological activity of the obtained halo- and sulfur-containing derivatives of 2(5*H*)-furanone revealed substances possessing an antiphlogistic action and also the ability to suppress the processes of the formation and growth of biofilms by various strains of pathogenic and opportunistic microorganisms [93–95].

A convenient approach is developed to the synthesis of thio derivatives of 5-hydroxy-3-pyrrolin-2 -one based on reactions of ammonia, amines, aminoalcohols, and hydrazines with appropriate 5-alkoxy-2(5*H*)-furanones [96] (Scheme 2.24).

The research of **Assistant-Professor A.V. Nemtarev** and his team (since 2015) is focused on the study of the component composition of specimens of the flora of Russia and neighboring countries and the study of the biological activity of some components followed by chemical modification of the most valuable among them aiming at attaining the required level of activity. Special attention is directed in the course of these studies on the implementation and utilization of advanced procedures, like supercritical (carbon dioxide) fluid extraction. This investigation is carried out together with the Laboratory of phosphorus-containing analogs of natural compounds at the Arbuzov Institute of Organic and Physical Chemistry of Kazan Scientific Center of the Russian Academy of Sciences (Correspondent Member of the Russian Academy of Sciences, Professor V.F. Mironov) and with the scientific and educational pharmaceutical center at Kazan Federal University (Candidate of biological sciences Assistant-Professor T.I. Abdullin, Doctor of medical sciences, Professor L.E. Ziganshina).

One of the most available specimen from the penta-cyclic triterpenoids, betulin [3-lup-20(29)-en-3β,28-diol] was chosen as the object of study; its content in the outer bark of birch was up to 30–35% (Scheme 2.25). It possesses a cytotoxicity and antiproliferative activity with respect to tumor cells and is considered as a promising platform for the synthesis of new antitumor drugs.

In the framework of current studies approaches were developed to mono- and bisphosphorylated betulin derivatives consisting in primary betulin esterification with haloalkanecarboxylic acids followed by their phosphorylation with triphenylphosphine [97, 98] Among the obtained compounds products were found exhibiting a pronounced antitumor activity on the par or exceeding in a number of cases that of vinblastine and doxorubicin.

A procedure was developed for the preparation of C^2-phisphonioalkyl derivatives based on the reaction

of O-methyl-2-methylidene-3-oxolup-20(29)-en-28-oate (obtained by the formaldehyde condensation with *O*-methylbetulonate in the presence of potassium carbonate) with triphenylphosphonium triflate [99] (Scheme 2.26).

Laboratory "Chemo informatics and molecular modeling" under the supervision of **Professor A.A. Varnek** (University of Strasbourg, France) and **Assistant-Professor T.I. Madzhidov** applies the approaches of chemo informatics and molecular simulation to the solution of diverse chemical problems. In the laboratory a universal approach is developed to the treatment of the information on chemical reactions based on the presentation of reactions as a condensed graph (CGR) [100] (Fig. 2.5). In the laboratory a set of instruments was made permitting coding reactions in CGR and backwards, generating a set of descriptors and bit strings for reactions, performing various quests using CGR. The designing of CGR requires establishing the atom-atom mapping, i.e., correspondence of reagents atoms to the atoms of products. An approach was developed that allows with the use of CGR an extension of application of the principle of the shortest chemical distance to the use of adjusting the atom-atom mapping [101]. A new universal technique was developed using CGR that permits predicting the behavior of reactions in various solvents, among them, in water-organic mixtures. It was used to obtain models permitting the rate prediction for reactions of bimolecular nucleophilic substitution [102], among them those involving azides [103], where the dependence was found of the rate constant on the reagents concentration, and also for the reactions of bimolecular elimination [104] and Diels–Alder [105]. In a recent publication from the laboratory a promising procedure of descriptor displaying of reactions was presented based on the mixture representation of reagents and products and without necessary CGR creation that by an example of bimolecular elimination reactions showed the advantages before the other approaches to simulating the reaction characteristics [106]. With the use of new types of local fragment descriptors models were also developed for the prediction of the reactivity of compounds with respect to halogen [107] and hydrogen bonds [108]. In the course of development of these models a unique data base QSRR DB was compiled collecting the information on kinetic and thermodynamic characteristics of chemical reactions.

The prediction of optimum conditions for performing a chemical reaction is the most interesting point for the synthetic chemistry. To this end the similarity principle was applied postulating that similar reactions proceeded in similar conditions. CGR makes it possible to evaluate the similarity of reactions, and it was utilized in the development of an expert system [109] based on the analysis of 72000 deprotection reactions under the conditions of catalytic hydrogenation. This array was obtained by automatic treatment of "raw" data from the base Reaxys [110]. The high accuracy of predictions was demonstrated both on the internal control (accuracy 85–95%), and by external validation (accuracy 85%).

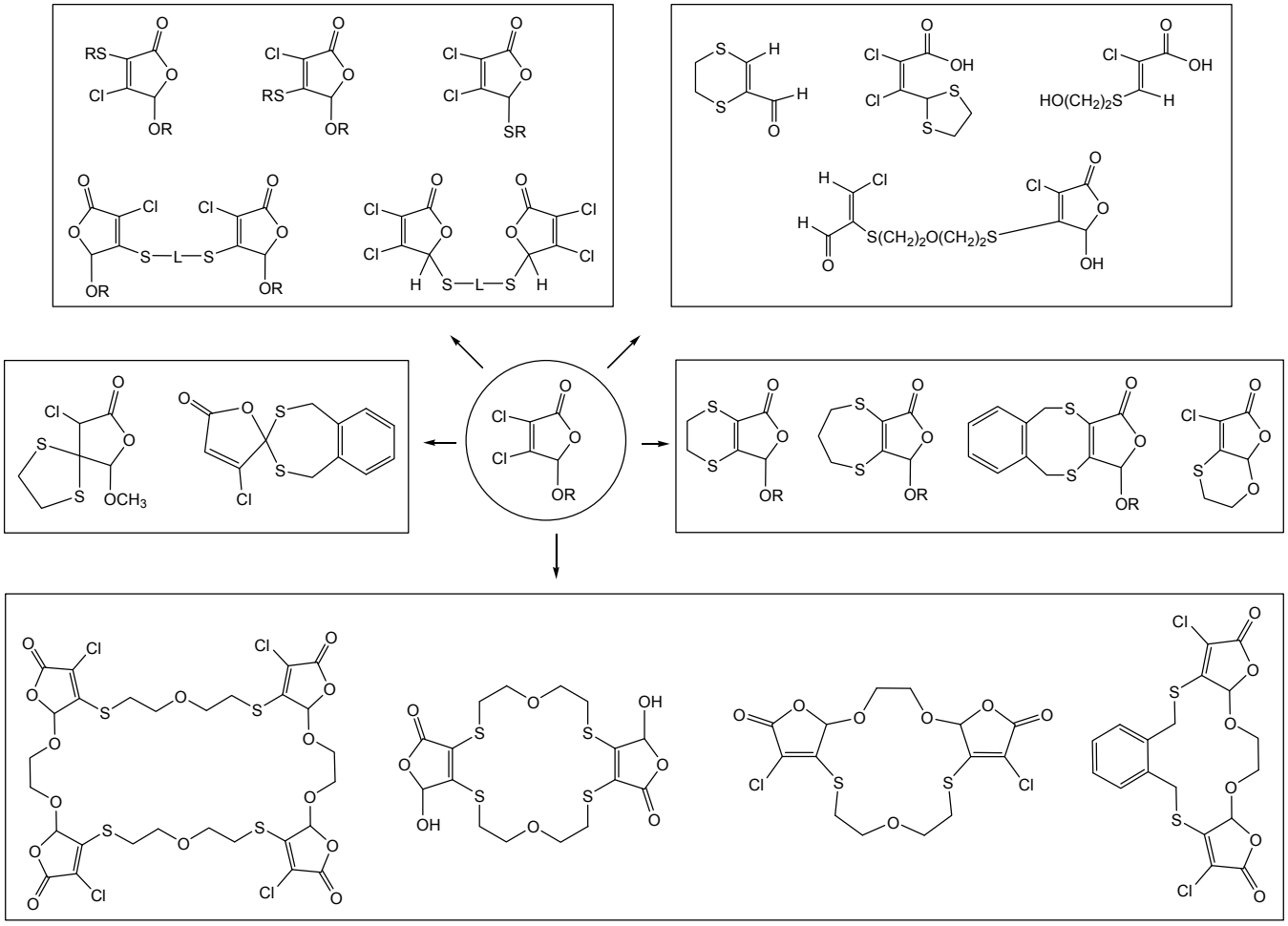
Within another direction of studies in the laboratory the research was focused on the investigation and analysis of the chemical space of molecules. It follows from Lipinski rule [111] that the number of orally admissible drugs is finite, and this number when estimated turns to be very large ($\sim 10^{33}$ without accounting for stereoisomers, $\sim 10^{36}$ when taking them into account) [112] for overcoming this number and synthesis.

In the framework of the collaboration between Kazan Federal University and University of Strasbourg new technique is developed of the analysis of the chemical space based on the generative topographic mapping [113]. The development of this approach made it possible to implement the GTM method not only for the visualization and analysis of the chemical space, but also for the modeling of the relationship structure–activity and for the evaluation of the range of the model applicability [114], the solution of the inverse modeling problem [115], analysis of large data [116]. This provides a possibility to search for compounds with a range of biological activity, e.g., possessing a definite range of activity towards intestinal transport proteins [117].

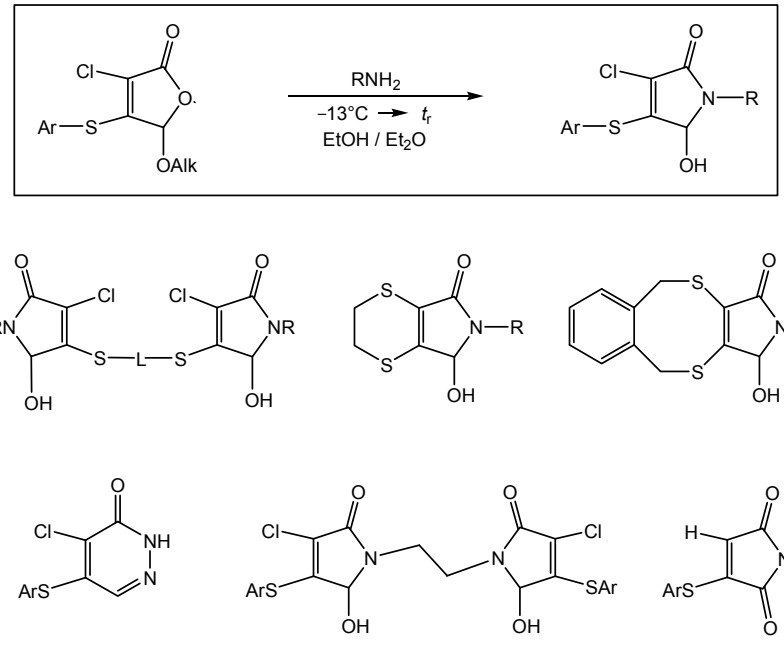
3. DEPARTMENT OF ORGANIC CHEMISTRY AT KAZAN NATIONAL RESEARCH TECHNOLOGICAL UNIVERSITY

Department of organic chemistry is one of the oldest in Kazan National Research Technological University: it has been founded in 1930, when the Kazan Institute of Chemical Engineering has been organized on the basis of the renown Butlerov Department of organic chemistry of Kazan State University. The founder and the first head of the department was the head of Kazan chemical school,

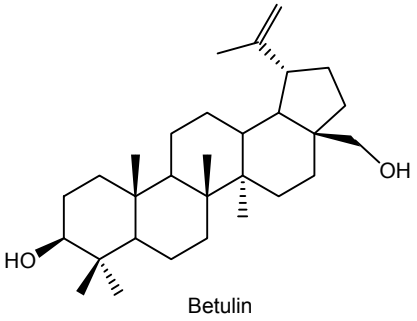
Scheme 2.23.



Scheme 2.24.

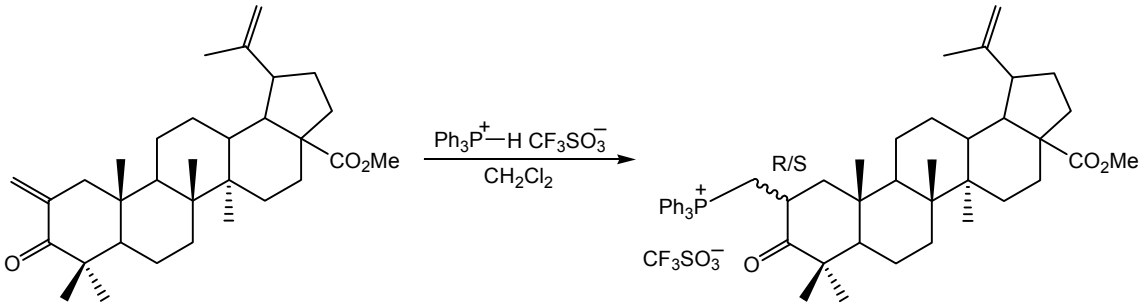


Scheme 2.25.



Betulin

Scheme 2.26.



the founder of the Russian school of orgnophosphorus compounds, **Academician A.E. Arbuzov**, who was the head of the department for 33 years (1930–1962). The main scientific field of the Department of organic chemistry of Kazan Institute of Chemical Engineering were always the investigations of organo-phosphorus compounds that were performed under the supervision of the heads of the department of organic chemistry **Professor A.I. Razumov** (1962–1980) and **Professor V.V. Moskwa** (1980–2000). The department of organic chemistry at Kazan National Research Technological University entered the new century not only with a large scientific baggage and with powerful potential but also with bright new ideas and tasks. Nowadays a fundamental scientific direction is developed here on the boundary of organic an organoelemental chemistry that may be described as "Targeted synthesis of complex polyfunctional organoelemental compounds with a desired 3D structure as the basis for development of new generation materials and technology". This direction started to develop with the appearance of the new **head of the department**, **Academician of the Russian Academy of Sciences O.G. Sinyashin**.

Nowadays 31 staff member is working at the department, among them 7 Professors, 15 Assistant-Professors. The scientific wealth of the department consists of over 3100 scientific publications in Russian and foreign journals, over 300 author's certificates and patents. In the department 12 Doctors of sciences and over 90 Candidates of sciences sustained their theses.

Several scientific directions of the department work may be mentioned. Targeted syntheses of polyfunctional organic compounds of desired structure

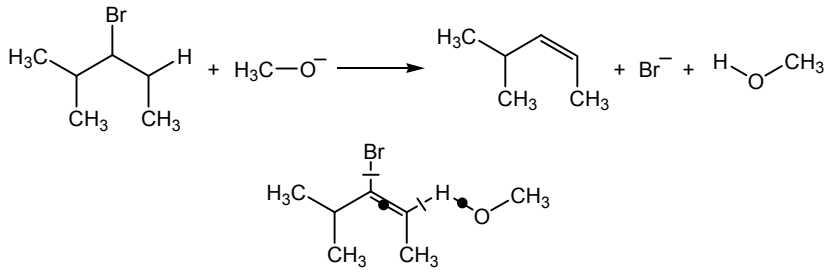


Fig. 2.5. An example of a condensed graph (below) corresponding to the elimination reaction (up). The forming double bond C=C is shown as a circle, the crossed bonds mean cleaved ordinary bonds C–H and C–Br.

by reactions of derivatives of P(III) and P(IV) acids, organic mono-, *gem*-di-, and trihalides and carbonyl compounds with *O*-, *P*-, *N*-nucleophiles. Reaction mechanism. Fine structure and biological activity (**Professor M.B. Gazizov**). The most important advances of M.B. Gazizov group are as follows: synthesis of intermediates of reactions between P(III) chlorides with aldehydes, anhydrides, and monoacetals of carboxylic acids which are key substances in the understanding the reaction mechanisms; revealing new reactions of *N*-alkyl-2-halo- or 2,2-dihaloaldimines with *O*,*O*-dialkyldithiophosphoric acids that never has been described in the world chemical literature; the synthesis of new for organic chemistry five-and six-membered heterocycles containing two phosphorus atoms of different coordination; nontrivial phosphoranes transformations with 1-phosphorylated alkoxy group by the opening of the phosphoryl group.

Studies in indole chemistry and investigation of its phosphorylated derivatives (**Professor P.A. Gurevich**). Now the synthesis is performed and the biological activity is tested of compounds obtained from 2-chloro-3*H*-indol-3-one.

Targeted synthesis and reactivity of polyfunctional *P*,*N*-containing compounds possessing a biological activity (**Professor E.L. Gavrilova**). The principal part of this direction is the synthesis of new hydrazides of arylhydroxyphosphorylacetic acids and their salts possessing a potential neurotropic activity; the synthesis and investigation of molecular complexes based on calix[4]resorcinol and hydrazides of phosphorylacetic acids aiming at development of means of drugs delivery to the central nervous system.

Study of kinetics of Diels–Alder diene synthesis (by an example of anthracene and 9-methylanthracene with maleic anhydride and of idanocyclone with styrene) in the conditions of thermal initiation and under microwave irradiation (**Assistant-Professor V.G. Uryadov**).

Development of synthesis method and the study of construction features of polynuclear fused bi-,tri-, and tetraheterocyclic systems as a way to designing ligands for complex formation and biologically active compounds, in particular, with antidiabetogenic properties (**Professor V.A. Mamedov**).

Designing of polyfunctional nanosystems using the fundamental principle of supramolecular chemistry "bottom-up": noncovalent controlled self-assembly of amphiphilic compounds, polymers, and metal ions. Rational selection of building blocks makes it possible to construct supramolecular systems of the new generation with the desired size and morphology and with controlled properties whose secondary (supramolecular) structure corresponds to a high intellectual level of designing, first of all, the possibility to adjust the properties of the systems by external influence (**Professor L.Ya. Zakharova**).

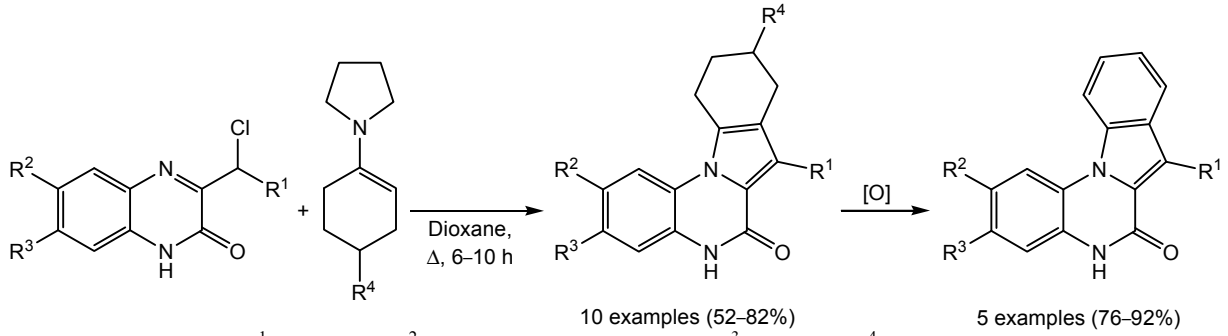
In 2014 the department of organic chemistry obtained a grant from the Russian Scientific Foundation for the project "Development of new synthetic methods for bi-, tri-, and tetracyclic compounds of heterocyclic series, preparation of nanosize water-soluble structures on their basis, and prospects of their biomedical application", and the studies on the project continued still. In this compilation some results are shown obtained within the work on this project: the opportunities to use the functionalized quinoxalin-2(1*H*)-ones in the syntheses of most diverse bi-,tri-, and tetraheterocyclic compounds both fused and linked with each other through C–C and C–N bonds, and the ways to increase the solubility of hydrophobic heterocyclic compounds using self-assembling amphiphilic systems.

One actively studied problem is the chemistry of heterocyclic compounds [118]. For instance, proceeding from the reaction of 3-α-chlorobenzylquinoxalin-2(1*H*)-ones with 1-cyclohexenylpyrrolidines indolo[1,2-*a*]quinoxalinones were synthesized, precursors of a number of indole and pyrazine alkaloids (Scheme 3.1) [119].

The reaction of chloropyruvates with 1-(cyclohex-1-enyl)piperidine and –pyrrolidine proceeds with the formation of various polysubstituted 4,5,6,7-tetrahydroindoles as a result of a cascade process including a substitution, cyclization, and addition. This approach was used for the preparation of diverse derivatives of tetrahydroindole which were mainly successfully aromatized (Scheme 3.2) [120–122].

Reactions of 3-aroylquinoxalin-2(1*H*)-ones with α-amino acids and their derivatives, with amines, amino alcohols, *N*-(3-aminopropyl)morpholine, and 1,6-diaminohexane in DMSO at 150°C occur with oxidative cyclocondensation thus providing a possibility to synthesize substituted imidazo[1,5-*a*]-quinoxalin-5(6*H*)-ones (Scheme 3.3). The advantages of this procedure consist in the possibility to introduce any desired substituent into the position *1* of imidazo-

Scheme 3.1.



R^1 = Ar, Alk; R^2 = H, Me, COOH, PhC(O); R^3 = H, Me; R^4 = H, *t*-Bu.

[1,5-*a*]quinoxalin-4(5*H*)-ones, the accessibility of versatile compounds with an aminomethyl fragment, a wide range of substrates, synthesis without metal complex catalysts [123].

Depending on the character of substituents in the position *3* the quinoxalin-2(1*H*)-ones can be utilized in the synthesis both of fused and non-fused biheterocyclic systems. For instance, 3-hydrazino-quinoxalin-2(1*H*)-one easily obtained from quinoxaline-2,3-(1*H*,4*H*)-dione and hydrazine hydrate readily reacts in boiling acetic acid solution (Scheme 3.4, *a*), with phenyl isothiocyanate first in toluene and then is acetic acid (Scheme 3.4, *b*), with maleic acid in acetic acid (Scheme 3.4, *c*) affording functionally substituted derivatives of [1,2,4]triazolo[4,3-*a*]qui-noxalin-4(5*H*)-one promising for the search for antidepressants, AMPA antagonists, compounds with antihistamine properties and antimicrobial activity [124]. The reaction of 3-hydrazinylquinoxalin-2(1*H*)-one with acetylacetone in methanol led to the formation of a derivative of 3-(pyrazol-1-yl)quinoxalin-2(1*H*)-one (Scheme 3.4, *d*) where two heterocyclic rings are linked by the C–N bond [124].

The synthesis of biheterocyclic systems was performed involving a quinoxalinones rearrangement under the action of nucleophilic reagents (Mamedov rearrangement) [118, 125–128]. The reaction of 3-benzoylquinoxalin-2(1*H*)-ones with enamines obtained *in situ* from ammonium acetate and the corresponding methyl aryl(hetaryl) ketones proceeds with the formation of the corresponding 1-(pyrrolyl)ben-zimidazolone derivatives in a good yield as a result of the Mamedov rearrangement involving a double rupture of C^3=N^4 and C^2–C^3 bonds (Scheme 3.5) [129, 130].

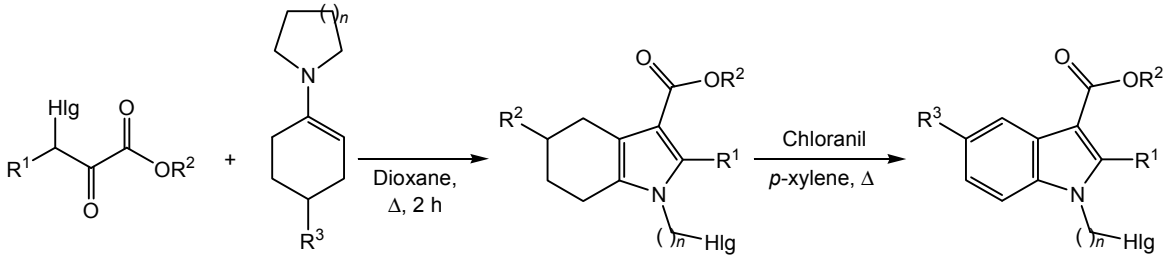
As a result of the Mamedov rearrangement the reaction of 3-(α-chloro-4-chlorobenzylquinoxalin-2-(1*H*)-one with *o*-phenylenediamine afforded an antitumor drug 2,2'-bibenzimidazole (Scheme 3.6) [126, 131].

The problem of solubility increase or of preparation of immobilized (container) forms of biologically active compounds is of high scientific and social importance. A separate direction in our investigations concerns designing new amphiphilic building blocks for constructing nanocontainers. In our studies a special attention is traditionally payed to cationic surfactants [132, 133], due to their high affinity to interphase biological surfaces, cell walls, natural anions, e.g., DNA.

One of efficient means of decreasing toxicity of cationic surfactants consists in the modification of supramolecular systems with hydrotropic additives like *N*-methylglucamine, hydroxylamine, choline, acid salts, etc. [134, 135]. In the system of the hexadecyl derivative of 1,4-diazabicyclo-[2.2.2]octane DABCO–16/*N*-methylglucamine a significant reduction of toxicity was reached with the conservation of a high antimicrobial activity and the solubilization characteristics were increased with respect to spectral probes and drugs [135]. In extension of these studies new amphiphilic compounds were synthesized containing a glucamine fragment, in particular, a surfactant with pH-sensitive characteristics *N*-methyl-*N*-cetylglucamine (GAM-16) and its quaternized analog GAM-16-I, which were investigated as building blocks for delivery systems (Fig. 3.1) [136].

An important quality of GAM-16 is its ability of solubilization of low polar organic compounds as shown by an example of hydrophobic spectral probes (Orange OT) and synthesized 3-methoxycarbonyl-2-phenyl-1-(4-chlorobutyl)-4,5,6,7-tetrahydroindole (IND-1) and its analogs (Fig. 3.2).

Scheme 3.2.



n = 1, 2 *n* = 4, 5 21 examples (63–98%) *n* = 4, 5 10 examples (68–85%)

R^1 = Ar, Alk; Hlg = Cl, Br; R^2 = Me, Et; R^3 = H, *t*-Bu.

For the quaternized analog of *N*,*N*-dimethyl-*N*-cetylglucammonium iodide (GAM-16-I) a special algorithm was developed for controlling the colloid properties and functional activity by optimization of the composition of supramolecular systems. The aggregating capability and solubilizing action of the systems based on GAM-16-I may be varied by adding organic salts: sodium tosylate (NaTos), sodium salicylate (NaSal), and sodium benzoate (NaBz) caused by effects of salting in/salting out, changes in the solvent structure, etc.

The effect of salts addition on the solubilizing the hydrophobic probe Orange OT in micelles of GAM-16-I was explored by an example of sodium salicylate. Regardless of the decrease in the *s* value at the salt addition the solubility of hydrophobic molecules of the GAM-16-I micelles occurs in a lower concentration range which provides a possibility to decrease the surfactant consumption and considerably decreases the toxicity of the nanosystems.

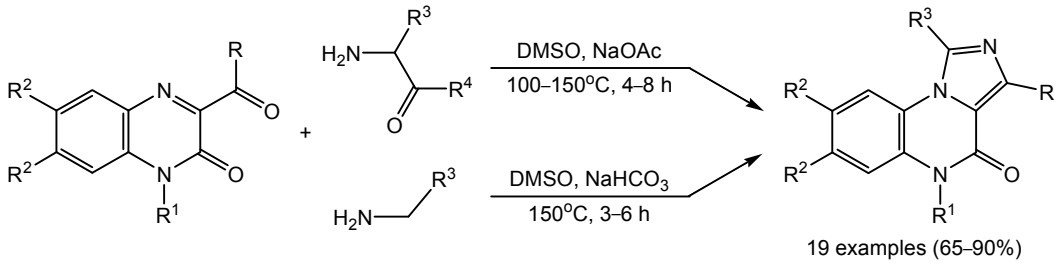
A separate direction of studies concerns the preparation of water soluble forms of antitumor drug 2,2'-bibenzimidazole (BBI) exhibiting antiviral and antitumor action (Fig. 3.2) [137, 138].

To increase the BBI solubility in water solutions additives of surfactants of diverse nature were applied: cationic surfactant cetyltrimethylammonium bromide (CTAB), anionic surfactant sodium dodecyl sulfate (SDS), and nonionic sirfactants Tween-80 and Tyloxapol. The BBI molecule contains four sites capable of taking part in acid-base equilibria, yet in the pH range 4–10 the neutral form of this compound dominates. The pH increase leads to increased intensity of BBI absorption regardless of the surfactant nature, yet in the solutions of cationic surfactants it is accompanied by the red shift of the absorption maximum, and in nonionic surfactants and in SDS a blue shift is observed.

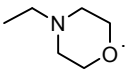
To increase further the solubilizing action compounds with hydrotropic properties were used: urea, choline chloride, and *N*-methylglucamine. The presence of *N*-methylglucamine enhances the solubilizing effect of CTAB 1.5–2 times, slightly decreases the action of nonionic surfactant Tween-80 and thrice decreases the SDS action, whereas choline 2–4 times improves the solubilizing capacity of micellar solutions notwithstanding the surfactant nature.

To decrease the toxicity of the system it was suggested to use GAM-16-I in combination with

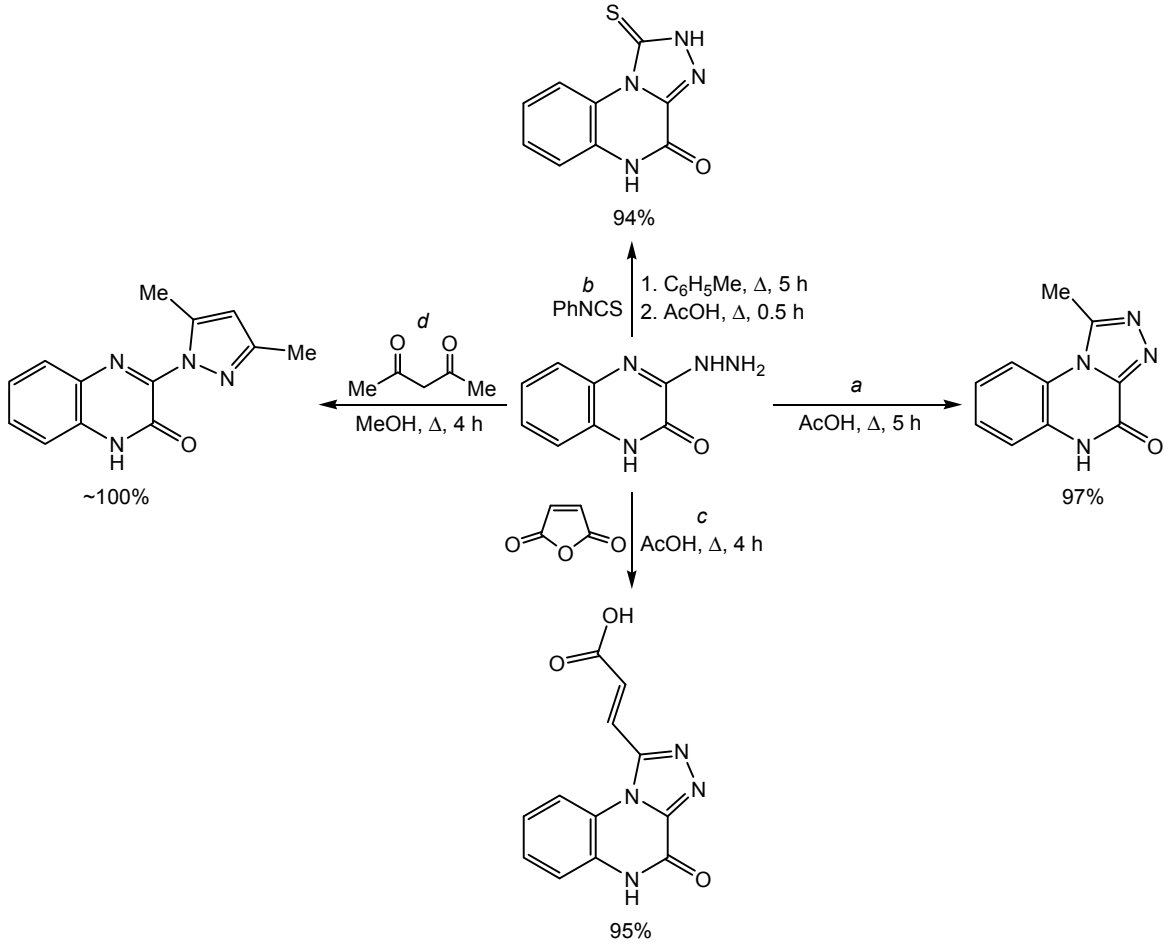
Scheme 3.3.



19 examples (65–90%)

R = Ar; R^1, R^2 = H, Alk; R^3 = H, Alk, $(CH_2)_nOH$, 

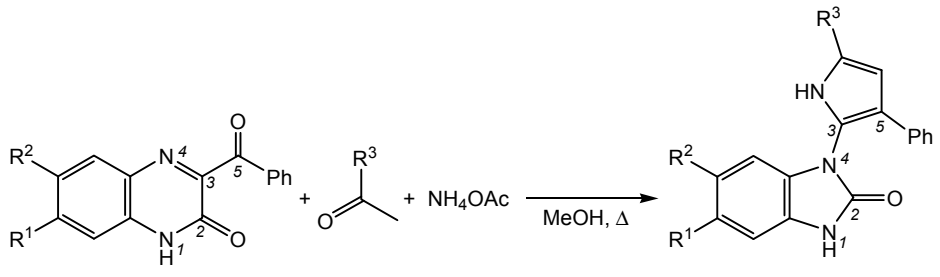
Scheme 3.4.



nontoxic *N*-methylglucamine at a molar ratio 1 : 1. Owing to its hydrotropic properties methylglucamine does not reduce the maximum obtained concentration of BBI, but makes it possible to significantly decrease the toxicity (LD_{50} 350 mg/kg).

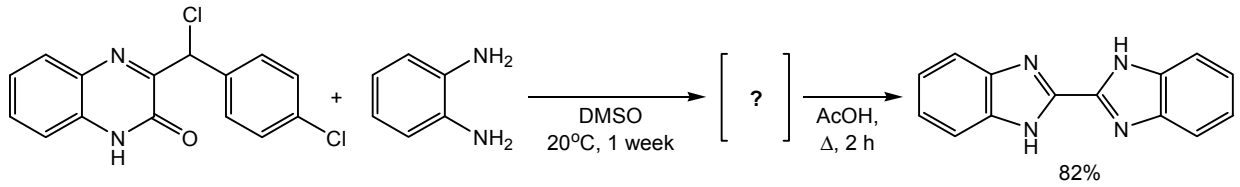
Another class of studied biologically active heterocyclic compounds are indole derivatives (Fig. 3.2). Along with the newly synthesized indoles investigation was performed using the known drugs, in particular an anti-inflammatory nonsteroidal pharmaceutical indomethacin, indoleacetic acid derivative (Fig. 3.2) [133, 139]. Geminal surfactant was synthesized with a morpholinium head group micelle-forming surfactant 14-*s*-14 (Fig. 3.1). The high efficiency of the latter in binding indomethacin is due

Scheme 3.5.



R^1, R^2 = H, Me, CO_2H, COPh; R^3 = Ar, Ht.

Scheme 3.6.



apparently to multifactor action combining the solubilization effect, electrostatic and specific intermolecular interactions.

The role of structural factors in the release of guest molecules was explored for the binary systems based on typical surfactants and amphiphilic macrocycles (calixarenes, cyclodextrins). To fulfill the task of the project calixarenes were synthesized containing fragments of natural amino acids ensuring reduced toxicity, affinity to biosubstrates and pH-dependent association mechanism.

New encapsulation protocols were developed for heterocyclic compounds with the use of binary compositions underlain by surfactants and cyclodextrins[140]. Bibenzimidazole derivatives were used as guest molecules for the synthesis of nanosize supramolecular ensembles based on β-cyclodextrin aimed to be used as delivery agents.

Promising systems for delivery of drugs and spectral probes are polymer-colloid nanocontainers [141–144] and polyelectrolyte capsules [145–147]. This research is aimed at designing new delivery systems combining the advantages of the amphiphilic formulations (simplicity of preparation, nanosize, biocompatibility) and high stability, resistance of polymer carriers against biodegradation. A simple protocol was developed for the formation of polyelectrolyte capsules by layered adsorption of oppositely charged polyelectrolytes on a dispersion of hydrophobic substrates excluding the application of

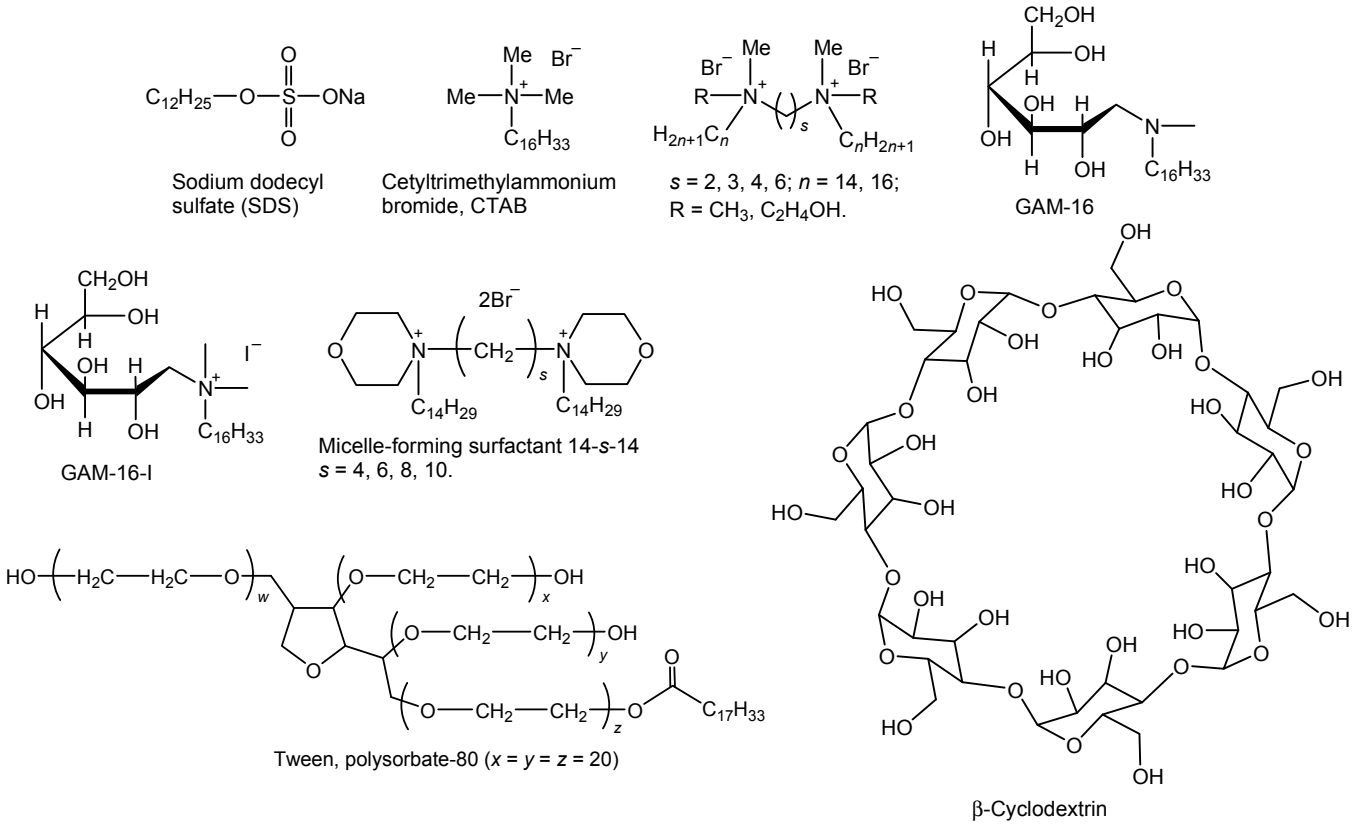


Fig. 3.1. Amphiphilic compounds

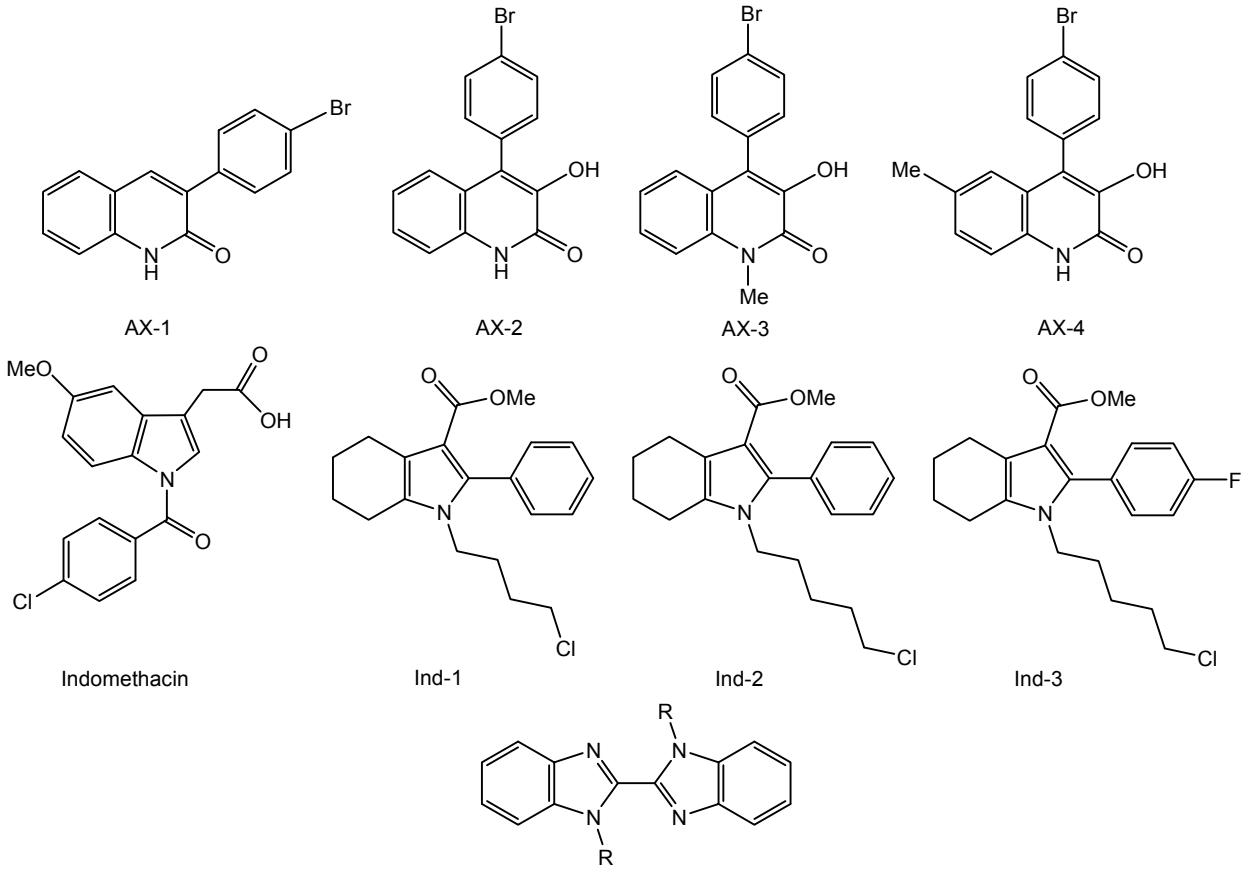


Fig. 3.2. Studied heterocyclic compounds.

mineral matrices. The obtained capsules possess a high colloid stability and a controlled permeability of walls thus providing them with a high potential for application.

4. DEPARTMENT OF ORGANIC CHEMISTRY AT SAINT PETERSBURG STATE UNIVERSITY

Department of organic chemistry at Saint Petersburg State University possesses a rich history and traditions [1]. Currently 11 Professors, 10 Assistant-Professors, 3 research fellows, and also 7 assistants and senior lecturers of the staff of the Institute of Chemistry of Saint Petersburg State University are working at the department. In 2016 the research at the department was carried out within the framework of projects supported by grants of the Russian Foundation for Basic Research (21 project, the supervisors of 9 grants are young scientists) and Russian Science Foundation (supervisors: M.A. Kuznetsov, M.Yu. Krasavin, A.F. Khlebnikov), one among them (under M.Yu. Krasavin) was performed within a large scale project "Translational Biomedicine at Saint Petersburg State University". One scientific study was performed for a state contract. This survey concisely describes the urgent trends in the research of the scientific teams of the department of organic chemistry at Saint Petersburg State University and the most important results obtained within the last 5 years.

Research in the group headed by I.A. Balova, **Director of the Institute of Chemistry** is focused on the synthesis and transformations of functionalized acetylene and diacetylene compounds, the preparation thereof of heterocyclic compounds [148–159], metal catalyzed reactions [153, 160–163]. In the synthesis of functionalized diacetylenes an original approach is used: the preparation of terminal diacetylenes from available and stable internal isomers by the diacetylene zipper reaction under the treatment with lithium 2-aminoethylamide (LAETA), followed by Sonogashira cross-coupling [149, 154–159] (Scheme 4.1).

The possibility of the use of potassium fluoride as a base in Sonogashira reactions of buta-1,3-diynylsilanes at the *one-pot* desilylation in the preparation of functionalized arylacetylenes as well as at introducing acetylene fragments in heterocyclic systems was demonstrated [149, 151–154, 156] (Scheme 4.2).

An effective strategy was suggested and developed for the synthesis of endiynes conjugated with various heterocycles, analogs of natural endiyne antibiotics. The synthetic approach is based on the electrophilic cyclization of *ortho*-functionalized (buta-1,3-diynyl)-arenes, as one pot procedure for the preparation of 2-ethynyl-3-iodoheteroindenes [152, 153, 156, 158] and isocoumarins [151], and the subsequent cross-coupling of the cyclization products with terminal acetylenes under Sonogashira protocol. The possibility to control regioselectivity of the introduction of various ethynyl substituents in the heterocycle and the tolerance of the developed method with respect to the multitude of functional groups are essentials advantages of the suggested approach to the synthesis of macrocyclic endiynes. The preparation of 12- and 11-membered macrocycles fused with a heterocyclic scaffold was performed for the first time using metathesis (Ring-Closing Metathesis) [153, 158]; in the synthesis of 9- and 10-membered macrocyclic endiynes Nicholas reaction was successfully utilized (Scheme 4.3). The latter compounds showed a considerable ability to damage DNA in experiments on plasmids.

Richter cyclization of ethynyl- and butadiynyl-substituted triazenes [154, 159] was applied to the preparation of fluorescent oligophenyleneethynylenes containing a cinnoline fragment and exhibiting chemosensor properties toward Pd(II) ions [154] (Scheme 4.4).

The development of new highly active heterogeneous [161] and homogeneous [163] catalysts based on acyclic diaminocarbene palladium(II) complexes for reactions of homo- and cross-coupling is one more important field of research. A fundamentally new approach was suggested for the simultaneous generation and immobilization of acyclic diaminocarbene palladium(II) complexes (ADC-Pd) on polystyrene surface [161] using the metal promoted nucleophilic addition of the NH_2 group of the benzhydrylamine resin to the isocyanide ligand in the palladium(II) complex (Scheme 4.5).

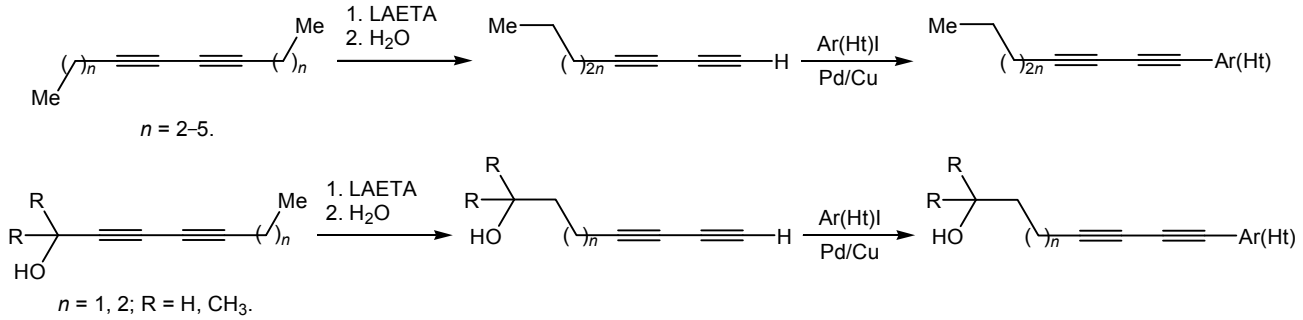
This type of heterogeneous precatalysts turned out to be effective as well in the conditions of Suzuki reaction, and in the Sonogashira cross-coupling it retained the high activity up to 8 cycles. This approach was also successfully applied to the synthesis of chiral acyclic diaminocarbene palladium(II) complex immobilized on polymer carrier [162].

The research team of **Doctor of Chemical Sciences**, **Professor A.V. Vasilyev** develops the methods of synthesis based on electrophilic activation of organic compounds under the action of Brønsted superacids, strong Lewis acids, and acidic zeolites. The principal results are compiled in reviews [164–167].

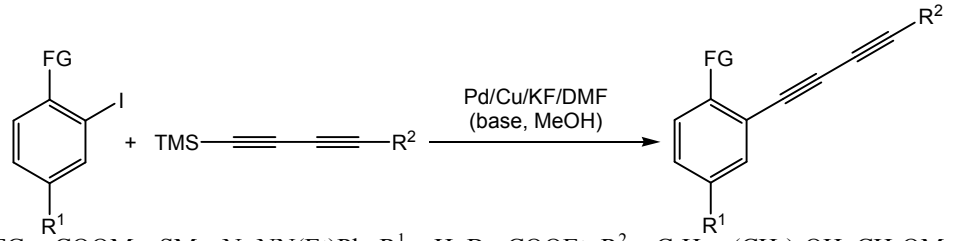
Methods were developed of arenes alkenylation and alkylation by cations generated from alkynes [168–170] and alkenes [171, 172] containing acceptor or heterocyclic substituents (Scheme 4.6). Intramolecular reactions of acetylene derivatives led to the formation of diverse carbocycles and heterocycles [165, 167, 169, 170].

In conditions of superelectrophilic activation in CF_3SO_3H 1,5-diarylpent-2-en-4-yn-1-ones (conjugated enynones) are protonated at the carbonyl group and multiple bonds affording cationic species possessing several electrophilic centers. As a result of intra- and intermolecular transformations these enynones furnish versatile indane series derivatives (Scheme 4.7) [173, 174].

Scheme 4.1.

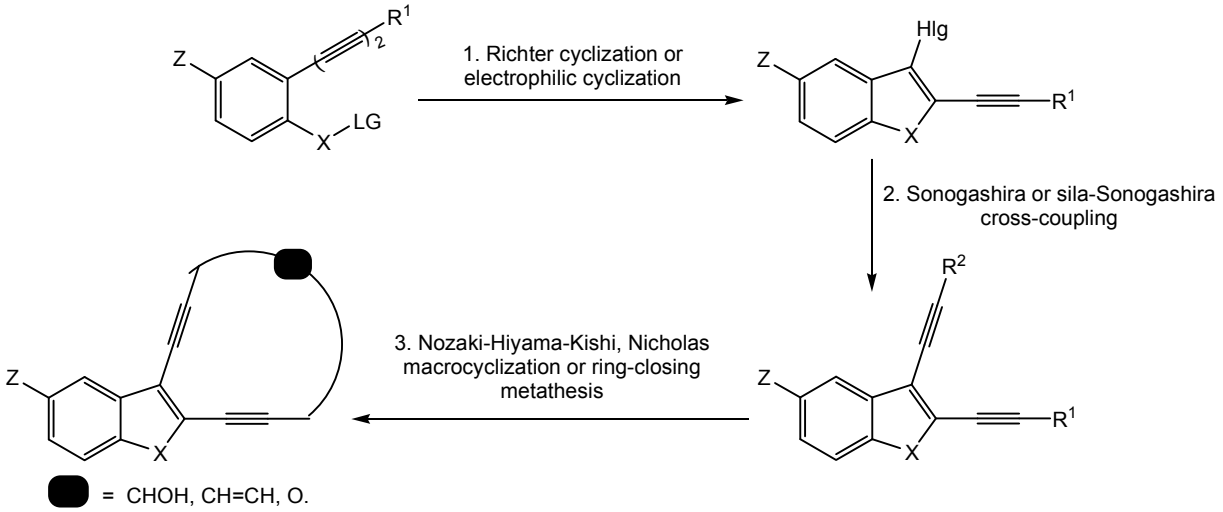


Scheme 4.2.



FG = COOMe, SMe, N=NN(Et)Ph; R^1 = H, Br, COOEt; R^2 = C_5H_{11}, $(CH_2)_2OH$, CH_2OMe.

Scheme 4.3.

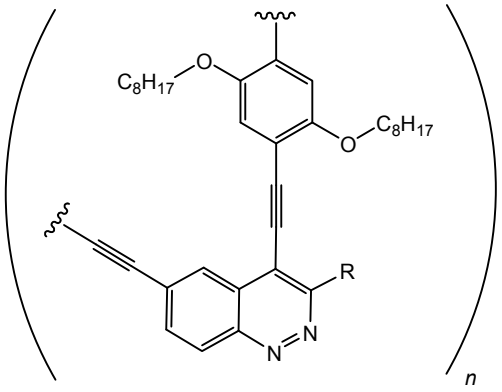


Phosphorus-containing allenes under the action of strong Brønsted or Lewis acids are converted in phosphaheterocycles and other compounds (Scheme 4.8). Cationic intermediates of these transformations are characterized and thoroughly studied by NMR methods [175–177].

The application of strong acid reagents provides a possibility to carry out versatile modifications of heterocyclic systems through reactions at the double bonds [178, 179], hydroxymethyl [180] or aldehyde groups [180, 181] in the side chains of heterocycles. For instance, proceeding from the transformations of 5-hydroxymethylfurfural (5-HMF) and 2,5-diformylfuran (2,5-DFF) a synthesis was performed of a large number of new compounds of furan series (Scheme 4.9) [180].

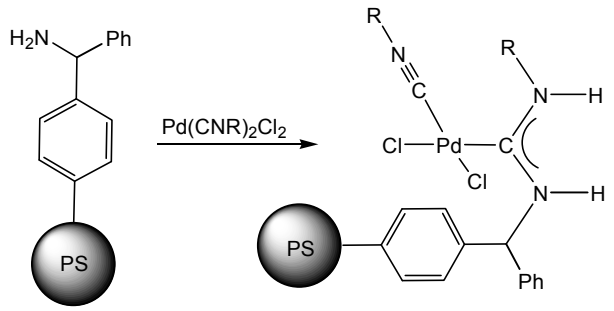
A separate direction concerns the synthesis and electrophilic activation of organofluorine compounds.

Scheme 4.4.



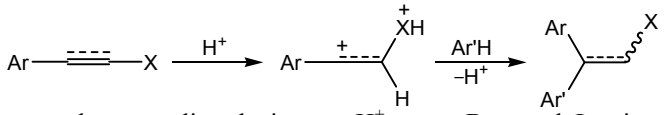
R = Bu, C_5H_{11}.

Scheme 4.5.



R = *t*-Bu, Cy.

Scheme 4.6.



X are electron-acceptor or heterocyclic substituents; H^+ means Brønsted, Lewis acids, acidic zeolites.

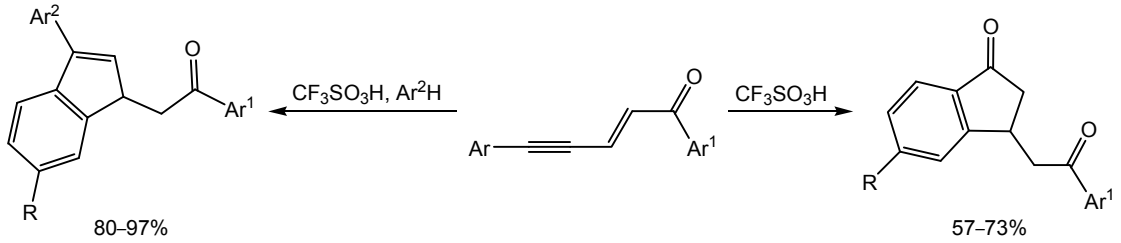
The protonation of CF_3-substituted alcohols, ketones, alkenes, and alkynes results in the generation of highly reactive carbocations whose subsequent reactions lead to the formation of fluorinated derivatives (Scheme 4.10) [168, 172, 182–185]. In the synthesized CF_3-indans their interesting biological activity was demonstrated [182].

The group led by **Doctor of Chemical Sciences**, **Professor M.Yu. Krasavin** is engaged in chemical pharmacology research: the new synthetic methods and new organic compounds are developed in so-called translational aspect, i.e. with some understanding of which biological targets may be affected by the compounds synthesized and what pharmacological effect can be expected. The principal goal pursued by this research team is to be able to recognize in the compounds synthesized the basis for biologically active compounds and to single out those methods which would maximize the chances to detect the desired biological activity. A research idea is considered realized if the following logical chain has been completed: synthetic idea → analysis of the pharmacophoric potential of the resulting compounds → practical development of the new synthetic methods → confirmation of the biological activity hypothesis → assessment of the translational potential of the structurally new chemical series (chemotype), i.e. suitability of the newly created compounds to be considered a future drug. A particular emphasis in this group is put on the development of new synthetic methodology (>50% of the group's publications in the last three years are in this area). The following principal research avenues have been developed in the Krasavin group over the last three years.

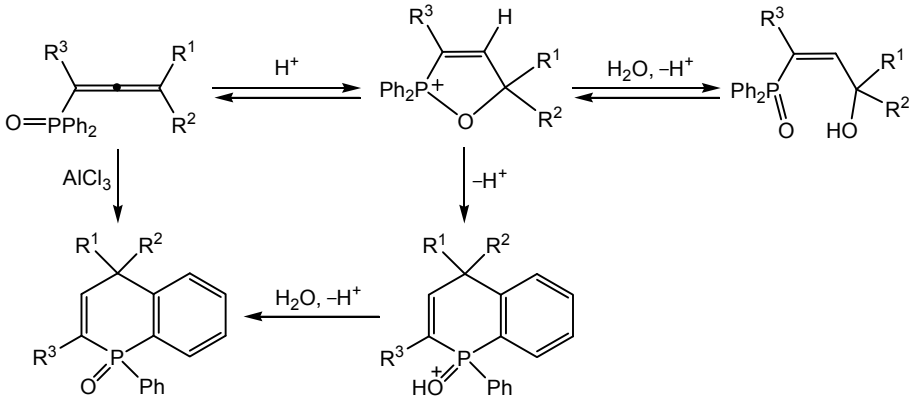
Multicomponent chemistry. The team has been investigating new aspects of the most important multicomponent reactions as well as pharmacological applications of the compounds resulting therefrom. In 2015, the scope of the formal cycloaddition between dicarboxylic acid anhydrides and imines (the so-called Castagnoli-Cushman reaction) was significantly expanded by employing in this reaction heteroatom-including anhydrides (Scheme 4.11) [186].

The same reaction (Scheme 4.12) was employed, for the first time, to synthesize ε-lactams (a privileged structure in drug design) using *o*-phenylenediacetic

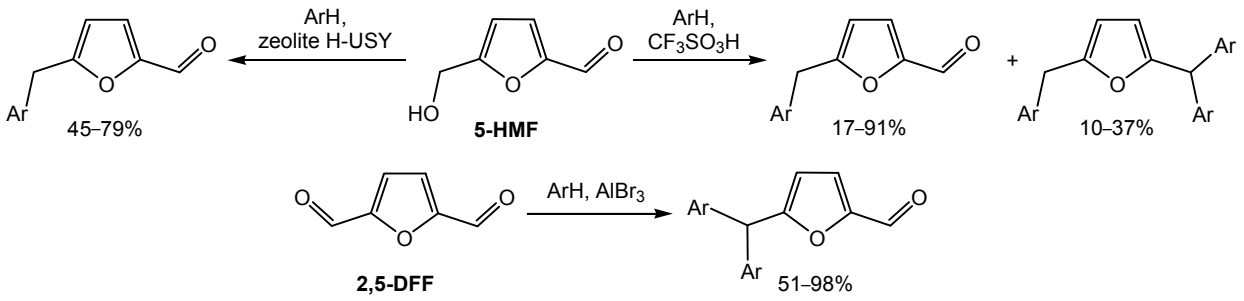
Scheme 4.7.



Scheme 4.8.



Scheme 4.9.



anhydride (earlier the reaction had been considered applicable to the synthesis of δ- and γ-lactams only) [187].

Employment in the Ugi reaction of a new type of cyclic imines – 3,3-disubstituted indolenine – followed by an intramolecular S_N2-type reaction – allowed obtaining sterically encumbered peptidomimetic structures based on the naturally occurring tetrahydropyrazine[1,2-*a*]indol-1,4-dione (Scheme 4.13) [188].

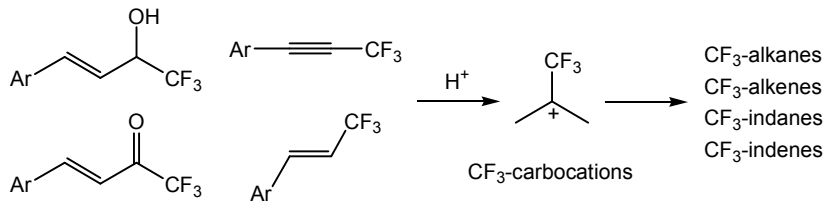
Engaging bifunctional ketocarboxylic acids in the Ugi reaction of *tert*-butoxycarbonyl-protected hydrazine afforded new type of antitubercular compounds belonging to the nitrofuran class of antibacterials, some of which turned out to be efficacious against multidrug-resistant strains of *M. tuberculosis* (Scheme 4.14) [189].

Cyclic azaketones have been shown to undergo the Prins reaction in 75% sulfuric acid (Scheme 4.15) [190]. The method represents a distinctly attractive alternative to the earlier described approaches employing expensive Lewis acids.

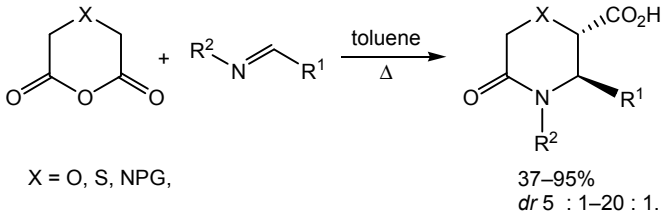
Using such an approach to spirocyclic amino alcohols allowed synthesizing a new highly active agonist of the free fatty acid receptor GPR40 via reductive alkylation reaction (Scheme 4.16) [191].

N-Arylation of 2-imidazolines. In 2012, the Krasavin group developed a new method for palladium-catalyzed *N*-arylation of 2-imidazolines (Scheme 4.17) [192]. A substantial limitation of this reaction was the possibility to employ only electron-deficient aromatic and heteroaromatic halides. Despite this obstacle, the reaction has already found a number of pharmacological applications, illustrative of which is the synthesis of selective human protein kinase inhibitors [193].

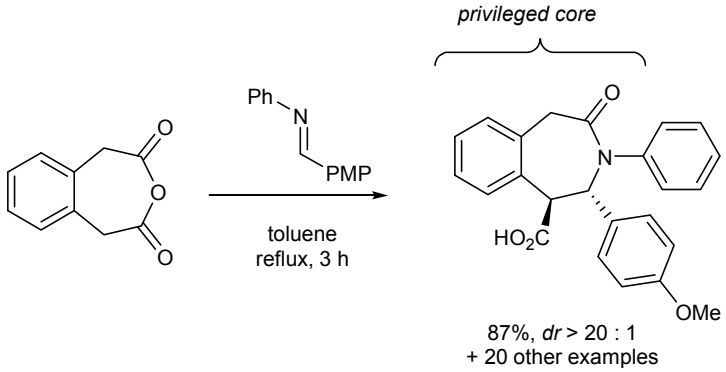
Scheme 4.10.



Scheme 4.11.



Scheme 4.12.



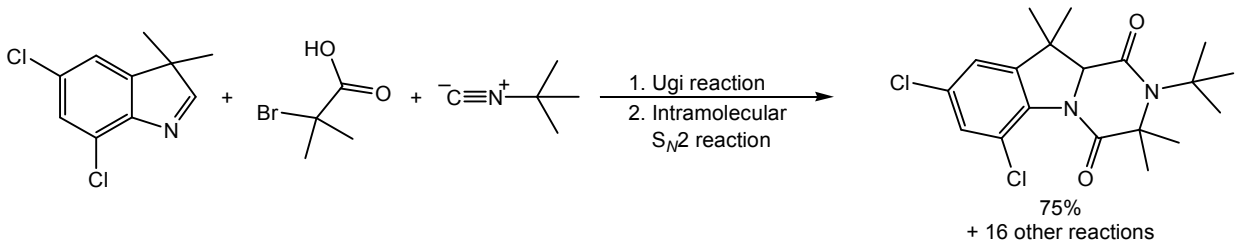
The aforementioned limitation of the Pd-catalyzed *N*-arylation of 2-imidazolines was successfully overcome in 2016, when this research team developed an alternative method for 2-imidazoline *N*-arylation employing the copper-catalyzed Chan-Evans-Lam protocol employing arylboronic acids (Scheme 4.18) [194].

New strategies to synthesize medium-sized ring compounds. Medium sized rings are widely represented in natural compounds but are severely lacking in the modern arsenal of synthetic compounds for biological activity discovery. Their synthesis is generally considered difficult due to entropic obstacles for the formation of such cycles. A productive strategy to obtain such cyclic compounds is the ring expansion reactions of substrates containing smaller rings. The Krasavin group is developing one such approach – the hydrolytic imidazoline ring expansion (dubbed HIRE). The validity of the HIRE protocol was for the first time demonstrated for tetracyclic benzazepines containing a fused imidazoline moiety (Scheme 4.19) [195].

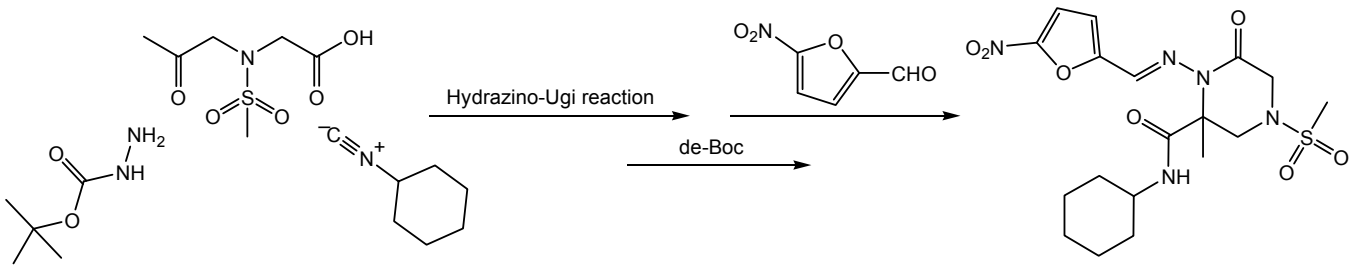
The studies of the research team of the head of the **Department of organic chemistry**, **Doctor of Chemical Sciences**, **Professor M.A. Kuznetsov** were related traditionally to two directions: chemistry of organic hydrazine derivatives and synthesis of versatile nitrogen heterocycles. Recently three previously unknown cyclopropylhydrazines were synthesized and their properties were investigated [196], and also *N*-aminosaccharin was prepared and explored [197] (Scheme 4.20).

An attention was paid to the synthesis of *N*-aminoaziridine derivatives by the method of oxidative aminoaziridination (the works were compiled in a survey [198]), and to the transformations of the obtained products. For instance, the phthalimido-aziridination of arylideneindandiones furnished spiroaziridines that were studied under thermolysis

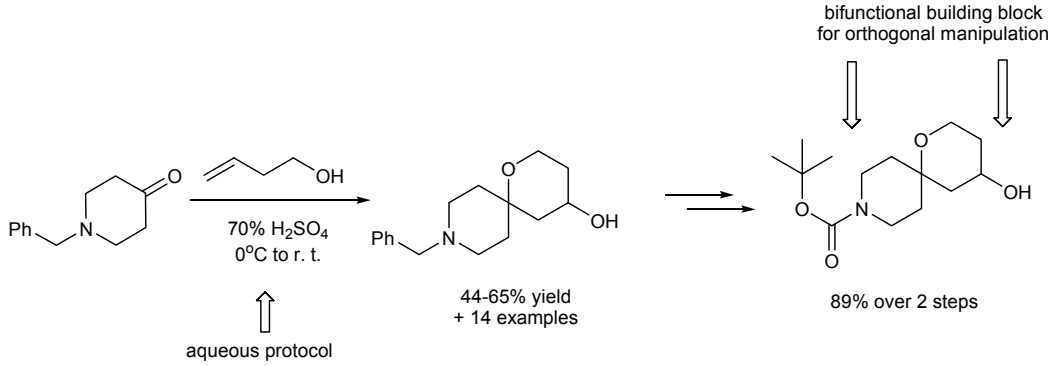
Scheme 4.13.



Scheme 4.14.



Scheme 4.15.



conditions in 1,3-dipolar cycloaddition reactions and transformations in oxazoles (Scheme 4.21) [199].

Three step synthesis was developed for 5-ethynyloxazoles from the derivatives of acrylic acids where the key stage was the electrocyclization of azomethine ylides generated thermally from the products of aziridination of 5-(trimethylsylyl)pent-1-en-4-yn-3-ones (Scheme 4.22) [200]. At the same time the phthalimidoaziridination of imines of unsaturated carbonyl compounds does not result in the expected imidoylaziridines or imidazoles but in the products of deeper transformations, pyrazolines [201].

A thermal rearrangement was explored of 2,3-diaryl-1-phthalimidoaziridine into imines [202] as well as the oxidative addition of *N*-aminophthalimide to 2-vinylfuran derivatives occurring at the endocyclic double bonds and leading to the ring opening into monophthaloylhydrazones of hexa-2,5-diene-1,4-diones (Scheme 4.23) [203].

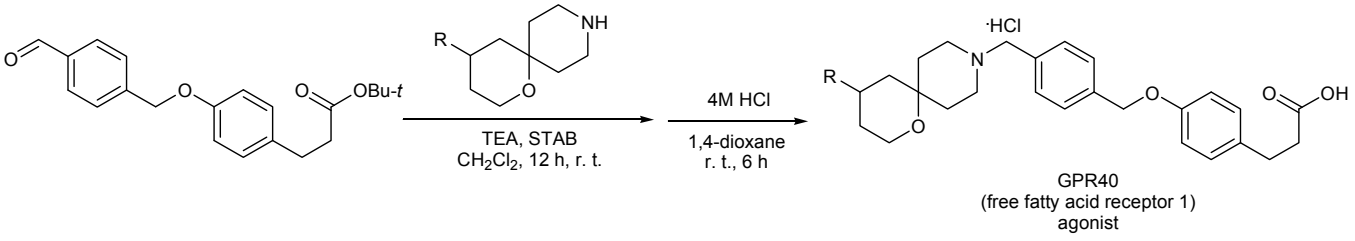
A procedure was developed of the preparation of 5-ethoxy-1-(trimethylsilyl)pent-1-en-4-yn-3-ones and their reactions were studied with a number of nitrogen nucleophiles resulting in the elaboration of new synthesis methods for a series of ethynyl- [204–206] and methylene-substituted heterocycles (Scheme 4.24) [207].

A possibility was shown of acid-catalyzed cyclization of the *ortho*-aryl(ethynyl)pyrimidines into benzo[*f*]quinazolines and spiro-fused tricyclic heterocycles (Scheme 4.25) [208].

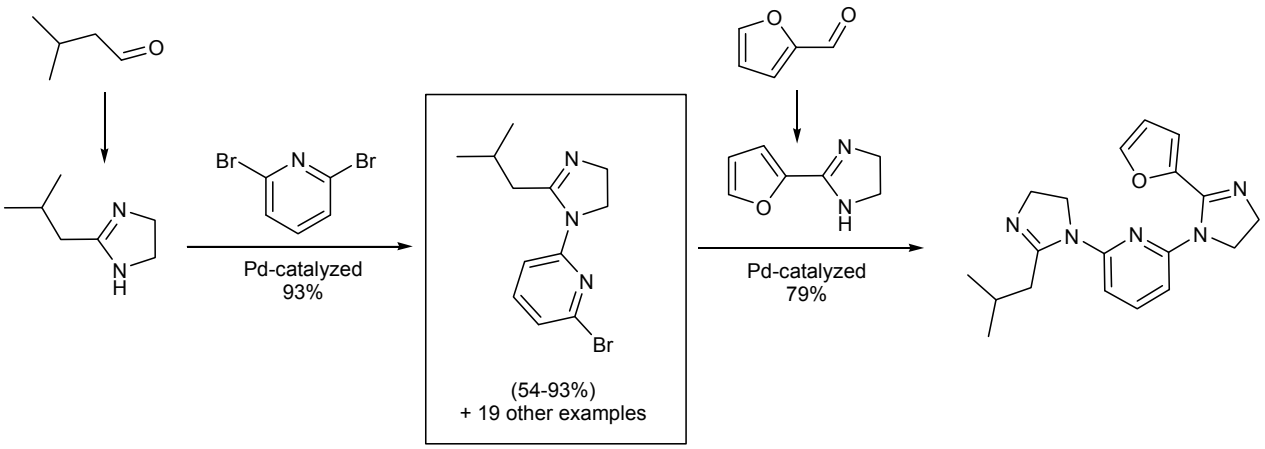
A procedure was developed of a selective pyrroles formylation into the position *3* by bringing sterically loaded formamides in Vilsmeier–Haack reaction [209]. The regioselectivity was studied of the reaction between unsymmetrical thioureas and maleic acid derivatives and the tautomerism of products in the solution [210, 211].

Highly functionalized bi-and tricyclic sultams were synthesized (Doctor of Chemical Sciences, Assistant-

Scheme 4.16.



Scheme 4.17.

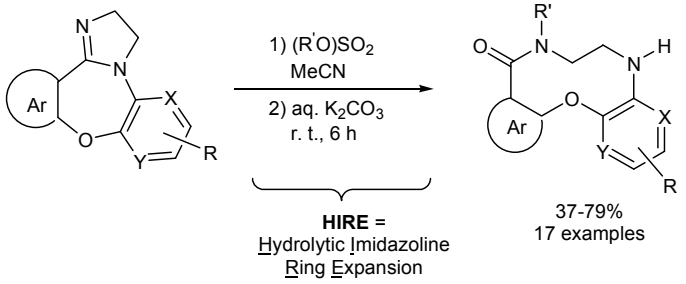


Scheme 4.18.

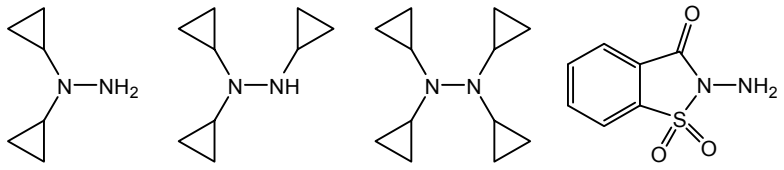
Professor V.V. Sokolov) (Scheme 4.26). These products are interesting as potential sulfamide compounds of new type [212–215].

The general direction of the research of Candidate of chemical sciences, Assistant-Professor P.S. Lobanov is the investigation of methods of synthesis, reactivity, and biological activity of five- and six-membered aromatic nitrogen heterocycles. As a result of the investigation of cyclocondensation of enediamines and enamines containing electron-acceptor groups with diverse types of aromatic dielectrophiles new convenient synthetic procedures were found for isoquinolines, indoles, cinnolines, as well as some their azaanalogs. For the first time a new type of *peri*-fused heterocycles was obtained: pyrimido[4,5,6-*de*][1,8]naphthiridines [216–223]. This research is summarized in reviews [224, 225]. The detailed exploration of the rearrangement of vinyl ethers of α-acylacetamidoximes revealed the synthetic opportunities and limitations of the reactions as the

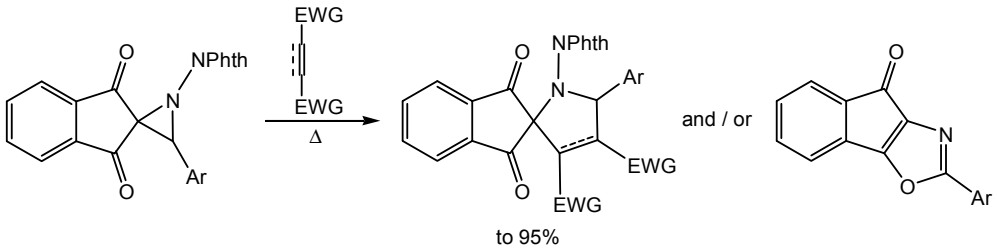
Scheme 4.19.



Scheme 4.20.

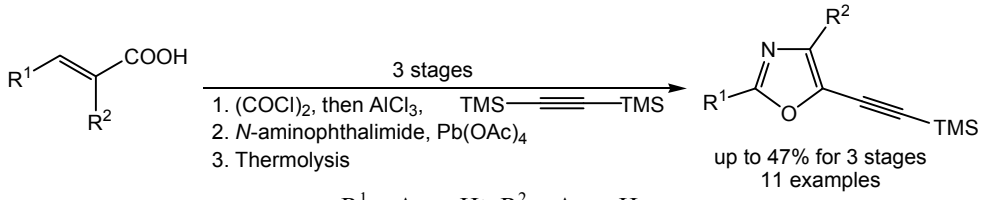


Scheme 4.21.



PhthN = phthalimido.

Scheme 4.22.



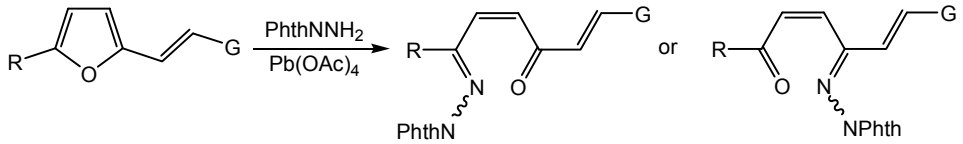
R^1 = Ar or Ht; R^2 = Ar or H.

method of 2-aminopyrroles preparation [226]. In collaboration with the team of Doctor of Biological Sciences A.O. Shpakov from the Sechenov Institute of Evolution Physiology and Biochemistry of the Russian Academy of Sciences the effect of structural factors was studied on the ability of new thienopyrimidine derivatives to activate the adenylate cyclase and affect the testosterone level [227–229]. A compound was found among the thienopyrimidines exhibiting a higher activity than the previously described species.

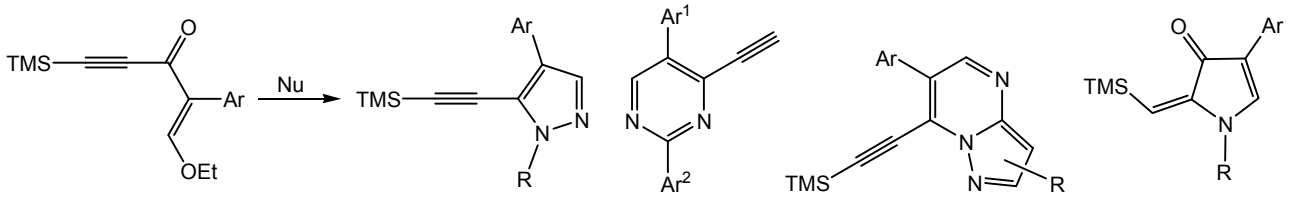
Among directions under study at the department for a long time is the chemistry of compounds with strained small rings. Within this subject the group of **Doctor of Chemical Sciences**, **Professor A.P. Molchanov** investigated the reactions of *N*-acyliminium cations with cyclopropenes. In the reaction of cyclopropenes with 1-aryl-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones formed both the products of formal cycloaddition, cyclopropa[*c*]isoindolo[2,1-*a*]-quinoline-1-carboxylates and the products with the three-membered ring opening, 3-(1*H*-inden-3-yl)-isoindolines (Scheme 4.27). A number of compounds obtained exhibit fluorescence [230].

Also the reactions of cyclopropene compounds with azomethine ylides generated from isatin and amino acids were studied for the first time. The derivatives of 2,3-diphenylcycloprop-2-ene-1-carboxylic acid, 1,2,3-triphenylcyclopropene, as well as 3,3-diphenylcyclo-propene were brought into the reaction (Scheme 4.28). This procedure is a good tool for the synthesis of fused

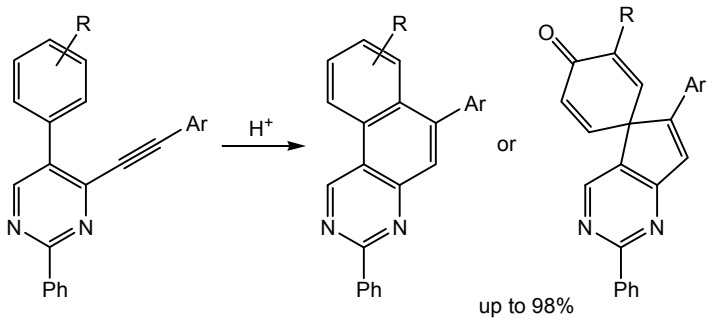
Scheme 4.23.



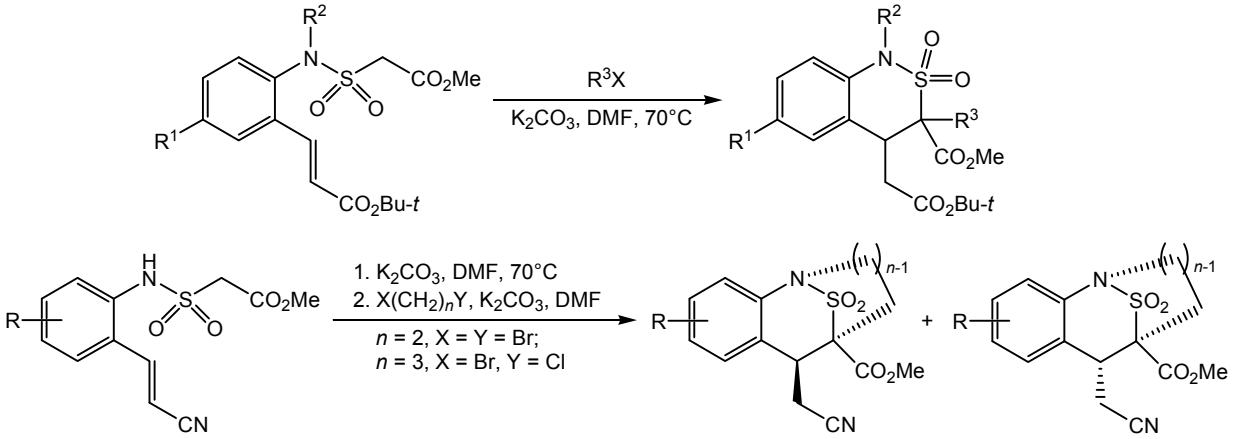
Scheme 4.24.



Scheme 4.25.



Scheme 4.26.



polycyclic systems with a cyclopropane fragment [231].

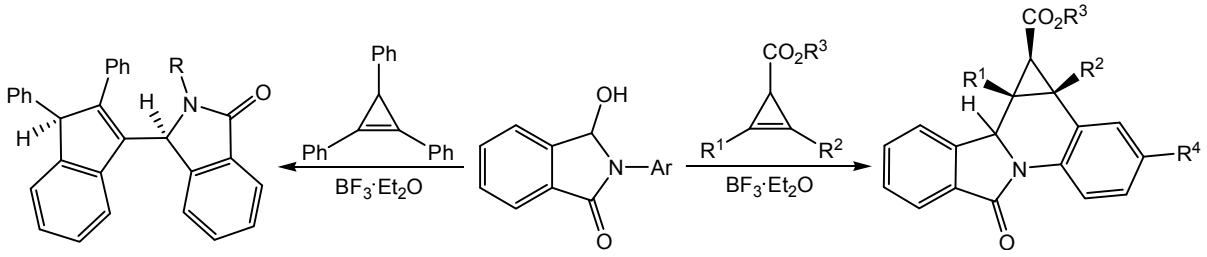
Pyrrolo[2,1-*a*]isoquinoline fragment is the basic part of erythrine alkaloids possessing anticancer, antibacterial, and antitumor activity as well as antiviral, antidepressant, and antioxidant properties. One of the widely spread methods of synthesis of these compounds is 1,3-dipolar cycloaddition of isoquinoline *N*-ylides to activated alkynes or olefins and the cyclization of acyliminium cations. The subject of studies were intramolecular reactions involving highly reactive *N*-acyliminium cations generated from hydroxypyrrolo[3,4-*d*]isoxazolones included in fused or spiro-fused heterocyclic systems (Scheme 4.29). The necessary hydroxypyrrolo[3,4-*d*]isoxazolones were synthesized from substituted maleimides or itaconimides by cycloaddition of nitrile oxides followed by the reduction of one carbonyl group. The regio- and stereoselectivity of reactions and the limits of the approach were established [232–234].

Pyrrole and indole fragments are also significant structural components of natural compounds possessing a wide range of pharmacological properties. This motivated the study of 1,3-dipolar cycloaddition to *N*-vinylpyrroles of nitrones, azomethine imines, and nitrile oxides. The application of various catalysts, in particular, Lewis acids made it possible both to increase the regio- and stereoslectivity of the [3+2]-process and to turn it into formal [3+3]-cycloaddition (Scheme 4.30) [235–237].

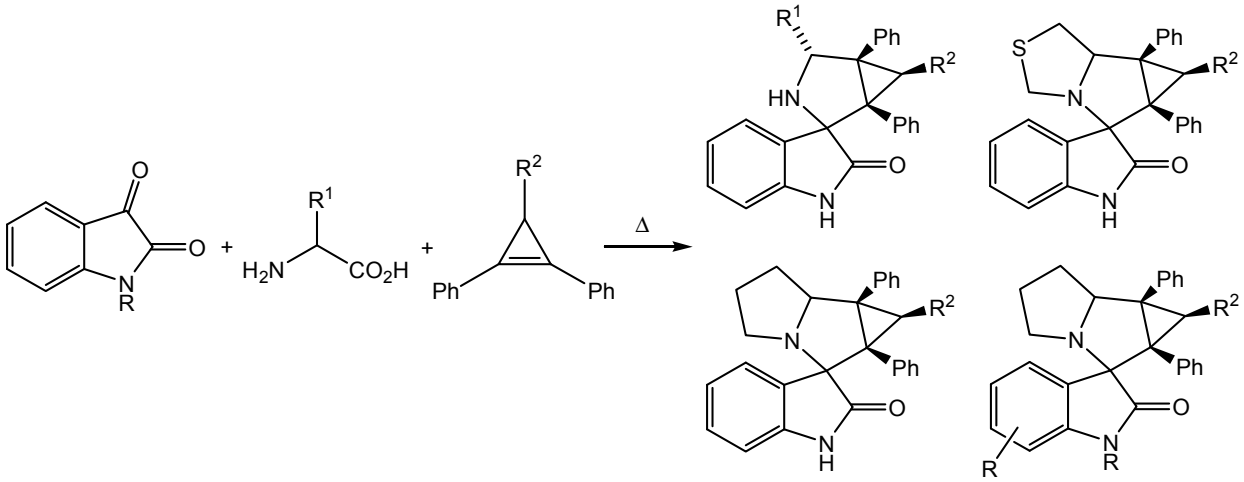
The research of scientific team under the supervision of **Doctors of Chemical Sciences**, **Professors V.A. Nikolaev** and **L.L. Rodina** develops in several directions including the study of polyfunctional diazocarbonyl compounds chemistry (DCC) in the ground and excited states, and also the synthesis of practically important molecules based on this research. In particular, they involves the study of reactions of previously unknown fluoroalkyl-containing diazodi-ketones (F-DCC) in the synthesis of fluorinated heterocyclic compounds, the investigation of DCC transformations catalyzed with transition metals (Rh, Cu, Ru) complexes or with Brønsted acids, looking for the new light-induced reactions of DCC, examination of their mechanism, and possibility of employment in synthetic practice.

The main purpose of research in the first direction consists in the development of the efficient methods

Scheme 4.27.



Scheme 4.28.



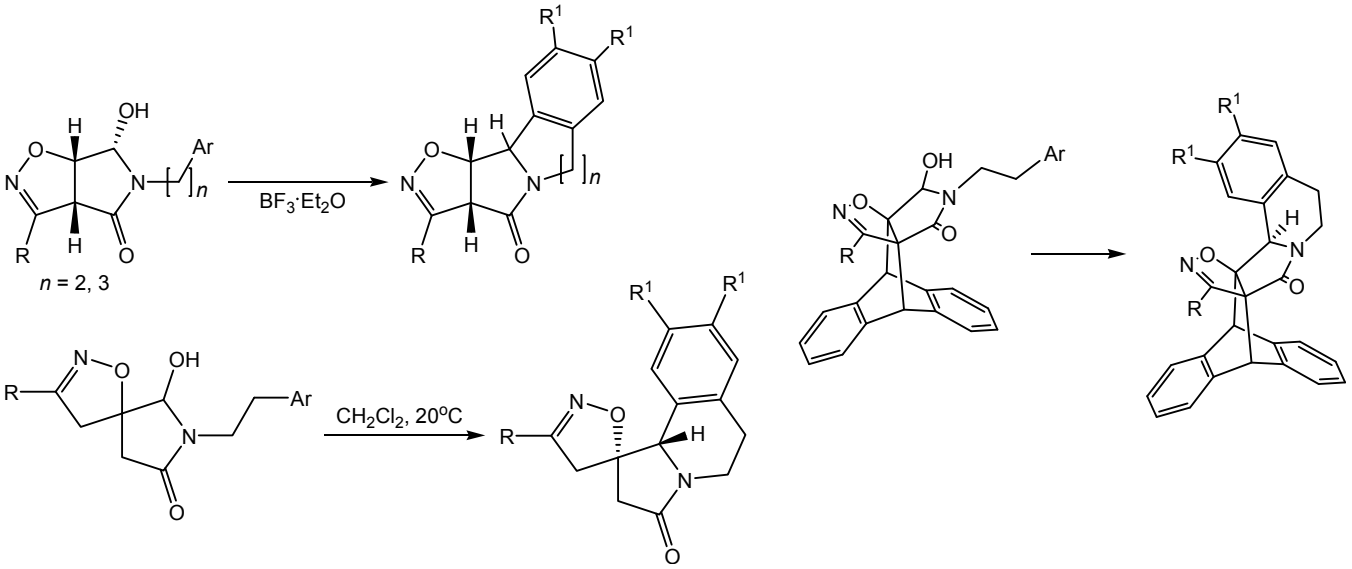
for the synthesis of new F-DCC and designing development therefrom of previously unavailable fluorinated heterocyclic molecules (Scheme 4.31) [238–242]. The studied F-DCC contain in their structures a fairly reactive CF_3CO fragment, which supplies them with opportunity to readily enter in reactions nontypical for DCC, in particular, in [2+2]-cycloaddition at the carbonyl group, and also in Wittig reaction. The first process allows preparation of fluoroalkyl containing pyrazoles [239], the second reaction proved to be a convenient synthetic approach to fluorinated vinyldiazocarbonyl compounds (F-VDCC) possessing a large synthetic potential (Scheme 4.31) [238–242].

As a result of the accomplished research it was established that the Rh(II)-catalyzed decomposition of F-VDCC led to intra-molecular [1,5]- and [1,3]-electrocyclization with the formation of CF_3-substituted thiophenes and cyclopropenes. The latter have a high reactivity and easily undergoes in further transformations (e.g., [4+2]-cycloaddition with diverse dienes) [240]. Thermal decomposition of F-VDCC furnishes mainly the transformation products of the formed carbenes [239]. In the presence of phosphines F-VDCC undergo either a direct or light-induced (due to the *E/Z*-isomerization) Wittig *diaza*-reaction resulting in the formation of fluoroalkyl-substituted pyridazines [238, 243].

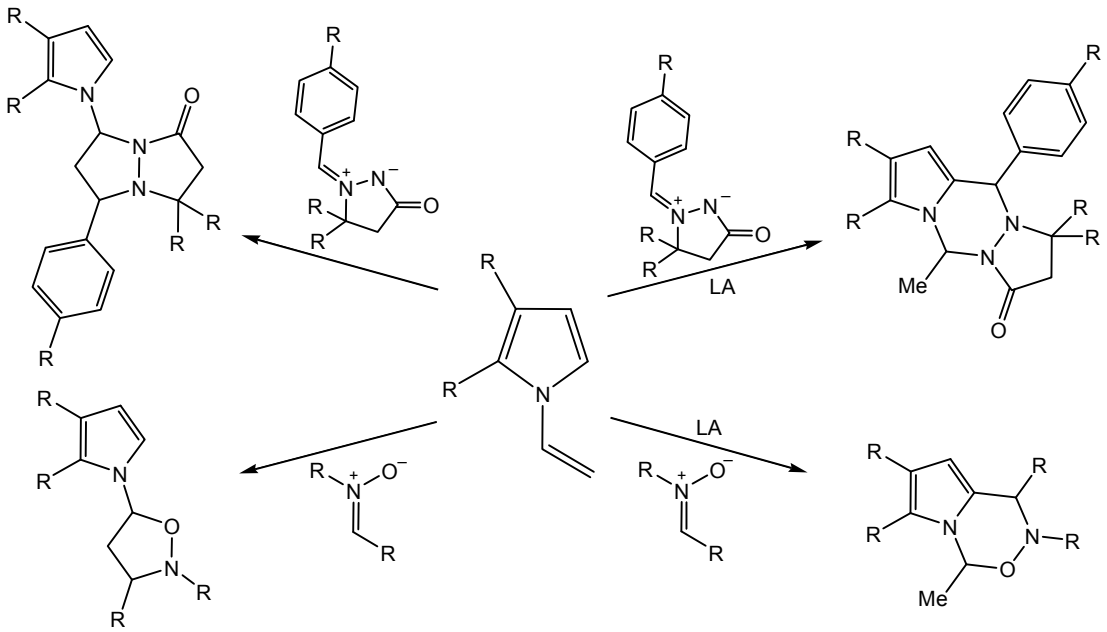
Another direction of this group research consists in exploring the main relationships governing the reactions of intermediate metal-carbenes and ylides generated at the catalytic decomposition of diazo compounds with polyfunctional amines, imides, sulfonimides, and other substrates containing in the structure of the molecule *N*, *O*, *S*-heteroatoms. These reactions attracted much attention, and in recent years a wide range of *intermolecular* reactions of *N*- and *O*-ylides with a series of electrophiles (C=O, C=N, and also with activated multiple bonds) have been studied extensively [244]. At the same time analogous *intramolecular* transformations providing the possibility to prepare various heterocyclic structures remain practically unexplored. To fill this gap a careful study was performed on the regularities of the Rh(II)-catalyzed reactions of diazo compounds with polyfunctional amines and thioamides containing in their structure additional electrophilic fragment. This research provided new efficient approaches to *N*- and *S*-heterocyclic structures (Scheme 4.32) [245, 246].

Alongside catalytic reactions thermal transformations of diverse class diazo compounds in reactions

Scheme 4.29.



Scheme 4.30.

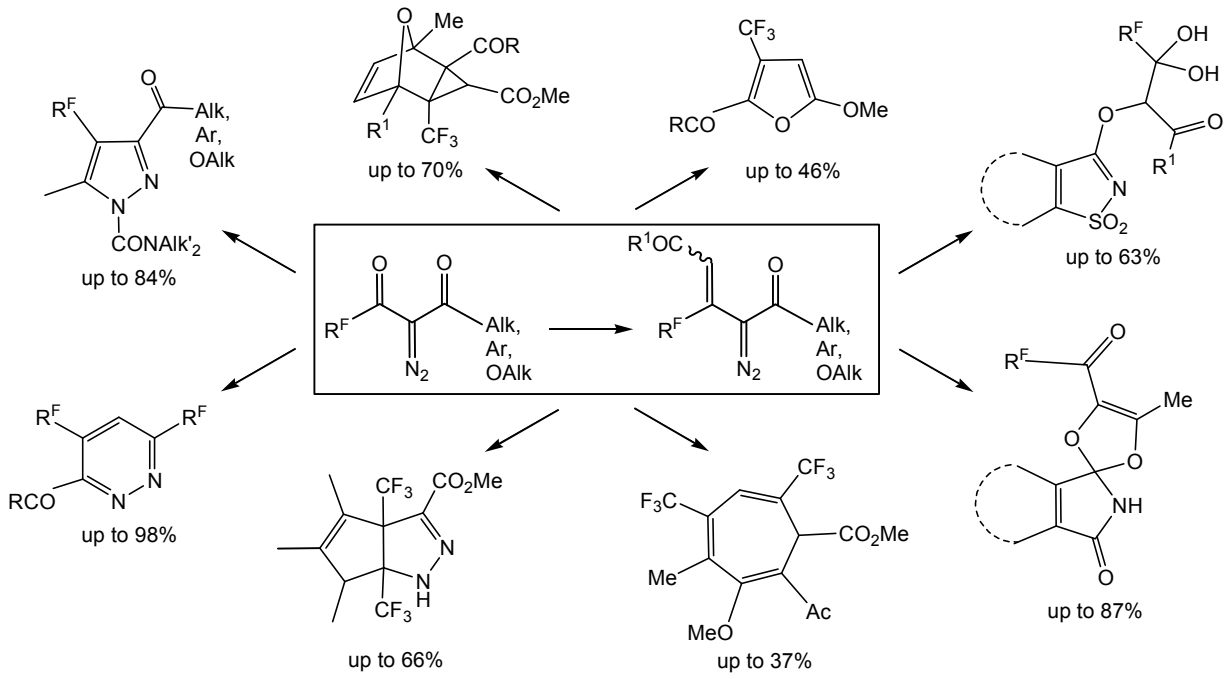


with polyfunctional amines in the presence of NaH were also explored. These processes were found to be a convenient synthetic approach to the structure of complex fused heterocyclic systems (Scheme 4.33) [247].

The transformations of DCC catalyzed by acids (same as thermal ones) are rarely used in the synthetic organic chemistry. Nevertheless, in the case of diazoketones of THF series the catalysis of strong Brønsted acids (or the thermolysis at high temperature) led to the formation of 3(2*H*)-furanones in virtually quantitative yields (Scheme 4.34). The obtained 3(2*H*)-furanones with 1,2-diaryl fragment and 4-SO_2X substituent in one of the rings are inhibitors of COX-2 enzyme and exhibit a high anti-inflammatory activity (NSAIDs) [248–250].

In the course of the studies on DCC reactions in the excited state the formation of the main intermediates was experimentally confirmed that were presumed to be formed on the way from the initial diazocarbonyl compounds to the products of their photochemical transformations, among them diazirines, carbenes, ketenes, ylides. The investigation of DCC photoche-

Scheme 4.31.



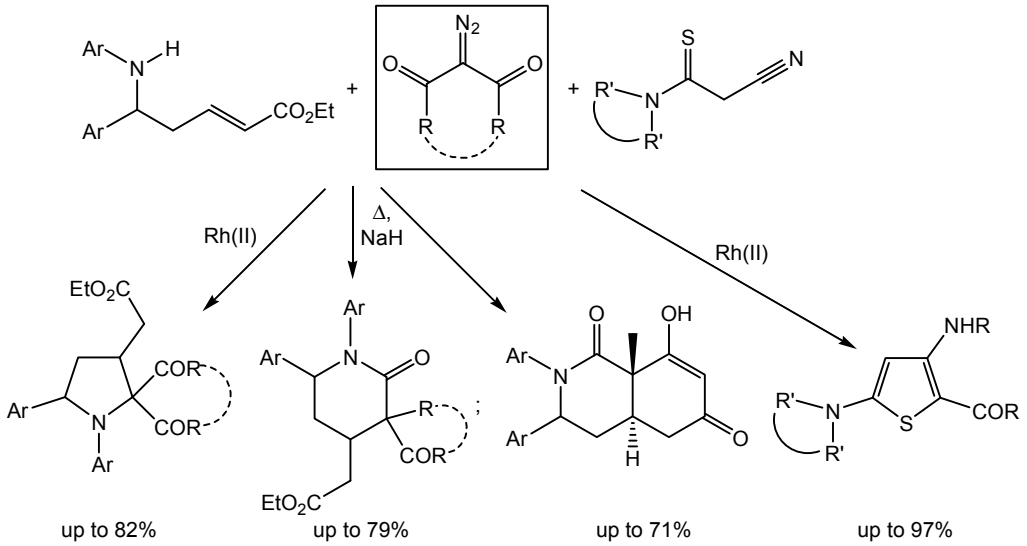
mical reactions and the identification of the intermediates of these processes is carried out together with colleagues from the Laser center of Saint Petersburg State University. One of the most recent achievements of the research team along this line is the development of a new method for the *N*-functionalization of the C–H bond in various organic substrates with the help of recently discovered photochemical reaction of DCC occurring without nitrogen elimination which provides a possibility to insert essentially a whole diazo compound molecule into the structure of the C–H-donor [251–253].

The research group of **Doctor of Chemical Sciences**, **Professor M.S. Novikov** develops new approaches to the synthesis of 4–6-membered *N*-, *N*,*O*-, and *N*,*N*-heterocycles through azapolyene intermediates. Azapolyene synthetic blocks did not attract much attention lately in the field of heterocyclic chemistry and were regarded exclusively as substrates for a limited range of [4+2]-cycloadditions. Yet in the last decade quite a number of new transformations were discovered of these highly unsaturated compounds resulting in a sharp change in the attention to these substances. The interests of the research group were focused on the new transformations of aza-, oxaza-, and diazapolyenes (Scheme 4.35) as well as their metal analogs which turned to be unique intermediates in the syntheses of various *N*-, *N*,*O*-, and *N*,*N*-heterocycles. The chemistry of these intermediates is tightly connected with the chemistry of 2*H*-azirine and isoxazole systems. The last advances of the latter are described in detail in three reviews published in collaboration by research teams of Professor A.F. Khlebnikov and Professor M.S. Novikov [254–256].

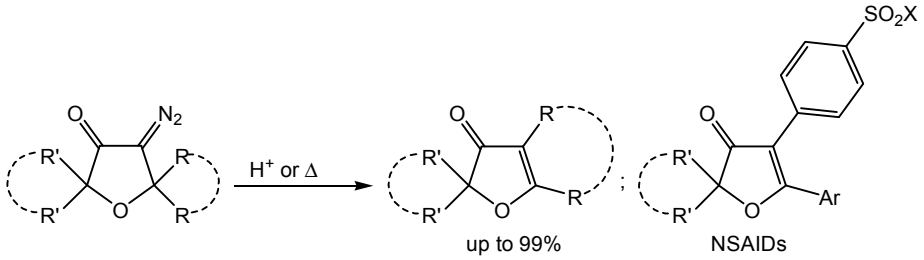
A powerful acceleration of the growth of the chemistry of these compounds was produced by the development of a convenient method of their preparation/generation by carbenoid mediated opening of azirine or isoxazole rings [255]. Since under certain conditions the interconversion isoxazole-azirine may be effectively performed the application of this method always permits the choice between these substrates accounting for their relative accessibility, stability, specific reactivity, tolerance to the substituents, etc. [256].

Heteropolyenes may either be relatively stable compounds or reactive intermediates generated *in situ*. The presence of one or more electron withdrawing groups in these heteropolyenes governs their propensity both to reactions with nucleophilic reagents and to thermal and catalytic cyclization. Heterocyclic systems shown in Scheme 4.35 are formed either through 1,4-, 1,5-, 1,6-cyclization of the heteropolyene or through a domino sequence “1,5-prototropic shift/1,2-prototropic shift/1,5-cyclization”.

Scheme 4.32.



Scheme 4.33.

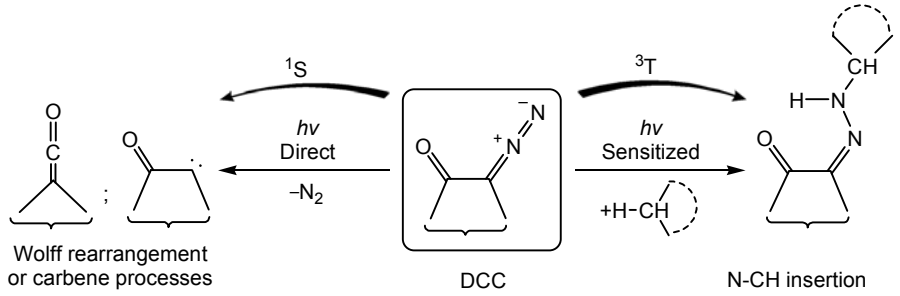


R = Ar; R' = Alk, Ar, cycloalk.

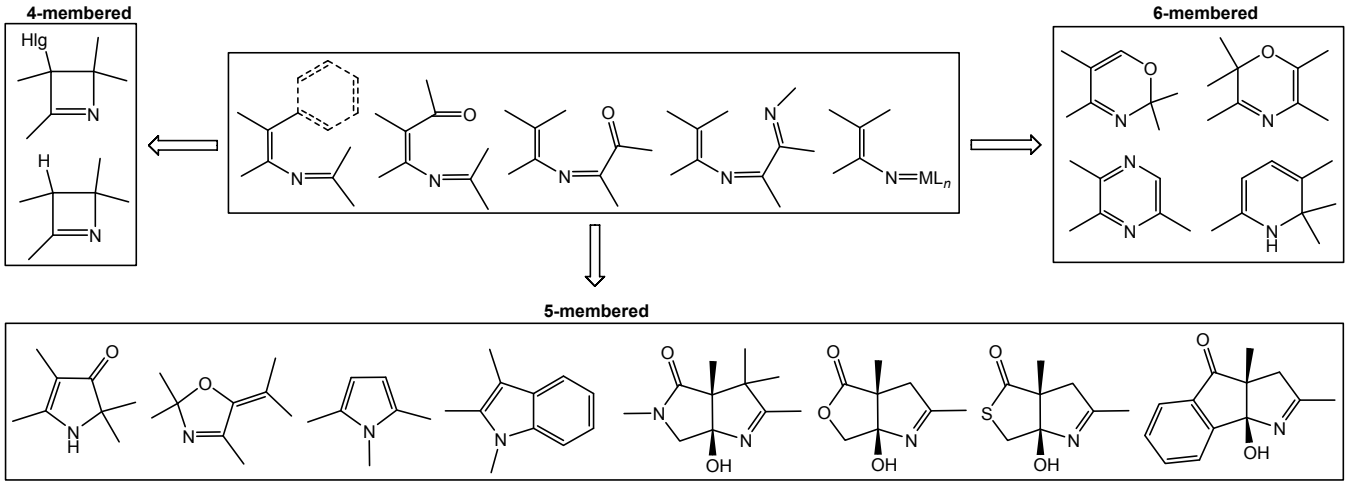
The 1,4-cyclization to 2,3-dihydroazetes is characteristic of 4-halo-substituted 2-azabuta-1,3-dienes obtained from diazo compounds and 2-haloazirines or their isomers, 4-haloisoxazoles, under catalysis with $Rh_2(OAc)_4$ (Scheme 4.36) [257]. The cyclization is reversible and proceeds at heating. An original procedure of the synthesis was developed for thermally stable non-halogenated dihydroazetes by treating an equilibrium mixture of brominated 2-azabutadiene and dihydroazete with tributylstannane in the presence of azobisisobutyronitrile [258]. A wide series of non-halogenated dihydroazetes was prepared, and some of them showed a high antitumor activity with a high apoptosis and low necrotic potential on a cell line of human monocyte leukemia THP-1 [258]. At the presence of an enolized acyl group at the C^1 atom of the azabutadiene along with 1,4-cyclization at boiling in dichloroethane a concurrent 1,5-cyclization to oxazolines is observed that becomes the only process at the temperature above 100°C or in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene.

1,5-Oxazahexa-1,3,5-trienes generated by the Rh(II)-catalyzed reaction of diazoesters with 2-formyl-

Scheme 4.34.



Scheme 4.35.



substituted azirines [259] or isoxazoles [260] proved to be convenient precursors of just two heterocycle classes: 2*H*-1,3-oxazines and 1*H*-pyrrol-3(2*H*)-ones (Scheme 4.37) [261]. Every one of these compounds may be prepared as a rule in a high yield by varying only two reaction parameters: temperature and solvent. Pyrrole derivatives are formed nearly quantitatively at high temperature from obtained oxazines, and according to DFT calculations the isomerization occurs through successive 1,5-prototropic shift, 1,2-prototropic shift, 1,5-cyclization involving imidoylketene and azomethine ylide intermediates.

Method of synthesis developed in 2013 for non-fused 2*H*-1,4-oxazines consisting in 1,6-cyclization of 1,4-oxazahexa-1,3,5-trienes generated from azirines and diazoketoesters [261] or diazoketones [262] in the presence of $Rh_2(OAc)_2$ remains still practically the only plausible method of their preparation (Scheme 4.38) [263].

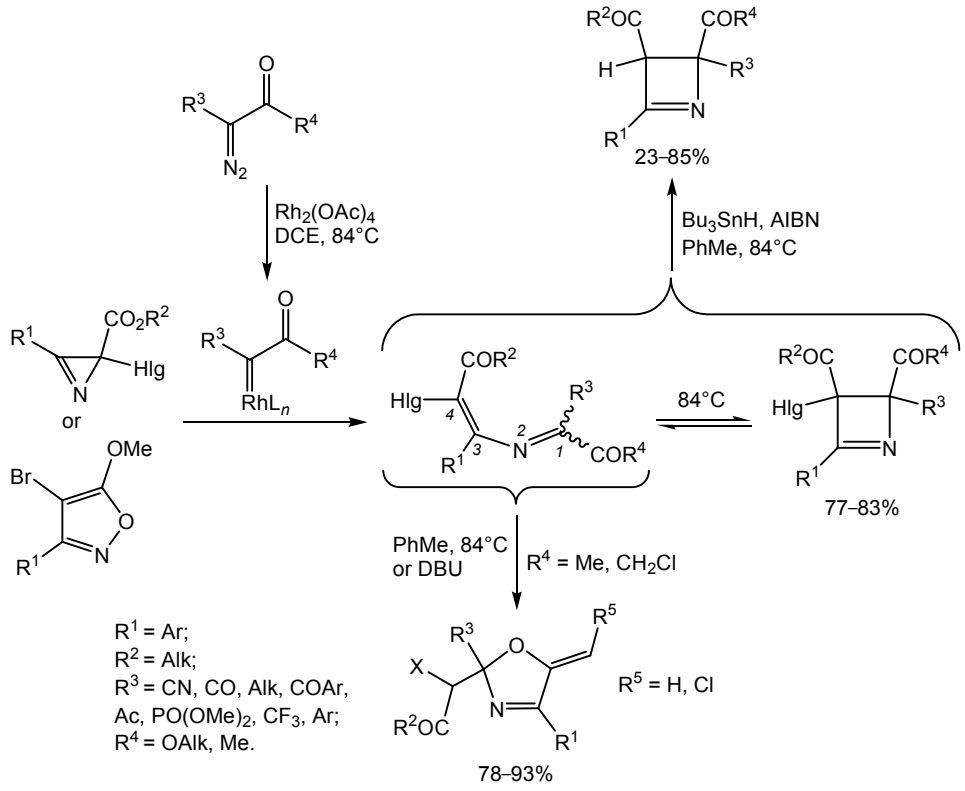
Recently a thermal 1,5-cyclization of 4(*Z*)-aryl-substituted 2-azabutadienes was discovered which had underlain the synthesis of indoles from azirines or 2*H*-1,4-oxazines (Scheme 4.39) [264]. According to DFT calculations for this cyclization a pseudopericyclic mechanism was postulated [264]. Such cyclizations proceeding through an azomethine-ylide intermediate is sufficiently general and is characteristic also of 2-azahexa-1,3,5-trienes [265] and 1,4-diazahexa-1,3,5-trienes [266] that undergo cyclization into pyrrole derivatives.

The application of rhodium iminocarbenoids for the generation of azopolyene intermediates opens interesting prospects for the synthesis of new pyrazine and 3-aminopyrrole derivatives. To implement the "iminocarbenoid" scheme of the synthesis of 1,2-dihydropyrazines and pyrazines the isoxazole and not aziridine substrates should be used. The former make it possible to generate exclusively 5(*Z*)-1,4-diazahexatrienes prone only to 1,6-cyclization into dihydropyra-zoles (Scheme 4.40) [266]. In this reaction azirines predominantly yield 5(*E*)-isomeric 1,4-diazahexatriene which are characterized by 1,5-cyclization in 3-aminopyrroles [266].

The use of metal analogs of azapolyenes, Cu(I)- and Cu(II)-vinylnitrene complexes, is one more direction where 2*H*-azirines may be successfully utilized as N–C–C synthetic blocks for the formation of new heterocyclic systems. An uncommon Cu(II)-catalyzed reaction was described in [267]: the coupling of 3-arylazirines with diazotetramic and diazotetronic acids where derivatives of triazole were formed with *ortho*-and spiro-fused bicyclic substituents at the atom N^2 (Scheme 4.41). This reaction is the first example of the formation of 1,2,3-triazole ring from the N–N and C–C–N synthetic blocks. Later, using this reaction an effective method of annulation of 5-membered cyclic enols with azirines under Cu(I)-NHC catalysis was developed, thus providing the access to a wide range of pyrrolo-fused systems with a hydroxyl group at the bridgehead atom. [268, 269].

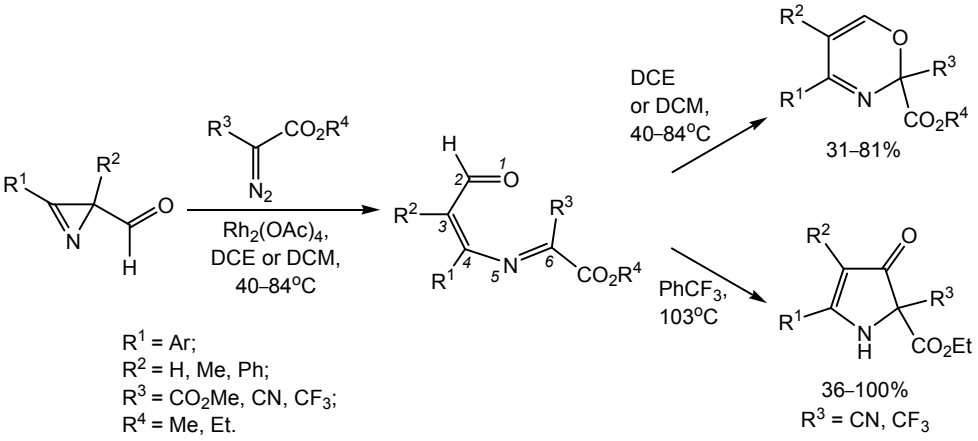
In the research team of **Doctor of Chemical Sciences**, **Professor A.F. Khlebnikov** research is carried out on the synthesis, investigation of the chemistry, and synthetic applications of azirines [254–256, 270–277] and aziridines [278–284], whose high reactivity is due to the ring strain, and also of

Scheme 4.36.

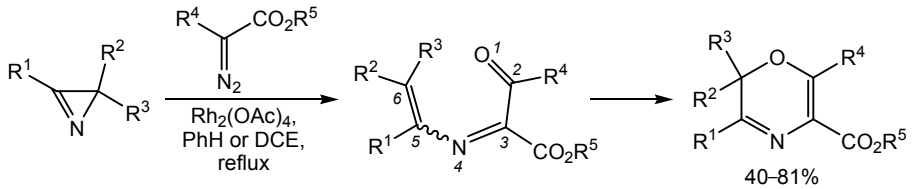


isoxazoles where the reactivity is related to a large extent to the presence of a labile N–O bond [285–289]. Various aspects of the chemistry of azirines [254–256], aziridines [278], and isoxazoles [285] are summarized in recently published surveys. The goal of the research consists in the development of new efficient sources of active ylides [275, 278, 280–284, 289–291], betaine [270, 271, 275, 277, 287, 288] and carbene [270, 271, 290, 291] intermediates for designing complex heterocyclic systems with useful properties. For the theoretical estimation of the energy characteristics of the studied reactions and equilibria, rational selection of reaction partners and elucidation of the reaction mechanisms quantum-chemical calculations were used by the method of density functional theory [270, 271, 273–277, 279, 280, 282, 283, 287, 288, 290–292]. As a result of the performed research a new strategy was established for the synthesis of 3-heterylpyrroles [277], synthetic methods were developed for new pyrrole-containing heterocyclic systems [270–277, 287–295],

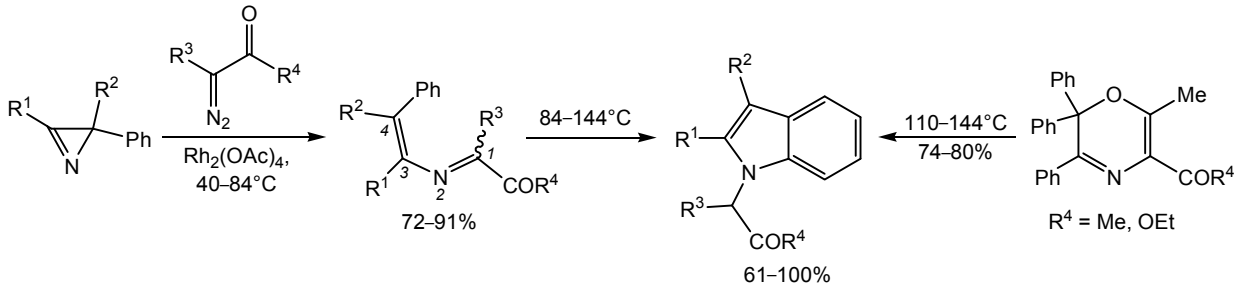
Scheme 4.37.



Scheme 4.38.



Scheme 4.39.



in particular, for those possessing fluorescence [270, 273, 287] for the application to the fluorescent bioimaging [272, 273] and as ligands for new metal complexes [270, 271, 273, 275] (Scheme 4.42).

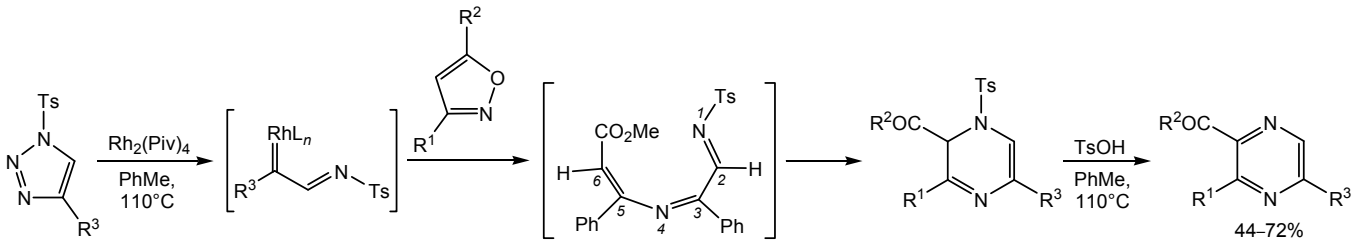
Relay multicatalytic schemes were developed for effective synthesis of nitrogen heterocycles (pyrrole [288, 289] and pyridine [286] derivatives), among the other ways, by the use of isoxazole-azirine isomerization for switching the reactivity [256] (Scheme 4.43).

Aziridine-ylide approach underlies the design of nanosize fullerene- and porphyrin-containing ensembles with the properties ensuring their application in photovoltaics and systems with nonlinear optical properties [279–284] (Scheme 4.44).

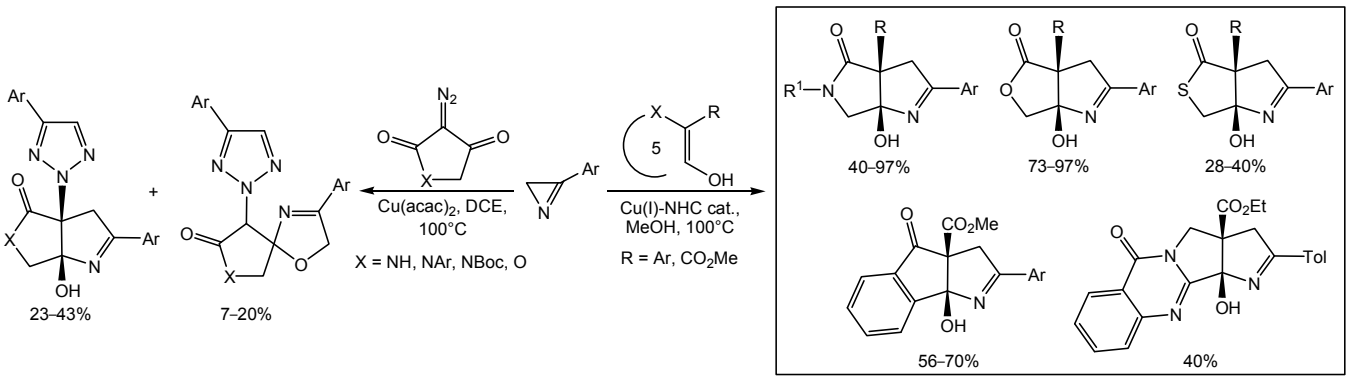
Two scientific teams out of ten at the department of organic chemistry perform research in the field of organic analysis, traditional for this department, which has started with the ***laboratory of organic analysis***, founded by **Professor I.A. Favorskaya**, and ***laboratory of gas chromatography***, founded by **Professor B.V. Ioffe**.

The research team of **Doctor of Chemical Sciences**, **Professor I.G. Zenkevich** is working in the field of chemometrics, development and refinement of chromatographic (GLC, HPLC), chromato-spectral (GC-MS, HPLC-UV, HPLC-MS) methods of analysis of organic compounds both in connection with analytical issues and the general problems of organic chemistry. First type of tasks includes the refinement of the methods of quantitative analysis regardless of analytes nature that is outside of the scope of the present survey. Yet the identification of organic compounds in all cases requires the consideration of their physicochemical characteristics. An approach was developed providing a possibility to calculate with a great accuracy the values of the majority of "classic" physicochemical characteristics of homologs (normal boiling points, refraction indices, density, viscosity, surface tension, ionization energy, etc.) [293–295], dissociation constants of organic acids [296, 297], various chromatographic parameters [298], and even octane numbers of hydrocarbons [299]. The criterion of the possibility of chromatographic and GC-MS analysis of thermally unstable analytes was suggested

Scheme 4.40.



Scheme 4.41.

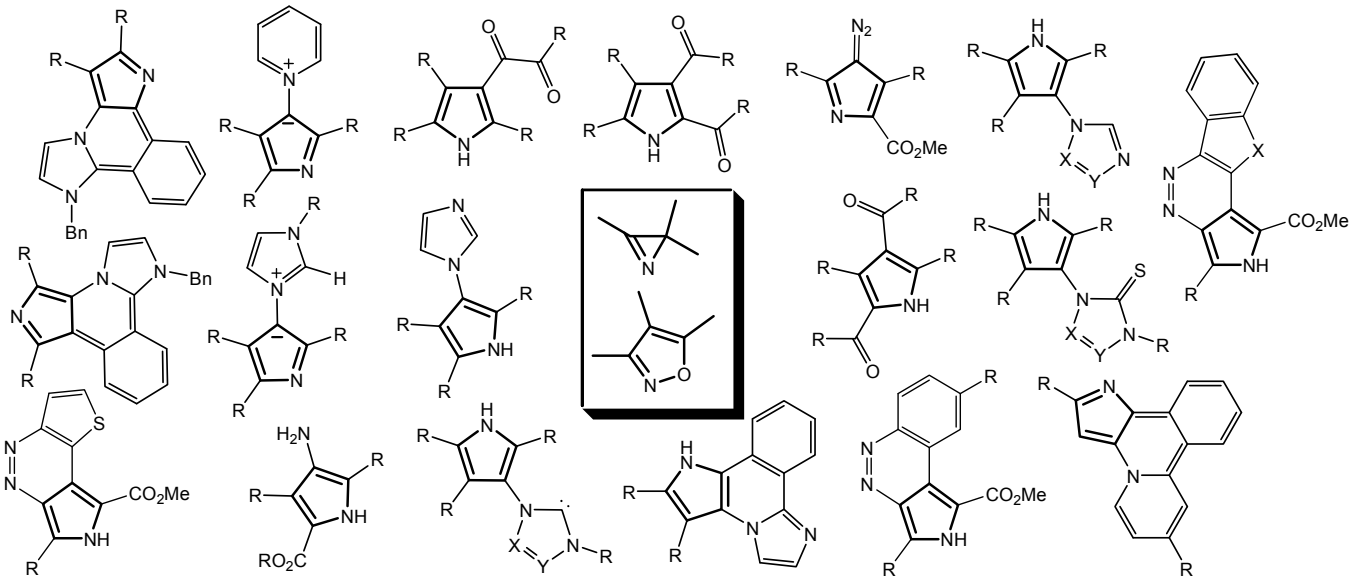


resulting from a thoroughly performed decoding of the composition of reaction mixtures from the synthesis of diazocarbonyl compounds [300, 301]. Monoesters of organic dicarboxylic acids were characterized for the first time by the examples of phthalates and maleates. In the course of gas-chromatographic separation they are converted in anhydrides [302, 303], which results in the high toxicity of monoalkyl phthalates.

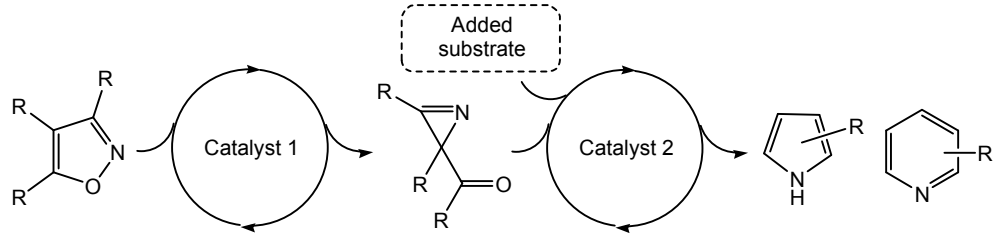
The possibility to analyze unstable compounds like peroxides and hydroperoxides in case when the chromatographic systems correspond to the modern requirements of inertness [304] was demonstrated by the example of dibenzyl ether hydroperoxide [305]. The degradation of 1,1-dimethylhydrazine in the presence of sulfur leads to the formation of another unstable compound, dimethylthionitrosamine $(CH_3)_2NN{=}S$ [306]. In two last cases as well as in the case of 3,4-dichloro-1,2,5-oxadiazole 2-oxide, forming in trace amounts at the nitrosating dichloromethane [307], the establishment of the structure is based on mass spectra combined with chromatographic retention parameters.

The preparation of derivatives of compounds to be analyzed is used for the optimization of their chromatographic separation and detecting. For instance, the conversion of alkyl-substituted phenols into iodine derivatives reduced their detection limit in water environment to 0.01–0.10 μg/L [308, 309]. The application of dimethylformamide dimethylacetal (DMFDMA) for the conversion of carboxylic acids into methyl esters and the aminocompounds into *N*-dimethylaminomethylene derivatives is known for a long time, but the systematic characteristics of the respective amino acids derivatives by mass spectra and retention indices has been performed only in 2015. The

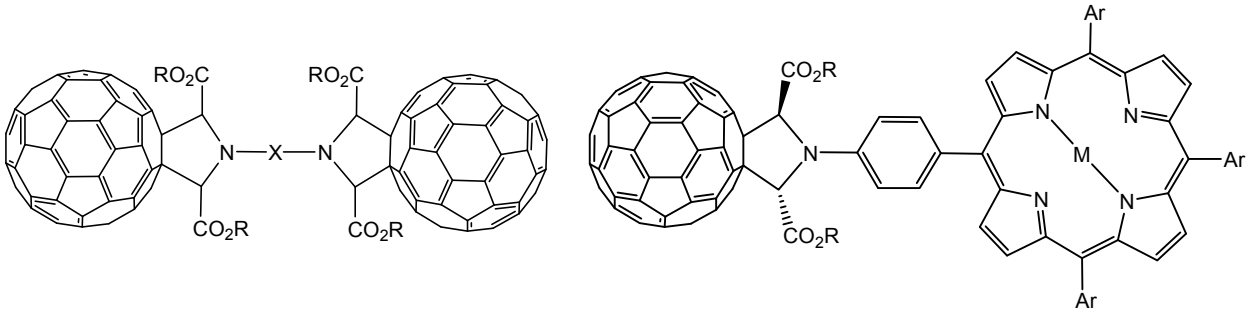
Scheme 4.42.



Scheme 4.43.



Scheme 4.44.



comparison of *RI* values of carbonyl compounds and the products of their reactions with DMFDMA makes it possible to refine the understanding of the nature of carbonyl groups, in particular, to recognize aliphatic and aromatic carbonyl compounds as well as to distinguish them from alkyl aryl ketones [310, 311].

A detailed analysis of published data, especially after 2008, permit to reveal a dangerous trend in presenting the data of GC-MS analysis without critical consideration of the lists of identified components of complex samples. Some reasons of this trend are discussed in [312], and an interesting example is the "discovery" of spiro[2.4]hepta-4,6-diene in various natural substrates that has been stated in dozens of publications in 2002–2016. The special consideration of the issue [313] demonstrated that in all cases it was an erroneous identification of toluene C_7H_8 isomeric to this substance that both possessed a similar mass spectrum and materially coinciding retention index on standard nonpolar phases. The conclusion on the properties of the differences in the values of single-dimensional characteristics or analytical parameters became an important element of the theoretical problems in the identification of organic compounds [314].

The work of the scientific team of **Doctor of Chemical Sciences**, **Professor L.A. Kartsova** are directed on the development of selective chromatographic (HPLC, HPTLC, HILIC) and electrophoretic (CZE, CEC, MEKC) determination of biologically active analytes (proteins, amino acids, steroid hormones and NPC, catecholamines, catechins, etc.) in complex matrices involving organized media (macrocyclic and ion-pair agents, dendrite polymers, micelles , microemulsions). Whereas the work of this group belongs to a greater extent to the field of analytical chemistry it is not described in this review.

5. DEPARTMENT OF ORGANIC CHEMISTRY AT LOMONOSOV MOSCOW STATE UNIVERSITY

Department of organic chemistry at Lomonosov Moscow State University is the largest department of this type in Russia. The research in seven laboratories of the department includes versatile directions of organic chemistry and related topics.

Laboratory of organoelemental compounds under the guidance of **Academician I.P. Beletskaya** focused traditionally its attention on diverse types of catalytic processes for building up carbon–carbon and carbon–heteroatom bonds. Catalysis with palladium is one of the main directions of research in the laboratory. Lately more and more attention is payed to the catalysis with palladium nanoparticles and to the replacement of the expensive palladium by essentially cheaper copper.

In the framework of classical homogeneous catalysis by the complexes of zero valent palladium a large amount of work is carried out concerning the synthesis of diverse nitrogen- and oxygen-containing macrocyclic and macropolycyclic compounds applying amination reactions of aryl and hetroaryl halides. To

this day many dozens of compounds of versatile architecture were synthesized including in their structure endocyclic and exocyclic chromophore and fluorophore groups. These compounds underlie creation of colorimetric and fluorescent sensors for metal cations [315, 316] (Scheme 5.1).

A large attention was directed on designing polyporphyrin conjugates; involving Pd(0)-catalyzed amination di- and triporphyrin systems were obtained, some structures were used to prepare molecular tweezers that changed the geometry of a molecule at complex formation [317] (Scheme 5.2).

Homogeneous catalysis with complexes of palladium and of the other noble metals is also applied to the homogeneous enantioselective hydrogenation of unsaturated substrates containing carbon–carbon and carbon–heteroatom multiple bonds (e.g., α-imino-, α-oxo-, α-hydroxyimino-, or α-phenylhydrazonophosphonate) [318] (Scheme 5.3). Based on the reactions of 1,3-dipolar cycloaddition of diazocompounds to 1-substituted vinylphosphonates a new strategy was developed for the synthesis of substituted 1-aminocyclopropylphosphonic acids and cyclopropylphosphonates with functional groups [319].

In the field of nanocatalysts we explored the main reactions of the formation of C(sp^2)–C(sp^2), C(sp^2)–C (*sp*) bonds catalyzed by nanopalladium catalysts (PdNPs). We investigated reaction of Heck, Suzuki, carbonylation, cyanation catalized by PdNPs which were stabilized by two types of polymers: polyvinylstyrene copolymer with polyethylene oxide and polyvinylimidazole copolymer with polyvinylcaprolactam. Much attention was payed to the issues of the organometallic reactions mechanism, to the evaluation of the nucleophilicity of the involved species, to the problems of "leaching" that have a great importance for prolonged uses of the catalyst and for the understanding of the reaction mechanisms [320]. We succeeded to show that PdNPs can be no less and sometimes more active catalysts than homogeneous palladium complexes with expensive and toxic ligands [321] (Scheme 5.4).

Cheaper copper nanoparticles immobilized on aluminum oxide were successfully used in heterogenic catalytic carboxylation of terminal alkynes [322]. The reduction of anhydrous copper salt $CuCl_2$ was used in the synthesis of CuNPs on various inorganic solid substrates (TiO_2, MK-10, zeolite, carbon). The CuNPs prepared by this procedure are of small size (1–2 nm), and their catalytic activity has been tested by the examples of the formation of bonds C–C (Sonogashira reaction), C–S (thiophenol arylation), and C–N (arylation of benzimidazole, imidazole, pyrazole, indole). The substrate nature strongly affects the results of the reactions, moreover, this influence is different for different reactions [323]. Sonogashira reaction is successfully catalyzed by a complex of univalent copper with a phosphorus-substituted phenanthroline immobilized on titanium oxide giving quantitative yields of products [324] (Scheme 5.5).

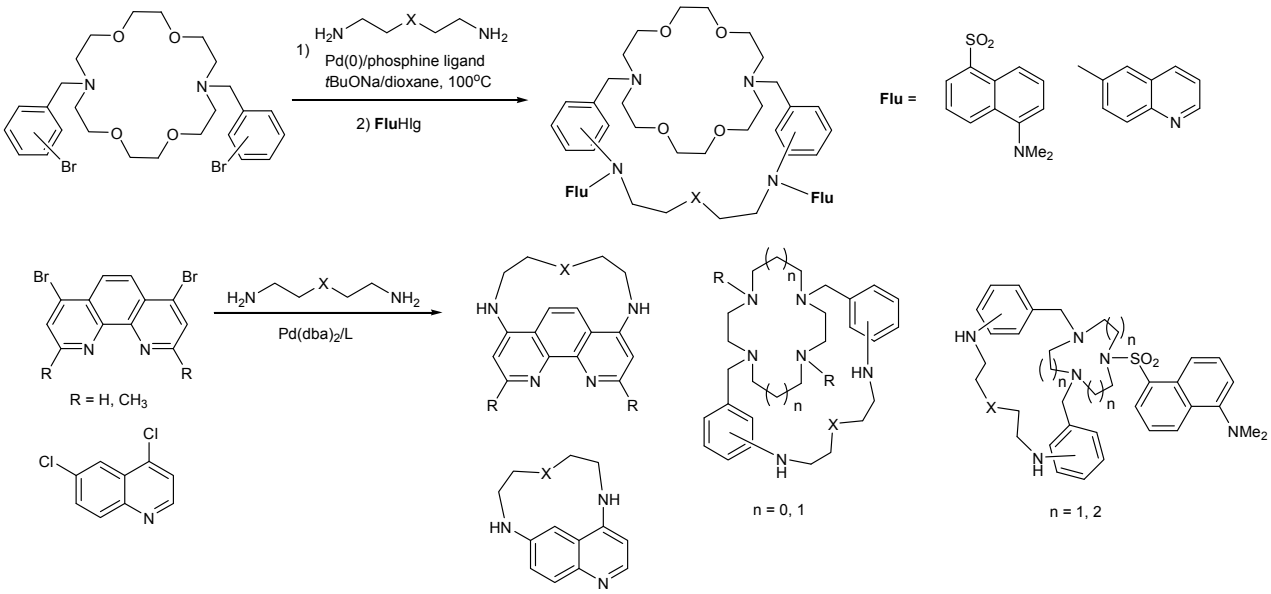
The use of the complex of univalent copper for the formation of C–N bonds is actively studied on arylation and heteroarylation of biologically active adamantane-containing amines, natural di- and polyamines [325]. Studies were performed on various ways of steroids molecules modification: basing on the copper-catalyzed reactions a new approach was developed to the synthesis of azolyl- and alkynyl-substituted steroids [326, 327], using palladium-catalyzed amination and copper-catalyzed 1,3-dipolar cycloaddition a number of polydentate ligands was prepared containing in their structure several rigid steroid scaffolds, in particular, steroid-containing macrocyclic systems [328]. The complex formation of these ligands with cations and anions is currently under study [329] (Scheme 5.6).

With the help of copper-catalyzed "click"-reactions a synthesis has been performed of porphyrin conjugates of diverse architecture, the unique optical characteristics of these molecules are investigated now [330] (Scheme 5.7).

Alongside with the copper-catalyzed substitution reactions the addition to alkynes of phosphorus- and sulfur-containing compounds is extensively explored. For instance, the hydrosulfenylation [331], hydrophosphorylation [332] of the triple bond was successfully performed, as well as additional dimerization of alkynes with enynes formation [333]. Recently in the laboratory of organoelemental compounds studies are started on the use of gold complexes as catalysts [334, 335].

In the field of catalysis, regarding also asymmetric one, involving Lewis acids and their chiral complexes a large amount of work was carried out on the investigation of Friedel–Crafts reactions between indole and various Michael acceptors. In these reactions magnesium and calcium salts show excellent catalytic properties. The replacement of transition

Scheme 5.1.

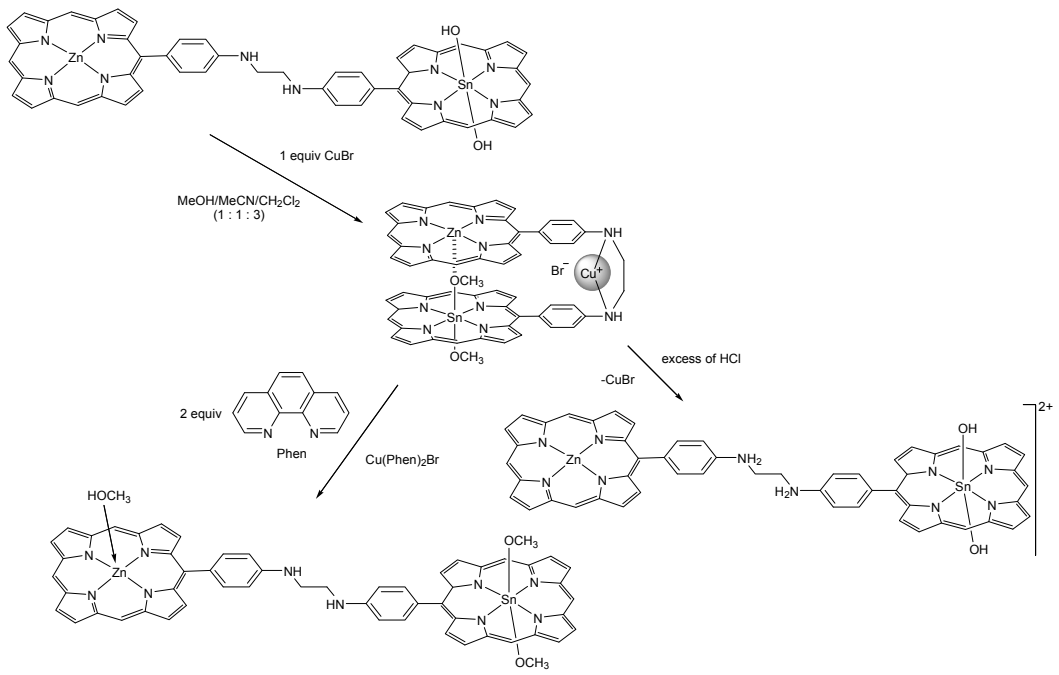


metals and lanthanides salts by the salts of the main group metals is an important phenomenon in this field. The best yields of the products of indole alkylation exceed 99%, and the enantioselectivity reached 92% [336] (Scheme 5.8).

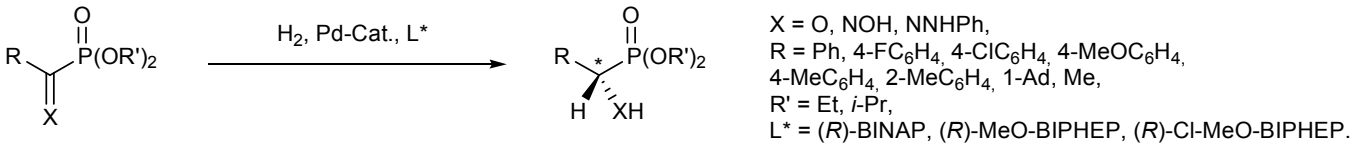
Development of catalysis of Friedel-Crafts and Michael reactions with Cu(II) complexes with chiral bisoxazoline (BOX) ligands occurs applying ligands immobilized on Merrifield polymer. As a result the asymmetric indoles addition to Michael acceptors proceeds in high yields (up to 99%) and enantioselectivity (up to 97%). These reaction parameters are conserved after recyclization within five cycles nearly without changes [337] (Scheme 5.9).

Indole addition was also explored in reactions with vinylphosphonates catalyzed by Cu(II) complexes with bipyridine. As a result potentially biologically active phosphorus derivatives of this heterocycle were

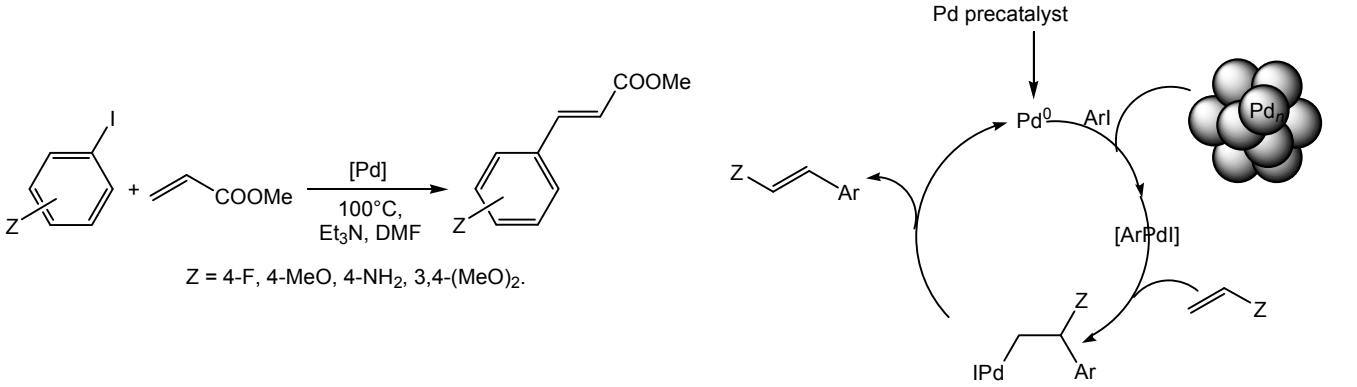
Scheme 5.2.



Scheme 5.3.



Scheme 5.4.



formed [338]. The enantioselective addition of indoles and pyrroles to phthalimidomethylenemalonate was investigated in the presence of bivalent copper complex with a chiral BOX ligand. Yields and the enantiomeric purity of the product reached 99% (Scheme 5.10).

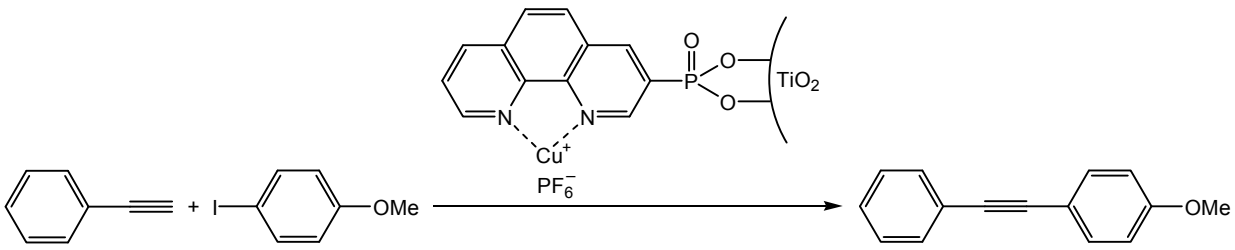
For the study of the catalytic enantioselective addition of alkynes to imines a ligand PyBOX was synthesized immobilized on polyethylene glycol. In the process under optimized conditions the value *ee* 92% was attained, the recyclization results of the immobilized ligand showed that it was sufficiently stable in the reaction process and isolation and may be used many times [339] (Scheme 5.11).

A new organic catalyst was prepared, prolinol derivative immobilized on polystyrene, which was tested in two reactions: α-amination of saturated aldehydes and in Michael reaction of cinnamic aldehyde with dibenzyl malonate; therewith the optical purity of the target compounds reached 99% [340, 341] (Scheme 5.12).

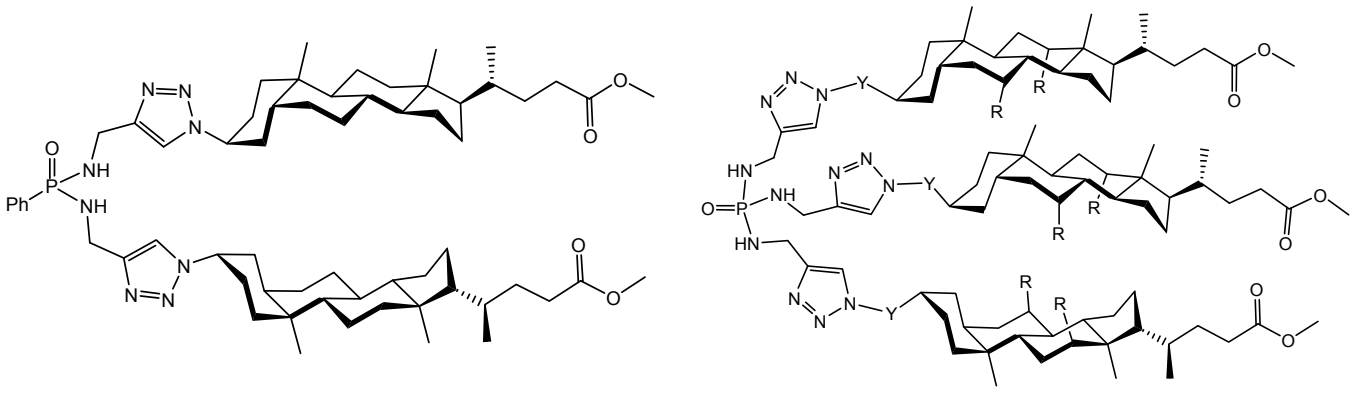
Some aspects of the activity of the laboratory of organoelemental compounds are out of the scope of the catalytic chemistry. A significant interest presents the development of the method of preparation of the previously undescribed hybrid macroheterocyclic system that occupies the position between porphyrins and phthalocyanines, tetrabenzo-5,15-diazaporphyrin [342], the study of physicochemical characteristics of these compounds that has been shown to be promising as sensitized dyes for making Graetzel solar cells [343].

Another traditional direction in the field of physical organic chemistry is also continued in the laboratory: the study of reactivity of metal-centered nuclophiles by an example of the anions of transition metal carbonyls. A double reactivity of such nucleophiles is demonstrated: the ability to attack organic halides RX both at the carbon atom (common nucleophilic substitution) and at the halogen atom (halophilic attack). A unique scale was constructed for the nucleophilicity and halophilicity of metal-centered and common *C*,*S*,*O*,*N*-nucleophiles [344, 345].

Scheme 5.5.



Scheme 5.6.



Pincher ligands Tripodal ligands

Laboratory of organic synthesis under the guidance of **head of the Department**, **Professor V.G. Nenaidenko** develops a wide range of synthetic issues. Subjects dealt with in the laboratory include the development of new procedures for the preparation of practically important compounds, catalysis (with metal complexes, asymmetric, organic catalysis), the chemistry of fluorine-containing compounds, the chemistry of heterocyclic compounds, investigation of multicomponent reactions involving isocyanides, quantum-chemical calculations.

For many years the scientific team under the guidance of V.G. Nenaidenko studies fluorine-containing compounds. One of the key problems in this respect is designing of molecules containing the fluorine atom or a fluorinated substituent in strictly defined position of the molecule. The preparation of fluorine-containing building blocks makes it possible to solve many problems in this field [346, 347]. For instance, proceeding from acetylene CF_3-ketones a regioselective method was developed for the synthesis of 3- and 5-trifluoromethylated pyrazoles, in particular, of Celebrex drug [348] (Scheme 5.13).

A stereoselective synthesis was developed for fluorosubstituted nitrostyrenes. These compounds open wide opportunities for the synthesis of versatile monofluorinated molecules [349] (Scheme 5.14).

V.G. Nenaidenko with the collaborators discovered and implemented in the synthetic practice a fundamentally new reaction of catalytic olefination, the reaction of *N*-unsubstituted hydrazones with polyhaloalkanes in the presence of CuCl affording substituted alkenes [350]. Recently this reaction found further extension: the reaction of polyhaloalkanes with *N*-substituted hydrazones led to the formation of diazadienes, new building blocks with valuable synthetic opportunities [351] (Scheme 5.15).

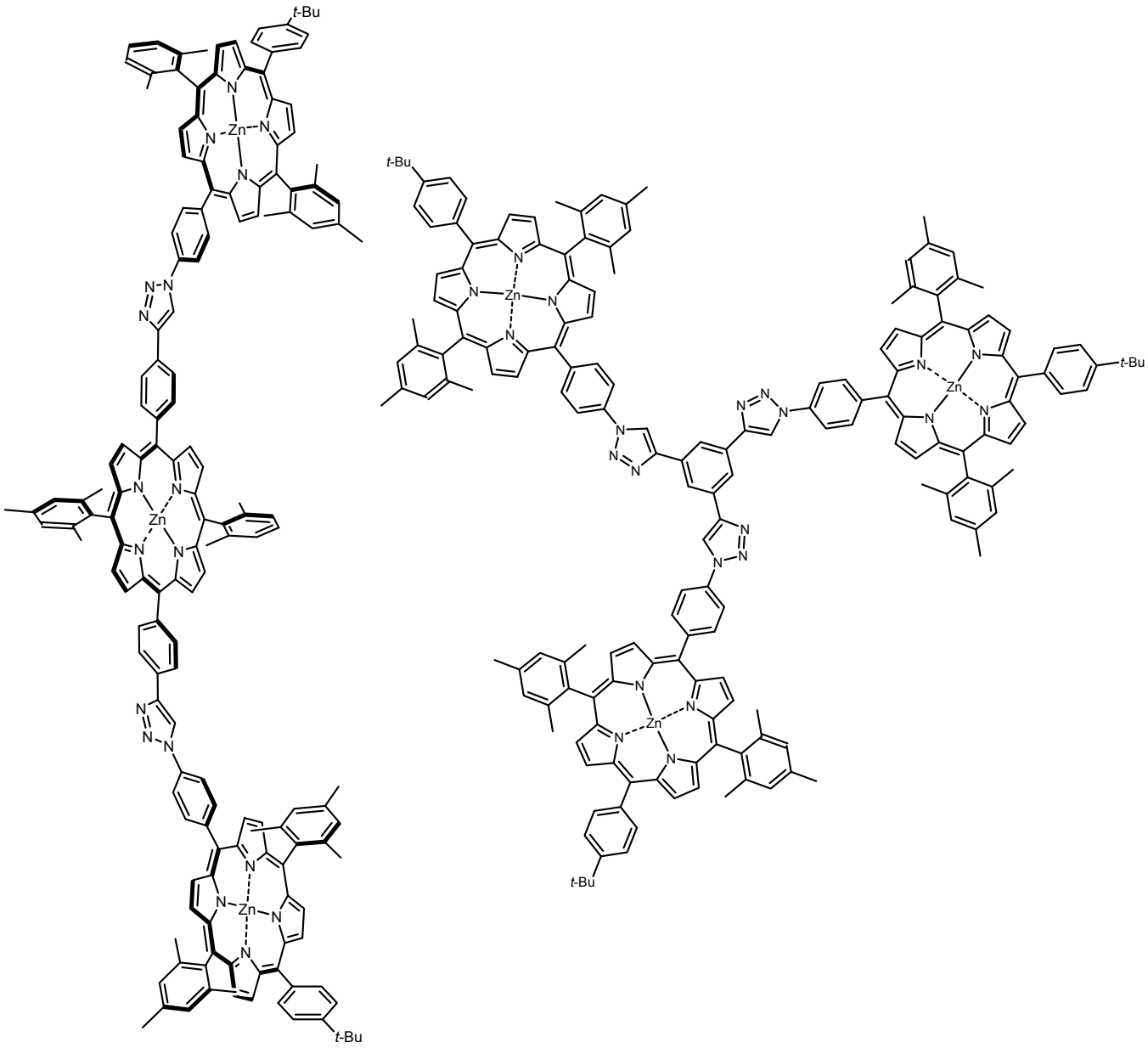
In the group of V.G. Nenaidenko a new class of substances was discovered, heterocyclic circulenes [352–355] that are representatives of polyfused thiophenes and are of great interest as materials for electronics and nanotechnology. Recently the structural transformations were successfully observed that the thiophene circulene suffers under the effect of electron beam. To this end a stack of circulene molecules was placed in a carbon nanotube. The subsequent action of electrons caused the band structure formation that consisted of carbon and sulfur (Scheme 5.16) [356].

One more direction developed in the laboratory of V.G. Nenaidenko is the multicomponent reactions involving isocyanides which provide a possibility to effectively prepare peptides and peptidomimetics [357–360]. The other type of compounds attractive because of their biological activity is various amines produced from cyclic ketimines (Scheme 5.17) [361–363].

The research of the group of **V.V. Dunina** concerns the preparation of new cyclopalladated complexes, development of new methods of their production and estimation of their potential in practical applications [364–367]. Thus within the last decade a series of aza- and phosphapalladocycles was obtained in an enantiomerically pure state. These were fundamentally new structurally and/or sterochemically new types of central, planar, and axial chirality (Scheme 5.18). The application of these complexes in various catalytic processes in now under investigation [368].

The group of **E.V. Babaev** for a long time explores the chemistry of indolizine and its heteroanalogs.

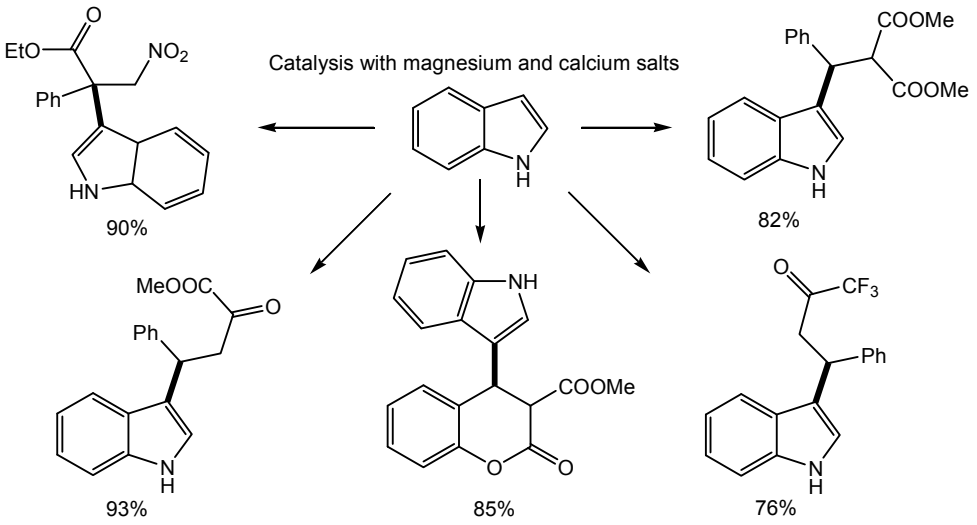
Scheme 5.7.



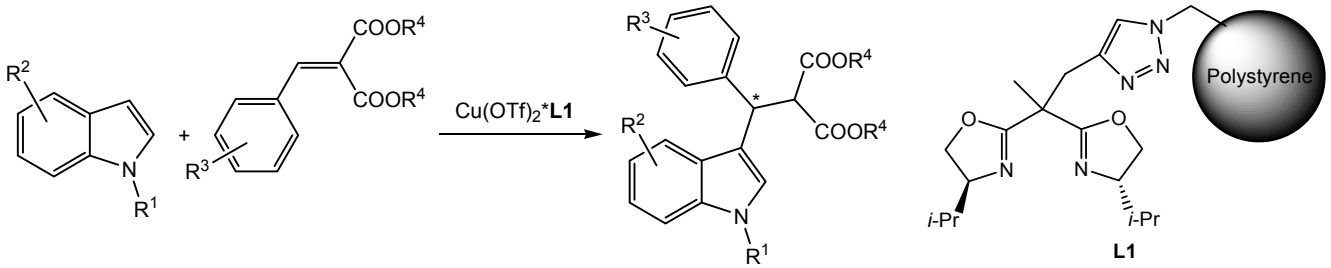
Various procedures of functionalization of these heterocycle are studied including the electrophilic and nucleophilic substitution, cross-coupling, and cycloaddition [369–371]. The heterocycles interconversions are investigated: of pyri(mi)dines into imid(ox)azoles, oxazoles in pyrroles [372], azolopyridines in indolizines. These studies underlie the development of effective synthetic methods for natural compounds [373]. In the scope of this group interests are also new reactions of 2-halopyridinium salts, the synthesis of uncommon mesoionic substances, solid phase synthesis, dendrimers preparation, and super bright fluorescence (Scheme 5.19) [374].

The work of **N.A. Bumagin** is focused on the development of highly efficient catalytic systems for cross-coupling reactions in water environment. Lately methods of the synthesis were developed for polyheterofunctional 1,2-azoles, their complexes with palladium and nickel were obtained [375]. Isoxazole-1,2,3-triazole palladium complexes $LPdCl_2$ are catalysts of cross-coupling in water environment active

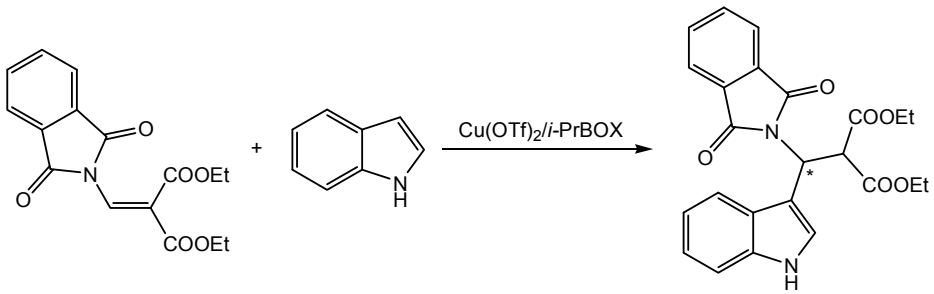
Scheme 5.8.



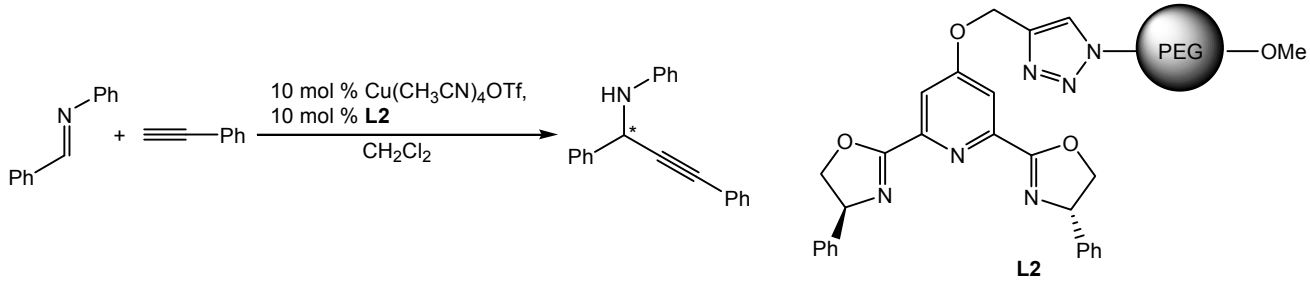
Scheme 5.9.



Scheme 5.10.



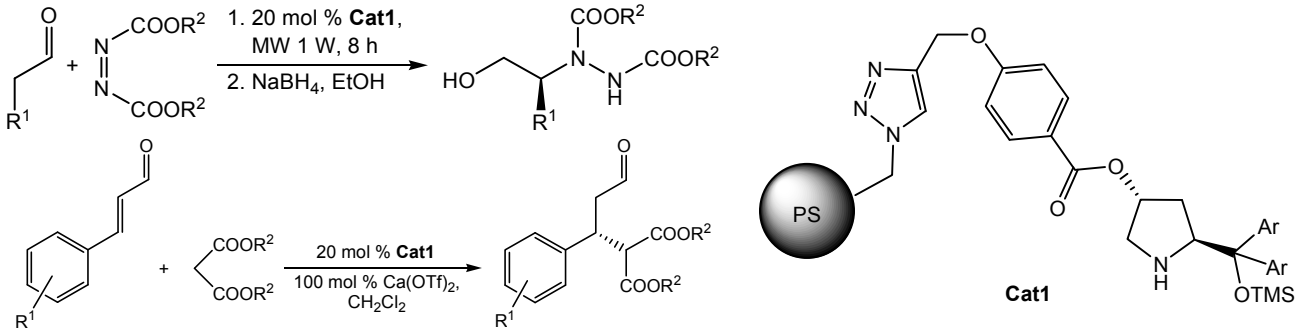
Scheme 5.11.



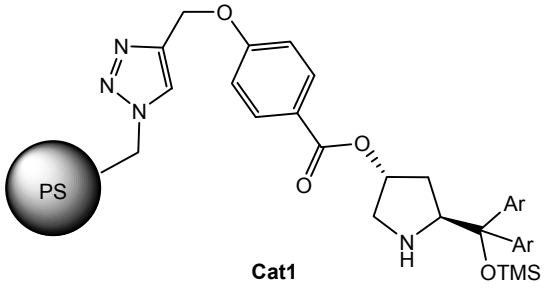
to such high degree that they can be used in trace amounts (1–10 ppm). A high catalytic activity is also found in palladium complexes with accessible aminopyridines L_2PdCl_2 and $[L_4Pd]Cl_2$, L = DMAP, 4-aminopyridine, etc. (Scheme 5.20) [376].

For the first time a promising and very active catalyst was developed for cross-coupling and reduction reactions underlain by nickel boride modified with isoxazole-1,2,3-triazole ligands and doped with palladium, Pd–Ni–B–L [377]. The ability

Scheme 5.12.



Scheme 5.13.



of composites Pd–Ni–B–L to form stable colloid solutions in methanol opens a way to their simple application on porous carriers and thus preparation of active reusable heterogenic catalysts.

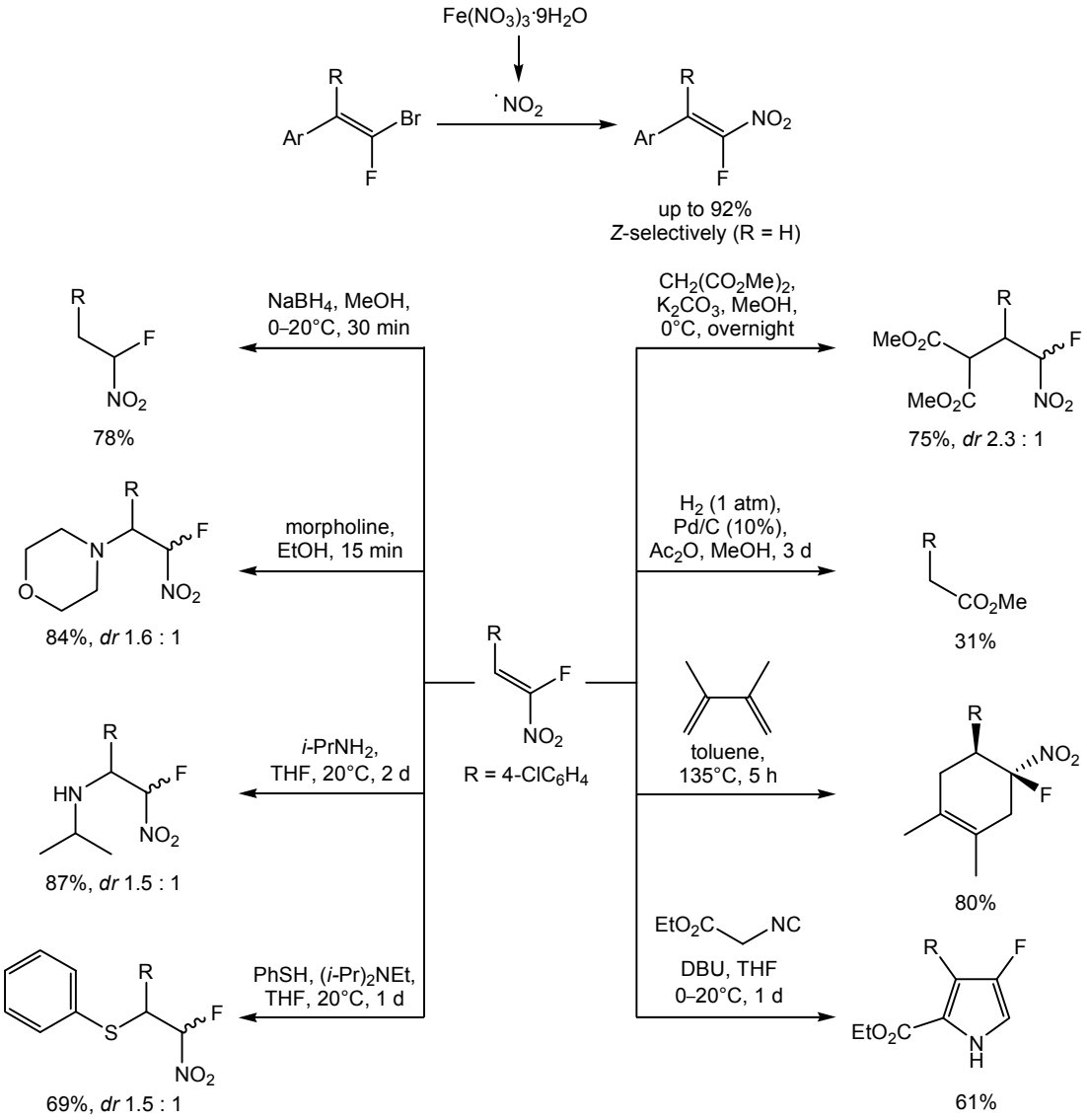
In the last decade **Ya.A. Ustynyuk** has been developing a new strategy of designing highly selective receptors for cations and anions [378, 379], which is underlain by the application of supercomputer simulation in the preliminary stage of research with the subsequent convergence assembly of target structure from large structural blocks. In the course of this work a series of receptors was obtained possessing unique extraction properties that opened new opportunities for solving crucially important tasks in the technology of lanthanides and actinides separation at the recovery of radioactive wastes and in the other important fields (Fig. 5.1) [380–383].

The group of **V.M. Dem'yanovich** and **I.N. Shishkina** studies the problems of asymmetric synthesis. Recently they explored metalation of chiral phenylethanol and *N*,*N*-dimethylphenylethylamine [384–386]. Subsequent reactions with ketones provide the possibility of the synthesis of chiral derivatives of hydrogenated isobenzofurans and isochromene. The obtained compounds contain a fragment that is an important structural unit of several drugs and that is present in a large number of natural compounds (Scheme 5.21).

Main directions of research of ***laboratory of supramolecular chemistry and nanotechnology of organic materials*** (founded in October, 2011, **head of the Laboratory Correspondent Member of the Russian Academy of Sciences**, **Professor S.P. Gromov**, proxy **Professor of the Russian Academy of Sciences S.Z. Vatsadze**) are as follows: synthesis of organic ligands and tectons for designing organic and coordination supramolecular ensembles; investigation of self-assembly and self-organization processes in solutions, crystals, liquid crystals, and gels; the study of photophysical properties and photochemical transformations of supramolecular nanosize systems and organic materials prepared thereof; designing of photoswitching molecular devices and photogoverned molecular machines; design, synthesis, and application of ligands for radiopharmaceuticals, devices of organic electronics and biovisualization. Within 2012–2017 the laboratory has achieved the following results.

Styryl dyes have been synthesized having an ammonioalkyl *N*-substituent, which are capable of spontaneous dimerization in solutions that is conserved also in the crystalline state. In the dimeric complexes a stereospecific reaction occurs of [2+2]-photocycloaddition (PCA) with the formation of cyclobutane derivatives at the irradiation with light in solution or single crystals without their destruction. The

Scheme 5.14.



possibility was demonstrated of performing retro-PCA reaction on the obtained cyclobutane derivatives resulting in initial dyes (Scheme 5.22) [387, 388].

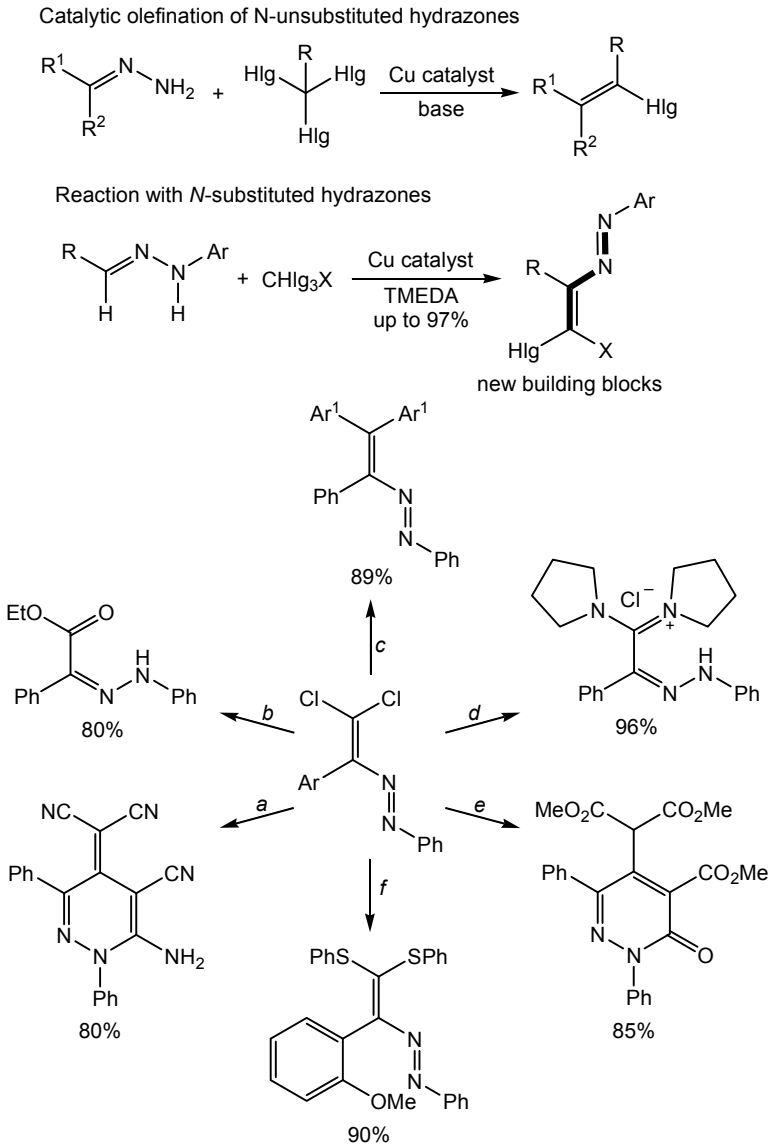
A synthesis was developed of biscrown-containing dibenzylidene derivatives of cyclopentanone, cyclohexanone, and cyclobutanone (dienones) based on formylbenzo-15(18)-crown-5(6)-ethers [389] (Scheme 5.23). Photophysical and photochemical properties of bisazacrown-containing dienones and model compounds, promising components of photoactive supramolecular structures were explored [390, 391].

A crystallochemical description was performed for topochemical reaction of PCA, the reasons of no reaction in some packing motifs and the causes of reaction occurrence without destruction of single crystals, and also the possibility of occurring both of the direct and reverse photochemical reaction in the same single crystal (Fig. 5.2) [392].

Photolysis of styryl dye (SD) solutions in the presence of cucurbit[8]uril (CB[8]) was investigated. In the solution inclusion complexes SD@CB[8] and $(SD)_2$@CB[8] are present. The system can operate in a cyclic mode as a supramolecular assembler of a stereospecific PCA reaction of SD dye with the formation of the cyclobutane derivative (C) (Scheme 5.24) [393].

A new supramolecular synthon was introduced, a complex of bidentate bispidine with 3d-metal. A series

Scheme 5.15.



Hlg = Cl, Br; X = Cl, Br, CN, CO_2Et, CF_3.
a: $CH_2(CN)_2$, NaH, THF, 20°C, 5 h; *b*: EtOH, reflux, 2 h; *c*: $Ar^1B(OH)_2$, S-Phos, K_3PO_4;
d: pyrrolidine, THF, 20°C, 5 h; *e*: dimethyl malonate, NaH, THF, 20°C, 5 h; *f*: PhSH, NaH, THF, 20°C, 6 h.

of complexes was synthesized of dimethyl bispidinone with salts of Cu(II), Ni(II), Co(II) [394] (Scheme 5.25).

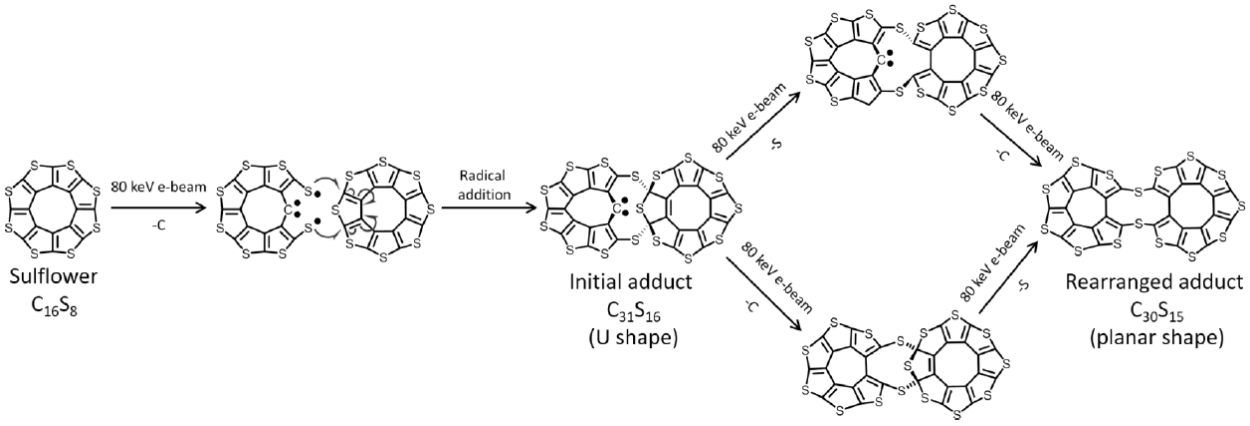
For the first time supramolecular gels and metallic gels based on bispidine derivatives were prepared and studied by combination of physicochemical analysis methods providing information on molecular structure, nanostructure, and microscopic properties of objects [395].

Among ferrocene-containing polymers promising nanomaterials were found capable of selectively binding hydrogen [396], and in this case the properties of the material could be affected by external action, namely, new stimulotropic materials were obtained.

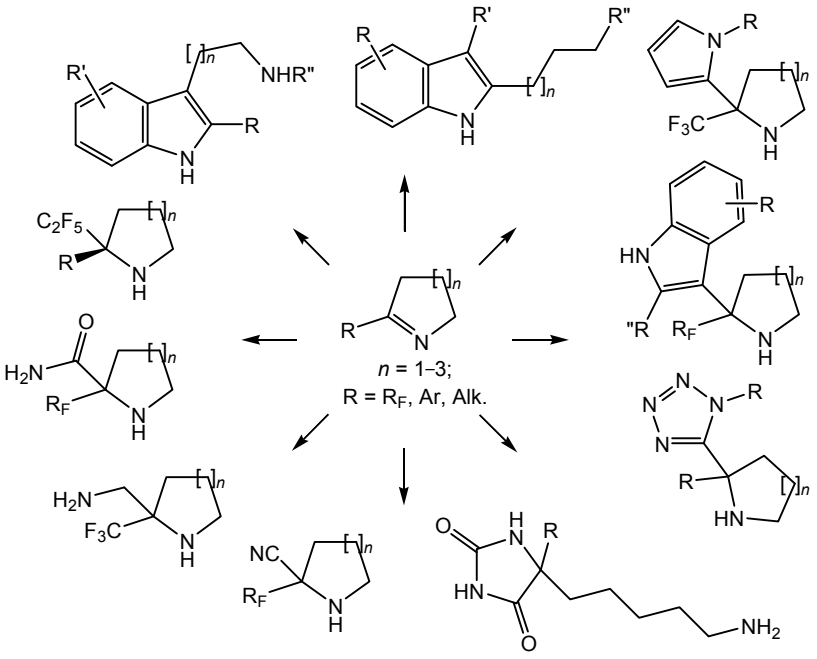
Docking was performed for a wide spectrum of bispidines, in particular, ferrocene-containing, into active sites of thrombin and factor Xa. The bispidine scaffold ensures the necessary spatial arrangement of all substituents and the ferrocene fragment ideally fills the S4 pocket [397].

A purposeful selection and detailed systematic investigation was performed on a series of diazamono-

Scheme 5.16.



Scheme 5.17.



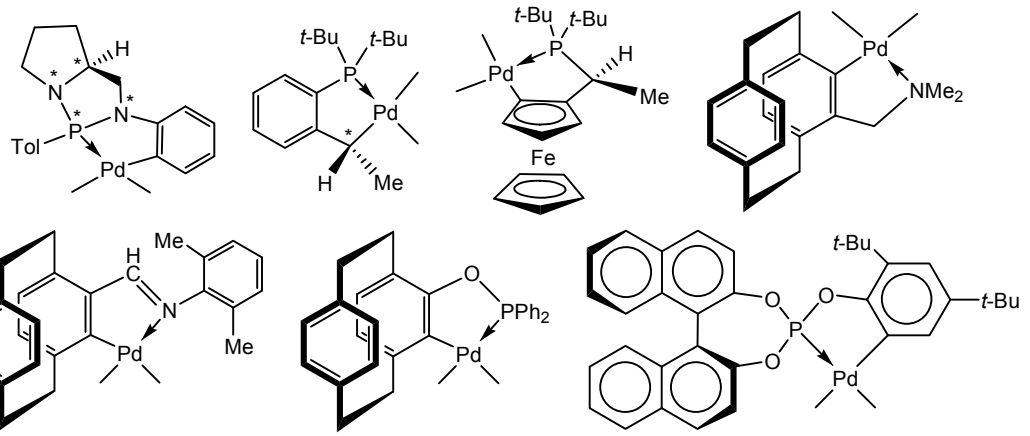
and bicyclic ligands able to effectively form chelate complexes with copper(II) ions promising for the study on cognitive processes and the effect of irradiation on the neuropsychological state of humans [398] (Scheme 5.26).

A synthesis was developed of biscrown-containing 1,3- and 1,4-distyrylbenzenes, their complex formation was studied with cations of alkali and alkaline-earth metals; at complex formation with ions of a large ionic radius unusual bissandwich complexes were formed interesting for further research [399, 400] (Scheme 5.27).

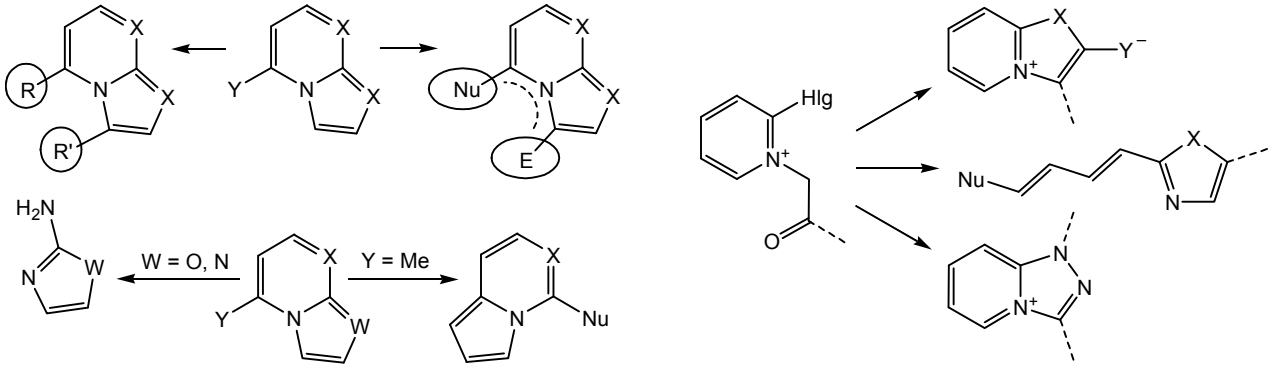
A synthesis was elaborated of lanthanide pyrazolecarboxylates (and of some other kinds of heterocyclic carboxylic acids with a heteroatom in the *ortho*-position with respect to the carboxy group) with atomic accuracy exhibiting luminescence properties in the visible range promising for biologic and medical applications [401] as well as for making OLED devices (Scheme 5.28).

In collaboration with colleagues from the University of Florida (USA) a concept was created of stereoelectronic chameleons: functional groups of organic, inorganic, and organoelemental compounds, possessing both donor and acceptor properties. Under certain conditions the same functional groups of chemical compounds are capable to exhibit both properties of donors and acceptors of electron density. The demonstration of a definite effect is determined by

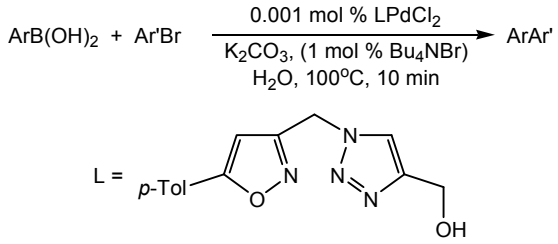
Scheme 5.18.



Scheme 5.19.



Scheme 5.20.



the spatial arrangement of the fragments of the molecule with respect to its main part or by the mutual position of two or more interacting molecules [402].

The scope of research themes of the ***laboratory of coordination organometallic compounds*** (**head of the laboratory Professor D.A. Lemenovskii**) was historically connected with the synthesis and the study of physiologically active organoelemental and organometallic compounds, with the design of new types of ligands and complexes of transition and rare earth metals [403]. Recently the main direction of research in the laboratory was the development of homogeneous catalysts and processes aimed at the preparation of new functional materials [404–410].

One of such processes is a nonclassical Ziegler–Natta catalysis in the chemistry of α-olefins. In contrast to the traditional Ziegler–Natta and single-centered polymerization catalysis the nonclassical approaches make it possible to prepare products like vinylidene dimers and α-olefins oligomers of low molecular weight and on the other hand, to prepare molecules including hundreds of thousands of monomer units. For the selective dimerization and oligomerization of α-olefins catalyzed by zirconocenes in the presence of minimum amount of organoaluminum activator a conception of mechanism was advanced (Fig. 5.3) extending the theoretical understanding of the nature of the single-center polymerization mechanism. The superhigh molecular weights of polymers are achieved by applying nontraditional reaction media, perfluorohydrocarbons. The products of nonclassical Ziegler–Natta catalysis

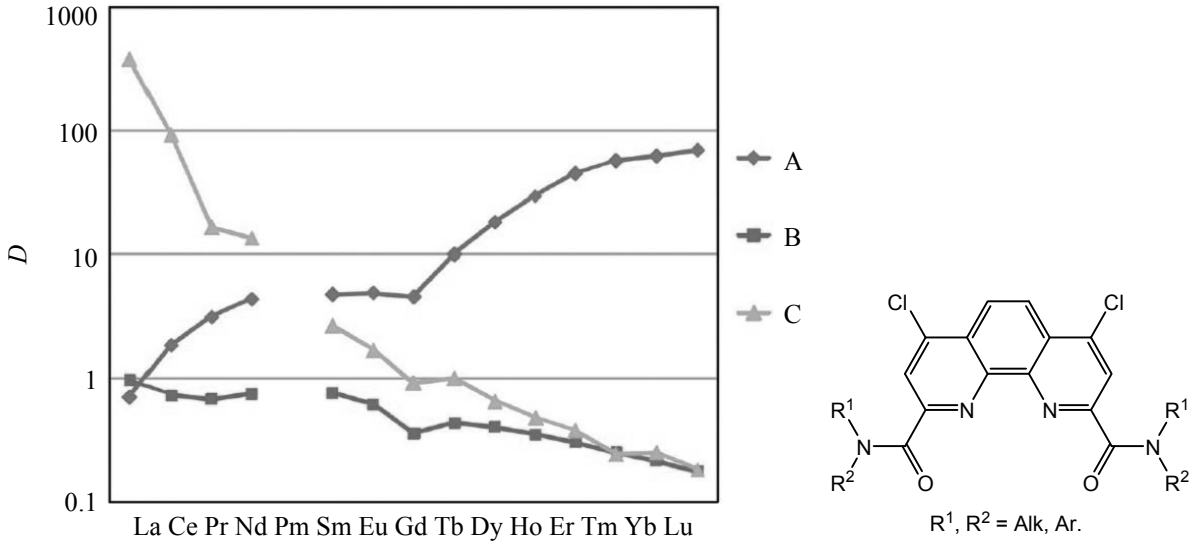


Fig. 5.1. Distribution coefficients of lanthanide ions at the extraction with the developed ligands.

may be efficiently applied to the production of motor oils and lubricants, as additives affecting the viscosity and rheology of oil and petroleum products. Functional derivatives of α-olefin dimers with adjustable lipophilicity show high efficiency in lanthanides extraction [411]. The controlled ethylene oligomerization with the chain transfer catalyzed with sandwich lanthanide complexes [409] opens opportunity to the preparation of oligoethylene block copolymers with cyclic esters. The classic polymerization of cyclic esters is no less important trend in the research of this laboratory. The development of new effective catalysts for the polymerization of lactones and lactides [410] opens the way to polymer materials for biomedical applications.

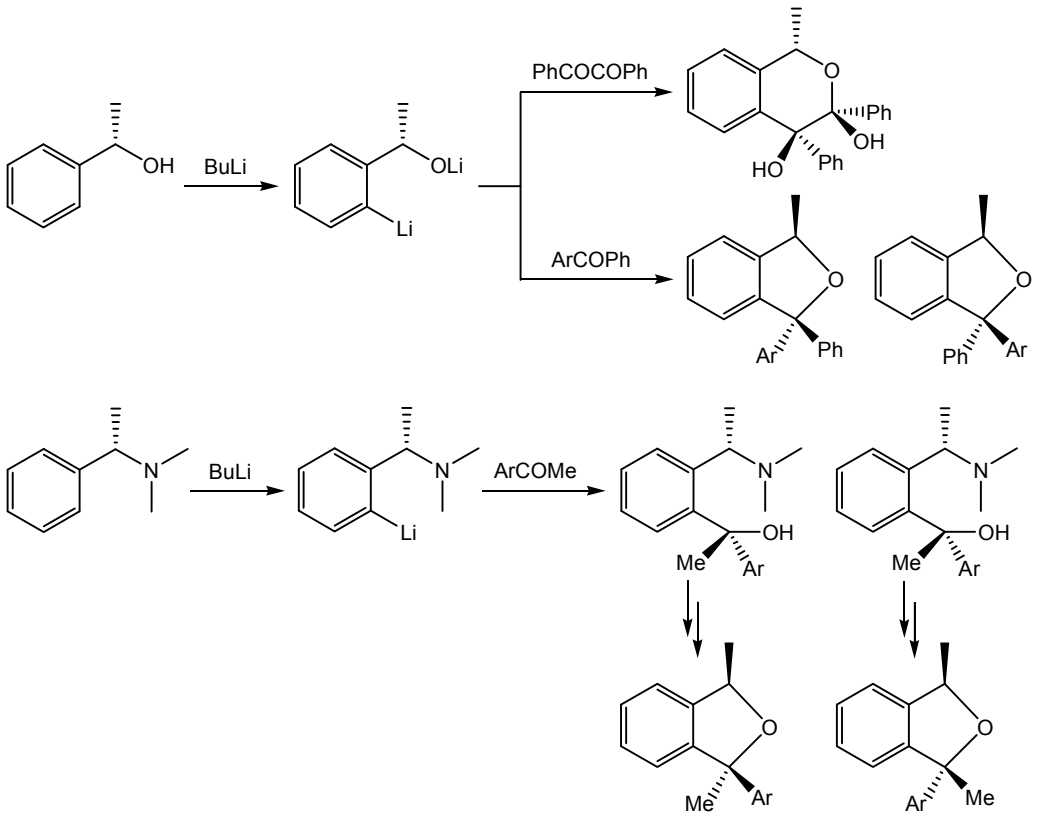
In the laboratory new materials and their precursors are developed. One among important directions of this activity is the establishment of technologic complex providing a possibility to obtain double and triple copolymers proceeding from acrylonitrile, precursors of carbon fiber [412]. Especially promising is the research on the synthesis of polyacrylonitrile in supercritical media [413]. The implementation of this project will provide a possibility to make an environmentally friendly process for the production of the precursor of the carbon fiber.

Yet another direction of research in the laboratory is the synthesis and study of the structure of organometallic compounds containing a prolonged structural fragment both a rigid one built of the scaffolds of biphenyl, terphenyl, and acetylene and a flexible fragment consisting of an alkyl chain [414–417]. Such compounds are metallomezogens, i.e., materials exhibiting liquid crystal properties that may be controlled and changed varying for instance the valence state of the metal. The structure of these complexes may govern their thermal, optical, electronic, and magnetic characteristics. First of all ferrocene and gold derivatives should be mentioned. The so-called aurophilic interactions are fairly characteristic of gold which result in the formation of bonds between molecules. The interactions Au…Au often result in the formation of weird structures, e.g., infinite bands in the crystal of the isocyanide complex of gold thiophenolate (Scheme 5.29).

A similar packing is observed in the crystals of bi- and terphenyl ferrocene derivatives containing no gold. The similarity in this case consists in the fact that the bulky ferrocenyl fragment does not hamper the formation of bands of gold atoms (Fig. 5.3) or similar bands of biphenyl fragments bound by van der Waals forces. Lately the work was focused on the purposeful synthesis of compounds where the ferrocenyl moiety was connected with a rod fragment with a terminal functional group (Scheme 5.30).

The compounds of this type are prepared by the reaction of ferrocene alkynylation with terminal alkynes that was discovered in the laboratory. This reaction is used to obtain ferrocenylacetylene, and from 4-bromophenylferrocene and 4-bromophenyl-ethynylferrocene the corresponding boroxines were prepared. The cross-

Scheme 5.21.

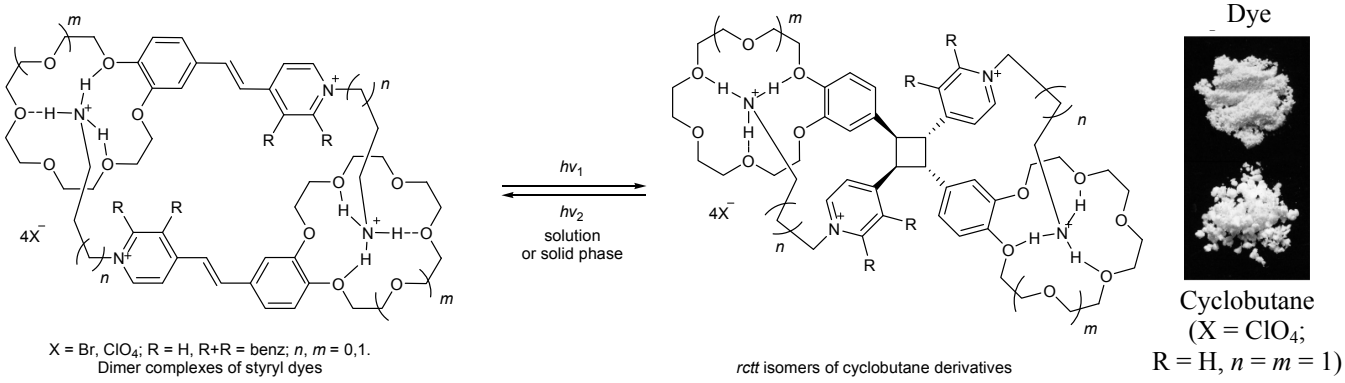


coupling of these boroxines as well as ferrocenylacetylene with aryl iodides and bromides led to the formation of a series of various ferrocenyl compounds with a rod-like part in the structure. It turned out that a number of such compounds containing a terminal heterocyclic fragment exhibit a pronounced cytotoxicity, in particular, to the human cells of ovarion tumor SCOV3 and of breast tumor MDA-MB-231.

The scope of research interests of the ***laboratory of physicochemical analytical methods of the structure of matter*** (**head of laboratory Professor A.T. Lebedev**) includes forecasting the direction and yield of chemical reactions in solutions basing on mass spectra of initial reagents, as well as research in the field of chemical ecology and proteomics.

All known rearrangements of organic compounds successfully occur not only in solutions but also in the gas phase under the conditions of mass spectrometric experiments. Interesting information was obtained on the transformations of diazocompounds, *ortho*-

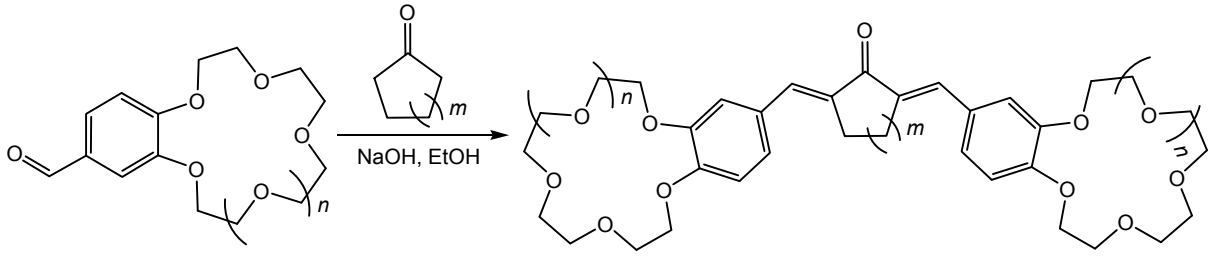
Scheme 5.22.



X = Br, ClO_4; R = H, R+R = benz; *n*, *m* = 0,1.
Dimer complexes of styryl dyes

rctt isomers of cyclobutane derivatives

Scheme 5.23.



$n = 1, 2$; $m = 0–2$.

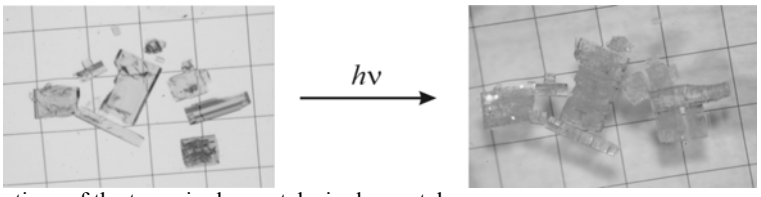
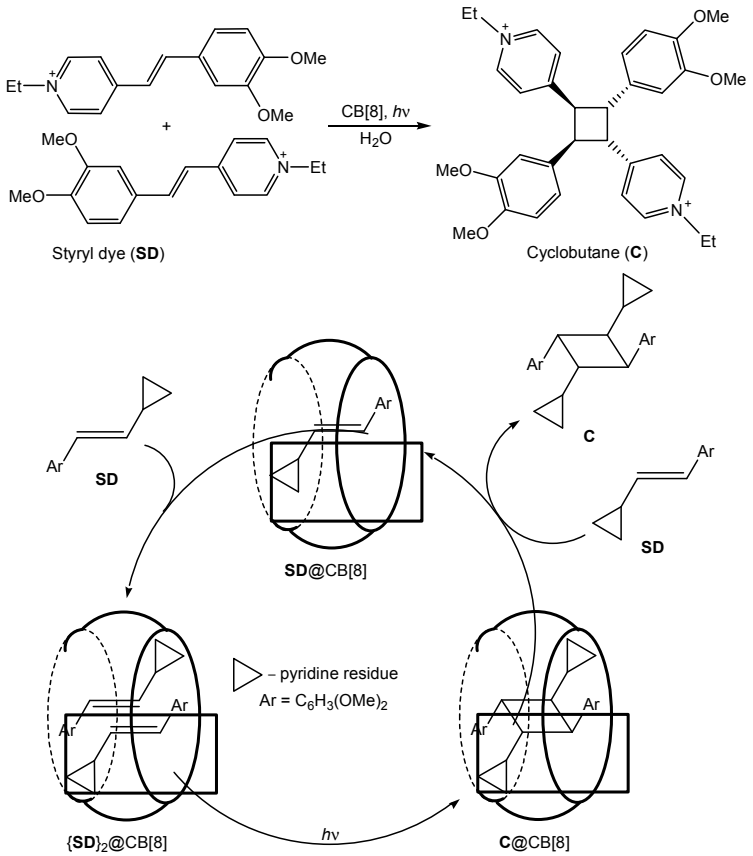


Fig. 5.2. Topochemical reactions of the type single crystal–single crystal.

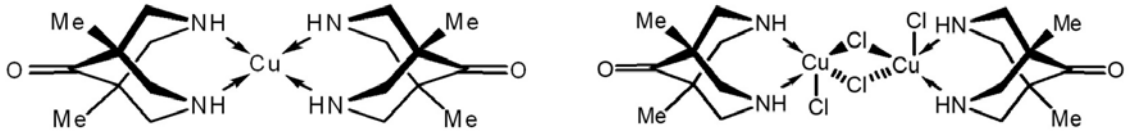
substituted phenylcyclopropanes, polysubstituted pyridines, versatile triazoles and thiadiazoles, and the other heterocyclic compounds [418]. Mass spectrometry is a reliable identification method of isomeric structure, of products of transformation in environment, of natural compounds. A large number of publications of staff members of the laboratory concern this direction [419–422].

Mass spectrometry of environmental objects is a world-wide important field of research since the obtained results provide a possibility to make correct

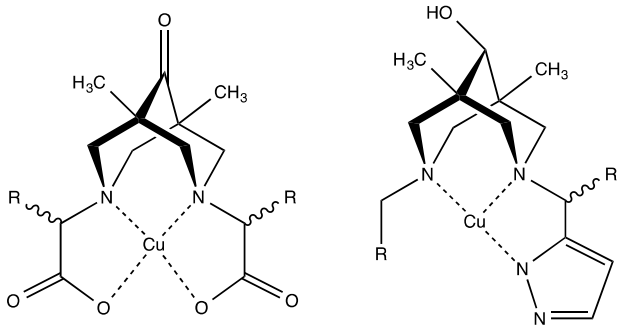
Scheme 5.24.



Scheme 5.25.

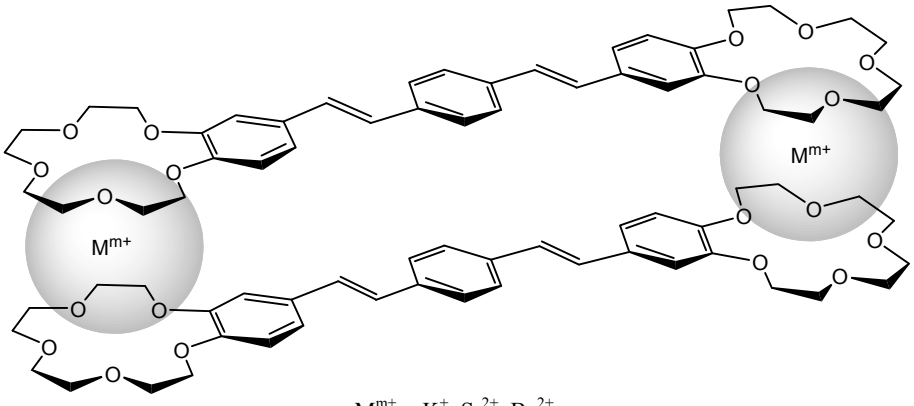


Scheme 5.26.



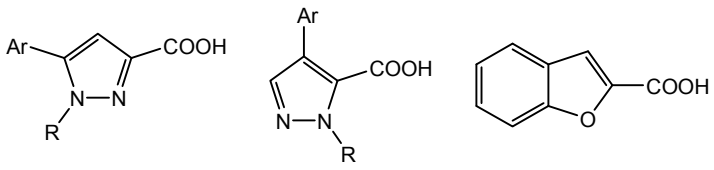
decisions on the conservation of the human health and ecosystems as a whole. In the laboratory of the physicochemical analytic methods this direction is connected with the study of contamination with organic compounds of water, earth, snow, air, biota in various regions of Europe and Asia, with the study of side products of drinking water disinfection [423–425]. Much attention is payed to the application of the most efficient methods of mass spectrometry including double-beam GC-MS, tandem mass spectrometry, high resolution mass spectrometry. The principal attention is focused on the search for new eco toxicants, compilation of lists of priority pollutants, detailed study of xenobiotics transformations in the environment. In particular, an efficient method was suggested of estimation of air pollution basing on the analysis of snow samples [423], lists of priority pollutants were compiled for Moscow [423], Baikal [424], and some other territories, the study of Arctic pollution was started. As examples of the study of transformation of natural and anthropogenic organic compounds under the conditions of preparation of drinking water publications [422, 425] may be cited.

Scheme 5.27.



$M^{m+} = K^+, Sr^{2+}, Ba^{2+}$.

Scheme 5.28.



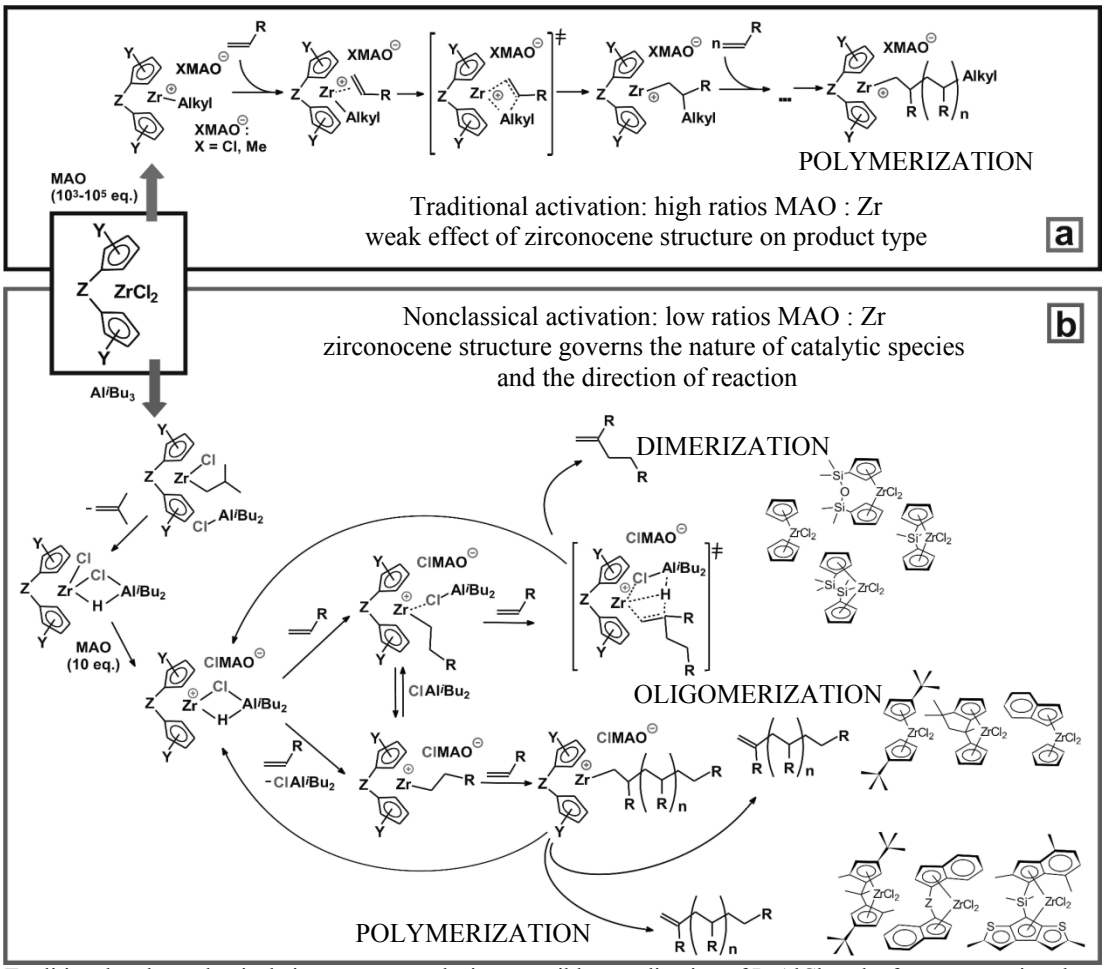
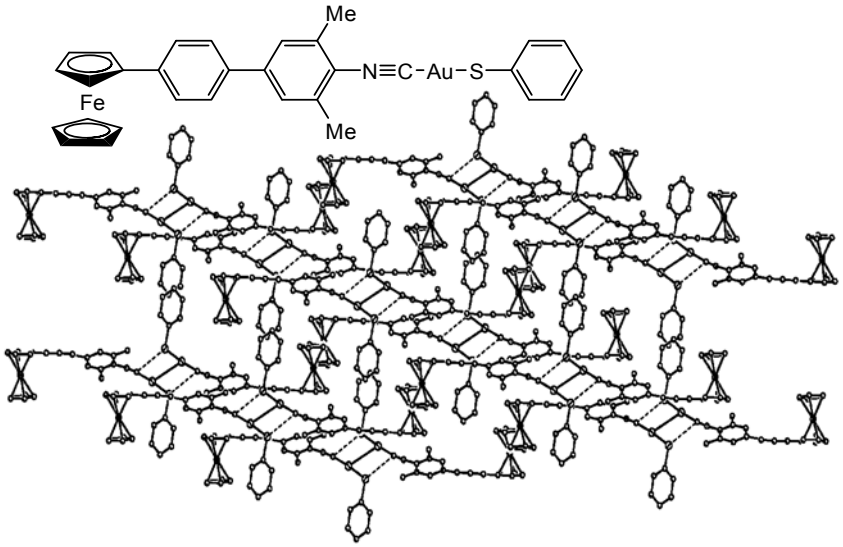


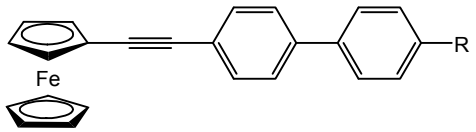
Fig. 5.3. Traditional and nonclassical zirconocene catalysis: reversible coordination of R_2AlCl as the factor governing the way of α-olefins transformation.

The microbial resistance to antibiotics is a serious problem for the modern pharmacology. One among the solutions to the problem is the preparation of drugs with another operation mechanism. A promising way consists in the application of natural antimicrobial compounds. In particular, a peptide secretion of amphibian is the only weapon of these animals both against the microorganisms and against predators. Yet the frogs live on our planet already for hundreds of millions of years. Ten years ago in the laboratory of physicochemical analytical methods research was commenced on sequencing of frog peptides. Within this time interval sequences were established in the laboratory for over 200 peptides, the method of mass spectrometric sequencing was considerably refined, reliable methods were suggested for overcoming the difficulties due to peptide length, the presence of disulfide bridges as well as the presence of isobaric and isomeric amino acids in the chain, to the cyclization of short peptides. An approach was found permitting establishing the amino acid sequence of any natural peptides [426–432]. A reliable method was implemented for differentiating isomeric leucine and isoleucine in the chain of a protein or a peptide applying tandem mass spectrometry [426], the problems were solved of sequencing inside disulfide cycles [427], and of short peptides cyclization [428]. Mass spectrometry made it possible not only to solve the issues of peptides sequencing, but also taxonomic problems. In particular, the studies provided a possibility to find peptides-biomarkers for distinguishing frogs of related kinds and even different populations of the same kind [429]. Frog peptides make it possible to classify reliably these amphibians. Moreover the use of isotope shifts and mass defects easily obtained from the clusters of molecular ions would suggest the type of biological activity of new peptides [429].

Scheme 5.29.



Scheme 5.30.



R = NO_2, NH_2, $(CH_2)_3COOH$.

Electrochemical methods alongside the solution of analytical problems may be used for directed redox activation of desired reaction sites in the reagent molecule thus providing an additional powerful instrument in the hands of synthetic chemist performing a directional organic synthesis. The contemporary requirements of the chemistry of stable progress put at the forefront the questions of environmental safety as well as of regio- and stereoselectivity of chemical processes. The electrochemical activation of reactions providing highly reactive species without the application of active metals and other ecotoxicants is in accordance with these trends, and it is widely used in the organic synthesis already for a long time. The pioneering direction in this field of research is the combination of directed electrochemical activation of the reagent on an electrode and the traditional ways of chiral induction in solution. This approach may be realized by introducing the reagent in the coordination sphere of a metal complex with a chiral ligand surrounding followed by electrochemically activated reactions. The efficiency of the suggested approach was demonstrated by an example of directed functionalization of amino acids in the coordination sphere of Ni(II) [433–436]. This allowed the preparation of direct precursors of optically pure formerly inaccessible amino acids of great practical interest. In particular, we prepared first specimens of functionalized α-fullerene-substituted amino acids [435]. Moreover, the stereoisomeric ($^{f,t}A$ and $^{f,t}C$) 1,4-adducts of C60 were isolated for the first time in the individual state [435]. Earlier this class compounds was obtained only as racemates.

The problems of chemical ecology are in the focus of attention in the ***laboratory of physical organic chemistry*** (**head of the laboratory Professor V.S. Petrosyan**). Lately everywhere, Russia included, the natural water sources are polluted with cyanobacteria and consequently with heterocyclic cyanotoxins preventing the use of these water sources for drinking water and recreation, in particular, for fish farming for amateur fishing. One among promising biotechnologies in this respect is the introduction (algalization) in the natural reservoir of a strain of green microalgae Chlorella vulgaris IFR no. C-111 [437–439]. Due to the special features of the development of this strain and the products of its life that contain hydrogen peroxide the cyanobacteria suffer a fast degradation. Recently a series of studies was carried out concerning

the exploration and refinement of this procedure. Several water reservoirs in Moscow suburbs were subjected to successive algalization [437–439].

Since 2008 a series of works performed in the laboratory concerns the selection of bioindicator of quality of water coming to the water treatment plant from natural water sources. These indicators should in shortest time provide information of the deteriorated water quality. A system was developed of continuous control of the natural water coming to the plant with respect to priority toxicants, among them those of organic and organometallic nature based on optical cardiography of freshwater mollusks [440]. For the development of this system the authors' group headed by V.S. Petrosyan was awarded in 2011 the National ecologic prize "EcoMir" (I place in the nomination "Scientific and technical achievements"). The threshold values were determined for the concentrations of versatile toxicants (heavy metals and organophosphorus pesticides) and optimization was carried out of the operation of this system [441, 442], and also an alternative approach was elaborated to the indication of the stress effect based on detecting the "simultaneous" changes in the characteristics of cardiorithms of mollusks regardless of their initial state and the character of changes. To qualitative and quantitative investigation the mixtures were subjected of organohalogen compounds forming in the course of natural water treatment [438, 439, 443].

In the ***laboratory of biologically active organic compounds*** since its foundation in 1969 the methodological basics of the preparation of new nitrogen heterocyclic compounds were traditionally performed: the general effective methods of the synthesis of substituted indoles and isomeric azaindoles, pyrazole derivatives, as well as the other nitrogen heterocycles. Another direction of research consists in looking for new reactions of activated electrophilic addition of weak electrophiles.

The research group of the **head of the laboratory**, **Doctor of Chemical Sciences**, **Professor N.V. Zyk** carries out the search for new electrophilic reagents for the reactions of electrophilic addition to unsaturated compounds (alkenes, alkynes, arenes, hetarenes, and cyclopropanes) of weak electrophiles activated with Lewis acids of diverse character. A method was developed of sulfate-activated electrophilic addition of *N*-, *S*-, and Hlg-containing electrophiles to alkenes at the use of sulfur trioxide (Scheme 5.31) [444].

The possibility of electrophilic nitrosation of cyclopropane ring was demonstrated accompanied with the subsequent heterocyclization (Scheme 5.32) [445, 446].

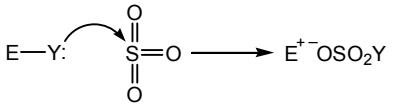
A simple, convenient, and universal synthetic method was developed for substituted sulfides, selenides, nitrates, nitrites, halides using as coreagents for weak electrophiles activation accessible inorganic compounds: phosphorus and silicon oxohalides and halides (Scheme 5.33) [447, 448].

The main research direction of the group of **Doctor of Chemical Sciences**, **Professor E.K. Beloglazkina** consisted in modeling the active centers of metalloenzymes and preparation of their synthetic analogs, low molecular model systems capable of performing various processes of synthetic organic chemistry with the efficiency and selectivity comparable with those in biochemical conditions. In most cases the maximum activity of the metal complex catalyst is attained at an appropriate choice of organic ligand providing the geometry of the coordination surrounding of the metal ion close to that present in the natural enzyme and the similarity of the redox characteristics of the model metal complex to those of the native enzyme. A series was prepared of copper- and cobalt-containing coordination compounds, functional analogs of N_2O [449] and NO-reductases [450], as well as nickel-containing complexes, catalysts of electrochemically induced alkylation reactions. Also the reactivity of organic ligands is studied in reactions with transition metal salts (oxidation and dehydrogenation of the ligand, nucleophilic substitution in the ligand molecule in the course of complex formation, heterocyclization and recyclization) (Scheme 5.34) [451].

In the group of **Doctor of Chemical Sciences**, **Professor A.G. Mazhuga** syntheses of new organic and coordination compounds are realized aimed at the search for new antitumor drugs. A series was synthesized and explored of 5-arylidene-substituted hydantoins, 2-thiohydantoins, and their *S*-alkylated derivatives, 1,3-oxazolones, imidazolones, and a number of dispirocompounds, products of 1,3-dipolar addition to the above mentioned heterocycles of azomethine ylides generated as a result of condensation–decarboxylation of *N*-alkylated amino acids and isatins (Scheme 5.35) [452].

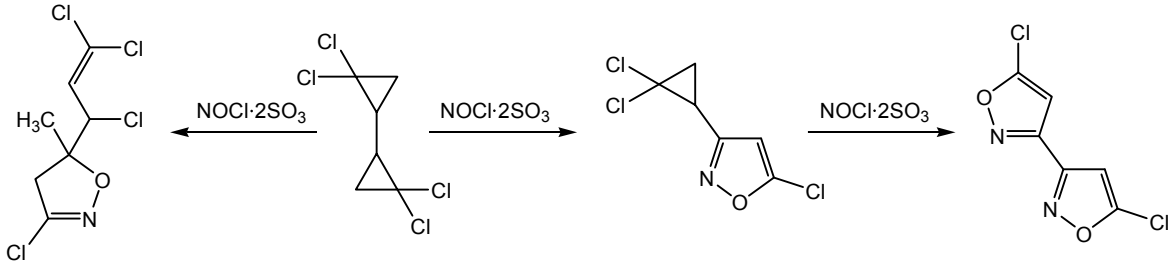
A general strategy was developed of the synthesis of biologically active coordination compounds of transition

Scheme 5.31.



E = Hlg, ArS, NO, NO_2; Y = Hlg, OR, NR_2, SO_2R etc.

Scheme 5.32.



metals with organic ligands of the series of imidazol-4-ones and imidazolin-4-ones based on the reliable synthesis methods found empirically and including a set of structural blocks, methods of their preparation, sequence and procedures for introducing the blocks in the structure of the molecule (Scheme 5.36) [453].

The research group of **Leading Researcher**, **Professor M.A. Yurovskaya** explores the methodological basics of the preparation of new nitrogen heterocyclic compounds. New convenient methods were developed of the synthesis of substituted indoles, isomeric azaindoles, azabenzofurans, and other nitrogen heterocycles [454–456]. Two fundamentally new approaches were advanced for the target of creating universal and efficient synthetic methods for this class compounds, involving in Fischer reaction the *N*-oxides of isomeric ketones pyridylhydrazones and extending to the synthesis of derivatives of isomeric azaindoles the previously developed method based of the intramolecular C–N bond formation catalyzed by copper and iron salts. The group has also a large practice in the synthesis of pyrazol-2-ines containing functional substituents in various positions of the pyrazoline ring. This provides a possibility to plan the synthesis of previously unknown substituted pyrazol-2-ines both proceeding from substituted benzaldehydes and from substituted arylhydrazines [457].

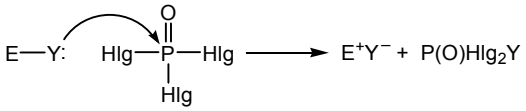
The field of studies of the scientific group of Doctor of Chemical Sciences, Professor V.I. Terenin is the chemistry of fused heterocycles with bridging nitrogen atoms [458]. Besides new synthetic aspects of Fischer reaction are investigated [459].

6. DEPARTMENT OF CHEMISTRY AT PIROGOV RUSSIAN NATIONAL RESEARCH MEDICAL UNIVERSITY

The modern stage of scientific studies started in 1973 when Yu.I. Baukov became the head of the department. He graduated from the Chemical Faculty of Lomonosov Moscow State University and was the disciple of Academician A.N. Nesmeyanov and Professor I.F. Lutsenko. Since 2011 the head of the department is V.V. Negrebetskiy that in 1992 graduated from Mendeleev Institute of Chemical Technology, now University of Chemical Technology of Russia. Research and development activity of the department includes several priority directions.

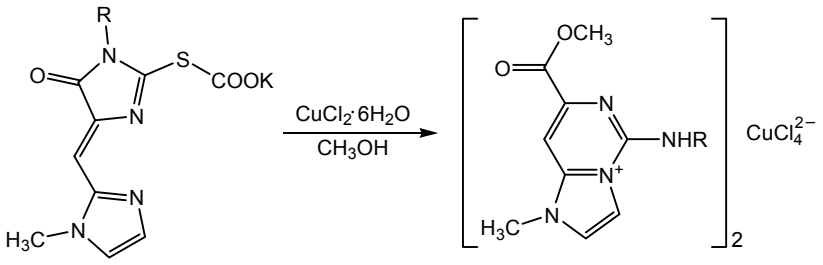
Hypervalent compounds of silicon, germanium and tin. Characteristic features of hypervalent (penta- and hexacoordinate) complexes is a coordination bond O–M (M = Si, Ge, Sn) determining the whole combination of physical, chemical, and biological properties of such complexes: unusual structure, frequently increased reactivity compared to common

Scheme 5.33.

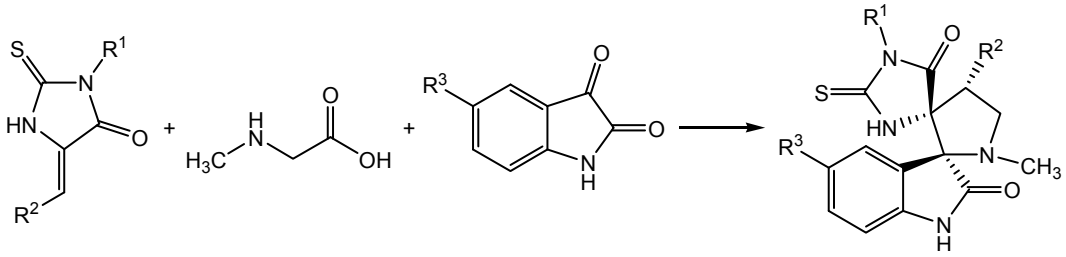


E = ArS, ArSe, NO; Y = NR_2, OR etc.

Scheme 5.34.



Scheme 5.35.



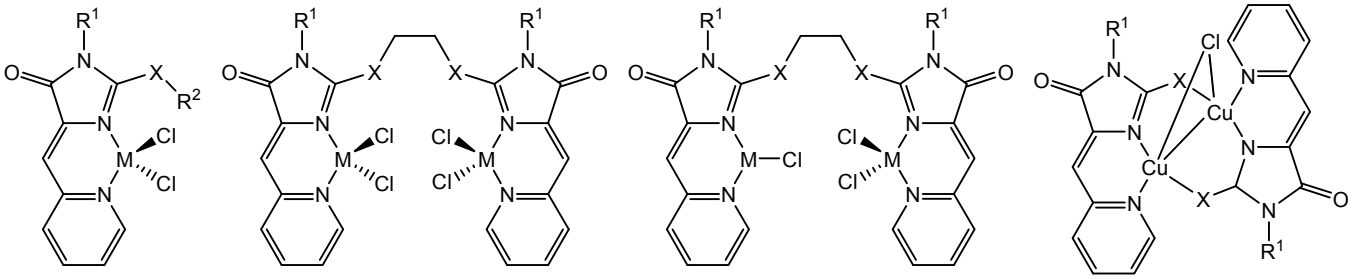
tetracoordinate compounds, stereochemical nonrigidity, and specific bioactivity. Neutral monochelate pentacoordinate [460–466] and bischelate hexacoordinate [467, 468] intra-complex compounds containing bidentate *C*,*O*-coordinating ligands were synthesized and investigated (Scheme 6.1).

The ionic intra-complex compounds has been obtained containing bidentate *O*,*O*- and *C*,*O*-coordinating ligands: bischelated pentacoordinate cationic complexes $\{XSi[OCH(R)C(O)NMe_2]_2\}Y$ (X= Cl, Alk, Ph, $BrCH_2$; R = H, Ph; Y = Cl, HCl_2, $HgBr_3$), tetrafluoroborates $[(LCH_2)_2Si(F)]BF_4$ (LCH_2 is monoanionic *N*-(methyl)acetamidomethyl, 2-oxoperhydroazepinomethyl, 2,2-dimethylbenzo-1,3-oxazin-4-one-3-methyl, and 4-methyl-2-oxoquinolinomethyl *C*,*O*-coordinating ligands) [469], germylium ions $\{ClGe[OCH_2C(O)NMe_2]_2\}HgCl_3$ [470], and enantolactam derivative, triflate $(L^8CH_2)_2Ge(Cl)OTf$ [468], and also tris chelate anionic hypercoordinated "mixed" complexes with a single potential *C*,*O*-chelate and two *O*,*O*-chelate ligands [471, 472] (**principal researcher A.G. Shipov** and **principal researcher A.A. Korlyukov**) (Scheme 6.2).

The work of **Assistant-Professors N.A. Kalashnikova** and **S.Yu. Bylikin** was focused on the synthesis and investigation of cationic (O,S)-bis chelates of silicon and germanium $[MeSi(CH_2COONMe_2)_2]Cl$ and $[MeSi(CH_2COONMe_2)_2]Br$ [473], and also new types of silacyclanes, a bicyclic silacyclane with a proline fragment [470] and 1-organosulfonyl-2-sila-5-piperazinones [474], precursors of hypercoordinated complexes in reactions of silacycle opening at the Si–N bond effected by various reagents (Scheme 6.3).

For many years these investigations are being performed in collaboration with Irkutsk Chemistry

Scheme 5.36.



X = S, Se; M = Cu, Co.

University of Siberian Branch of Russian Academy of Sciences (Academician M.G. Voronkov, Professor V.A. Pestunovich), laboratory of X-ray crystal analysis of Nesmeyanov Institute of Organoelemental Compounds of Russian Academy of Sciences (Corresponding Members of Russian Academy of Sciences Yu.T. Struchkov, M.Yu. Antipin, Doctor of Chemical Sciences A.A. Korlyukov), Razuvaev Institute of Organometallic Chemistry of Russian Academy of Sciences, Nizhniy Novgorod (Professor A.N. Egorochkin), Chemical Faculty of Lomonosov Moscow State University (group of Assistant-Professor G.S. Zaitseva), the Open University (Great Britain, Professors A. Bassindale and P. Taylor) [460–477].

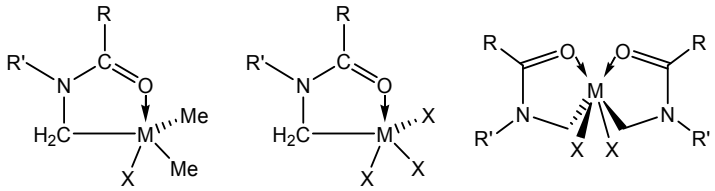
Chemistry of physiologically active compounds (nootropics and antioxidants). Nootropic drug phenotropil (karphedon), by nootropic activity significantly exceeding pyracetam and other known nootropics, possessing significant psychoactivating, anticonvulsant, antihypoxic, antitoxic and adaptogenic properties, was synthesized for the first time by researchers of department of chemistry of Russian National Research Medical University [478] (Scheme 6.4). For these results Professor Yu.I. Baukov, principal researcher A.G. Shipov, and senior researcher E.P. Kramarova were awarded a prize by the State foundation of intellectual project VIRA in science, industry, education and enlightment (2006). A new promising composition was patented exceeding phenotropil by a number of characteristics [479].

Methods of synthesis, investigation of structure and bioactivity of new zwitter ionic complexes of pentacoordinated silicon based on α-amino and α-hydroxy acids are intensively developed [480] (Scheme 6.5). Similar complexes of hypervalent silicon may be promising as medicines for treating lateral amiotrophic sclerosis, and also may demonstrate cardioprotective properties.

In continuation of the study of new heterocyclic system of 2-sila-5-piperazinone derivatives [474] at present a strategy has been developed of the synthesis on their basis of previously unknown *N*-sulfonyl derivatives of amino acids (glycine, alanine, proline, sarcosine). Besides, the synthesis and investigation of biological activity of new compounds is realized for chemically modified bioflavonoids, in particular, for known biologically active compound quercetin, directed on improving their antioxidant and antitumor action.

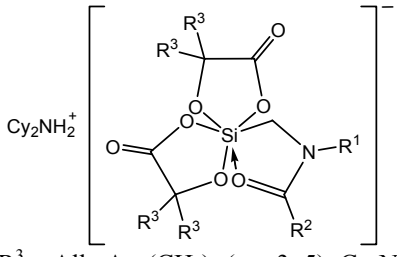
Preclinic tests and photochemical antibacterial therapy. In present time the department of chemistry along with department of medical chemistry and toxicology realizes preclinical tests (*in vitro* and *in vivo*) of potentially biologically active compounds either of our own preparations, or for other organizations. Investigations *in vivo* on laboratory test-systems (rodents) are realized in vivarium of barrier type, where animals are contained, not carrying specific pathogenic microflora, so these animals do not have hidden chronical diseases that may make unseen positive effect of application of drug, and also mask

Scheme 6.1.



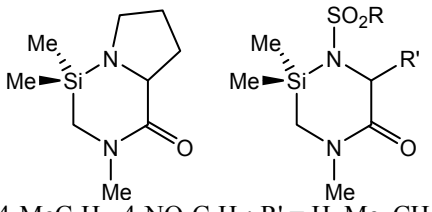
M = Si, Ge, Sn; X = Hlg; R, R' = Alk, Ar, $(CH_2)_n$ (*n* = 3–5); RC(=O) is a fragment of N-organosulfonylproline.

Scheme 6.2.



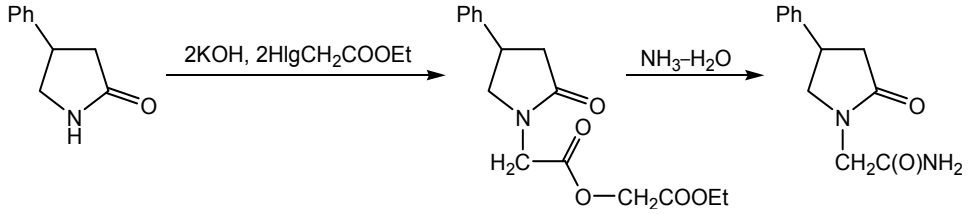
R^1, R^2 = H, Alk, Ar; R^3, R^3 = Alk, Ar, $(CH_2)_n$ (*n* = 3–5); Cy_2NH_2 is dicyclohexylamine.

Scheme 6.3.



R = Me, 4-MeC_6H_4, 4-$NO_2C_6H_4$; R' = H, Me, CH_2CHMe_2.

Scheme 6.4.



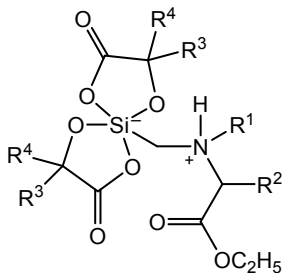
negative effects (animals of SPF type). Investigations are realized in GLP form.

Basing on measurements of absorption spectra of zinc phtalocyanine (ZnPc) tetrasulfonated cooper phthalocyanine and ($CuPcS_4$) in DMSO at increasing concentration of ZnPc and $CuPcS_4$ (from 1 to 14 μmol/L) a lack of aggregating ability of phtalocyanines in investigated conditions was established, while the corresponding spectra possess a typical form: B-band (Soret band) in the range 300–400 nm, electron-vibration band at 615 nm, strong absorption Q-band at 675 nm. Merocyanine 540, potential photosensitizer for photodynamic therapy, aggregates in aqueous solutions of NaCl at concentrations of salt exceeding critical concentration of aggregates formation [481].

7. DEPARTMENT OF ORGANIC CHEMISTRY AT MENDELEEV UNIVERSITY OF CHEMICAL TECHNOLOGY OF RUSSIA

Investigations of the department (**head of department Professor of Russian Academy of Sciences A.E. Shchekotikhin**) traditionally concern the development of the chemistry of heterocyclic compounds and their practical application. One of themes of the department (**Professor V.F. Traven'**) corresponds to the synthesis of coumarin derivatives and their analogs, and also to the development therefrom of fluorophores, fluorescent markers, photochromes, solvatochromic and sensor materials (**Assistant-Professors T.A. Chibisova**, **N.A. Pozharskaya**, **I.V. Ivanov** and others). Another field of investigations of the department is connected with the synthesis and investigation of properties of biologically active compounds. During the studies that started in nineteen eighties under the guidance of Professor N.N. Suvorov involving the synthesis and investigation of polyfused indol derivatives it was discovered that naphthoindoles (pyrroloanthraqinones) possessed a high biological potential. Therefore lately a thorough attention is directed on the development of methodology of the synthesis of hetarene-anthracenediones, on the systematic investigation of their chemical and biological properties, and on establishing structure–activity relationships.

Scheme 6.5.



Hlg = Cl, Br.

The investigation of derivatives of naphtho[2,3-*f*]-isatin-5,10-dione (naphtho[2,3-*f*]indole-2,3,5,10-tetraone) is a new direction in investigation of polyfused analogs of isatin. A preparative method was developed furnishing 4,11-dimethoxynaphtho[2,3-*f*]-isatin-5,10-dione and its *N*-alkyl derivatives, based on chlorination of naphtho[2,3-*f*]indole-5,10-diones with sulfuryl chloride with subsequent hydrolysis in acetic acid (Scheme 7.1) [482]. Besides effective methods were found of demethylation of 4,11-dimethoxynaphtho[2,3-*f*]-isatin-5,10-diones.

4,11-Dimethoxynaphtho[2,3-*f*]isatin-5,10-dione was transformed into acetonide, oxime, and thiosemicarbazone, structural analog of antiviral drug methisazone (Scheme 7.2). Moreover a method was developed of modification of naphthoisatins into derivatives of 2-aminonaphtho[2,3-*f*]indole-3,5,10-trione consisting in the halogenation of isatin by phosphorous pentachloride followed by treating with alkylamines [482].

Gramin analogs of in the series of naphtho[2,3-*f*]-indole-5,10-dione possess a high biological activity. Series of new 3-aminomethylnaphtho[2,3-*f*]indole-5,10-diones were synthesized, containing residues of cyclic diamines, where the most promising were the derivatives of 3-aminopyrrolidine (Scheme 7.3) [483].

3-Aminomethylnaphtho[2,3-*f*]indole-5,10-diones in submicromolar concentrations inhibit the growth of tumorous cells. In tests *in vivo* on model of lymphoid malignancy P388 it was discovered that the derivative of (*R*)-3-aminopyrrolidine possessed a high antitumor activity and in a dose of 30 mg/kg increases life span of animals by 55%, while its antipode summons toxic death of animals at the same mode of administration [484].

The modification of naphthoindole (Scheme 7.3) applying "scaffold hopping approach" resulted in identification of multitarget antitumor 4,11-dihydroxyanthra[2,3-*b*]furan-3-carboxamides [484]. The discovered chemotype not only possesses a high antitumor activity, but is also attractive by the synthetic accessibility of this class of derivatives (Scheme 7.4).

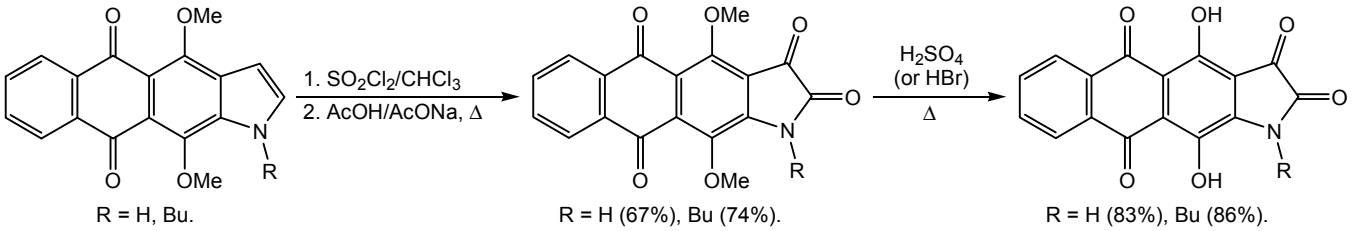
Amides of anthrafuran-3-carboxylic acid bind to DNA and block the activity of topoisomerases 1 and 2, and also of a number of protein kinases that is the reason of their high cytotoxic activity and the ability to overcome MDR mechanisms of tumor cells [486]. An alternative method was developed for the preparation of derivatives of anthra[2,3-*b*]furan-3-carboxylic acids based on similar method of heterocycle fusion [485]. The key stage is the formylation at the activated methylene group of esters of 2-(3-haloanthraquinon-2-yl)acetic acids. Claisen condensation of esters with methyl formiate in the presence of NaH gives esters of 2-(3-haloanthraquinon-2-yl)-2-formylacetic acids (Scheme 7.5). The cyclization of obtained esters in the presence of K_3PO_4 and CuI results in the desired methyl ester of 4,11-dimethoxy-5,10-dioxoanthra[2,3-*b*]furan-3-carboxylic acid in a moderate yield (35–43%).

An original scheme was developed for the synthesis of hetaroarenanthracenediones containing primary amino groups in positions *4*, *11* based on the oxidative dealkylation of alkylamino groups [486]. While *peri*-alkoxy groups in hetaroarenanthraquinones are activated for nucleophilic substitution due to the acceptor effect of the quinone fragment, this method was effective also for the preparation of 4,11-diamino derivatives. By the reaction with *n*-butylamine a series of 4,11-dibutylamino derivatives was synthesized, which were subjected to the oxidative dealkylation and treatment with $(n\text{-Bu})_4NOH$ in DMSO to obtain a number of furan- and thiophene-fused derivatives of anthraquinone (Scheme 7.6).

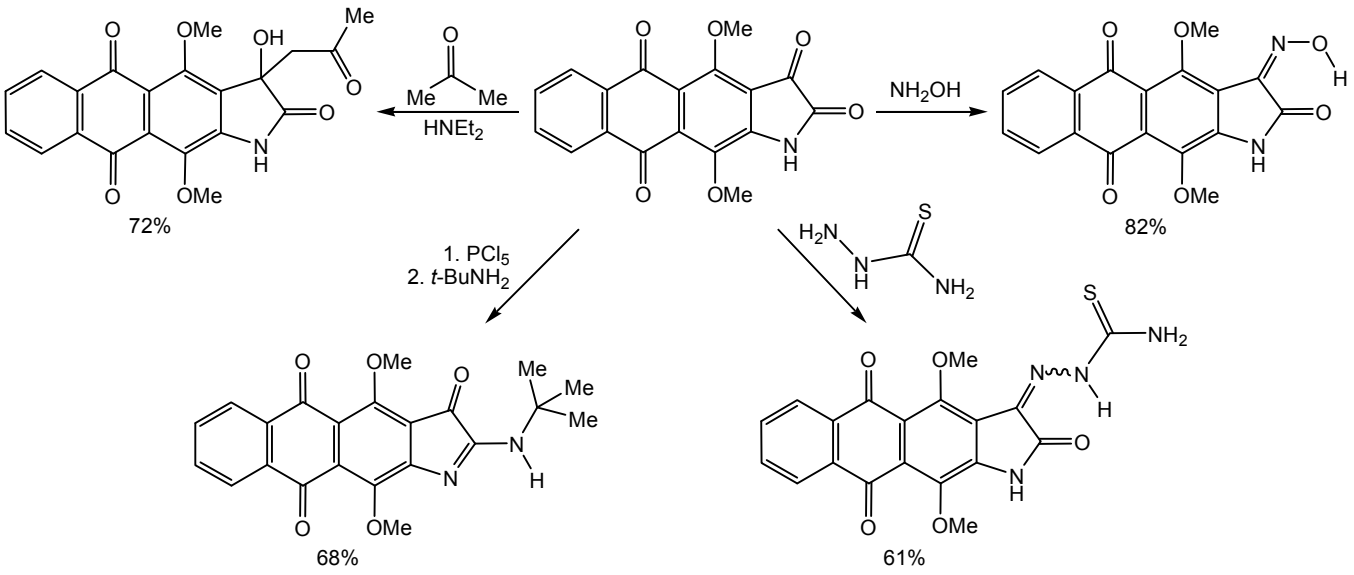
4,11-Bis(aminoalkylamino) derivatives of hetaroarenanthracenediones are another important chemotype demonstrating promising characteristics for development of new antitumor compounds based on anthraquinone. By reaction of 4,11-dimethoxyanthra[2,3-*b*]thiophene-5,10-diones and 4,11-dimethoxyanthra[2,3-*b*]furan-5,10-diones with diaminoalkanes a series of thiophen- and furan-fused analogs of antitumor drug Ametantrone was obtained [487, 488]. By transformation of the terminal amino groups (R^1 = R^2 = R^3 = H) of hetaroarenanthraquinones into guanidine group by treatment with pyrazolocarboxamide bisguanidines were obtained (Scheme 7.7). The screening of the antiproliferative activity showed that the majority of derivatives block the growth of tumor cells in submicromolecular concentrations, and anthrafuranes exceed activity of the sulfur-containing analogs. Bisguanidines of the series of 4,11-diamino derivatives were the most active inhibitors of topoisomerases 1 and 2.

High antitumor potential of 4,11-diamino derivatives of anthra[2,3-*b*]furan-5,10-diones and their multitarget effect on the series of intracell targets stimulated the search for new universal paths of their

Scheme 7.1.



Scheme 7.2.

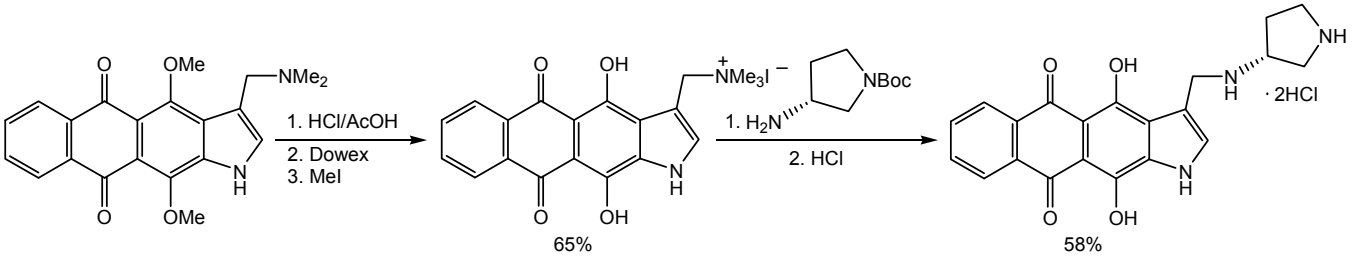


synthesis, allowing to realize diversification of substituents in heterocyclic scaffold [489]. A new highly effective method was developed for the preparation of 2-substituted 4,11-dimethoxyanthra[2,3-*b*]furan-5,10-diones based on Pd-catalyzed cross-coupling/heterocyclization (Scheme 7.8) [490, 491].

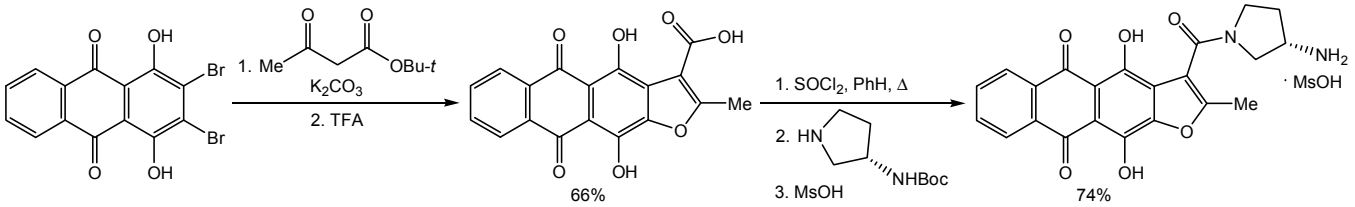
Angular derivatives of anthracene-9,10-dione are also interesting for the search of antitumor compounds and are investigated by research groups in many countries. In the course of collaboration with NDMC of Taiwan 4-substituted anthra[1,2-*c*][1,2,5]-thiadiazole-6,11-diones were synthesized and their biological properties were investigated (Scheme 7.9). Subsequent reactions of anthra[1,2-*c*][1,2,5]-thiadiazole-6,11-dione with alkyl- and arylmercaptans catalyzed with iron(III) chloride or cooper(II) acetate afforded a series of 4-*S*-substituted derivatives [492]. For the most active compound (R = *i*-Pr) the average concentration inhibiting to 50% the growth of cells on a panel of NCI-60 human tumor cell lines was GI_{50} = 1.6 μmol/L.

New direction of scientific research of the department was the investigation of chemical properties of polyfunctional antibiotics and the search for promising ways of their transformation. Thus selective methods were developed for modification of macrolide antibiotic oligomycin A. The most interesting is the modification of the hydroxy group in

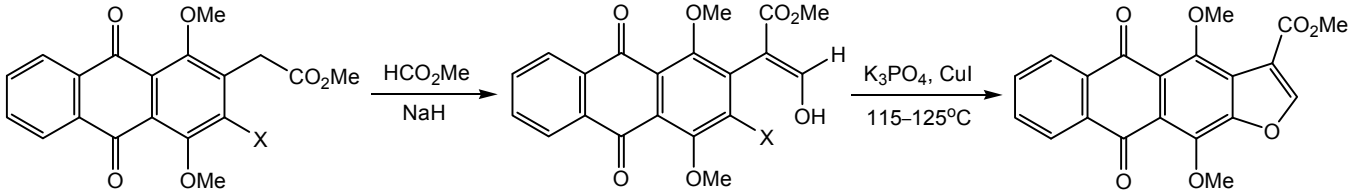
Scheme 7.3.



Scheme 7.4.



Scheme 7.5.



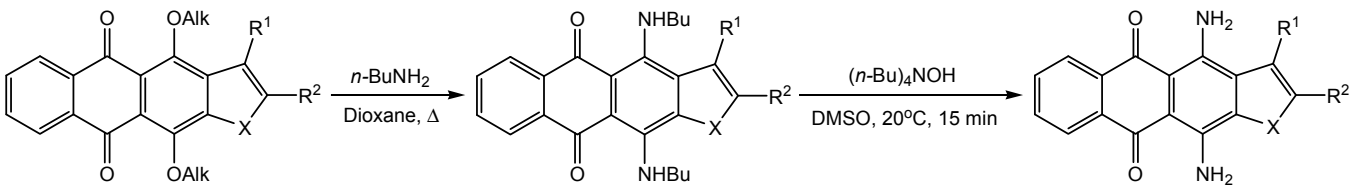
the position *33* of oligomycin, because it is important for binding with target ATP-synthase. Aiming at the preparation of semisynthetic oligomycins a method of the synthesis of 33-halo derivatives of oligomycin A was developed (Scheme 7.10) [493].

Introduction of a bromine atom in the side chain of oligomycin A reduces the activity of the derivative practically 500 times with respect to actinomycetes *Streptomyces fradiae* ATCC-19609 (the strain hypersensitive to oligomycin A and its derivatives) and *S. albus* ATCC-21132. One more example of modification of the position *33* of oligomycin A was the synthesis of 33-dehydrooligomycin A (Scheme 7.10) [494]. The transformation of group $C^{33}OH$ into a keto group results in increasing the antiproliferative activity of the derivative (comparing to the initial one) with respect to the cell line of myeloid leukemia K562 and in decreasing the cytotoxicity with respect to the normal human cells. The hydrogenation of the antibiotic on palladium catalyst occurs both at α,β-unsaturated bond of lactone and at the diene system in the positions C^{16}–C^{19} providing 2,3,16,17,18,19-hexahydrooligomycin (Scheme 7.10) [495]. The reduction of all C–C bonds results in a significant decrease in the biological activity of oligomycin A with respect to *S. fradiae* and filamentous fungi, and also reduces the toxicity of antibiotic in comparison to the cells of mammals. However perhydrooligomycin A preserves a high activity against *Candida spp.*, including the strain *C. crusei* resistent to fluconazole.

One of the most promising directions in the construction of highly productive systems of recording information, capable on preserving, reproducing, and processing high amounts of data, is the preparation of polylayer polymer optical disks providing dozens of times increase in their information capacity as compared to contemporary carriers. In such polylayer optical disks the information recording is performed using photofluorescent registering media containing fluorescent precursors, effective fluorophores in a latent form. However the required UV radiation is frequently considerably hard and may cause the deterioration of photoproduct.

The radiation of the precursor in the presence of acid photogenerator (APG) is less destructive. The role

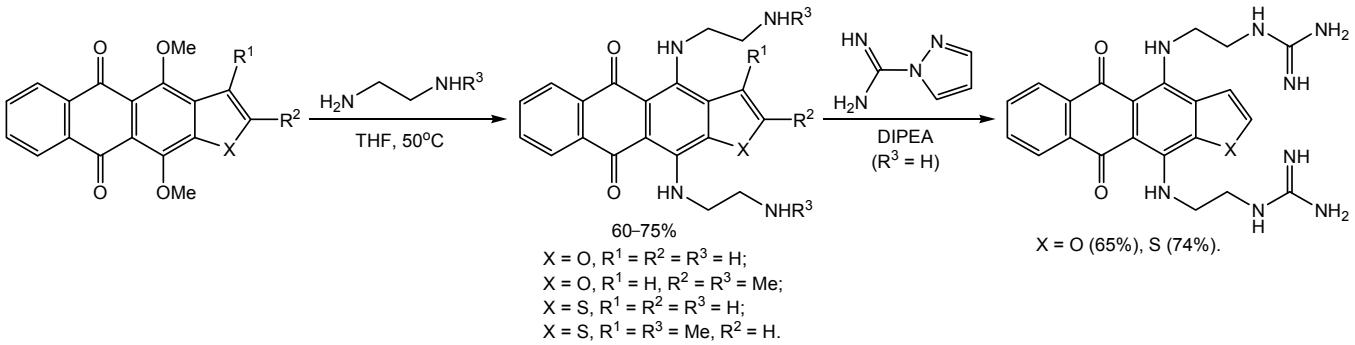
Scheme 7.6.



X = O, R^1 = R^2 = H;
X = O, R^1 = H, R^2 = Ph;
X = O, R^1 = CO_2Et, R^2 = Me;
X = S, R^1 = R^2 = H;
X = S, R^1 = Me, R^2 = H.

X = O, R^1 = R^2 = H;
X = O, R^1 = H, R^2 = Ph;
X = O, R^1 = CO_2Et, R^2 = Me;
X = S, R^1 = R^2 = H;
X = S, R^1 = Me, R^2 = H.

Scheme 7.7.

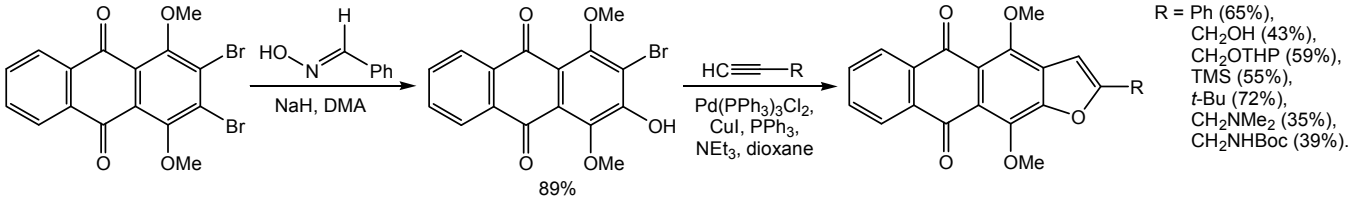


of APG here is to transform the molecules of fluorescent precursor (cleavage of protective group [496, 497], opening of lactone/lactam cycle of leuko-base [498–500], protonation of amino groups) in order to change the intensity of the fluorescent signal or to shift it into the range of longer waves. As APG photosensitive, thermally stable compounds are applied that after excitation with light of suitable length undergo photochemical transformation with acid generation.

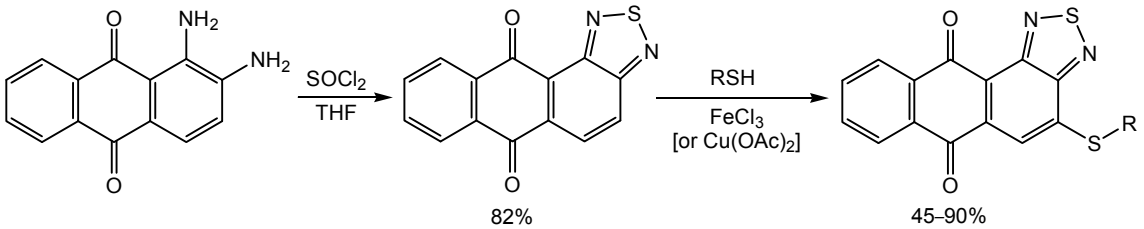
Dihydrohetarenes are highly promising photogenerators, capable under radiation to undergo dehydrogenation with generation of protons at softer radiation. Previously at the department a reaction of photodehydrogenation of 4-hydroxy-3-pyrazolinylcoumarins was discovered. These compounds are accessible in preparative yields and undergo photodehydrogenation at irradiation (420 nm) in solution of tetrachloromethane at room temperature affording practically in quantitative yield the corresponding pyrazole [501–507]. This reaction proceeds not only in CCl_4, but in other solvents in the presence of substrates containing trihalomethyl fragments. It occurs smoothly, for example, in toluene in the presence of hexachloroethane. Similar transformations undergo various aryl(hetaryl)pyrazolines, and also other dihydrohetarenes: Hantzsch dihydropyridi-nes, pyrrolines, benzothiazolines. It may be assumed that the reaction of photodehydrogenation of dihydrohetarenes proceeds by the scheme similar to, e.g., photoinduced reaction of pyrazolines (Scheme 7.11).

Aryl(hetaryl)pyrazolines are suitable as APG for opening lactone forms and activation of fluorescence of rhodamine dyes. This was demonstrated by an example of lactone forms of Rhodamine B and Rhodamine 19 [505]. Thus the irradiation of a toluene solution of pyrazoline and lactone Rodamine B in the presence of hexachloroethane results in pink coloration of the solution (absorption band λ_{max} 560 nm) and the appearance of a fluorescence band with a maximum at 587 nm that indicates the accumulation of the open form of Rodamine B in solution (Scheme 7.12).

Scheme 7.8.

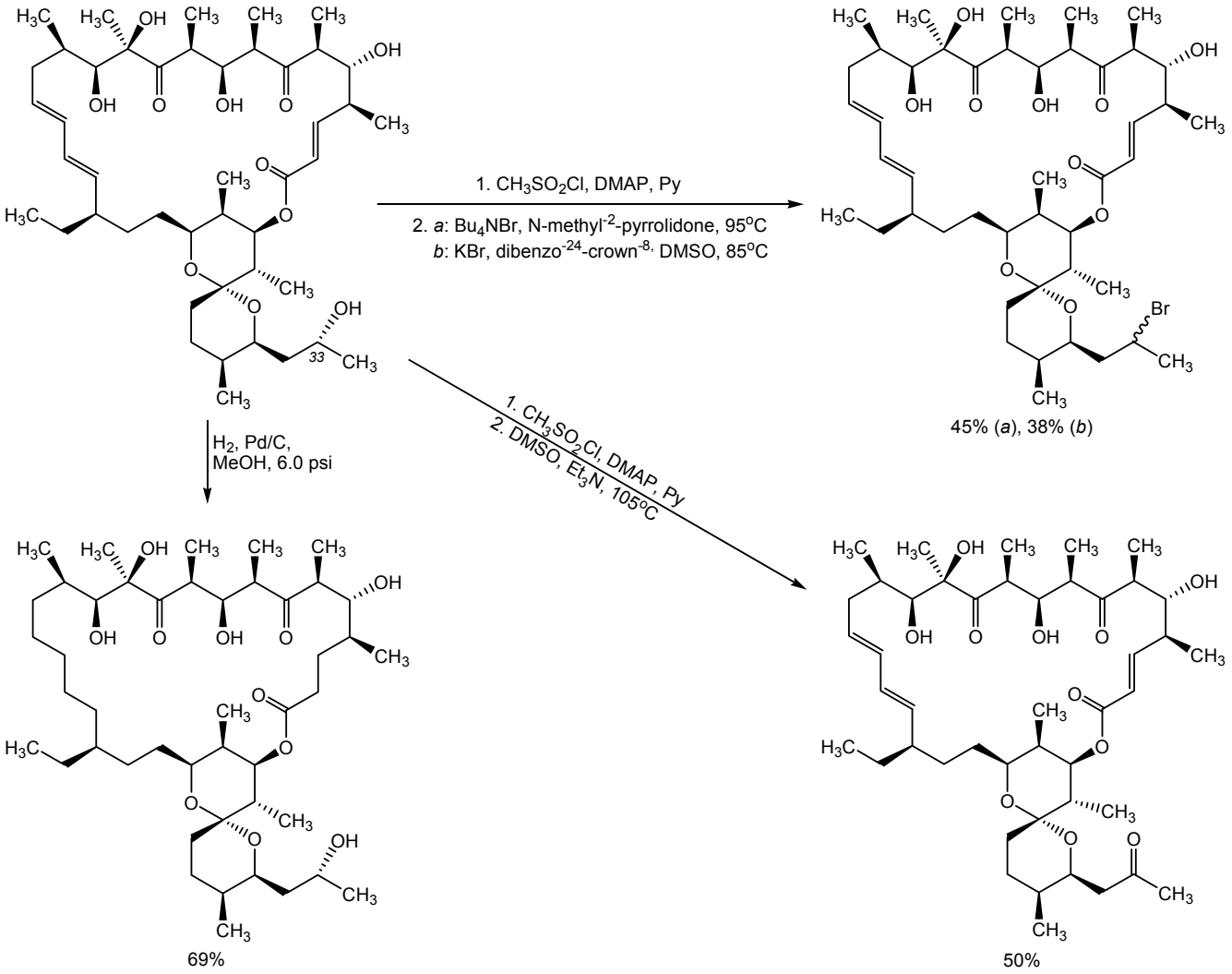


Scheme 7.9.



R = Alk, Ar.

Scheme 7.10.



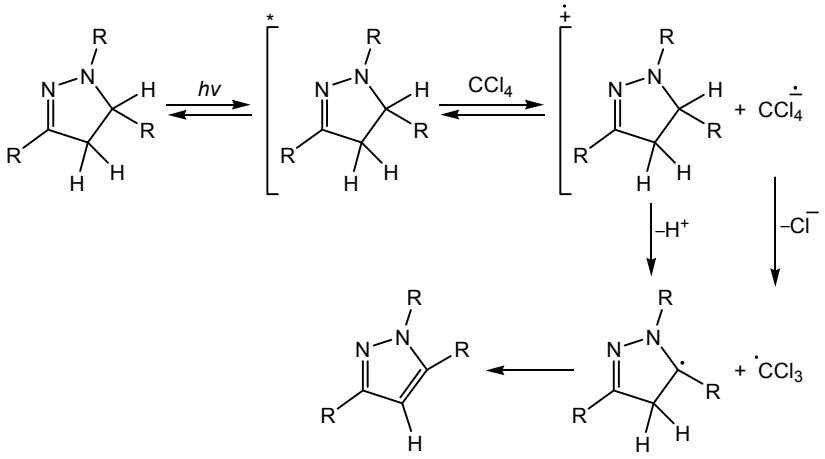
The irradiation on aryl(hetaryl)pyrazolines in polymeric films in the presence of hexachloroethane and lactones of rhodamine dyes is also followed by activation of fluorescence of dyes. This fact shows the promising properties of the studied media for optical recording of information with fluorescent readout [507]. As in case of solutions, the irradiation of lactone Rhodamine B in poly(methyl methacrylate) film in the absence of pyrazoline does not result in any spectral changes.

Data on successful application of photogenerators of acidity to destruction of cancer cells was obtained. Photodynamic therapy (PDT) of cancerous diseases in classic version is based on the action of singlet oxygen generated during the irradiation of dye-sensitizer in cancerous tissues. However the affected cancerous tissues are distinguished by deteriorated vascular system that lowers the PDT effectivity. Methods not connected with the transfer of singlet oxygen may turn out to be an effective alternative. First patents on the application of photogenerators of acidity of the type 2-nitrobenzaldehyde for targeted therapy of cancerous diseases were obtained [508]. Actuality of the synthesis of new photogenerators of acidity capable to work close to the IR absorption range thus is evident also for biochemical issues. Condensed heteroaromatic compounds possessing a developed π-electron system are highly promising for these goals [509].

8. DEPARTMENT OF ORGANIC CHEMISTRY AT PEOPLES' FRIENDSHIP UNIVERSITY OF RUSSIA

Since the moment of foundation in 1960 the department was really a department of heterocyclic chemistry. To 2005 three distinct scientific directions formed in

Scheme 7.11.



the department: Tandem transformations of (hetero)-fused azaheterocycles under the effect of activated alkynes; intramolecular [4+2]-cycloaddition in *N*-alkenyl-substituted furfurylamines (IMDAF reaction); oxidative transformations of piperidines derivatives. A little later (in year 2009) they were supplemented by the theme of domino-reaction of *N*-cyanomethyl salts of azaheterocycles with *ortho*-hydroxybenzaldehydes.

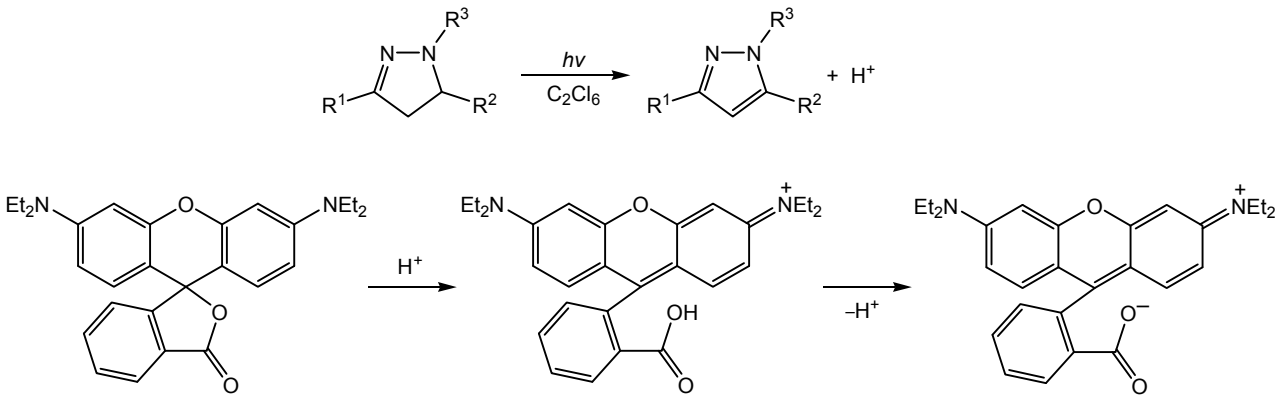
Tandem transformations of (hetero)fused azaheterocycles under effect of activated alkynes. The reaction of ring expansion of fused tetrahydropyridine cycle under the effect of activated alkynes [510] discovered at the department in 2002 (**Doctor of chemical sciences A.V. Varlamov**, **Doctor of chemical sciences L.G. Voskresenskii**, and **Candidate of chemical sciences T.N. Borisova**) in the following years was intensively studieded on diverse substrates (Scheme 8.1) that allowed finding new channels of transformations and establishing the application limits of this interesting transformation [511, 512].

Within further development of this topic new multicomponent reactions were found with participation of isonitriles (Scheme 8.2) [513], the ring expansion by three carbon atoms of tetrahydropyridine ring in quaternary salts of carbolinium was described [514] (Scheme 8.3), and a unique synthesis was developed of heterocyclic allenes, derivatives of benzazecine (Scheme 8.4) [515].

Intramolecular [4+2]-cycloaddition in *N*-alkenyl -substituted furfurylamines (IMDAF reaction). Another intensively developed direction of research at the department (**Candidate of chemical sciences F.I. Zubkov** and **Doctor of chemical sciences A.V. Varlamov**) is the investigation of intramolecular Diels–Alder reaction of furans (IntraMolecular Diels-Alder Furan IMDAF) [516]. Due to accessibility of initial reagents this transformation was explored mainly by an example of the reaction of substituted and fused furfurylamines with anhydrides of αβ-unsaturated carboxylic acids.

First study on this subject consisted in the synthesis and aromatization of 3a,6-epoxyisoindoles in phospho-

Scheme 7.12.



ric acid (Scheme 8.5) [517]. Later it was established [518] that the basic catalysis of epoxide cycle opening was more effective, and yields of 7-isoindolocarboxylic acids were higher, especially at aromatization of epoxyisoindoles fused with other ali(hetero)cycles. The simplicity of experimental arrangement distinguishes this approach from the previously described acid-catalyzed methods of opening of 7-oxobicyclo[2.2.1]heptene fragment.

Continuation of these studies consisted in the application of phosphoric acid for realization of the simultaneous reaction of aromatization – electrophilic cyclization in 3-allylepoxyisoindoles [519–521] that easily formed at acylation with maleic anhydride of homoallylamines, products of reaction of aldimines with allyl- or methallylmagnesium halides.

Heating of methallyl-substituted oxabicycloheptenes (n = 0, R^1 = Me) in H_3PO_4 in one stage affords isoindolo[2,1-*a*]quinolinecarboxylic acids in moderate to good yields (Scheme 8.6). The cyclization of allyl analogs (n = 0, R^1 = H) demands more rigid conditions. In the last case mixtures of diastereomers of 5-monomethyl-substituted (R^1 = H) are formed with respect to the positions of atoms H^5 and H^{6a} in the ratio 3.5 : 1–12 : 1 with *cis*-isomer prevailing.

Similarly the acylation with maleic anhydride of α-furyl-*N*-benzylaminobutenes (n = 1) leads as a result of IMDAF reaction to epoxyisoindoloazepinecarboxylic acids in up to quantitative yields (Scheme 8.7). Processing of obtained epoxy derivatives with polyphosphoric acid makes it possible to synthesize practically interesting isoindolobenzazepinecarboxylic acids.

The structural motif of a series of physiologically active alkaloids is a scaffold of isoindolo[1,2-*a*]-isoquinoline. Basing on IMDAF reaction between hydrated 1-furylisoquinolines and anhydrides of αβ-unsaturated acids a new approach was suggested to alkaloids jamthin and novamine [522, 523] (Scheme 8.7). 1-Furyl-1,2,3,4-tetrahydroisoquinolines (obtained by reactions Pictet–Spengler or Bischler–Napiralski) react with unsaturated anhydrides in relatively mild conditions (25–110°C) giving exclusively *exo*-adducts resulting from [4+2]-cycloaddition. Only at the application of citraconic anhydride a mixture of regioisomers **A** and **B** formed distinguished by the position of methyl group. Further acid- or base-catalyzed opening of epoxide bridge in the formed adducts and simultaneous aromatization results in the formation of close structural analogs of alkaloids mentioned above.

The procedures described above based on successive reactions of acylation/intramolecular cycloaddition of unsaturated anhydrides to furfurylamine fragment of tetrahydroisoquinolines was successfully extended also to 2-furyltetrahydroqui-nolines, providing a possibility to carry out a synthesis of isoindolo[2,1-*a*]quinoline-carboxylic acids in one stage (Scheme 8.8). So, three component condensation of furfural, substituted anilines, and *N*-vinylpyrrolidine in the presence of *p*-TsOH in yield up to 98% furnished 2-furyl-tetrahydroquinolines that at boiling in toluene with maleiic anhydride underwent IMDAF reaction with the formation of the system of isoindolo-[2,1-*a*]quinoline (Scheme 8.8) [524].

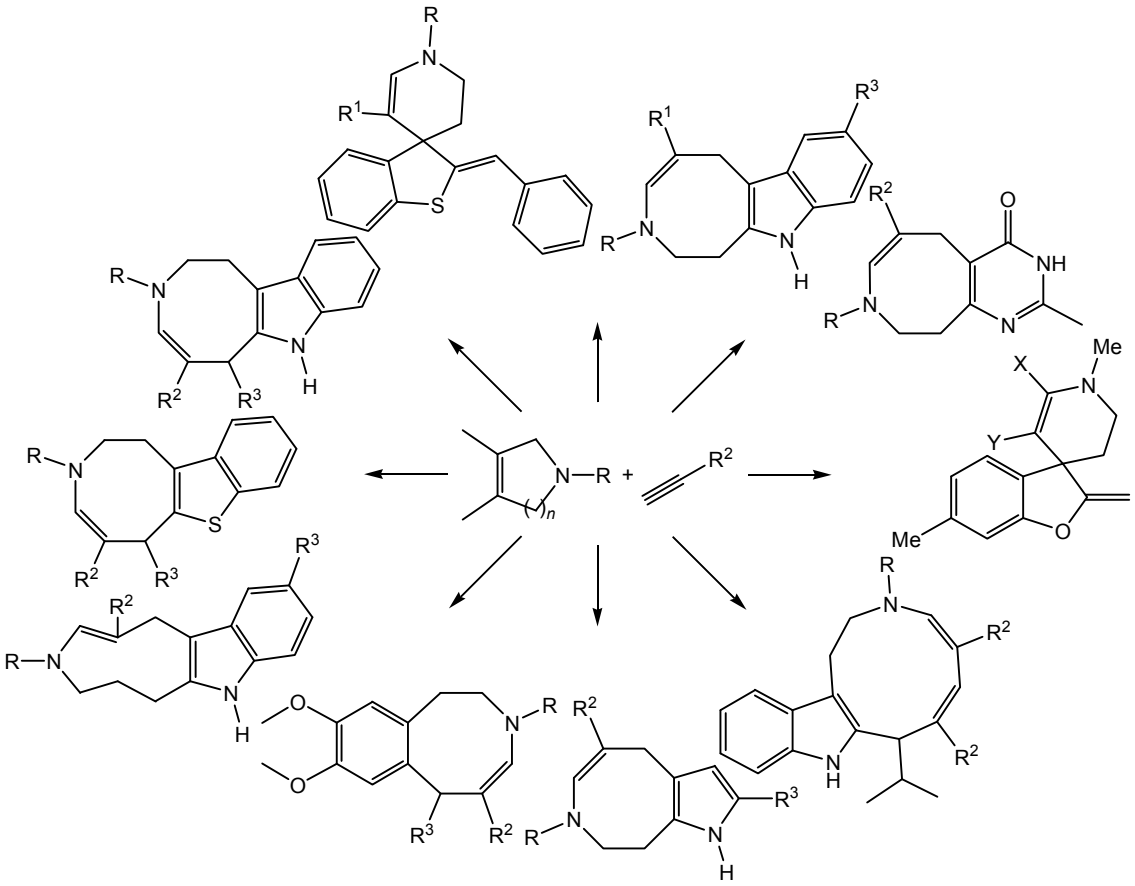
2,6-Difuryl-substituted piperidines, piperidin-4-ols, and piperidin-4-ones react with maleic anhydride or acryloyl chloride only at one furan ring with the formation of 8,10a-epoxypyrido[2,1-*a*]isoindoles and their 7-carboxylic acids, products of IMDAF reaction (Scheme 8.9) [525]. The cycloaddition proceeds regio- and stereoselectively, and in case of unsymmetrically substituted initial substrate, also chemoselectively.

In 2014 an original method of synthesis was advanced for epoxyisoindoles fused with oxazine, oxazole, thiazine, thiazole, pyrimidine and other heterocyclic fragments, and also with their benzofused analogs [526]. The condensation of furfurals with 1,2- and 1,3-binucleophiles (aminoalcohols, aminothiols, diamines) proceeds smoothly and results in acyclic isomethines that are in tautomeric equilibrium with their cyclic forms. The presence in the latter of a furfurylamine fragment allows a realization of the chemoselective tandem reaction of *N*-acylation/[4+2]-cycloaddition, ending with the formation of fused epoxyisoindolones in one stage (Scheme 8.10).

Depending on nature of heteroatom X, the size of the fused ring (n), and temperature of reaction the cycloadducts may form either as a single diastereo-oisomer, or as a mixture of position isomers with respect to the nodal proton (Scheme 8.11).

Intramolecular [4+2]-cycloaddition in vynil-arenes (IMDAV reaction). The development of strategy of consecutive acylation/intermolecular [4+2]-cycloaddition of furfurylamines by anhydrides of unsaturated carboxylic acids (IMDAF reaction) was an introduction into similar transformations of their vinylogous compounds, easily accessible (3-furyl)-allylamines (Scheme 8.12) [527].

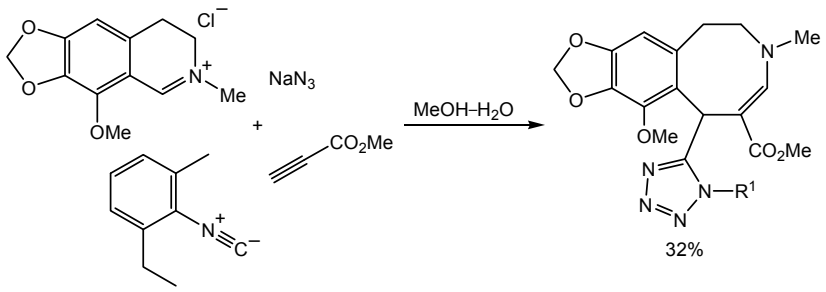
Scheme 8.1.



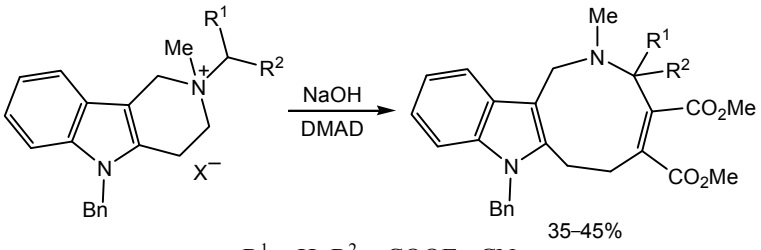
In this case in the intramolecular Diels-Alder reaction only one double bond of furan and the vinyl fragment of the formed maleinamide (IMDAV reaction) take part as the diene component. Initial reagents for these transformations are accessible furyl acroleins that through intermediate azomethines are converted into R^2-*N*-allylamines. The latter without additional purification are introduced into IMDAV reaction (Scheme 8.13) and through the stage of acylation/[4+2]-cycloaddition/proton shift are transformed into the target furo[2,3-*f*]isoindoles. The reaction proceeds stereospecifically with the formation of a single diastereomer. In reaction not only (3-fur-2-yl)allylamines may be introduced, but also their regioisomers (3-fur-3-yl)-allylamines as well as vinylthiophenes and styrenes of similar structure.

Wagner-Meerwein rearrangement in epoxyisoindols. Epoxyisoindoles synthesized as described above, while possessing several reactive sites, may be involved in a wide range of transformations. However the most interesting reaction from theoretical and aesthetic point of view is the skeletal Wagner-Meerwein rearrangement to which are susceptible

Scheme 8.2.

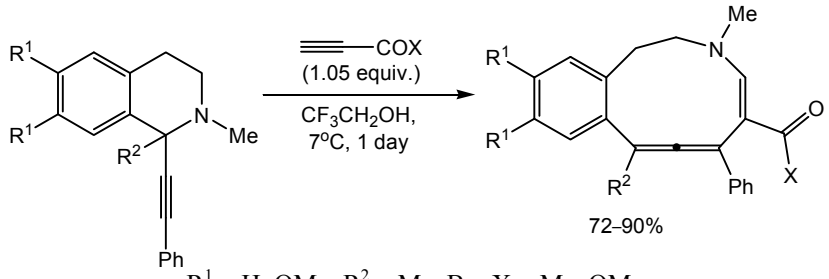


Scheme 8.3.



R^1 = H; R^2 = COOEt, CN

Scheme 8.4.



R^1 = H, OMe; R^2 = Me, Bn; X = Me, OMe.

almost all synthesized diepoxyisoindoles that are easily obtained at the treatment of monoepoxyisoindoles with *meta*-chloroperbenzoic acid (*m*-CPBA) [528]. The best conditions for cation-catalyzed rearrangement of diepoxides is the application of acetic anhydride as solvent and boron trifluoride etherate as Lewis acid. Under identical conditions methyl esters with *exo*-oriented ester group undergo the skeleton rearrangement (Scheme 8.14).

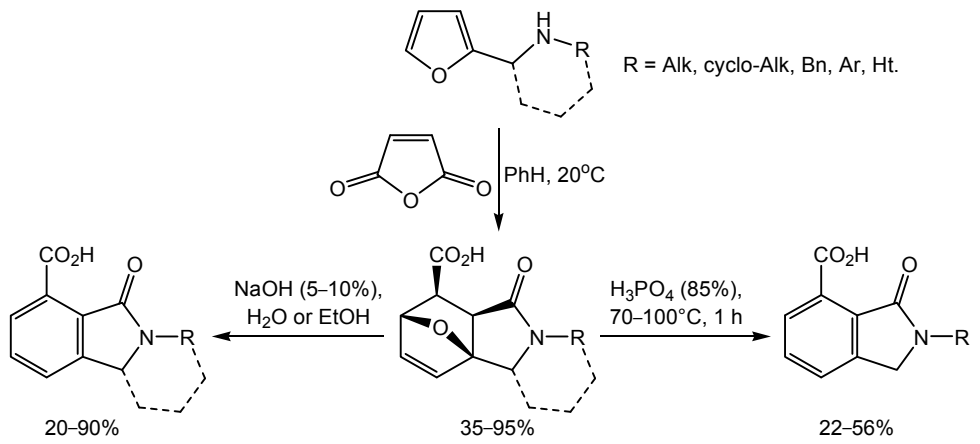
On the contrary, diepoxides with the *endo*-oriented ester group undergo only intramolecular cyclization transforming into the corresponding lactones (Scheme 8.15).

Oxidative transformations of tetrahydropyridine derivatives with a conjugated exocyclic double bond. This direction of studies of the department was performed by the group of Professor A.T. Soldatenkov. Oxidative C–C- and C–N-coupling reactions of tetrahydropyridines with C–H- and C–N-acids were described (Scheme 8.16) [529].

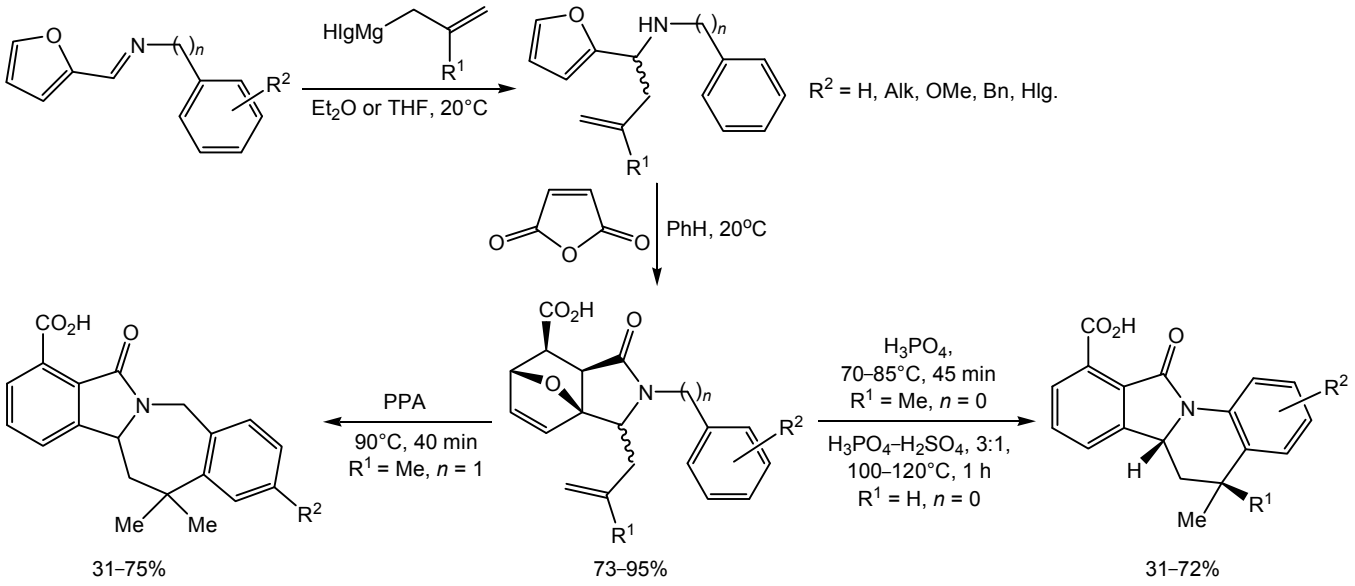
Basing on oxidized form of tetrahydropyridine derivatives bicyclic heterocycles, including boron containing, were successfully synthesized (Scheme 8.17) [530].

Domino-reaction of *N*-cyanomethyl salts of azaheterocycles with *ortho*-hydroxybenzaldehydes. First publication on this topic (**Doctor of chemical sciences L.G. Voskresenskiy** and **Candidate of chemical sciences A.A. Festa**) appeared in 2010. Basing on the reaction of *N*-(cyanomethyl)iso-

Scheme 8.5.

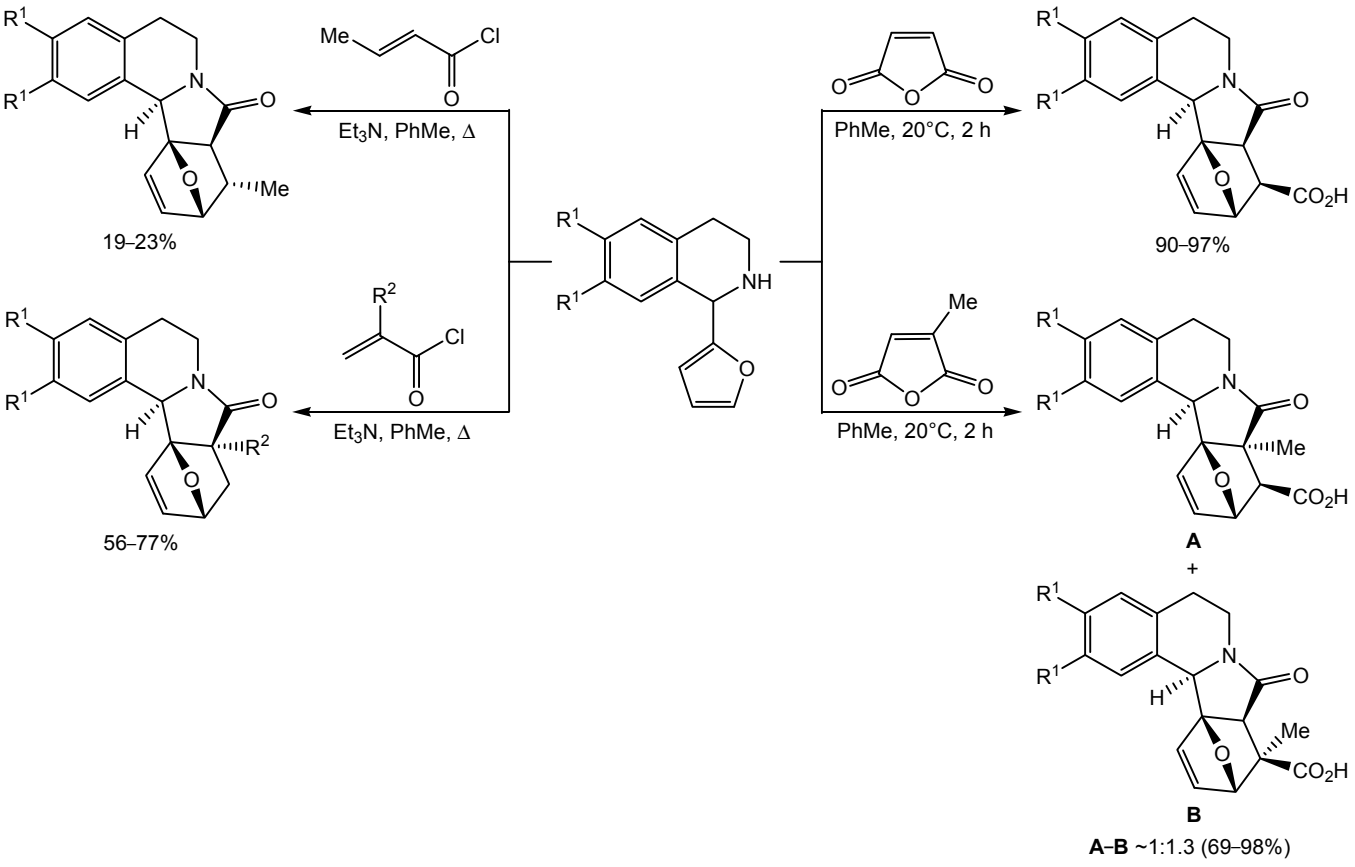


Scheme 8.6.

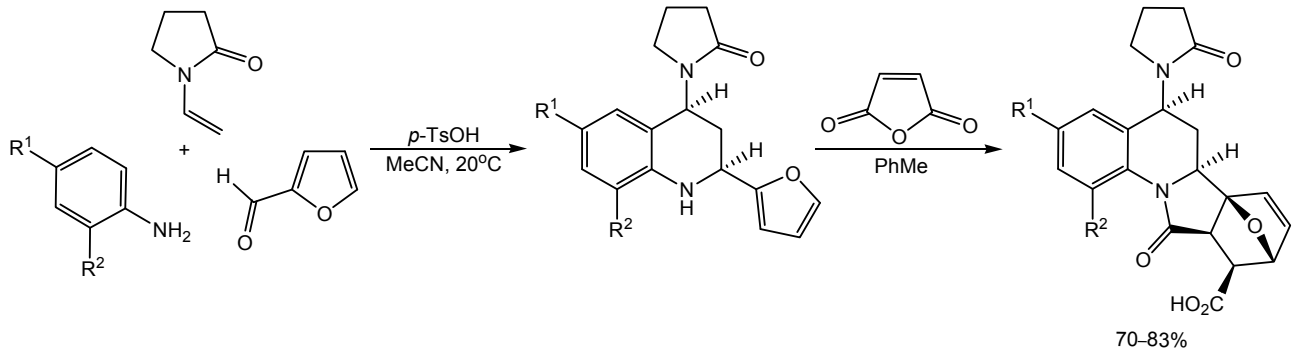


quinolinium salts with *orto*-hydroxybenzaldehydes dominoapproach was developed to the synthesis of chromenoimidazoquinolines. It is assumed that the sequence of reactions includes Knoevenagel condensation, nucleophilic cyclization with the formation of 2-iminochromene intermediate **C**, another nucleophilic cyclization resulting in the closure of imidazole ring, and aromatization (Scheme 8.18) [531].

Scheme 8.7.

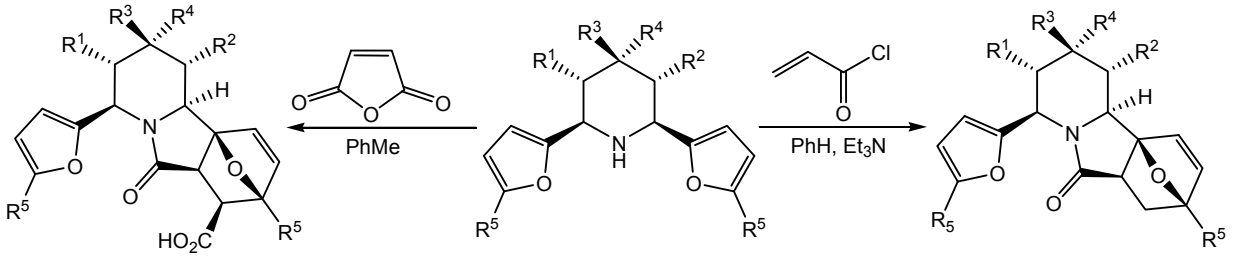


Scheme 8.8.



R^1 = H, Me, OMe, Hlg; R^2 = H, OMe.

Scheme 8.9.

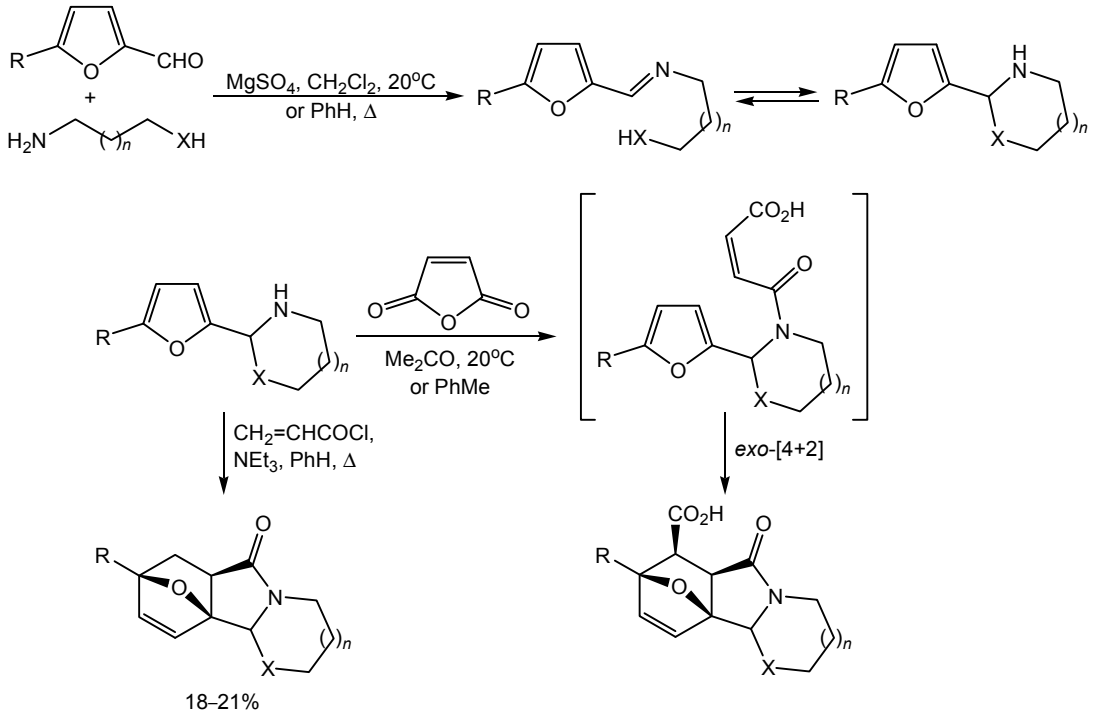


R^1 = Me, Et, Ph, CH_2CO_2Et; R^2 = Me, Ph, CH_2CO_2Et; R^3 = H, Me, Ph; R^4 = H, OH; R^3+R^4 = O; R^5 = H, Me.

Similarly thiosalicilaldehyde reacts giving thiochromenoimidazoisoquinolines (Scheme 8.19) [532].

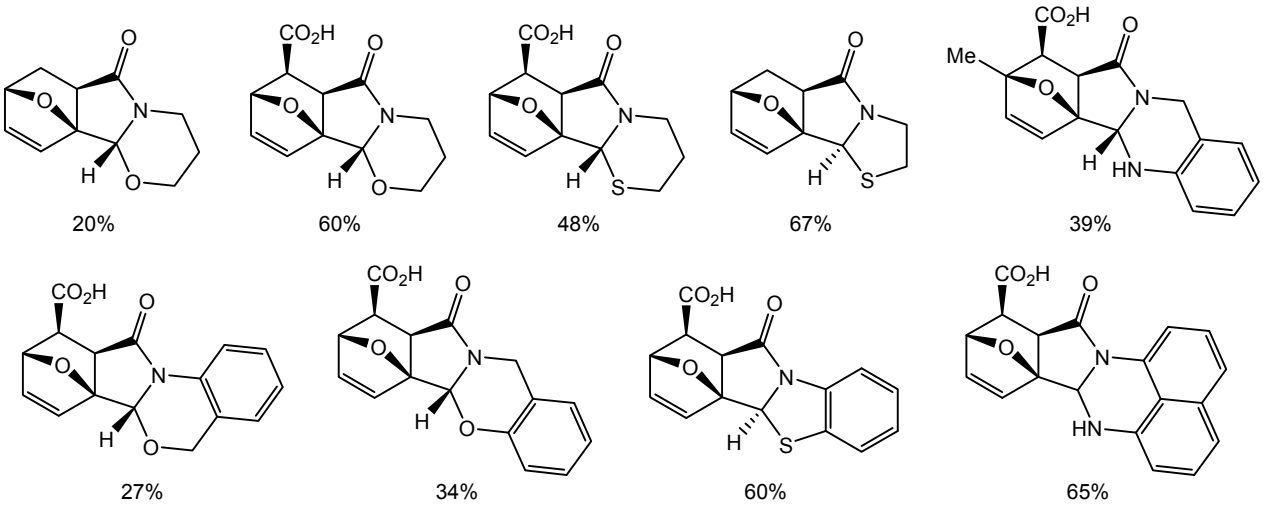
The developed procedure may be extended to the other azinium salts, for example, chromenimidazoles

Scheme 8.10.



R = H, Me, Br, I, NO_2, Ph, *m*-$C_6H_4NO_2$, *o*-$C_6H_4NO_2$; *n* = 0, 1; X = O, S, NH.

Scheme 8.11.



were obtained fused with β-carboline scaffold (Scheme 8.20) [533].

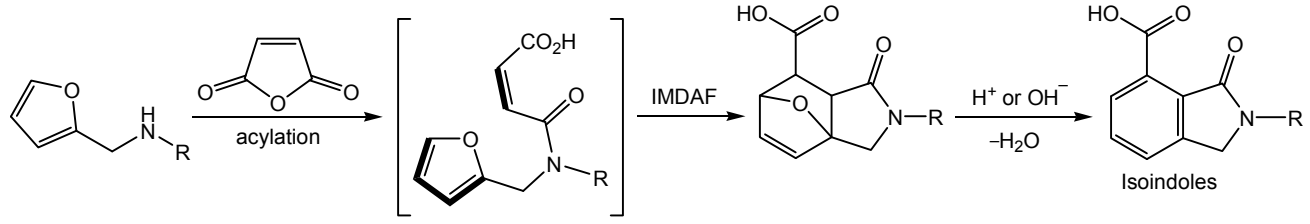
Although bringing 7-azaindoles cyanomethyl salts into similar reactions encountered some difficulties connected with the hydrolysis of iminium intermediates, it was possible to obtain at the application of microwave radiation the target polyfused compounds, analogs of alkaloids of *isogranulatimide A* and *C*. Also the products of reaction of cyanomethyl salts of all isomeric azaindoles with *orto*-hydroxybenzaldehydes were obtained (Scheme 8.21) [534].

Interesting and unexpected course of reaction was discovered for *N*-cyanomethyl thiazolium salts. Presumably, the reaction starts with Knoevenagel condensation and cyclization resulting in 2-imino-chromene cycle. However further nucleophilic attack of iminium anion on the atom C^2 of thiazole ring results in the ring opening and recyclization of chromene at the atom C^4 with the formation of chromenoimidazothiazine (Scheme 8.22). The obtained compounds demonstrate high cytotoxic activity [535].

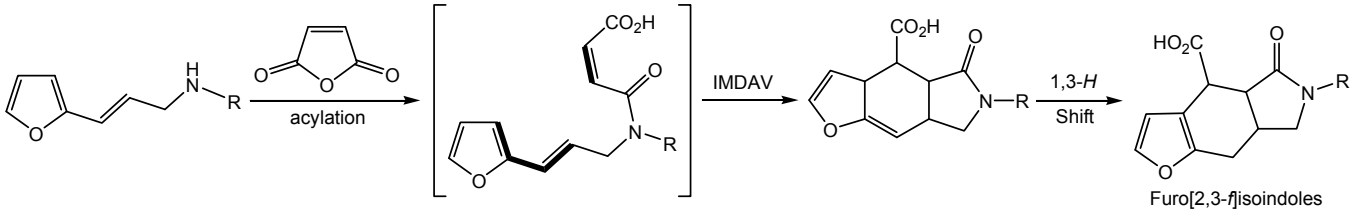
9. DEPARTMENT OF ORGANIC CHEMISTRY AT IVANOVO STATE UNIVERSITY OF CHEMISTY AND TECHNOLOGY

Starting from 1970th the department is engaged in research in the field of synthesis and investigation of physicochemical, coordination, and application

Scheme 8.12.

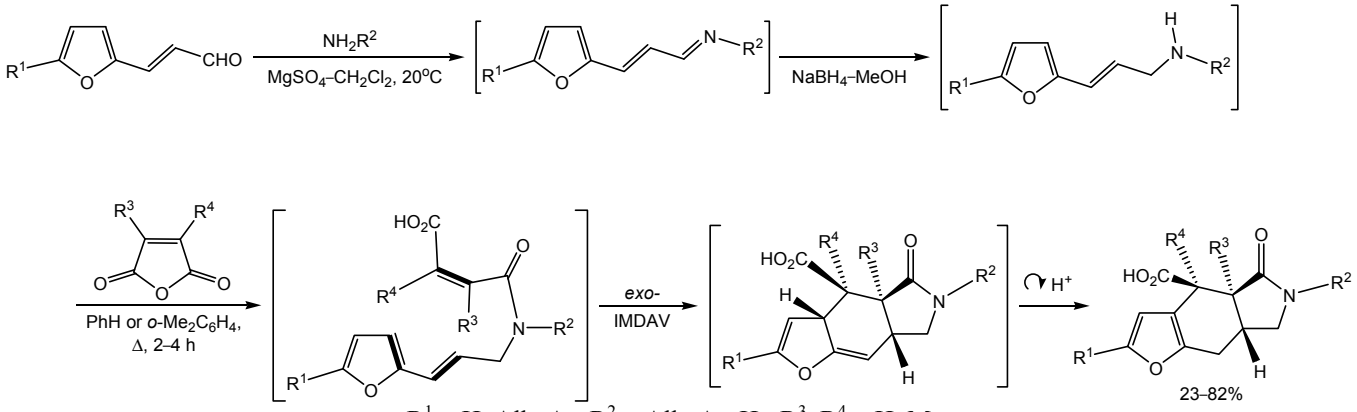


Intramolecular Diels-Alder reaction with furan.



Intramolecular Diels-Alder reaction with vinylarene.

Scheme 8.13.

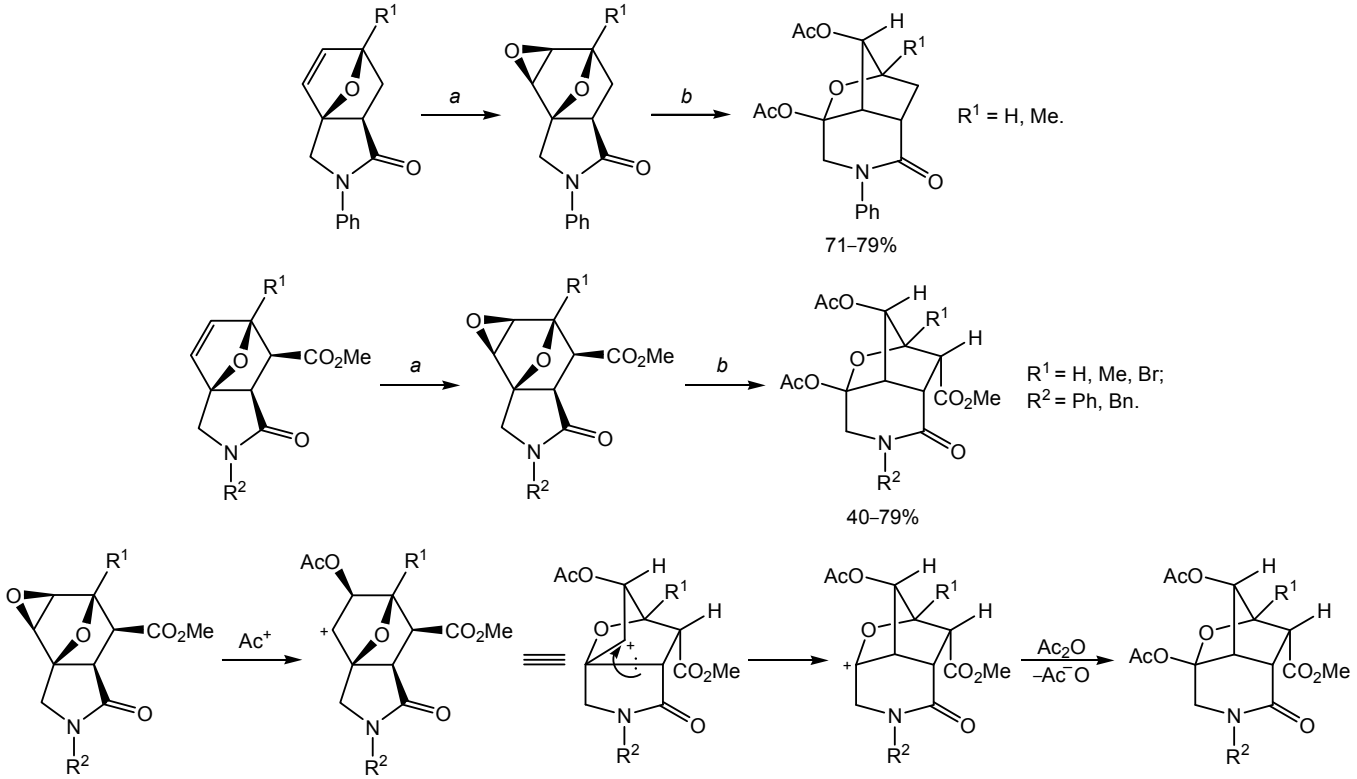


R^1 = H, Alk, Ar; R^2 = Alk, Ar, Ht; R^3, R^4 = H, Me.

properties of macroheterocyclic compounds: porphyrines, *meso*-azaporphyrines, porphyra-zines, phtalocyanines, and their analogs. At present the staff of the department consists of 5 Professors, 2 Assistant-Professors, 6 researchers (among them 2 Professors), which actively develop this scientific field, bases of which were founded by **Professor B.D. Berezin**, head of the department in 1973–1995 [1, 536].

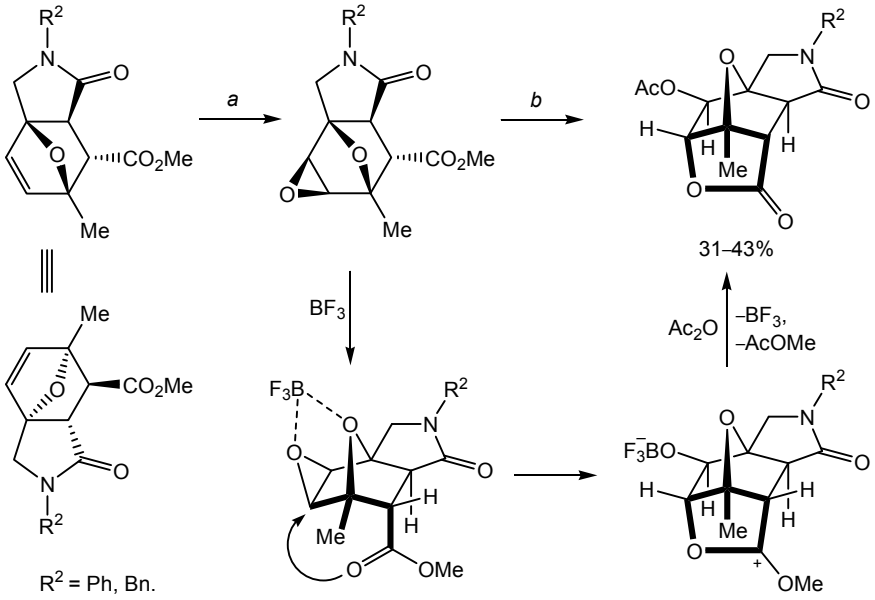
In 2014–2017 the research activities of the department were realized either in the framework of the State contract of the Russian Ministry of Education and Science (3 projects), or under the support of three grants of Russian Science Foundation (supervisors **Professors D.B. Berezin**, **S.A. Syrbu**, and **P.A. Stuzhin**), and also grants of Russian Foundation of Basic Research and President's grants for young scientists. Besides that scientific staff of the

Scheme 8.14.



Reagents and conditions: *a* – *m*-CPBA–CH_2Cl_2, 20°C, 2 d; *b* – $BF_3 \cdot OEt_2$–Ac_2O, 5→25°C, 4 h.

Scheme 8.15.



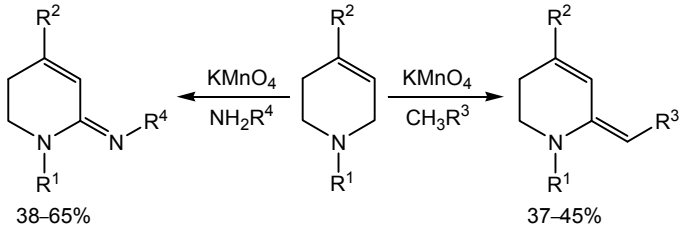
Reagents and conditions: *a* – *m*-CPBA–CH_2Cl_2, 20°C, 2 d; *b* – $BF_3 \cdot OEt_2$–Ac_2O, 5→25°C, 4 h.

department, being part of the Research Institute of macroheterocyclic compounds at Ivanovo State University of Chemistry and Technology (**scientific Director Corresponding Member of Russian Academy of Sciences O.I. Koifman**), participates in the project of Russian Science Foundation (support of existing scientific labs and departments), where responsible performers are Professors of the department **O.A. Golubchikov**, **P.A. Stuzhin**, and **O.G. Khelevina**).

In the group of **Professor A.S. Semeikin** effective methods were developed for the synthesis of *meso*-aryl-substituted porphyrins by condensation of pyrrole with aldehydes providing products in the highest yields recorded for this type of compounds (up to 50%) (Scheme 9.1) [537–539].

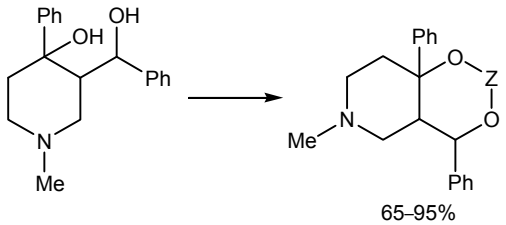
In collaboration with **Professor S.A. Syrbu** the reduction of nitro derivatives and hydrolysis of methoxy derivatives were performed to obtain amino

Scheme 8.16.



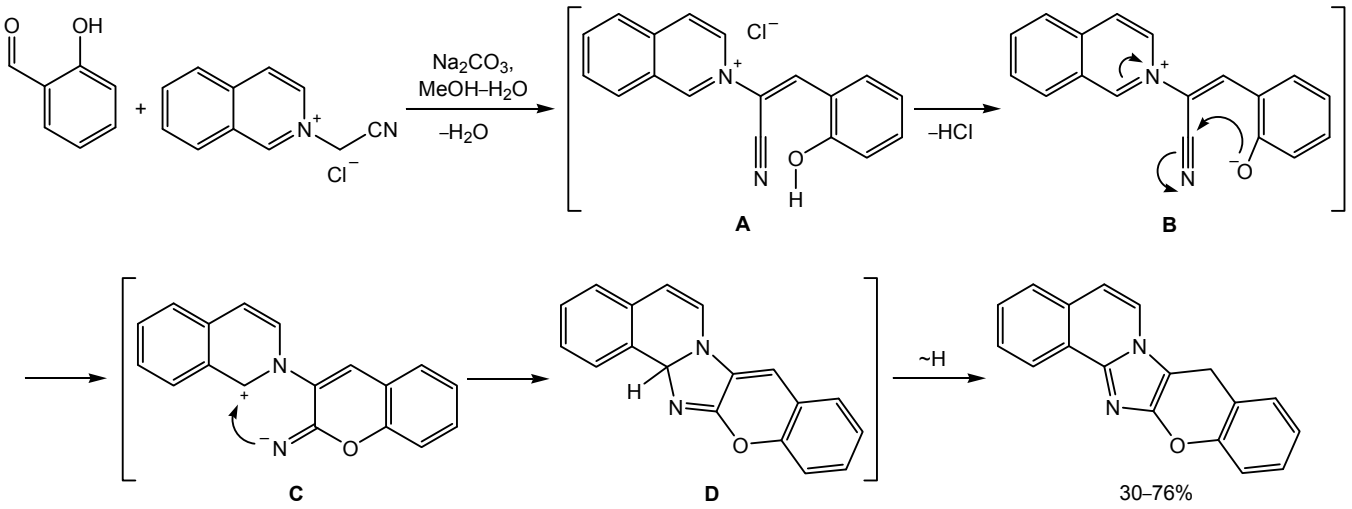
R^1 = Alk; R^2 = Ar, 4-Py; R^3 = COAlk, COAr; COHt, NO_2; R^4 = Ar.

Scheme 8.17.



Z = $BOCHMe_2$, BOH, BAr, CH_2.

Scheme 8.18.



and hydroxyl derivatives that along with carboxy porphyrins and the corresponding acid chlorides served as initial compounds for the synthesis of various functional derivatives [R = NHR, NHCOR, OAlk, OCOAlk, $O(CH_2)_nHlg$, $O(CH_2)_nOR$, NN^+, SCN, N=NAr, CONHR, COOR etc.] [540, 541].

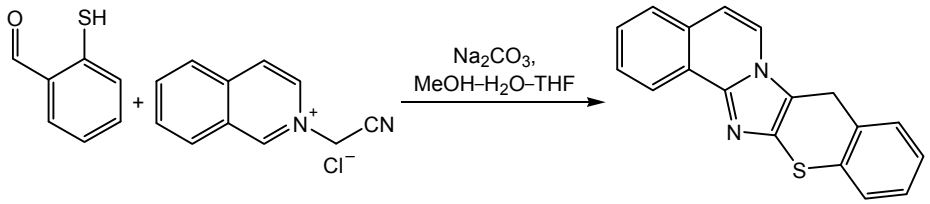
Effective methods were developed for the catalytic synthesis of monosubstituted and unsymmetrical porphyrins by condensation of a mixture of benzaldehydes with pyrrole in xylene catalysed with trifluoroacetic acid (Scheme 9.2) [540, 542–544].

In the group of **Professor O.A. Golubchikov** by condensation of pyrrole with aromatic dialdehydes a series was obtained of cyclophane dimers [R = $(CH_2)_n$, n = 2, 3, 4; *ortho*- or *meta*-bridges] [545], whose coordination compounds were of interest as catalysts of multielectron redox reactions (Scheme 9.3). Dimers with bridges in the *meta*-position (n = 1, 3) as well as an *ortho*-dimer (n = 3), possess a planar structure of the spatially close tetrapyrrole nuclei. The dimers with an even number of bridges are distinguished by the spatially strained structure of bridges and porphyrin scaffold that has a ruffled dome structure. From *ortho*-dialdehydes with n>4 only monomeric porphyrins can be obtained, because in this case the length of methylene chain is enough to form a bond between two neighbouring phenyl fragments.

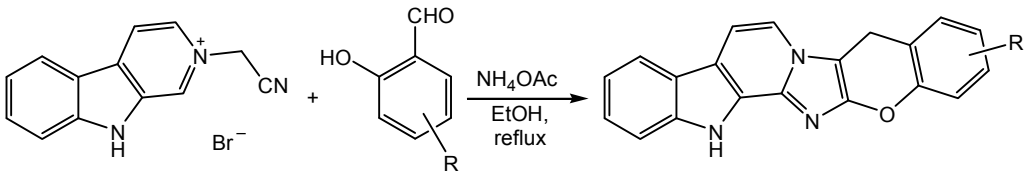
Under the guidance of **Assistant-Professor E.M. Kuvshinova** methods of synthesis were developed of aplanar dodeca- and polynitro-substituted porphyrins and their coordination properties were investigated [546, 547] (Scheme 9.4). These properties significantly differ from those of planar porphyrins. These substances show a high basicity and increased acidity [548].

For the synthesis of 5,15-diphenylporphyrins with electron-donor and electron-acceptor substituents in the benzene rings two methods were developed (Scheme 9.5) [549].

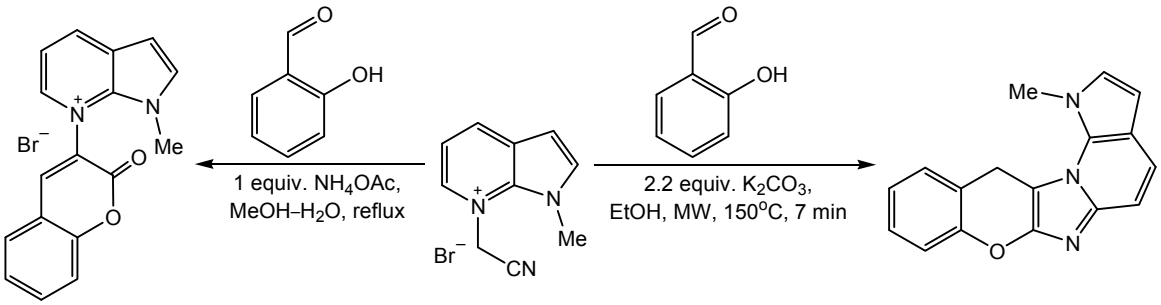
Scheme 8.19.

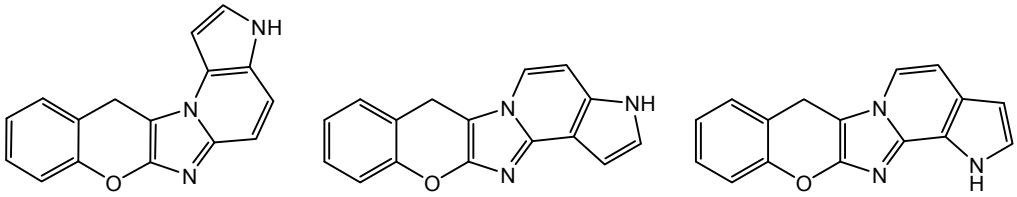


Scheme 8.20.

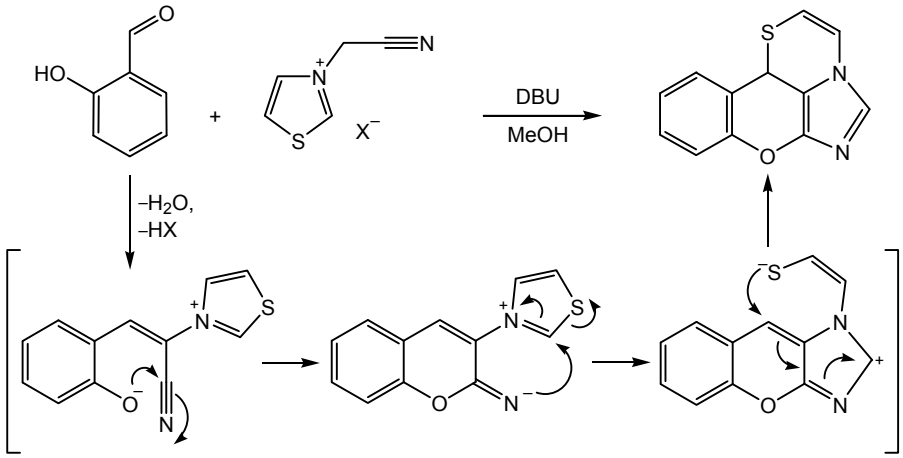


Scheme 8.21.





Scheme 8.22.



The first procedure involves a high temperature condensation of dipyrrolylmethanes with benzaldehydes in the presence of zinc acetate in basic solvents followed by demetallation of the obtained zinc complexes of porphyrins. The second method consists in the condensation of α,α'-unsubstituted dipyrrolylmethanes with aldehydes in chloroform, methylene chloride, acetonitrile, or methanol in the presence of trichloro- or trifluoroacetic acid at room temperature with subsequent oxidation of porphyrinogens. Initial dipyrrolylmethanes were obtained in several stages (Scheme 9.6).

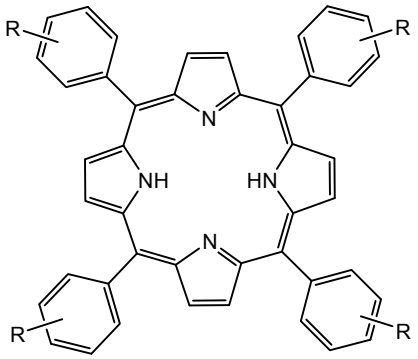
5,15-Disubstituted porphyrins may also be obtained by condensation of dipyrrolylmethanes with ethyl orthoformate in the presence of trifluoroacetic acid in chloroform [549]. Dipyrrolylmethanes enter a mixed-aldehyde condensation, where form three porphyrins; it is possible to isolate from the mixture the unsymmetrical macrocycle in case of a different polarity of aryl groups. A series of mono-*meso*-substituted porphyrins was obtained from dipyrrolylmethanes through intermediate biladienes-*a*,*c* (Scheme 9.7).

The condensation of dipyrrolylmethanes with dimeric benzaldehydes having phenyl rings linked through dioxymethylene bridges at the length of bridge of 3, 4 carbon atoms afforded dimeric cyclophane porphyrins [550] without spatial strain (Scheme 9.8).

At a higher length of bridge (5–6 carbon atoms) "overlapped" porphyrins are formed, which have a strained porphyrin ring. As fragments Z blocking the coordination center bulky residues were also used [551, 552] (Scheme 9.9). Complexes of overlapped porphyrins are interesting as carriers of molecular oxygen.

In the group of **Professor O.G. Khelevina** investigations are carried out on the physicochemical and

Scheme 9.1.



R = Me, Alk, OC_nH_{2n+1} (n = 1–16), Hlg, NO_2, COOH (*o*-, *m*-, *p*-isomers).

coordination properties of porphyrazines, method is developed of their synthesis and the opportunities are explored of their peripheral modification by reactions of electrophilic substitution [553]. Bromination of unsubstituted Mg-tetraazaporphyrin was used for preparation of a Mg-monobromotetraazaporphyrin [554]. The cocondensation of maleodinitrile and monophenylmaleodinitrile in the presence of magnesium butoxide in butanol allows obtaining Mg(II) complexes of tetraazaporphyrins bearing diverse numbers of phenyl rings in the macrocycle (Scheme 9.10) [555].

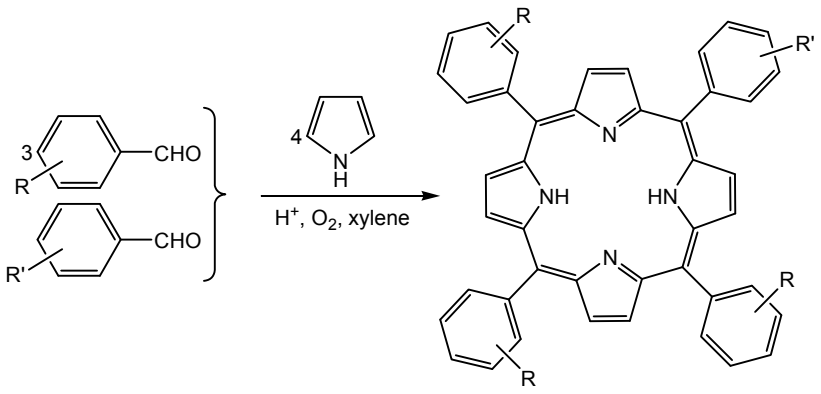
In collaboration with Professor M.K. Islyaikin (department of Technology of Fine Organic Synthesis) low-symmetrical triazoloporphyrazines were synthesized and their Ni-complexes were prepared [556, 557] whose acidic-basic properties were investigated (Scheme 9.11).

For 1,4-diazepinotribenzoporphyrazine obtained in collaboration with P.A. Stuzhin [558] reactions were discovered of 1,4-diazepine ring contraction with the formation of porphyrazines containing fused fragments of pyrazine, oxodihydropyrazine (by photooxidation) [559], and imidazole (by vacuum sublimation) (Scheme 9.12) [560].

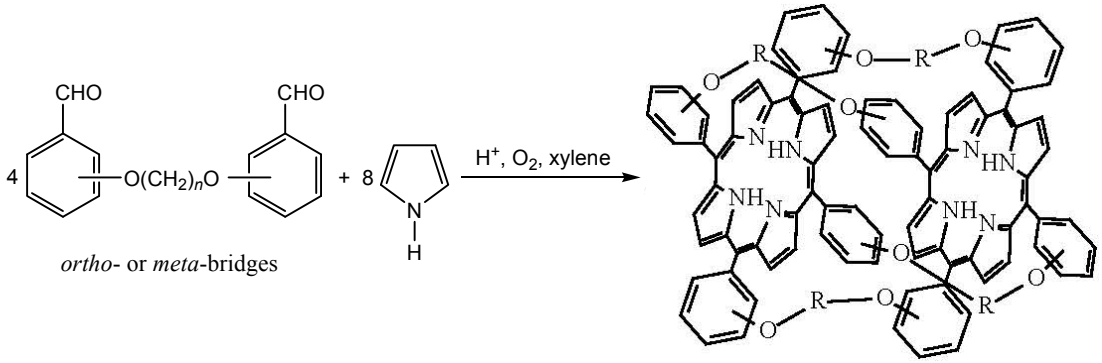
Under the guidance of **head of the department Professor P.A. Stuzhin** the synthesis was performed and investigation was carried out of new heterocyclic analogs of phtalocyanine, first of all, of electron-deficient porphyrazines containing fused heterocycles instead of benzene rings and also perfluorinated substituents. On the series of these compounds a systematic investigation was carried out of the effect of *meso*-azasubstitution and heterocyclic fusion on the acid-base properties of tetrapyrrole macrocycles. Coordination properties were studied of mono- and binuclear and organometal complexes with iron and other *p*- and *d*-metals. As a convenient precursor for porphyrazines with fused 5-, 6-, and 7-membered heterocycles diaminomaleodinitrile is used, dinitriles of different heterocyclic dicarboxylic acids are easily obtained therefrom (Scheme 9.13).

Porphyrazines with fused 1,2,5-thiadiazole and 1,2,5-selenadiazole fragments [$(XN_2)_4$PAM] (X = S,

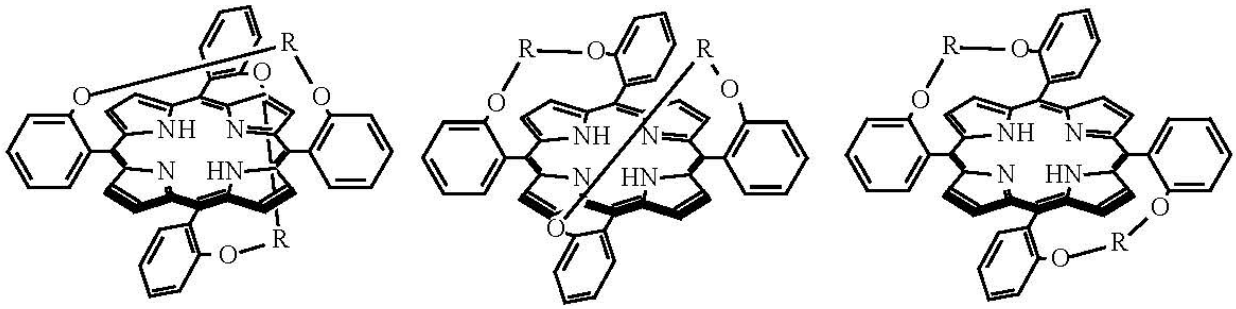
Scheme 9.2.



Scheme 9.3.



R = $(CH_2)_n$, n = 2, 3, 4.



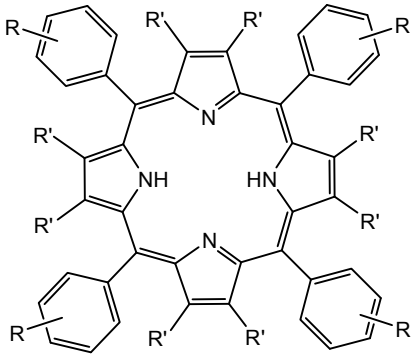
R = $(CH_2)_n$, n > 4.

Se) were first obtained and investigated together with Italian colleagues [561]. First Te-containing analogs [$(TeN_2)_4$PAM] were synthesized [562] (Scheme 9.14). Cyclotetramerisation of 1,2,5-chalcogenadiazol-3,4-dicarbonitriles in alcohol solution of lithium or magnesium alcoholates is the optimal method of synthesis of the corresponding porphyrazine macrocycles. Porphyrazine macrocycle is formed also by template cyclotetramerization of dinitriles (S, Se) in the presence of salts of *p*-metals, for example, Al^{III}, Ga^{III}, In^{III} halides or acetates. In the presence of BCl_3 the S-dinitrile undergoes cyclotrimerisation with the formation of boron subporphyrazine [$(SN_2)_3$SubPABCl] [563].

Mixed cyclocondensation of heterocyclic dinitriles with other 1,2-dicarbonitriles under these conditions leads to porphyrazines of unsymmetrical structure, for example, mono-1,2,5-chalcogenadiazoloporphyrazines [$R_6(XN_2)$PAM] [564]. Fusion of electron-deficient 1,2,5-chalcogenadiazole fragments increases the π-acceptor properties of macrocycles that makes their application promising as materials with conductivity of *n*-type [565].

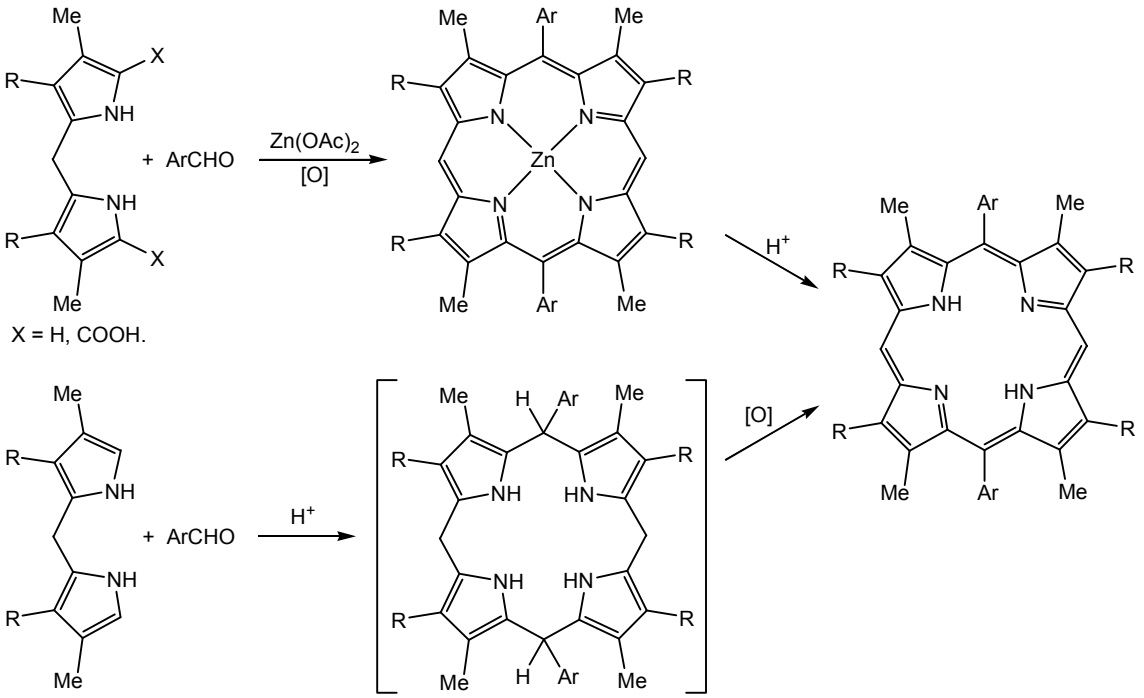
1,2,5-Selena- and 1,2,5-telluradiazoloporphyrazines (SePA and TePA) may be regarded as synthetic analogs of porphyrazines with vicinal amino, imino, or

Scheme 9.4.



R = H, OMe, Alk, NO_2; R' = Me, Et, Ph.

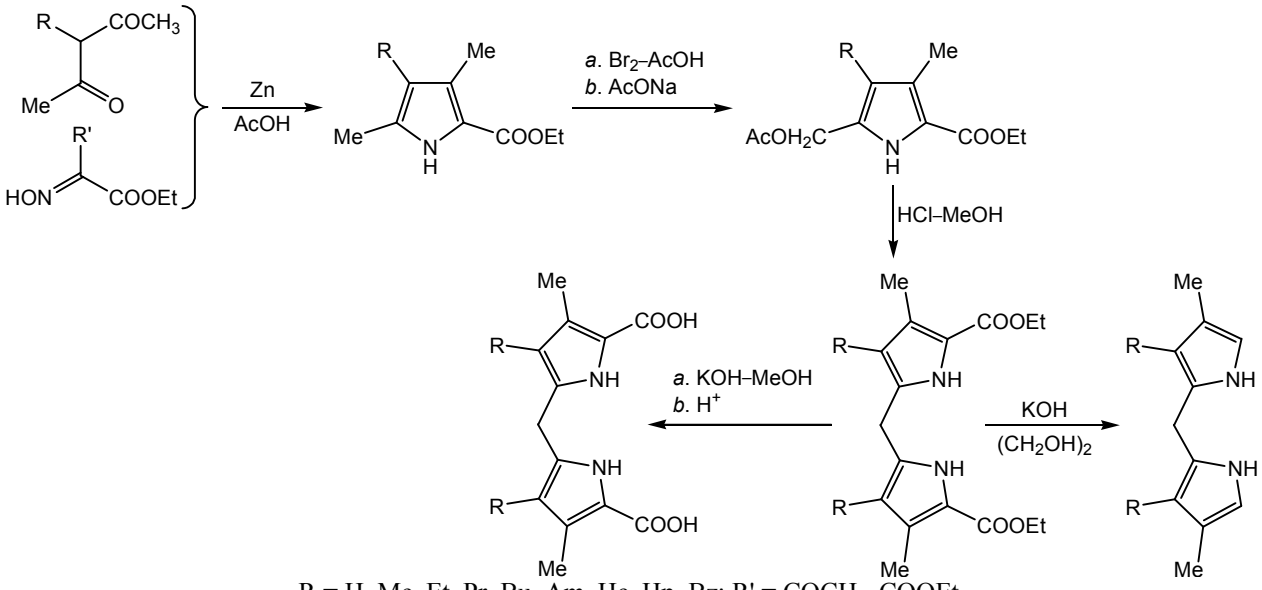
Scheme 9.5.



Ar = Ph, C_6H_4Y (Y = OAlk, Hlg, NO_2, COOH, NH_2, OH, and their derivatives).

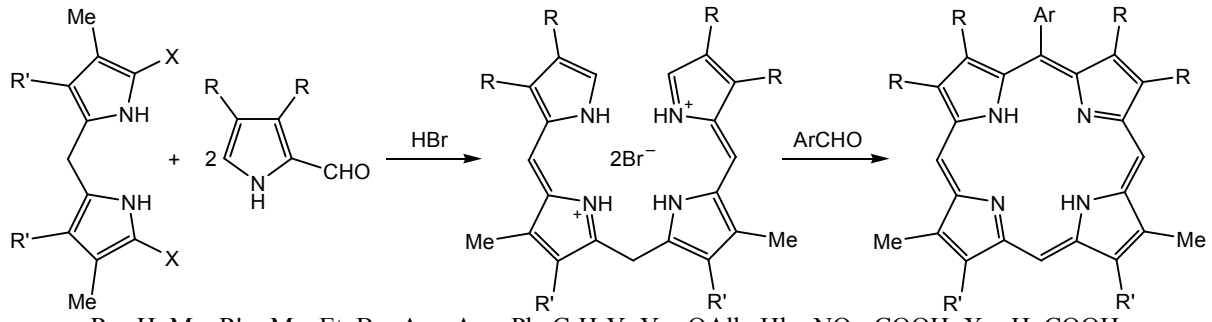
keto groups. Thus the reductive deselenation of 1,2,5-selenadiazoloporphyrazines under the treatment with H_2S gives vicinal porphyrazinediamines **A** that may further enter the condensation reactions with carbonyl compounds giving azomethine derivatives **B** or pyrazinoporphyrazines in case of α-diketones **C**, and also be oxidized providing of secoporphyrazines **D** and further pyrazinoporphyrazines **E** [566, 567]. 1,2,5-Telluradiazole ring is cleaved even easier, especially in acid conditions, and behaves as analog of vicinal diimines **F** and diketones **G**, forming pyrazine fragment **H** reacting with diamines [568] or **I** upon dimerization (Scheme 9.15).

Scheme 9.6.



R = H, Me, Et, Pr, Bu, Am, Hc, Hp, Bz; R' = $COCH_3$, COOEt.

Scheme 9.7.



R = H, Me; R' = Me, Et, Bu, Am; Ar = Ph, C_6H_4Y; Y = OAlk, Hlg, NO_2, COOH; X = H, COOH.

Lately in focus of attention fell also tetrapyrazinoporphyrazines [569], electron-deficiency of which was increased either due to perchlorination in [Cl_8TPyzPAM] [570], or due to the fusion of 1,2,5-thiadiazole fragments in [T(SN_2)PyzPAM] [571]. For the first time also a phosphorus complex was obtained [(R_8TPyzCA)P=O] containing a contacted tetrapyrazinocorrolazine macrocycle (Scheme 9.16) [572].

Studying of the acid-base properties of octaethyl-substituted tetrapyrazinoporphyrazine [Et_8TPyzPAH_2] revealed its high NH-acidity (pK_{a1} 7.77, pK_{a2} 7.80) and ability to easy deprotonation in basic media with generation of dianion stabilized by bifurcate hydrogen bond with two molecules of water [573]. This property may be utilized for measuring the degree of solvents drying, for example, of pyridine. An interesting feature of porphyrazines with fused 1,4-diazepine fragments is their propensity to dimerization [574] due to the formation of complementary hydrogen bonds between *meso*-atoms of one molecule and axial atom of hydrogen of CH_2 group of 1,4-diazepine fragment of the other molecule.

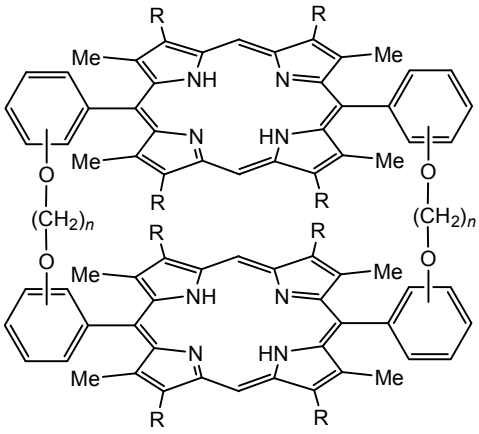
Perfluorooctaphenylporphyrazine [$F_{40}PAH_2$] and its complexes were obtained for the first time [575]. They proved to be the weakest porphyrazine bases, capable of click-reactions of fluorine nucleophilic substitution (Scheme 9.17).

The studies of **Professor O.A. Petrov** have revealed the effect of slow protons transfer in H-complexes of porphyrazines in the presence of amines and kinetic and structural aspects of this phenomenon are investigated [576–578].

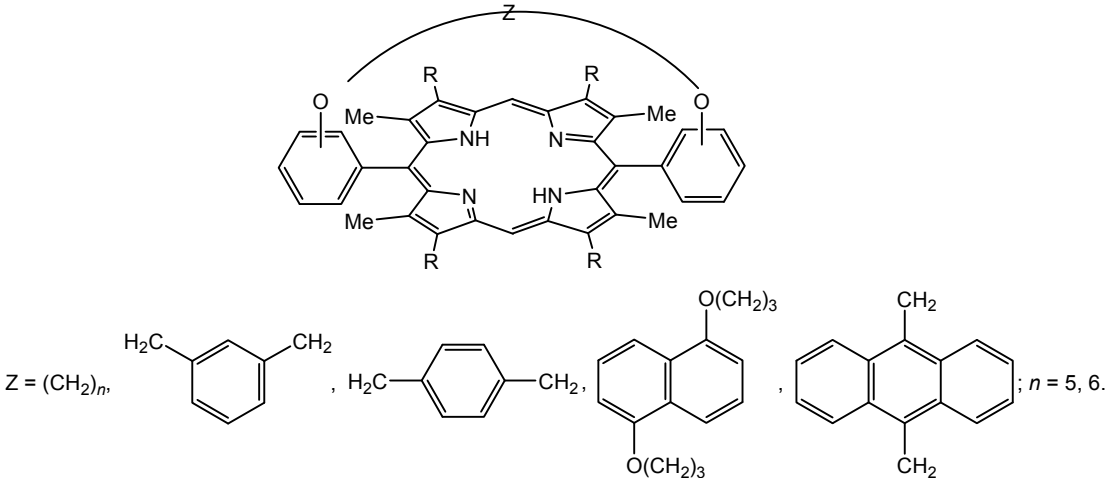
In the group of **Professor D.B. Berezin** the synthesis is performed of diverse tetrapyrrole macrocycles and their physicochemical and coordination properties are investigated. Various types of porphyrinoids were obtained: *N*-methyl-porphyrins, inverted porphyrins, corroles [579–582] and porphycenes (Scheme 9.18) [583].

Metals in complexes with these porphyrinoids are distinguished by non-typical grades of oxidation. Special aspects of such non-classic porphyrins were compiled in a monograph [584]. Other direction in this group is the investigation of biologically active

Scheme 9.8.



Scheme 9.9.



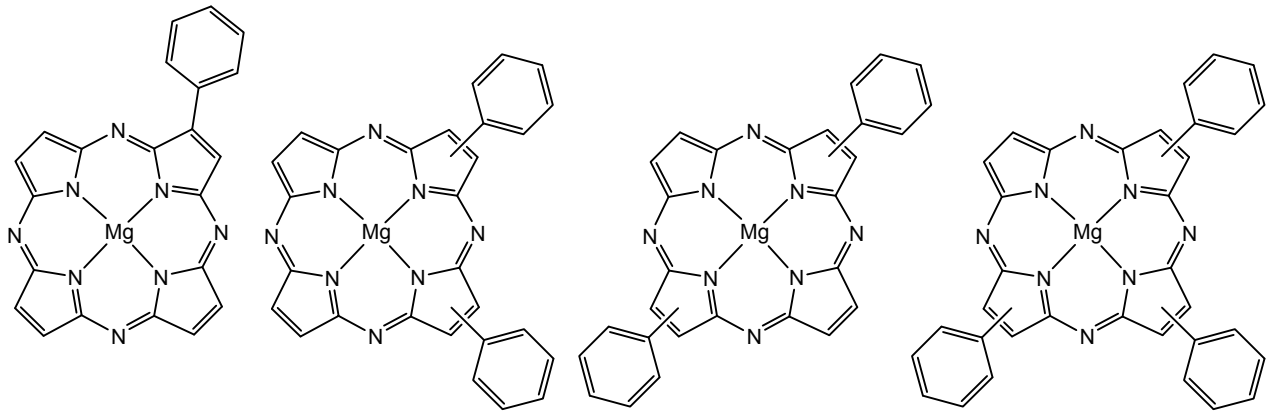
tetrapyrrol macrocycles, including amphiphilic chlorins (Scheme 9.19) [585, 586].

At the department the spectral, acid-base, coordination properties of macroheterocyclic compounds depending on their structure are systematically investigated. Methods were developed of the synthesis of their coordination derivatives with the majority of elements of the periodic table. The reaction mechanisms of complex formation of porphyrins, azaporphyrins, porphyrazines, and related compounds in aqueous and non-aqueous solutions, and also processes of dissociation of metal complexes in proton-donor surrounding were explained. Results of these investigations were generalized in a series of monographs "Advances in porphyrin chemistry" [587].

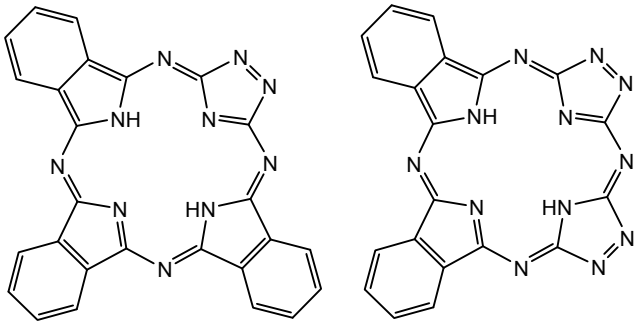
An important direction of studies is the exploration of the practical application of macroheterocyclic compounds. Under the guidance of **Professor D.B. Berezin** on museum and hospital stocks of microorganisms *in vitro* and *in vivo* testing was realized of different tetrapyrrole macrocycles as photosensitizers for antibacterial photodynamic therapy. The most effective were derivatives of chlorins containing cation groups or fragments of molecules which were antibacterial drugs (see structures above) [588]. Chlorins demonstrated low toxicity both with respect to erythrocytes *in vitro*, or in acute animal experiment [589].

Aiming at creation of polymeric materials possessing biological and catalytic activity, Professor O.A. Golubchikov with assistants developed methods of surface activation and subsequent modification of polypropylenes [590], cellulose, polyethylene terephthalate. Subsequent modification with pharmaceuticals (aspirin, indomethacin, gentamycin, dioxidine and cephazoline [591, 592]), porphyrins and phtalocyanines provides modified polypropylene fibres possessing significant antiphlogistic effect.

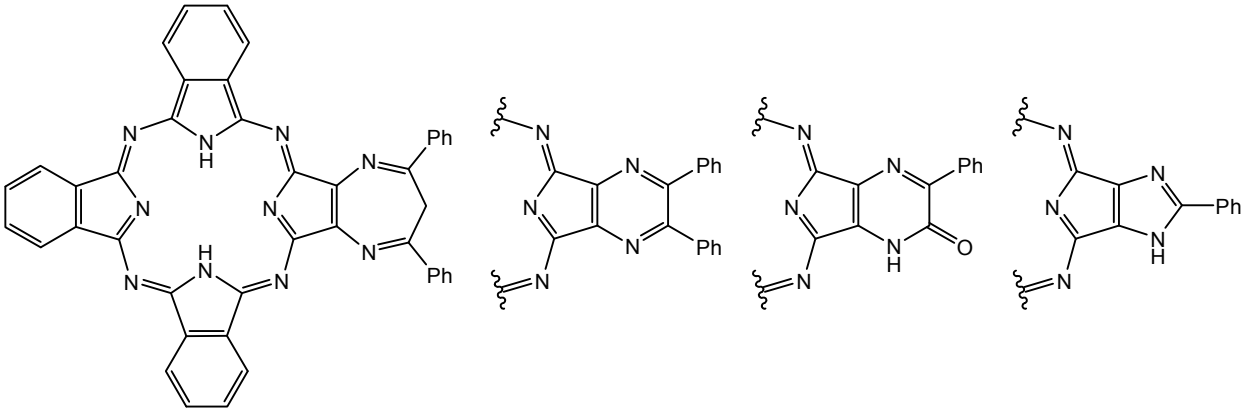
Scheme 9.10.



Scheme 9.11.

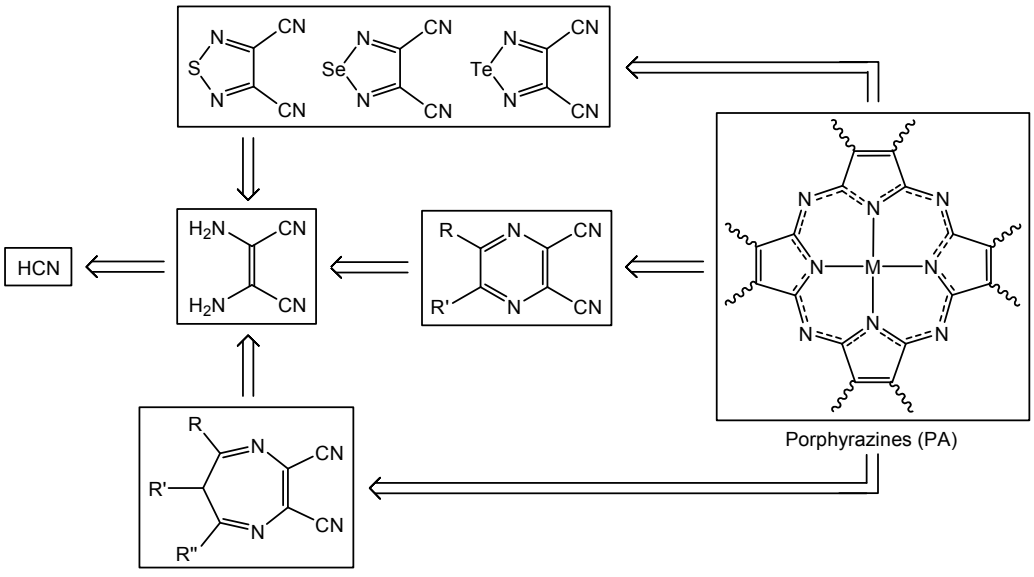


Scheme 9.12.

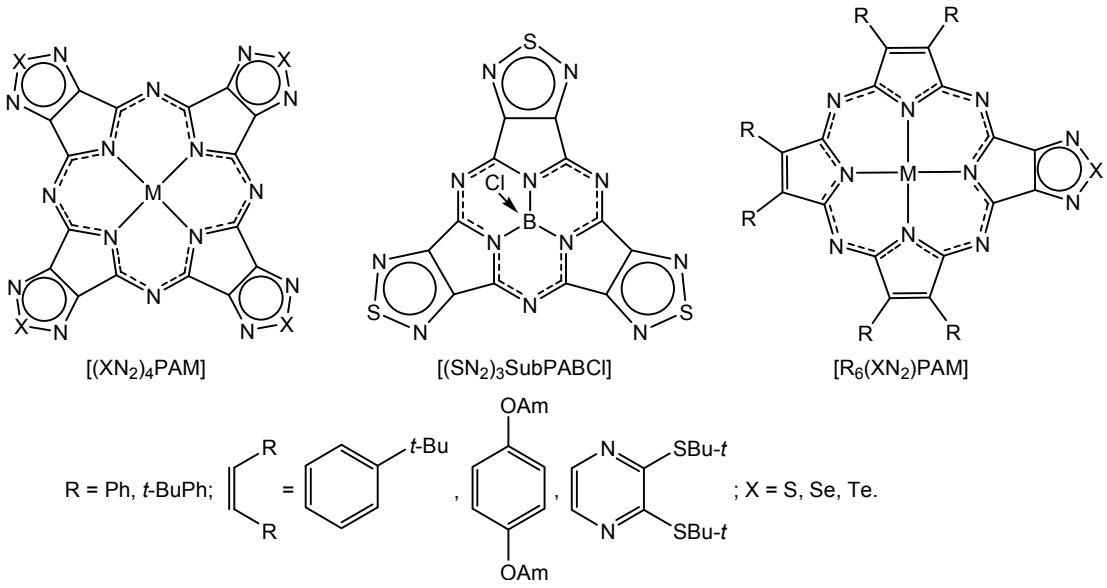


Professor O.A. Golubchikov with co-workers also study the activity of a wide range of tetrapyrrole macroheterocyclic compounds in homogeneous and heterogenic catalysis of thiols oxidation. The most effective were the coordination compounds of cobalt, catalytic activity of complexes grew in a series porphyrins < tetrabenzoporphyrins ≤ porphyrazines << phtalocyanines regardless of the nature of peripheral substituents [593, 594]. The mechanism of oxidation was explained, including the stage of forming and deterioration of triple coordination complex [595, 596].

Scheme 9.13.



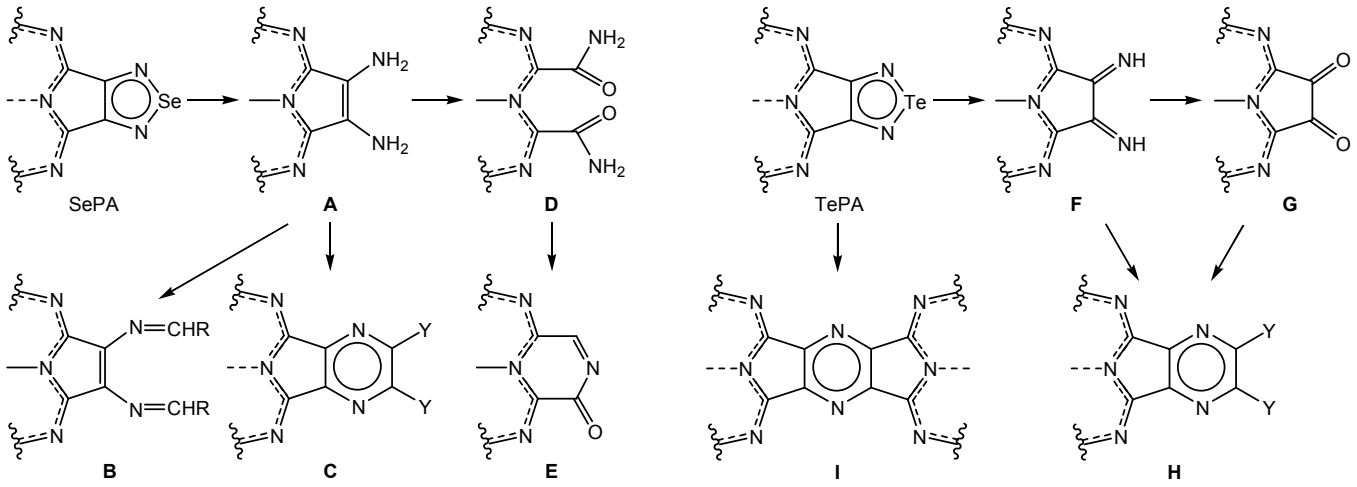
Scheme 9.14.



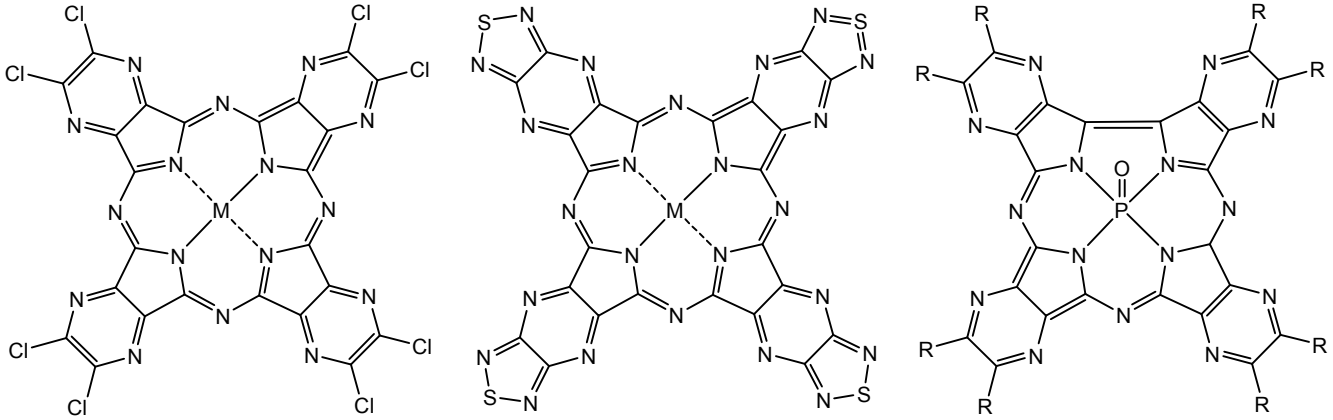
It was established for the first time [597, 598] that porphyrins and phtalocyanines are effective brighteners of standard electrolytes of nickelation, galvanic settlement of alloys nickel-cobalt and nickel-iron [and also copper plating and silvering (unpublished)]. They allow to increase reflective ability of galvanic coatings up to 80%. Exceptionally low amount of additives (0.5–50 mg/L) of ligands of macroheterocyclic compounds reduce the level of surface roughness 2–2.5 times, increase their uniformity, many times decrease the porosity and internal strains. That is explained by the high adsorptive activity of ligands, porphyrins and phtalocyanines.

Under the guidance of Professor O.G. Khelevina methods were developed of the preparation of elementosiloxane oligomers using as catalysts phtalocyaninates of cobalt, tin, iron, cooper (MPc) and octaphenylporphyrazinatocobalt (CoPA) [599–601]. The introduction of metalloporphyrazines into elementosiloxane oligomers significantly reduces the activation energy of structuring reaction. Metalloporphyrazines demonstrate a catalytic activity only at raised temperature (130–160°C). The following series of their catalytic activity was established: SnPc > CoPc ≈ CoPA > FePc > Pc. Boro-, alumo-, and titanosiloxane olygomers were synthesized and a method was developed of preparation of protective

Scheme 9.15.



Scheme 9.16.



textile materials on their basis. These materials possess attractive physico-mechanical properties and a resistance to the effect of open fire.

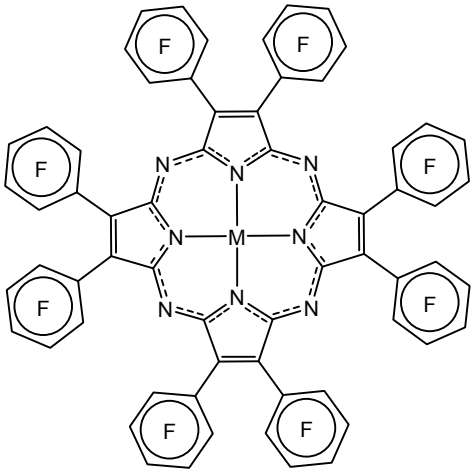
10. DEPARTMENT OF ORGANIC CHEMISTRY AT LOBACHEVSKY STATE UNIVERSITY OF NIZHNY NOVGOROD

In the last 15 years in the department of organic chemistry of State University of Nizhny Novgorod (**head Professor A.Yu. Fedorov**) research is actively performed concerning the development, synthesis and investigation of biological properties of compounds possessing antitumor action, particulary analogs of natural combretastatin A-4 and colchicines (Scheme 10.1).

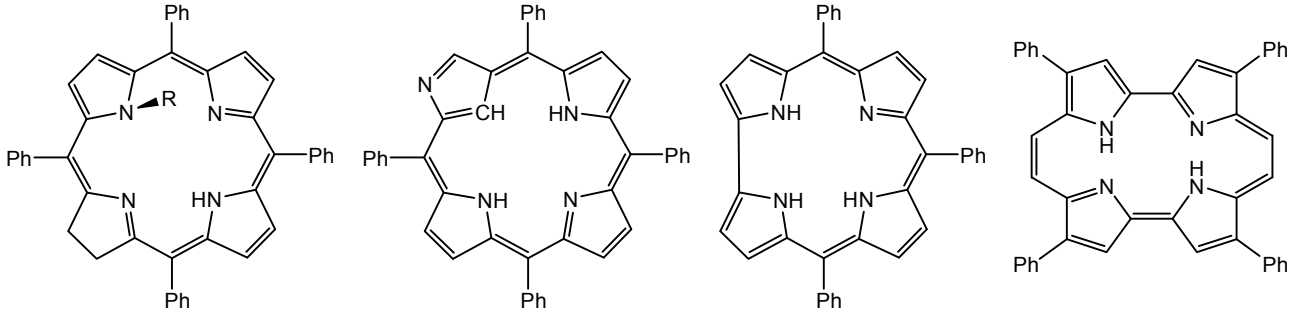
Coumarin derivatives are widely spread in nature and possess a broad spectrum of biological activity [602]. Basing on 4-hydroxycoumarins a number of biologically active compounds was obtained (Scheme 10.2). In the key stage of the synthesis of these compounds the reaction of cross-coupling or the reaction of reductive coupling were applied in the coordination sphere of nontransition metal.

Coumarin complexes of boron difluoride **1**, analogs of BODIPY dyes, were synthesized applying a sequence of reactions of acylation of 4-hydroxycoumarins at the position *3* followed by the reaction of cooper-catalyzed dipolar [4+2] azide-alkyne cycloaddition [603] and by complex formation with boron trifluoride (path *a*) [604]. As biological marker in conjugates of type **1** derivatives of carbohydrates were used capable to bind with lectin receptors. Fluorescent glycosides of 4-triazol-

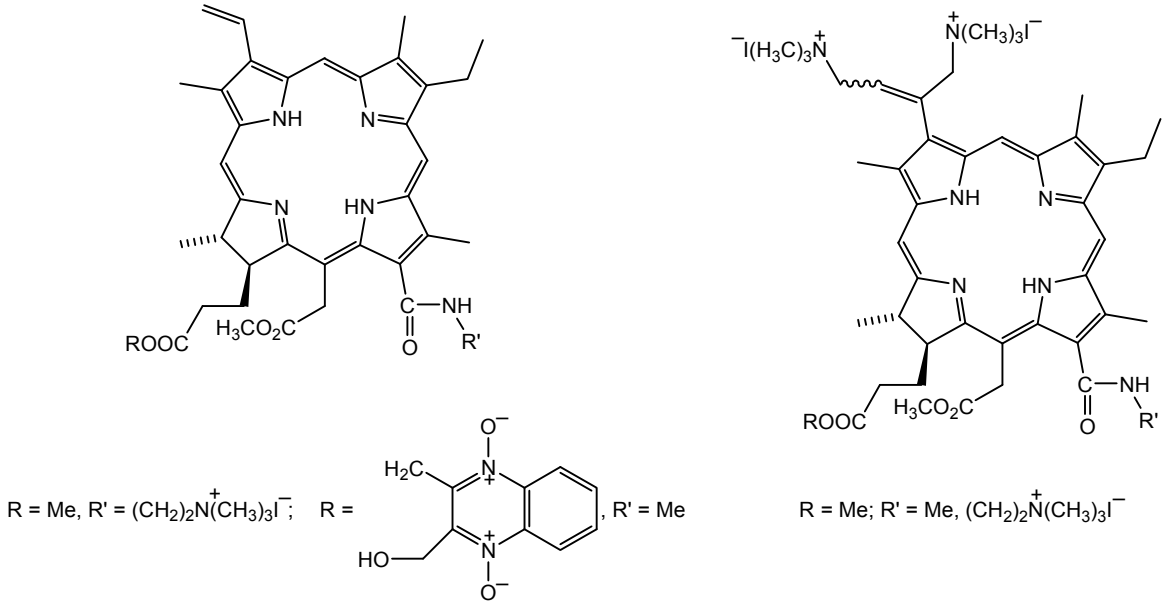
Scheme 9.17.



Scheme 9.18.



Scheme 9.19.



ylcoumarins **2** were obtained basing on coumarin 4-trifluoromethylsulfonates using Sonogashira cross-coupling and cooper-catalyzed click-reaction in the key stages (path *b*) [605].

4-Heteroarylcoumarins **3** and 4-aminocoumarins were synthesized by reactions of palladium-catalyzed cross-coupling of NH-heterocycles and amines with the corresponding triflates (path *c*) [606]. A series of related by structure 4-arylcoumarins, for example, compounds **4** and **5**, were obtained using arylboronic acids with the application of Suzuki-Miyaura reaction in the key stage [607–613].

For arylating the position *3* in 4-hydroxycoumarins the most effective approach are reactions of reductive coupling [614, 615], proceeding in coordination sphere of bismuth [616–618] and lead [619] (paths *d*, *e*, Scheme 10.2).

For the preparation of the desired polysubstituted coumarins **6** and **7** several types of polyfunctional arylating organometallic agents were developed [609, 619–623]. For example, 2-(chloromethyl)-phenyllead triacetate **10** (Scheme 10.3), obtained as a result of a cascade sequence of transmetallation reactions starting with dihalide **8**, reacts *in situ* with enolizable substrates (β-ketoesters, β-diketones, donor phenoles) affording organolead intermediates **11**. These adducts contain simultaneously one carbon nucleophilic center in the position *3* of the coumarin fragment and two carbon electrophilic centers. The subsequent reaction of reductive coupling occurring in the coordination sphere of lead results in the formation of new C–C bond giving ketone **12** with the elimination of lead diacetate. Enol form of ketone **13** in the presence of bases undergoes intramolecular reaction of nucleophile substitution resulting in tetracyclic compound **14**.

The distribution of electron density in 2-iodobenzyl chloride **8** corresponds to the charges in synthon **A** (Scheme 10.2). The presence of two halogens in the

molecule results in more electrophilic benzyl position. At replacement of iodine atom for boron the inversion of polarity occurs and a partial negative charge is generated on the aryl carbon atom (synthon **B**); further transformation, the introduction of lead triacetate instead of boron atom, brings back the positive charge on the carbon atom of aryl fragment, however, now this position is definitely more electrophilic than benzyl (synthon **C**). Therefore the attack of nucleophile occurs on the carbon atom bound with the lead atom but not at the benzyl position [619–622].

Application of reactions of reductive coupling using diverse polyfunctional aryl derivatives of lead or bismuth **15** allows synthesizing a large number of polymethoxy-substituted 3-arylcoumarins, as well as tetracyclic derivatives of benzopyrans, benzopyranones, and isoquinolines, some of which (**16–21**) are shown on Scheme 10.4 [609, 618, 621–623].

The investigation of antitumor activity of synthesized coumarins demonstrated that the best cytotoxicity and antimitotic properties exhibit 4-arylcoumarins **22–25** (Scheme 10.5). In case of coumarin derivatives leader compounds contain in cycle A one or two methoxy groups [608, 611–613], unlike combretastatin A-4 or colchicine that contain trimethoxy-substituted fragment A. Increasing the amount of methoxygroups in this fragment results in significant reduction of the agent–tubulin binding constant [611]. 3-Hydroxy-4-methoxyaryl fragment C in 4-arylcoumarins (ring B in combretastatin A-4) can be easily replaced by indole substituent [608] with preserving high antimitotic activity (**25**). In this connection an idea appeared to introduce heterocyclic fragment in the structure of colchicine. Before our investigations heterocyclic colchicinoids were not known [624].

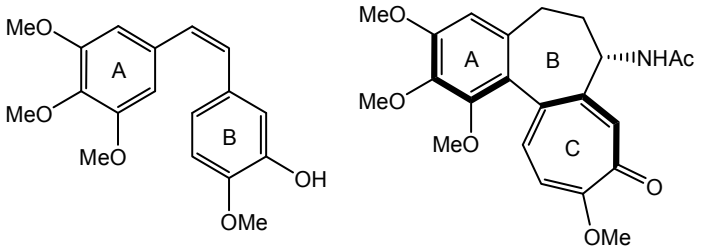
A complete synthesis of several colchicinoids basing on 3,4,5-trimethoxyphenylpropanoic acid **26** was carried out [625–627]. Acid **26** was converted in the corresponding iodine derivative *N*-methoxy-*N*-methylamide **27**. To create the target C–C bond between trimethoxyphenyl ring and indole fragment Weinreb ketone synthesis was applied using organocerium derivative of *N*-methylindole **28** (path *a*). The formation of seven-membered cycle B of allocolchicinoid **29** was performed by Pd-catalyzed reaction of C–H-activation in the position *3* of the indole fragment. The transformation of the carbonyl fragment using classic methods of organic chemistry resulted in colchicinoid **30a** [626]. For the synthesis of N–H-containing allocolchicinoid **30b** as the key stage the reaction of crotonic condensation was utilized of 2-iodo-3,4,5-trimethoxybenzaldehyde **31** and *SEM*-protected 2-acetylindole **32** [626] (path *b*) (Scheme 10.6).

To obtain isomeric colchicinoid with the reverse position of indole fragment methylindole was acylated at the position *3* using acylbenzotriazole **33** (path *c*). The subsequent catalytic reaction of C–H-activation resulted in forming tetracyclic colchicinoid **34** that in few stages was transformed into the target derivative **35** [626].

A total synthesis of tetracyclic colchicinoids **36–38** with other type of coupling of cyclic fragments also was realized (Scheme 10.7) [627, 628]. Biaryls **39a** and **39b**, obtained in five stages from arylpropionic acid **26**, were transformed into acid chlorides by treating with Ghosez's reagent; a subsequent acylation by Friedel–Crafts reaction using soft Lewis acids [$(i\text{-Bu})_2AlCl$ or $ZnCl_2$] and the transformation of functional groups furnished target colchicinoids **36–38**. Basing on derivatives **38** containing an azide substituent a series of lipophilic colchicinoids was obtained possessing common structure **41** [628].

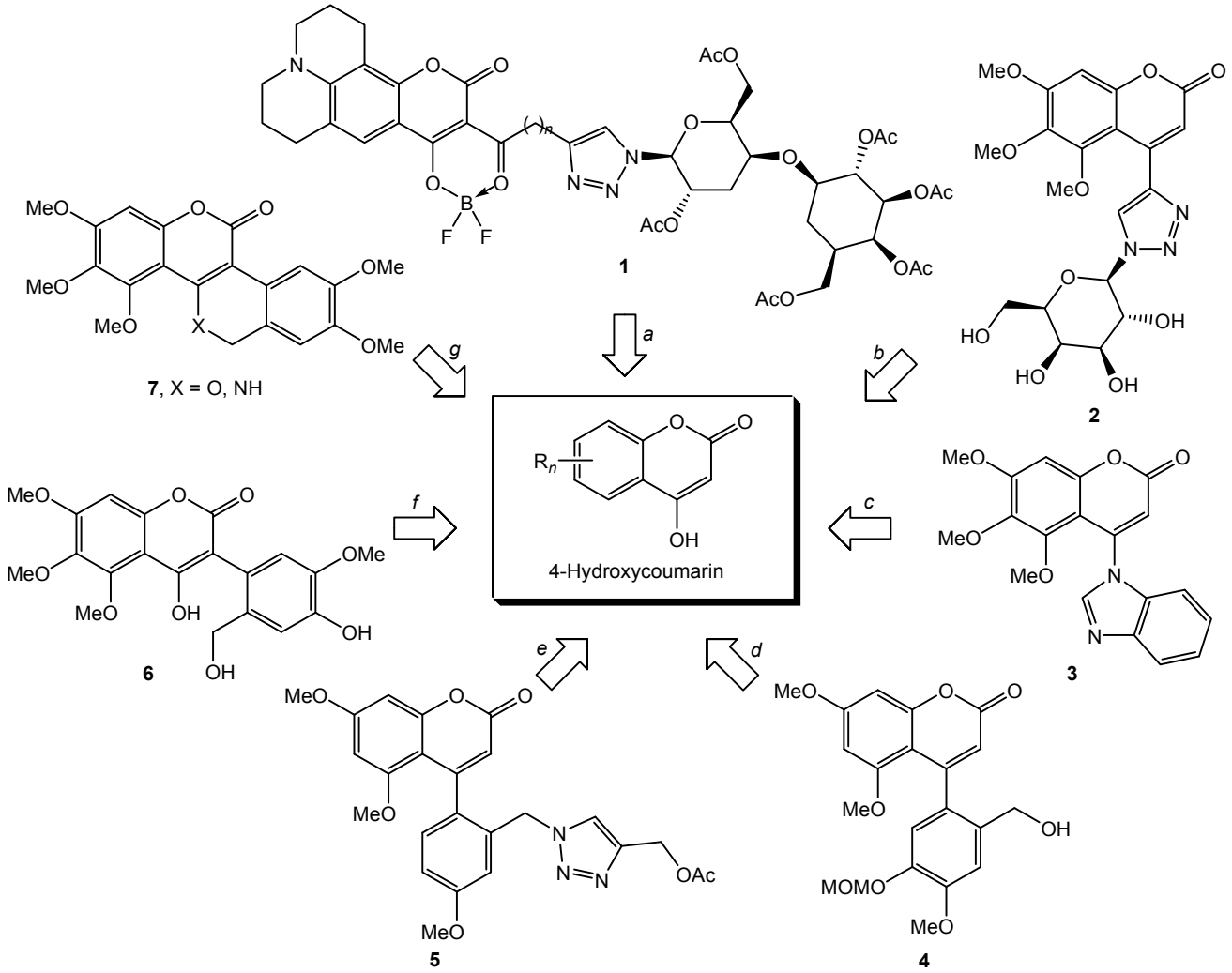
Derivatives **36–38** containing as "X" group carbonyl or hydroxyl fragment demonstrate an antiproliferative and apoptosis-inducing activity in low nanomolar and even subnanomolar concentrations, while not initiating necrotic effects.

Scheme 10.1.



Combretastatin A-4 (a*R*,7*S*)-Colchicine

Scheme 10.2.



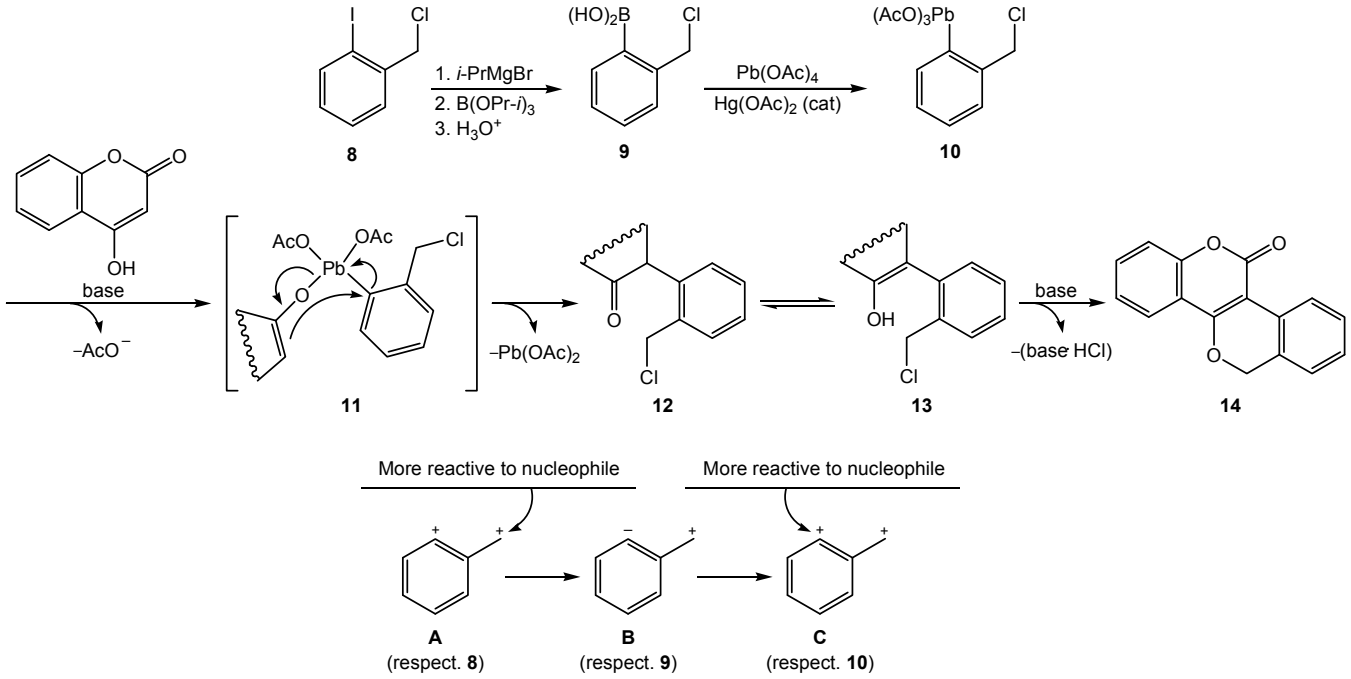
We also developed semisynthetic approach of 8–10 stages to non-racemic pyrolloallocolchicinoids underlain by natural colchicine. First colchicine undergoes bromination in the position *4* of ring A. In the next stage tropolone cycle C suffers contraction under the action of sodium methylate [629, 630] due to the 6-π-disrotative electrocyclization resulting in the formation of norcardiene intermediate **42**. The opening of cyclopropane fragment in adduct **43** leads to the formation of 4-bromoallocolchicinic acid **44** that enters Curtius reaction furnishing aniline **45**. The latter underwent iodination in the *ortho*-position to amino group that further was protected by trifluoracetate fragment, and thus obtained amide **46** was brought into tandem catalytic fusion (of Sonogashira cross-coupling/6-*endo*-*dig*-cyclization), resulting in nonracemic pyrolloallocolchicinoids **47** and **48a–48e** [630] exhibiting cytotoxic activity in subnanomolar concentrations with respect to a number of human tumor cell lines (Scheme 10.8).

Isostructural non-racemice furanoallocolchicinoids **49** were obtained from the natural colchicine only in three stages. Colchicine was transformed into iodocolchinol **50** in two stages [631]. The latter entered into catalytic tandem fusion with terminal alkynes resulting in the target non-racemic furanoallocolchicines **49a–49k** in good and high yields (Scheme 10.9).

Leader compound **49a** effectively inhibits growth of tumors in mice without lethality, weight loss, and neurological symptoms.

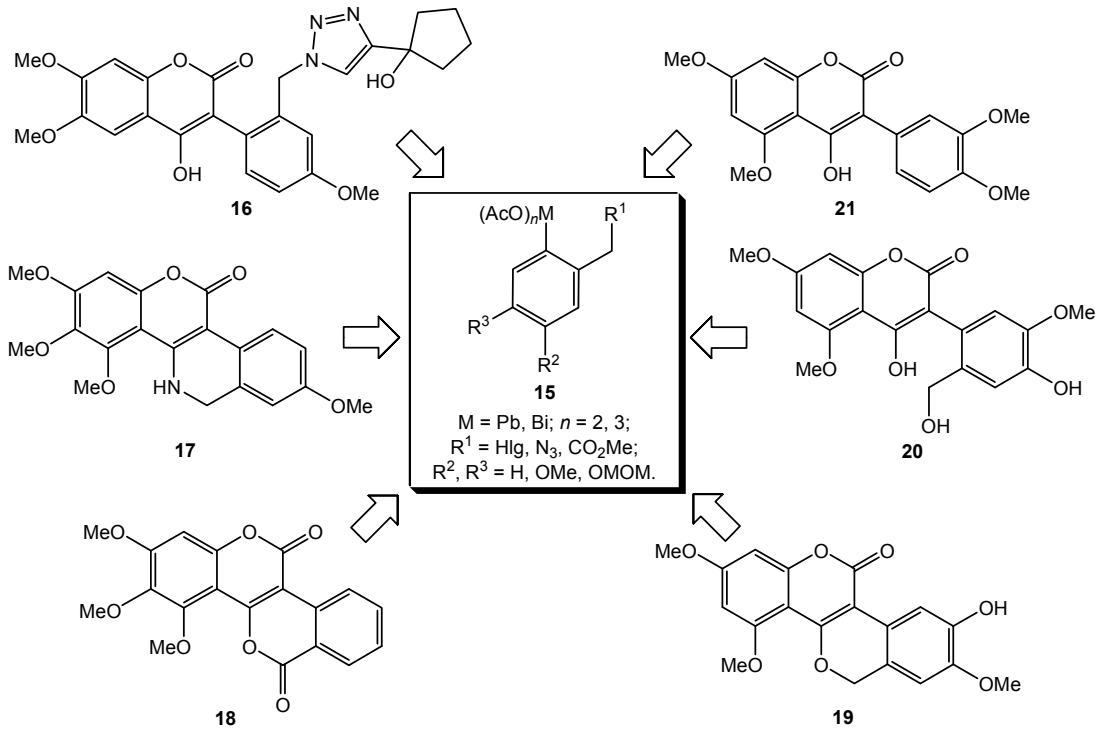
Among synthesized heterocyclic allocolchicinoides **36–38**, **47**, and **48** the highest antitumor activity is

Scheme 10.3.

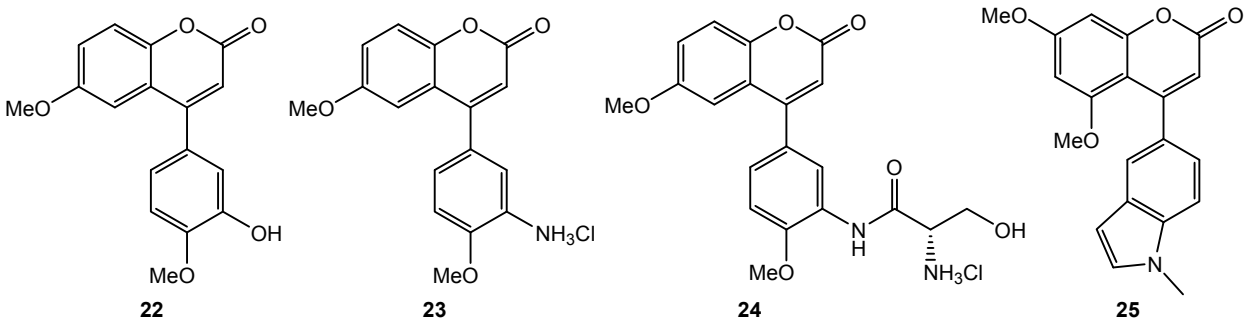


demonstrated by molecules containing a hydroxy group in benzyl or pseudobenzyl position. In this connection we decided to synthesize furanoallocolchicinoids **51** containing simultaneously two hydroxyls in benzyl and pseudobenzyl positions (Scheme 10.10). To this end iodocolchicinol **50**

Scheme 10.4.



Scheme 10.5.



obtained from colchicine was subjected to deacetylation and deacetyliodocolchinol **52** was obtained in an overall yield of 44% in 4 stages [632]. The reaction of transamination with application of Rapoport reagent allowed transforming amine **52** into ketone **53**. The latter underwent cascade cyclization in the presence of terminal alkynes with the formation of furans **54a**, **54b**, and **55**, whose carbonyl group was reduced to alcohol to obtain the target colchicinoids **51a**, **51b**, and **56**.

Compounds **51a** and **54a** are cytotoxic in low nanomolar concentrations with respect to a number of human tumor lines, they inhibit cell cycle in G2/M phase, inhibit tubulin polymerization, and also produce a number of interphase effects: excessive expression of tubulin and F-actin, hyperpolarization of mitochondrial and lysosomal membrane potentials [632].

To comprehend the high antiproliferative activity of heterocyclic allocolchicinoides containing hydroxy group in benzyl or pseudobenzyl positions, a hypothesis was offered on the capability of these molecules for covalent binding with cysteine fragments of cell protein tubulin. To check this hypothesis reactions of colchicinoides **49a** and **49b** with some thiols were performed [633]. Thiols of various structures easily react with the mentioned derivatives giving products of substitution of the hydroxy group **59–61** in high yields (Scheme 10.11).

To improve the pharmacokinetic parameters of the obtained colchicinoides pro-drug forms of the most active compounds were synthesized and systems of their address delivery were created. For this purpose 7 -triazolylcolchicinoides lipophilic derivatives were obtained that by extrusion method were introduced into lipid bilayer of liposomal nanoparticles basing on natural phosphatidylcholine and phosphatidyl inozite (Fig. 10.1, Scheme 10.12) [634].

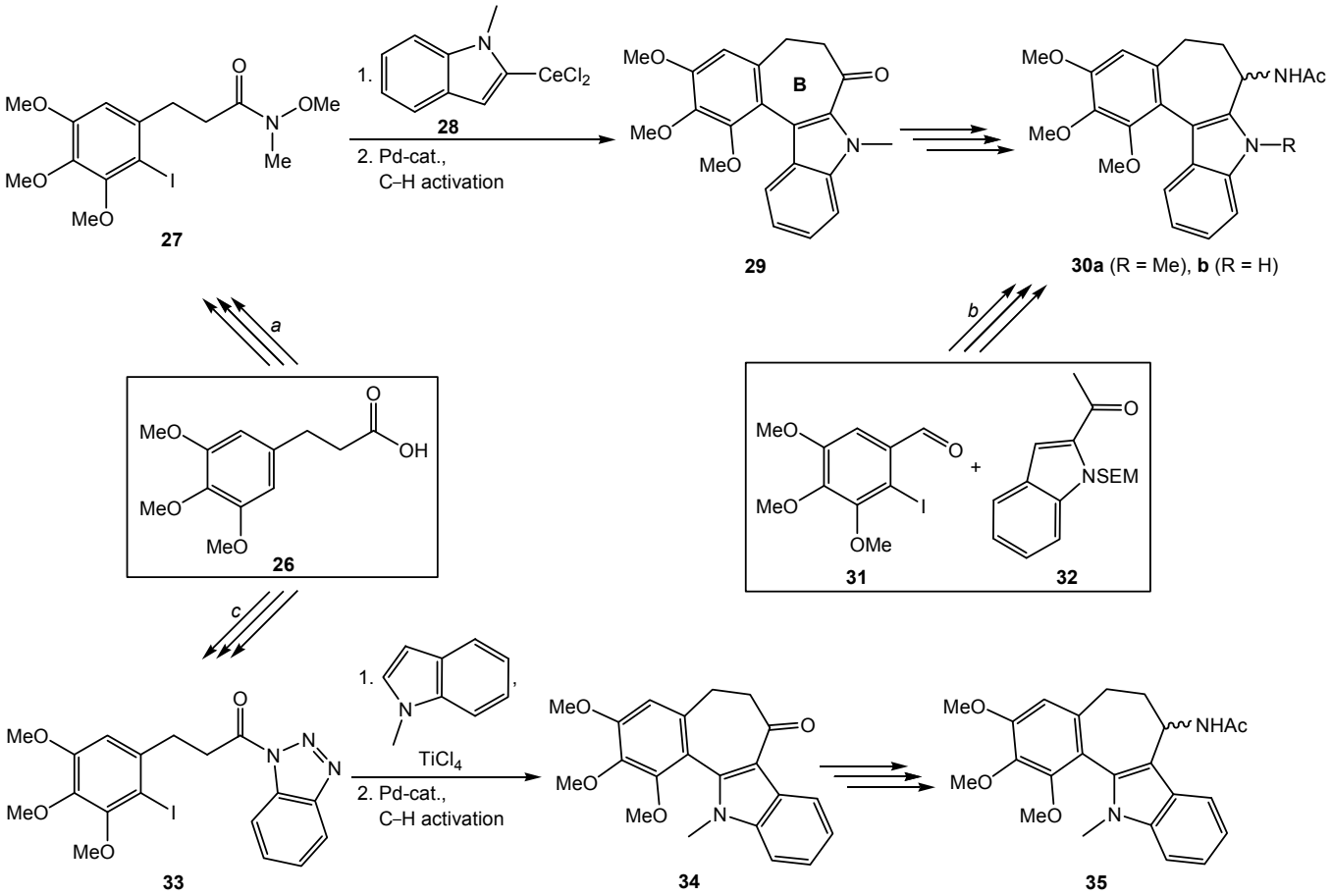
Lipid forms of colchicinoids were obtained proceeding from colchicine that first was subjected to deacetylation (Scheme 10.12). After the contraction of the tropolone ring in deacetylcolchicine with subsequent reaction of cooper-catalyzed diazotransfer using freshly prepared TfN_3 we obtained azides of colchicinoids **63–65** that easily reacted with alkynyl derivatives of fatty acids under conditions of cooper catalysis leading to the corresponding triazole-containing lipophilic colchicinoids, for example, **62**. The obtained therapeutical liposomes demonstrate high antitumor activity.

Conjugates of colchicinoides with chitosan **66** (molecular mass of chitosan ~40 kDa) were prepared (Fig. 10.2) [635]. NMR method demonstrated that the conjugate contained 45 colchicine fragments per one macromolecule of chitosan. The obtained conjugates **66** are more effective at inhibition of mice tumor growth than intact colchicinoid **49a**.

Also with application of click-chemistry we synthesized colchicine-tubulizine heterodimers **67** and **68** [636] (Scheme 10.13). Tubulizine is an effective antimitotic agent binding with the tubulizine site of tubulin protein [637]. Length of linker between colchicine and tubulizine fragments significantly affects *in vitro* cytotoxicity of obtained conjugates.

Besides the mentioned colchicinoid derivatives colchicine-like molecules **69** were obtained containing a 1,2,3-triazole fragment as the ring C [638]. With application of Negishi cross-coupling "block" methods were developed of the synthesis of combretastatins **70** [639] and isocombretastatines **10.73** [640] making it possible in mild conditions to quickly synthesize in good yields libraries of these effective antitumor agents (Scheme 10.14).

Scheme 10.6.



Hence, although colchicine is one of the oldest drugs applied to the treatment of Mediterranean fever, gout, and arthritis, it finds lately new areas of application in the treatment of phlogistic, cardiovascular, autoimmune and oncological diseases.

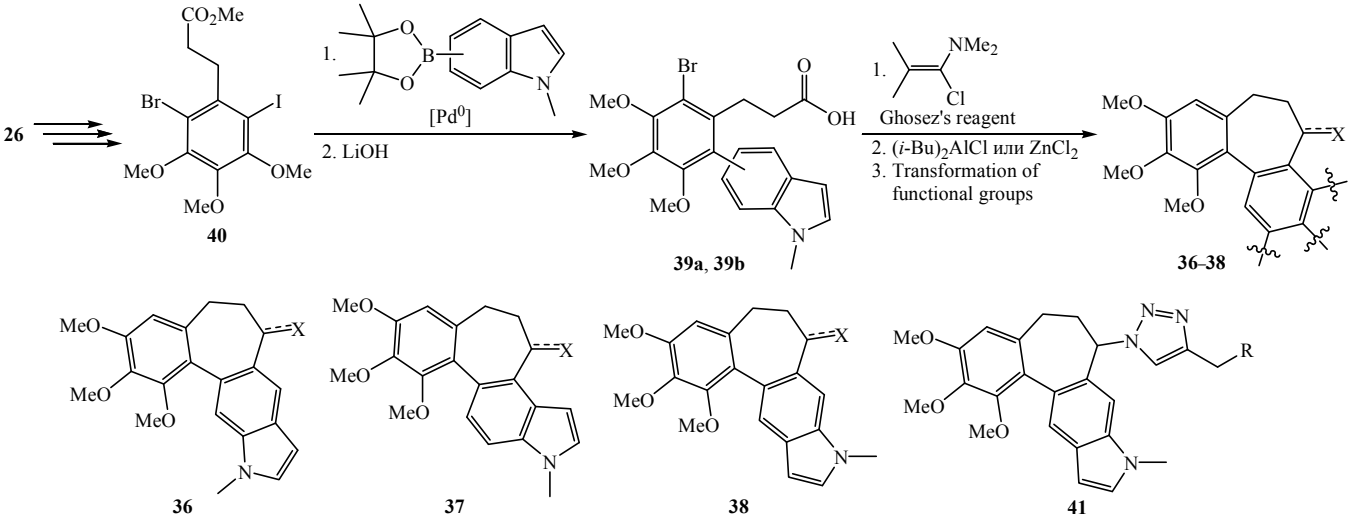
11. DEPARTMENT OF BIOTECHNOLOGY AND ORGANIC CHEMISTRY AT NATIONAL RESEARCH TOMSK POLYTECHNIC UNIVERSITY

Department was founded in 1901 by **Academician N.M. Kizhner** [641], it became the first center of organic chemistry in Asian part of Russia. In later years at the department a number of first rate results in aromatic iodination and the chemistry of hypervalent iodine compounds was obtained (Professors B.V. Tronov, A.N. Novikov, E.B. Merkushev, V.K. Chaikovskii), new reagents based on DMSO were discovered used for oxidation of alkenes and alkynes to 1,2-dicarbonyl compounds (**Professors V.D. Filimonov**, **M.S. Yusubov** and **E.A. Krasnokutskaya**), etc.

In the middle of the past century under the supervision of Professor L.P. Kulev at the department investigations of chemistry and technology of synthetic pharmaceutical compounds began and training of specialists for chemical-pharmaceutical industry was started. In particular, the known anticonvulsant drugs benzonal, benzoylbarbamyl, halonal, halodif, first synthetic antiviral preparation iodantipyrine for curing and pro-filactice of tick-borne encephalitis etc. were developed.

Ten years ago mild and effective method was developed for the preparation of aromatic and some heterocyclic iodides by diazotization of primary amines by the action of $NaNO_2$ in the presence of *p*-TsOH and KI in acetonitrile or water in 50–87% yields [642, 643]. Diazotization of anilines easily occurred under the effect of sulfated cationites and $NaNO_2$ in water, and the subsequent treatment of the products with KI afforded aromatic iodides ArI in 50–98% yields [644]. Similar results were achieved at diazotization – iodination of anilines under the

Scheme 10.7.



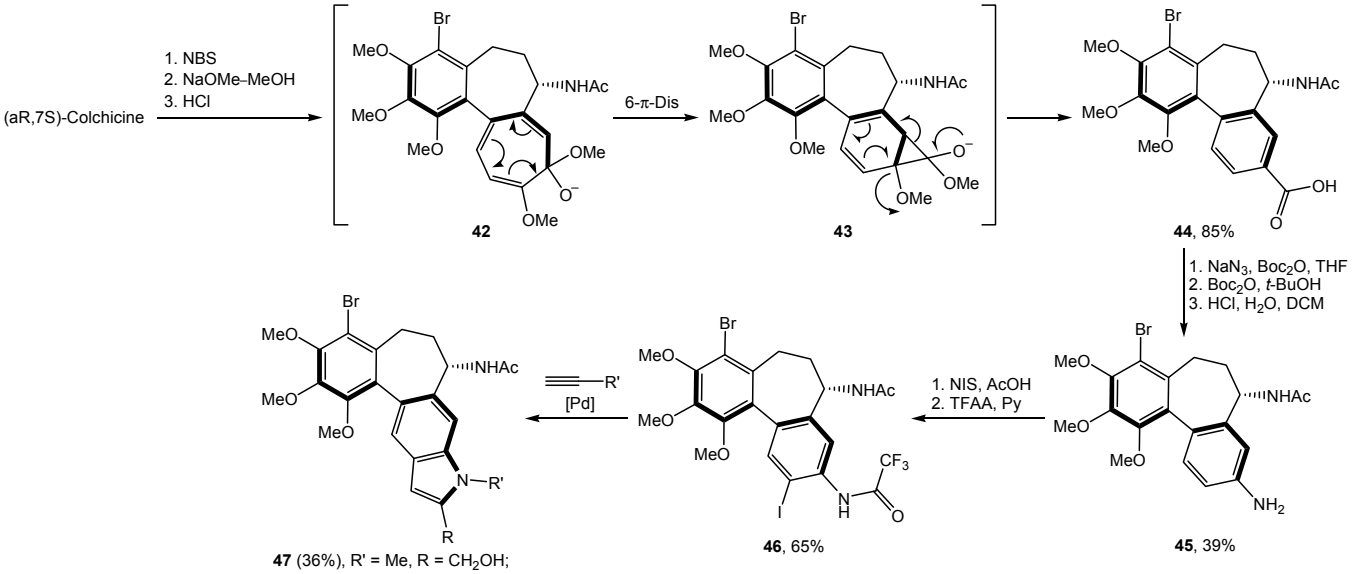
X = O, OH, N_3, NH_2, NHAc; R = OH, CH_2OH, $OC(O)C_{17}H_{33}$, $CH_2OC(O)C_{17}H_{33}$, $OC(O)C_{15}H_{31}$, $CH_2OC(O)C_{15}H_{31}$.

treatment with $NaHSO_4$ and $NaNO_2$ in aqueous paste [645] or at the application as the diazotization agent of anion-exchanging resins saturated with NO_2^- in the presence of *p*-TsOH [646].

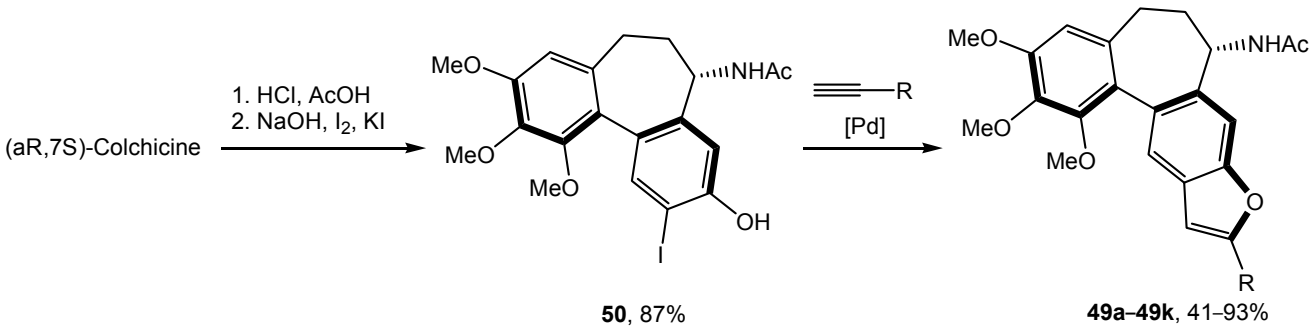
Primary products of these reactions are arendiazonium sulfonates, in particular, tosylates $ArN_2^+TsO^-$ (Scheme 11.1). We succeeded relatively recently to isolate for the first time the arenediazonium sulfonates and to identify them [647–650].

The developed method has a general character and is applicable to a wide series of aromatic amines both with donor and acceptor substituents; yields of salts reach 80% and more. The obtained sulfonates possess a number of advantages compared with the traditional diazonium salts. The most of salts are stable and explosive safe in dry isolated state and may be preserved at room temperature without changes, at least for several weeks [647, 648, 650]. An important advantage of these diazonium salts is a good solubility both in water and in low-polar solvents (DMSO, DMF, alcohols, ketones, acetonitrile, etc.), which distinguishes them beneficiary from diazonium tetrafluorborates. Moreover the sulfonates demonstrated

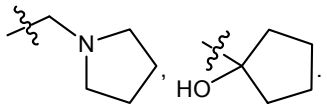
Scheme 10.8.



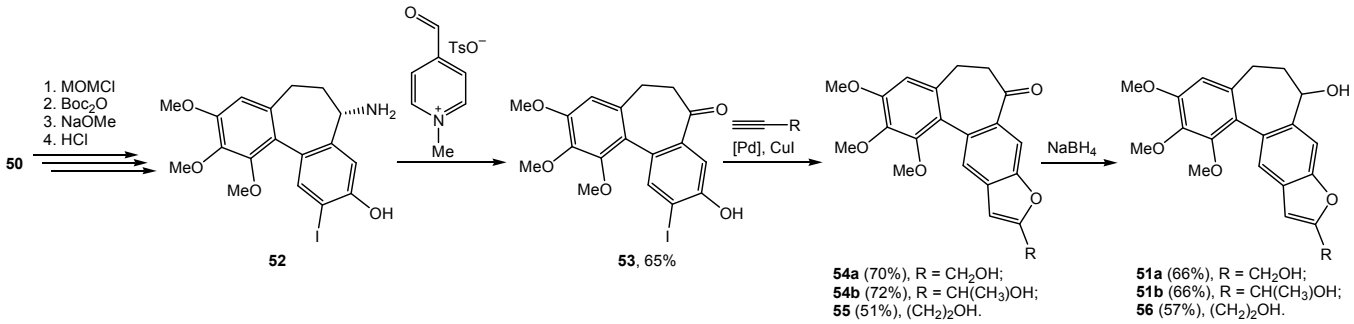
Scheme 10.9.



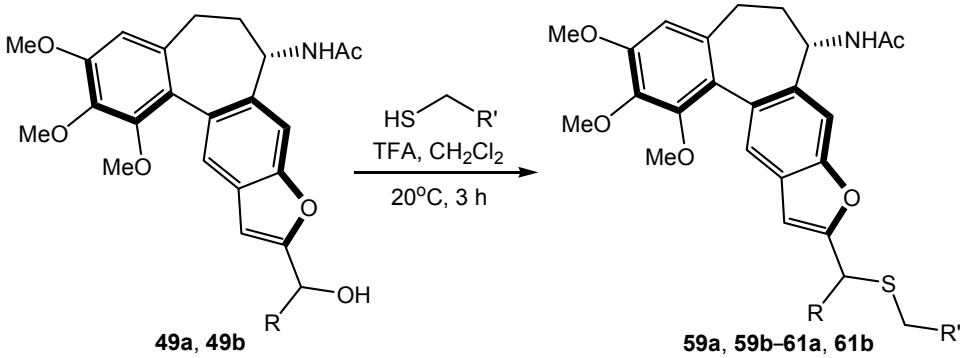
R = CH_2OH, CH_2OAc, $CH(CH_3)OH$, $(CH_2)_2OH$, $(CH_2)_8CO_2CH_3$, CH_2NEt_2, Ph, 2-Py,



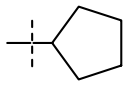
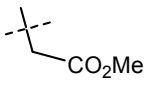
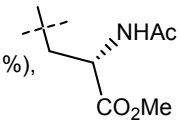
Scheme 10.10.



Scheme 10.11.



R = H (**a**), Me (**b**);

R' =  (**59a**, 83%; **59b**, 73%),  (**60a**, 81%; **60b**, 81%),  (**61a**, 97%; **61b**, 88%).

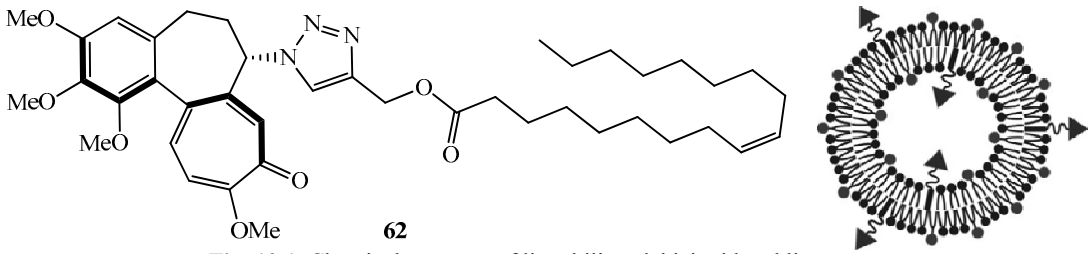


Fig. 10.1. Chemical structure of lipophilic colchicinoid and liposome.

Scheme 10.12.

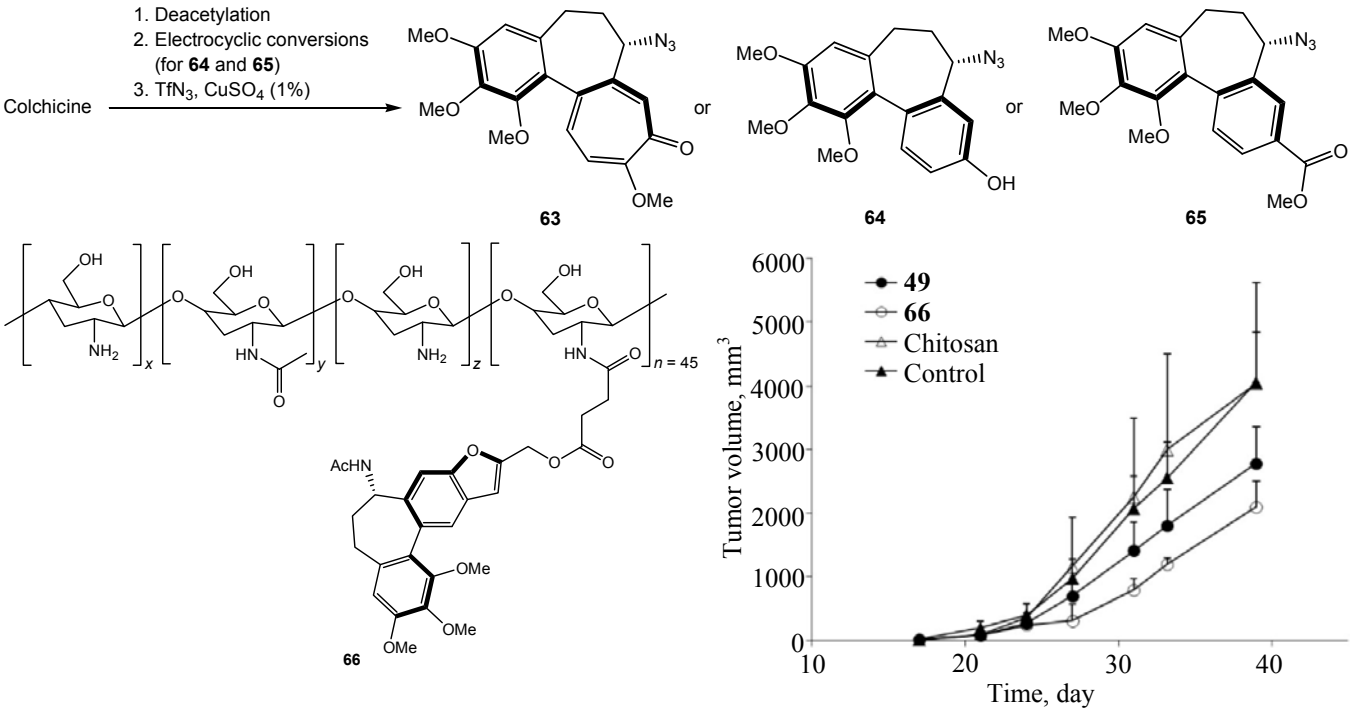


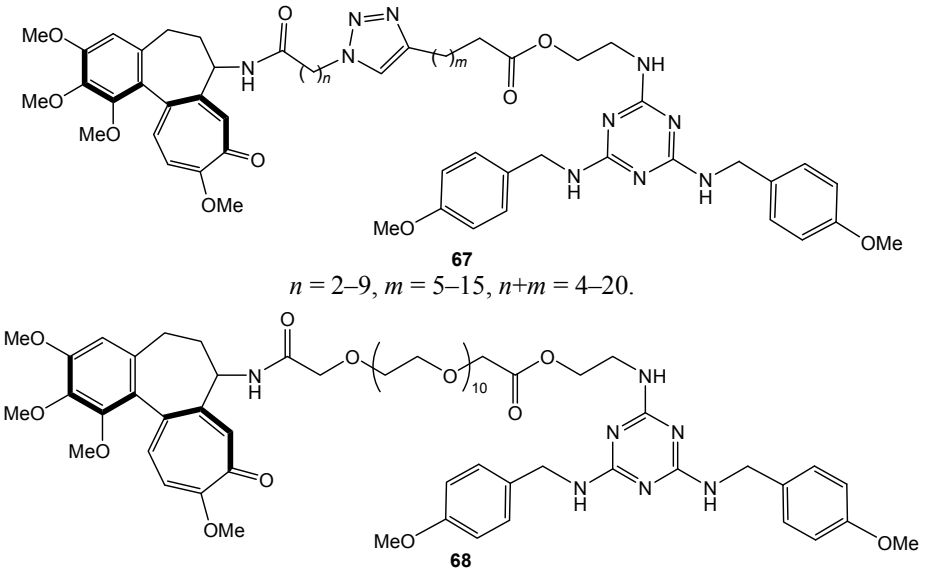
Fig. 10.2. Conjugate of colchicinoid with chitosan **66** and its antitumor activity.

lypophilicity unique for traditional diazonium salts and the capability to dissolve even in non-polar solvents (THF, CCl_4, benzene).

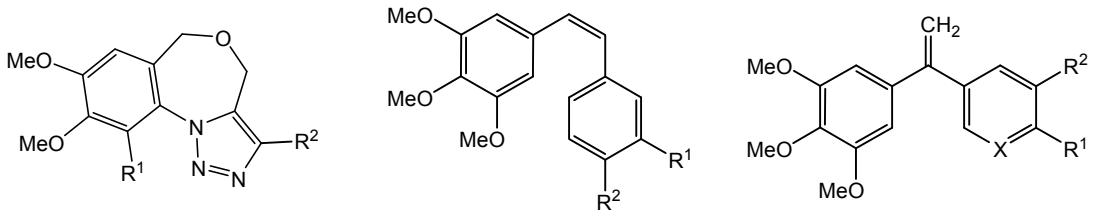
At the same time salts possess a high reactivity in typical "diazonium" reactions. In aqueous solution and mild conditions they are able to form in good yields aromatic iodides [642, 643, 646, 647], azides [651], triazenes [647], to arylate benzene and pyridine, to enter in reaction of azo-coupling, and under effect of Pd-catalyst to give products of C–C-condensations [647, 650–653] (Scheme 11.2).

For lypophilic sulfonates in non-polar surroundings new for diazonium chemistry transformations were also discovered. So, salts at heating in CCl_4 or

Scheme 10.13.



Scheme 10.14.



69 R^1 = H, OMe; R^2 = H, Me, Et.

70 R^1 = H, OH, F, Cl, CH_2OH, NHMe, $CH_2NHC(O)Me$, $CH_2NHC(O)(CH_2)_{12}Me$; R^2 = H, OMe, NHMe.

71 X = CH, N; R^1 = H, OMe, SMe, NHAc; R^2 = H, NHAc, NO_2, OH.

alkylbromides in the absence of cooper easily replace diazonium group for halogenes, giving in high yields aromatic chlorides and bromides ArHlg [648–650]. At heating of salts in chloroform they mostly eliminate nitrogen and are reduced to the corresponding arenes ArH. At investigation of reactions of diazotization of 2-, 3-, 4-amino- and 2,6-diaminopyridines, and also of 3-aminoquinoline in the presence of *p*-TsOH and TfOH initially formed pyridinediazonium sulfonates are unstable and spontaneously transform into the corresponding pyridyl and quinolyl tozylates and triflates [654, 655] (Scheme 11.3).

The developed methods are a good alternative to the known approaches to the preparation of pyridyl triflates and tozylates through acylation of pyridinoles by TsCl, TfCl, Tf_2O, Tf_2NR [656]. With application of diazotization in TfOH it was possible for the first time to obtain pyridines with triflate groups in positions *4* and *2*, *6*.

Another direction of studies at the department is the synthesis and investigation of derivatives of azoles as polydentate ligands (so-called "scorpionates" class). Universal and scalable methods were developed for the synthesis of bis(azolyl) derivatives with flexible polymethylene linkers of variable length (from 1 to 12 methylene group) by reactions of pyrazole, imidazole, 1,2,4-triazole, 1,2,3-benzotriazole, and 1,2,3-triazole with dibromo derivatives of alkanes in superbasic medium KOH–DMSO (Scheme 11.4) [657–659].

The obtained ligands were used in the course of preparation of coordination compounds with antiradical activity with respect to superoxide-anion [660], and also of specimens with new types of topology of linear coordination polymers and metal-organic scaffolds [640, 661]. They were also used in the syntheses of pyrazolium salts showing cytotoxicity with respect to tumor cells of promonocytic leukemia THP1 [639].

In reactions of pyrazoles with tetrabromethane ditopic ligands were obtained [662, 663] and used further for the preparation of coordination polymers of copper(II), possessing electrocatalytic activity [664, 665], and silver(I) with increased thermostability [666] (Scheme 11.5).

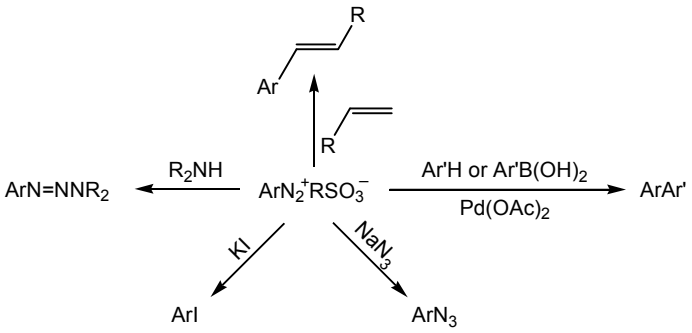
The mentioned investigations are realized in cooperation with Polzunov Altay State Technical University and Nikolaev Institute of Inorganic Chemistry of Siberian Branch of Russian Academy of Sciences.

Comparatively recently a new direction of research in the chemistry of carbohydrates was started at the department. Methods were developed of the total synthesis of esters of phenol glycosides [667–669], the main pharmacologically active components of medicinal plants of the family *Salicaceae* (willow, poplar). The development of new methods of the synthesis of glycosides of salicyl alcohols and salicylic acids is under study, an approach is suggested for the preparation of rare natural 2-O-acetylphenolglycosides [670] (Scheme 11.6). Together with Zelinskii Institute of Organic Chemistry of Russian Academy of Sciences a search is performed for new protective groups for the carbohydrate synthesis [671, 672].

Scheme 11.1.

$[NO^+]$ = *resin*-$NMe_3^+NO_2^-$, $NaNO_2$, AlkONO; R = 4-MeC_6H_4, 4-$C_{12}H_{25}C_6H_4$, CF_3.

Scheme 11.2.



To increase the effectivity of creation of new pharmaceuticals at the department modern methods of SAR and QSAR investigations are applied: molecular docking, virtual screening, pharmacophore modelling. Using these approaches promising linker compounds were found, possessing properties of inhibitors of elastase of human neutrophiles [673–676], agonists and antagonists of formylpeptide receptors [677].

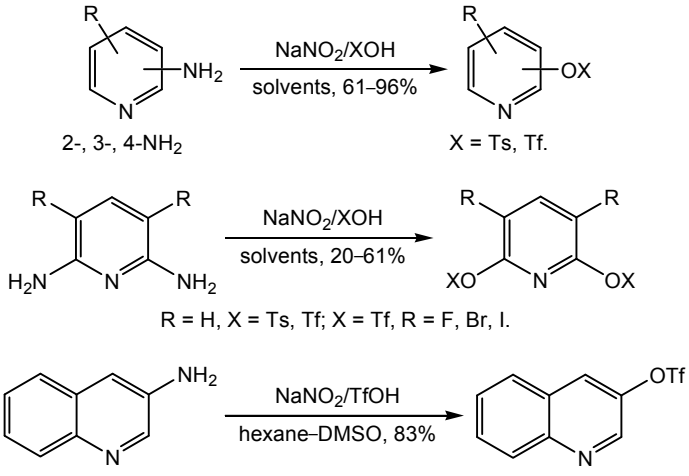
Lately attention is focused on the development of new inhibitors for enzymes of JNK family (c-Jun *N*-terminal kinase) that play significant role in phlogosis regulation, affect signaling pathways, leading to apoptosis and necrosis, regulate processes, from which depends damage to brain neurones and cardiomyocytes at ishemia/reperfusion. Besides that, JNK participates in embryonal development of heart, metabolism regulation, and normal functioning of myocardium. Basing on the data on spatial structure of enzyme JNK3 new inhibitors were investigated by methods of molecular docking to find that the most active among them were 11*H*-indeno-[1,2-*b*]quinoxalin-11-one oxime (IQ-1) and its sodium salt (IQ-1S). The synthesis of these compounds was carried out and the experimental studies confirmed the high activity of new JNK inhibitors in nanomolar concentrations [678, 679] (Scheme 11.7).

Moreover an ability of IQ-1S was discovered to act as effective donor of nitrogen oxide that opens good opportunities to create anti-ischemic drugs on its basis. Current investigations are realized at the department in cooperation with Montana State University (USA).

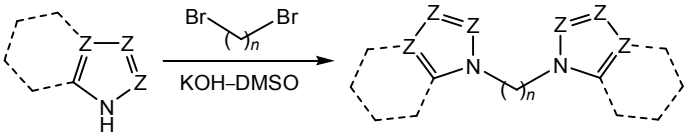
12. DEPARTMENT OF ORGANIC AND BIOLOGICAL CHEMISTRY AT DEMIDOV YAROSLAVL STATE UNIVERSITY

A set of studies, realized within last years at department, was focused on the complication of structures, containing a nitro group without its transformation. So a cycle of studies was performed on the optimization of heterophase process of forming a diphenyl oxide fragment of organic compounds containing either nitro or other functional groups in the

Scheme 11.3.

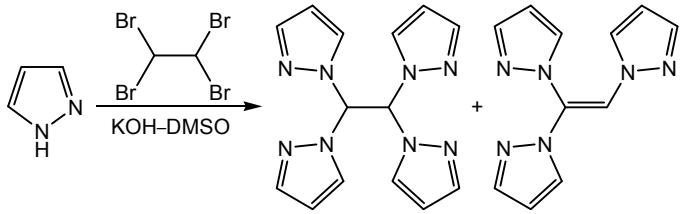


Scheme 11.4.



Z = CH, N; *n* = 1–12.

Scheme 11.5.



presence of original catalytic additives [680–682]. One of wide-spread methods of synthesis of substituted diphenyl ethers consists in the reaction of nitrohalobenzenes (or other activated substrates) with phenoxide-anions by S_NAr mechanism (Scheme 12.1).

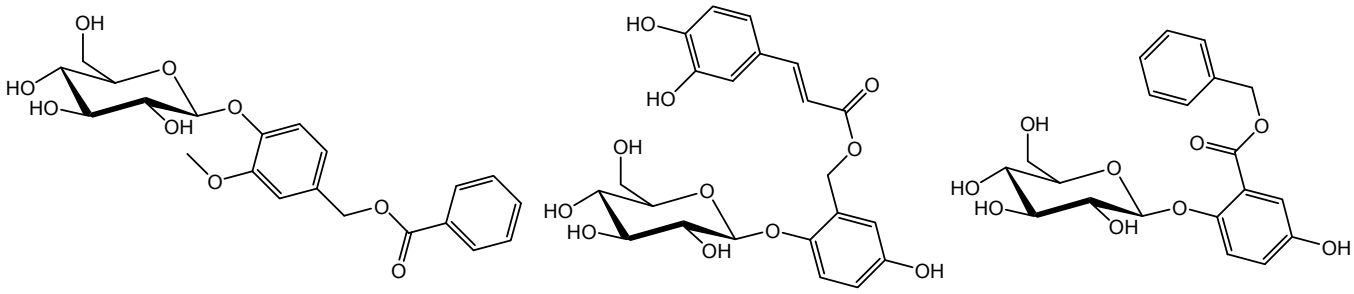
Phenoxides may be obtained directly in the course of the process by adding deprotonation agent (carbonates of alkali metals). The specific feature of this process is its occurring in two phases. Potassium carbonate is practically insoluble in aprotic dipolar solvents where the synthesis of diaryl ethers usually occurs. Therefore processes on the phase boarder occurs and, consequently, the characteristics of the solid phase play a significant role.

A promoting additive of iron(III) oxide was suggested in order to increase the rate of reaction between phenol and *p*-nitrochlorobenzenes in the presence of potassium carbonate [680]. The increase in the rate of the investigated process by hematite depends on the method of its preparation. The best results were obtained with iron(III) oxide synthesized from its sulfate. The nature of potassium carbonate activation in the presence of hematite consists in ionizing effect of iron oxide on the crystal lattice of potassium carbonate resulting finally in the emission of potassium ions into iron oxide and the formation of labile particles easing phenols deprotonation [681, 682].

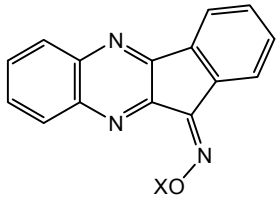
A series of studies performed at the department is connected with investigating the reaction of nucleophilic aromatic substitution of hydrogen in nitroarenes that often occurs with nitro group participation in further transformations. The object of investigations was the process of nitroarenes reaction with carbanions of arylacetonitriles, where depending on the structures of substrate and reagent a formation of different products occurs, from quionone oximes to heterocycles (Scheme 12.2). At the reaction of *para*-substituted nitroarenes with arylacetonitriles form 2,1-benzisoxazoles (anthraniles) (X ≠ H) [683]. Reaction of arylacetonitriles with nitroarenes without substituent in the *para*-position [684] (X = H), results in the formation of arylcyanomethylene-*para*-quinone monooximes [685].

These reactions proceed in monohydroxy aliphatic alcohols in the presence of high (at least twofold) excess of sodium or potassium hydroxide. The application of other solvents, bases, and also smaller amounts of alkali metal hydroxide results in the

Scheme 11.6.



Scheme 11.7.



X = H, Na

domination of side processes (substitution of halogenes and other nucleofuges, hydrolysis of cyano group, etc.). Quite a number of 5-R-3-aryl-2,1-benzisoxazoles was synthesized (Scheme 12.3) [686].

For unsymmetrical nitroaromatic compounds the reaction proceeds regiospecifically: for example, from 1,2-dichloro-4-nitrobenzene (Scheme 12.4) form anthranils of exclusively linear structure.

Limiting stage of the process is the formation of σ^H-complexes [687] **A** (Scheme 12.5).

At the investigation of arylacetonitriles reaction with nitroarenes without substituent in *para*-position the reversibility of the formation of arylcyanomethylene-*para*-quinone monooximes was experimentally proved [688], minor products of reaction of *para*-substituted nitroarenes with some arylacetonitriles were obtained in an individual state and characterized [689]. Quantum-chemical simulation of all stages of reaction of 4-nitrochlorobenzene with phenylacetonitrile resulting finally in the formation of 5-chloro-3-phenyl-2,1-benzisoxazole was performed, and also attempts were made at the isolation and identification of the intermediates in the reaction of 4-nitrochlorobenzene with various arylacetonitriles [690].

An interesting direction of further functionalization of 2,1-benzisoxazoles is the introduction of amino and nitro groups. In a system hydroxylamine sulfate–conc. H_2SO_4–vanadium(V) oxide (catalyst) 5-halo-3-phenyl-2,1-benzisoxazoles transform into 3-(4-aminophenyl)-5-halo-2,1-benzisoxazoles (Scheme 12.6) [686].

The direction of 2,1-benzisoxazoles reaction with nitrating reagents depends on reaction conditions [686] (Scheme 12.7).

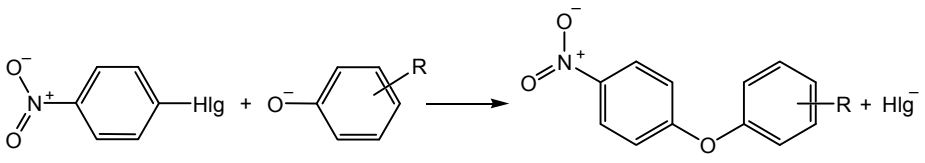
A new method was developed for the preparation of fused imidazole derivatives with a nodal nitrogen atom consisting in the reductive cyclization of *N*-[2-nitro-(het)aryl]pyridinium chloride salts (Scheme 12.8). The structure of key intermediate [691] was established and also the effect of different factors on this process: the nature of electron [692] and proton donors, temperature [693], and structure of the substrate [694].

The reductive cyclization was catalyzed by $TiCl_3$, $FeCl_2$, $SnCl_2$. As proton donors the lowest aliphatic alcohols were applied, their mixtures with 4% HCl and with hydrochloric acid of different concentrations. The reduction of pyridinium salt in alcohols results in the formation of the cyclization product in 95–96% yield. Conditions of synthesis were developed both for polycyclic derivatives of imidazole and 1-(2-aminoaryl)pyridine chlorides (Scheme 12.9).

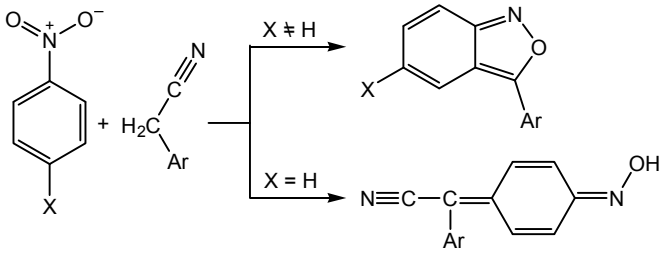
To comprehend the effect of different factors on the direction of reduction of *N*-(2-nitroaryl)-pyridinium salts investigations were performed on establishing the nature of the key particle formed in the course of the synthesis, whose participation resulted in the cyclization. The obtained data evidence that the key role belongs to hydroxylamine derivative (Scheme 12.10).

The application of stronger reducing agent ($TiCl_3$), raising the temperature and proton donor properties of the environment promote transformation of arylhydroxylamine into amino compound (path *a*), and at reduction in alcohol or weak acidic aqueous-alcoholic solution at 10–40°C a reductive hetero-cyclization occurs (path *b*). In collaboration with coworkers from Zelinskii Institute of Organic Chemistry of Russian Academy of Sciences

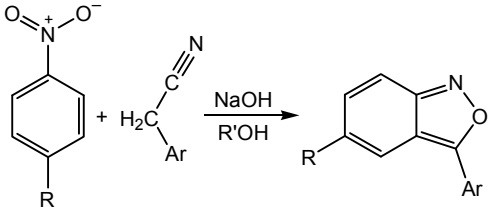
Scheme 12.1.

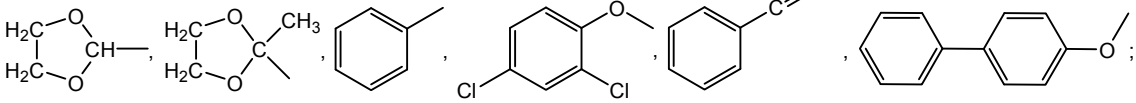


Scheme 12.2.



Scheme 12.3.



R = Cl, Br, I, COOH, 

Ar = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 2-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 2-$CH_3SC_6H_4$, 3,4-$Cl_2C_6H_3$, 3,4-$(C_2H_5O)_2C_6H_3$.

we applied electric current as a source of electrons [695, 696]. The performed studies made it possible to choose conditions of electrolysis allowing the preparation of chemically pure heterocyclic compounds in high yields.

The reactivity of substituted pyrido[1,2-*a*]benzimidazoles in reactions of nitration and halogenation was studied [697, 698] (Scheme 12.11).

In collaboration with researchers of Engelgardt Institute of Molecular Biology of Russian Academy of Sciences ability was studied of a series of obtained pyrido[1,2-*a*]benzimidazoles to embed into DNA molecules [699, 700]. All tested substances may be applied as intercalate agents in chromosomes analysis for increasing resolution capability of cytogenetic methods.

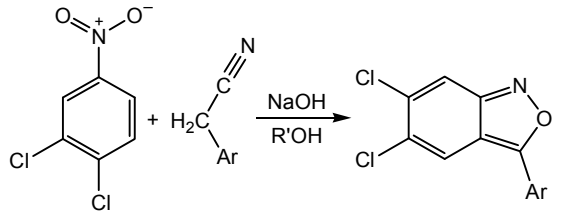
13. DEPARTMENT OF ORGANIC CHEMISTRY AT YAROSLAVL STATE TECHNICAL UNIVERSITY

The main directions of investigations are connected with the chemistry of heterocyclic compounds. Initially the interest in pyridazine-3(2*H*)-ones and their fused derivatives was due to the search for new biologically active compounds because of their known antiviral, cardiotonic, sedative, antibacterial, and analgesic activity. By an example of 6-arylpyridazine-3(2*H*)-ones the basic realized approaches to their synthesis and functionalization are illustrated (Scheme 13.1).

The investigation of the dehydrogenation of 4,5-dihydropyridazin-3(2*H*)-ones under the action of bromine demonstrated that electron-donor substituents *n*-R^8 noticeably lower the rate of dehydogenation, and electron-acceptor substituents increase it [701]. A new reagent was found for dehydrogenation of 4,5-dihydropyridazin-3(2*H*)-ones, chlorosulfonic acid, which made it possible to perform later a one-pot synthesis of sulfochlorides of a series of 6-arylpyridazin-3(2*H*)-ones basing on 4,5-dihydropyridazin-3(2*H*)-ones [702]. A new method of synthesis was developed of amines of 4-amino-6-arylpyridazin-3-(2*H*)-one series based on 4-oxo-4-arylbut-2-enoic acids [703].

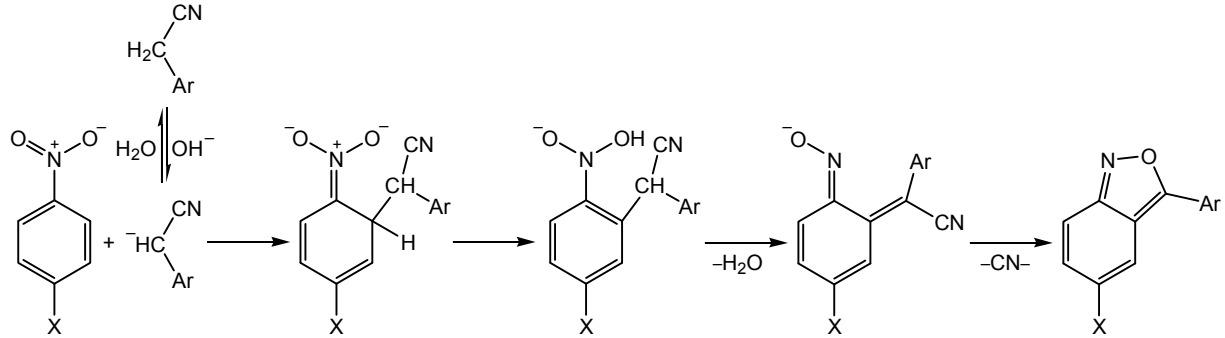
A spontaneous elimination was observed at the acylation of amines at R^1 = Ar. It is reasonable to obtain carboxylic acids (R = COOH) basing on 4-oxo-4-(4-carboxyphenyl)butanoic acid produced in its turn by the selective oxidation of the methyl group in the 4-oxo-4-(4-methylphenyl)butanoic acid in the presence of cobalt bromide catalyst. The combinatorial libraries

Scheme 12.4.



Ar = Ph, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 3,4-$(C_2H_5O)_2C_6H_3$.

Scheme 12.5.



A

of 3-(6-aminopyridazin-3-yl)benzenesulfonamide and 3-(6-chloropyridazin-3-yl)benzenesulfonamide [704] etc. were obtained. By Michael reaction using as nucleophilic agents compounds of pyridazine and phtalazine series and derivatives of maleic and itaconic acid as Michael acceptors we obtained new vicinal dicarboxylic acids [705] and their derivatives [706].

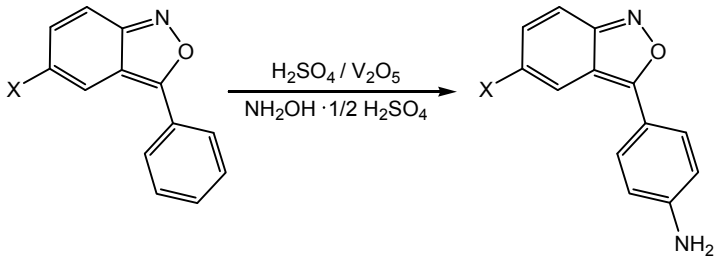
In continuation of these studies the possibility was investigated of the preparation of methoxyestr-1,3,5-(10)-triene[17,16-*c*]pyridazin-3[1](2*H*)-6[1]-one and 3-β-hydroxyandrost-5-ene[17,16-*c*]pyridazin-3[1](2*H*)-6[1]-one [707] by the reaction respectively of 3-methoxyextr-1,3,5(10)-trien-17-one and 3-β-hydroxy-androst-5-en-17-one with glyoxylic acid followed by treating with hydrazine hydrate (Scheme 13.2).

Methods were developed of carboxylic acids preparation containing a fragment of 3,5-substituted 1,2,4-oxadiazoles [708–712]. One-pot method of synthesis of (5-alkyl-1,2,4-oxadiazol-3-yl)benzoic acids [713] from the corresponding amide oximes and anhydrides with a subsequent selective oxidation of methyl group in the aromatic ring allows the preparation of desired acids in a yield over 85%. The oxidation was performed with air oxygen in the presence of cobalt bromide catalyst. A synthesis was carried out of 1,2,4-oxadiazole derivatives from amide oximes of aromatic series and acetonitrile at a pressure of 10 kbar and 100°C in a yield of 80% (Scheme 13.3) [714].

A procedure was developed for the preparation of new arylalicyclic tricarboxylic acids basing on accessible commercial compounds (Scheme 13.4) [715].

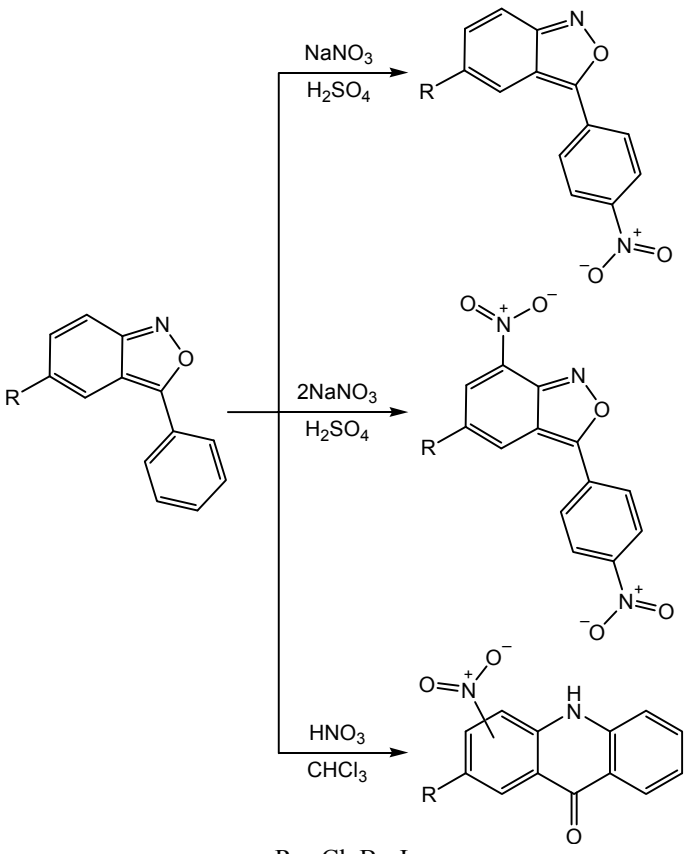
From similar row material a synthesis was performed of new optically active aminocarbocylic

Scheme 12.6.



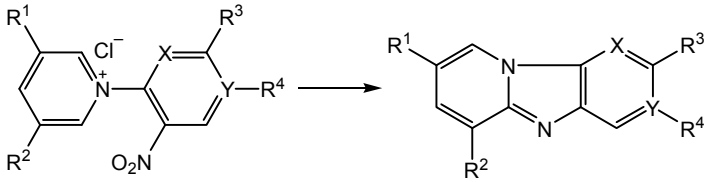
X = Cl, Br, I.

Scheme 12.7.

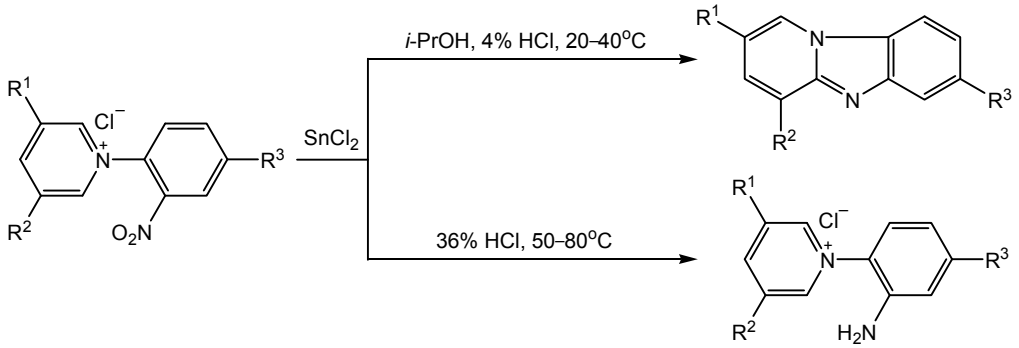


R = Cl, Br, I.

Scheme 12.8.



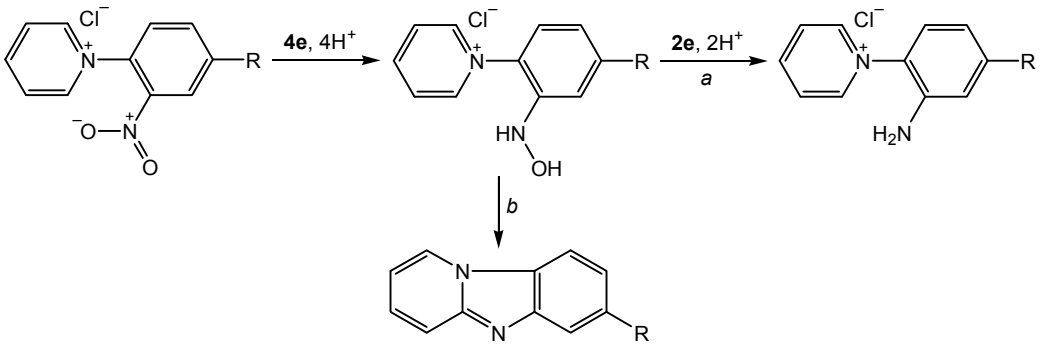
Scheme 12.9.



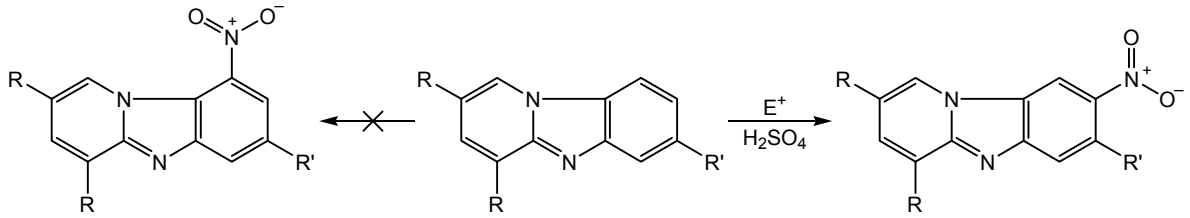
acids containing fragments of L-leucine or L-valine [716, 717] and optically active semi-aromatic polyamidoimides, possessing a plausible thermal stability (Scheme 13.5) [718].

The synthesized hemisuccinate of avermectin B_1 by biocide (antiparasitic) effect exceeds the known preparations of avermectin B_1 and closantel [719]. Therefore the other anhydrides of vicinal dicarboxylic

Scheme 12.10.



Scheme 12.11.



acids [720] and also cholic acids [721] were brought into the reaction of monoacylation of avermectin B_1 (Scheme 13.6). The reaction proceeds only at the hydroxy group in position *5* with the formation of 5-O-hemisuccinate, and even at the use of a large excess of anhydride it was impossible to obtain disubstituted derivatives. The problem of obtaining 4"-O-acyl derivatives of avermectin B_1 in all mentioned cases was solved by *tert*-butyldimethylsilyl protection of the 5-hydroxy group.

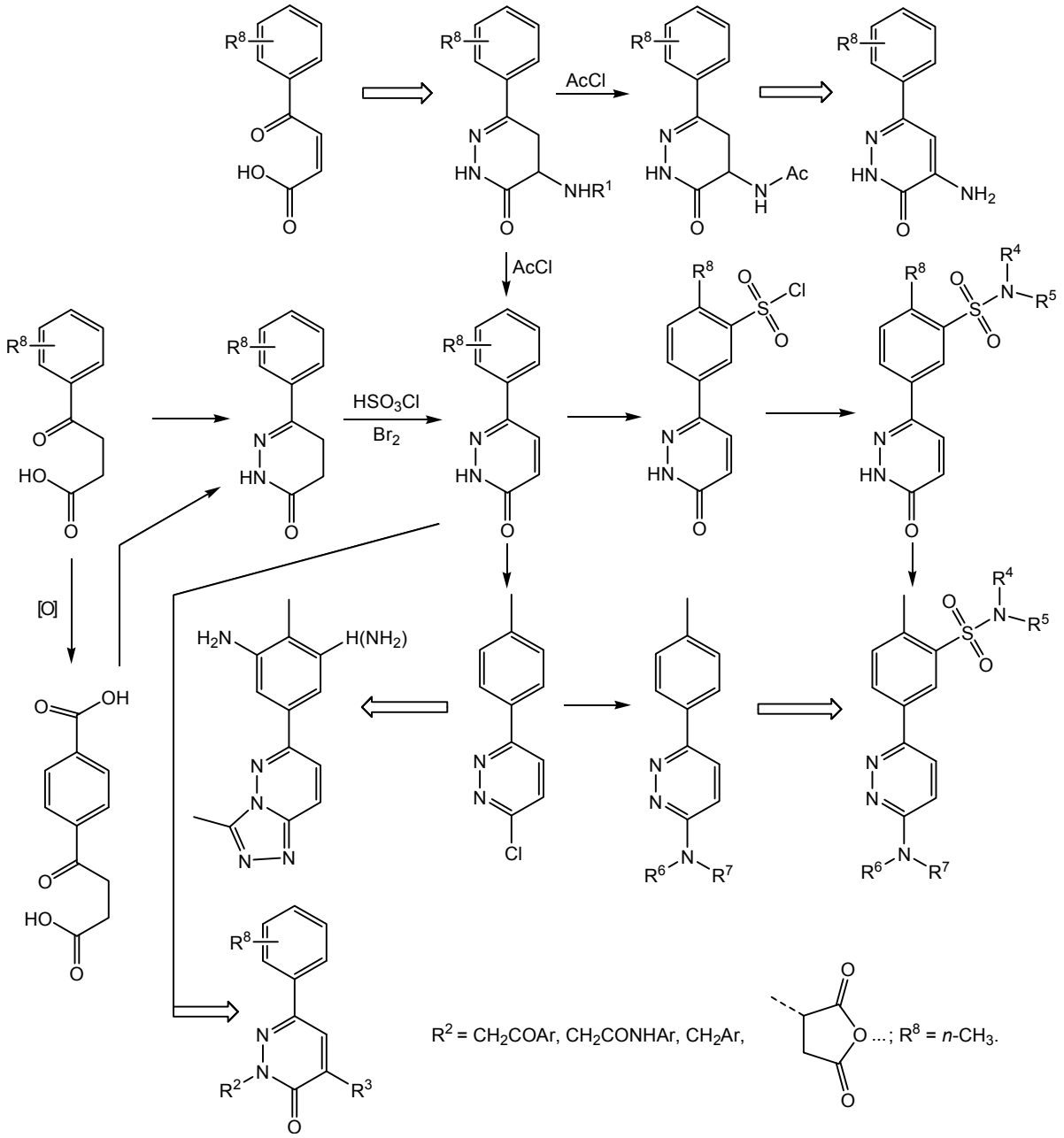
By reaction of avermectin B_1 with succinic anhydride at a super high pressure of 10 kbar a previously problematic 5-O-4"-O-disuccinate of avermectin B_1 was obtained, also interesting as potential antiparasitic agent [722]. Products were obtained of further functionalization of 5-O-hemisuccinate of avermectin B_1 [723].

14. DEPARTMENT OF ORGANIC AND BIOORGANIC CHEMISTRY AT CHERNYSHEVSKII SARATOV NATIONAL RESEARCH STATE UNIVERSITY

At the department (**head of department Professor O.V. Fedotova**) systematic research is in progress in the field of the chemistry of mono-, polycarbonyl compounds, products of their carbo- and heterocyclization, *N*, *O*, *S*, *Se*-containing five-, six-, seven-membered heterocycles, including those of complex structure (fused, bridged, spirocyclic), and also exploration of possible practical application of synthesized substances, first of all, as biologically active compounds in medicine, veterinary. New reactions were found for building up heterocyclic systems of diverse degrees of saturation, condensation, functionalization basing on accessible substrates.

Methods were developed for the preparation of *N*-,*O*-containing polyheterocyclic systems including 2*H*-chromen-2-one fragment: chromenopyrimidobenzimidazolones, dihydrochromenopyrazolopyridinones, -pyrimidinones, -quinazolinediones, polysubstituted 1,4-dihydropyridines, chromenoquinolines, -acridines [724–726]. Competing Biginelly reactions were discovered: condensation of 4-hydroxychromenones and aromatic aldehydes into arylmethylenebis-2*H*-chromen-2-ones; the possibility of participation of nucleophilic C^4 site of 1*H*-pyrazol-5-amine in forming dihydrochromenopyrazolopyridinones. The confirma-tion was obtained of predicted generality of behavior of 4-hydroxychromen-2-one and 3-substituted polyoxo compounds on its basis in multicomponent reactions with bis-azaheterocyclic nucleophiles of benzimidazole and pyrazole series involving endo- and exocyclic nitrogen atoms. A possibility was discovered of the formation of regioisomers of linear and angular structure and their separation; it concerns the position of the chromen-2-one fragment in hydrochromenopyrimidobenzimidazolones, products of modified Biginelly reaction. Tautomeric keto-enamine, enol-imine, amino-imine transformations were established in dihyd-

Scheme 13.1.



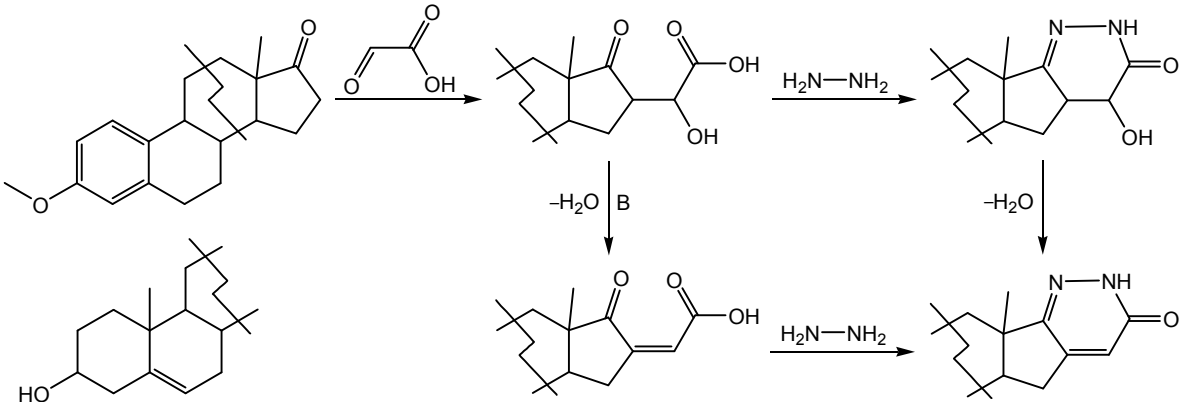
rochromenopyrazolopyridinones, -pyrimidinones, -quinazolinediones (Scheme 14.1).

Biginelly reaction was extended to acetoacetyl- and arylpropylchromen-2-ones. At the presence of a methyl substituent in the quinazoline fragment and a lactone carbonyl in the chromenone segment the carbocyclization and hemiketalization was observed providing polyheteroatomic systems. In two component condensation with the same reagents angular chromenopyrimidines were obtained.

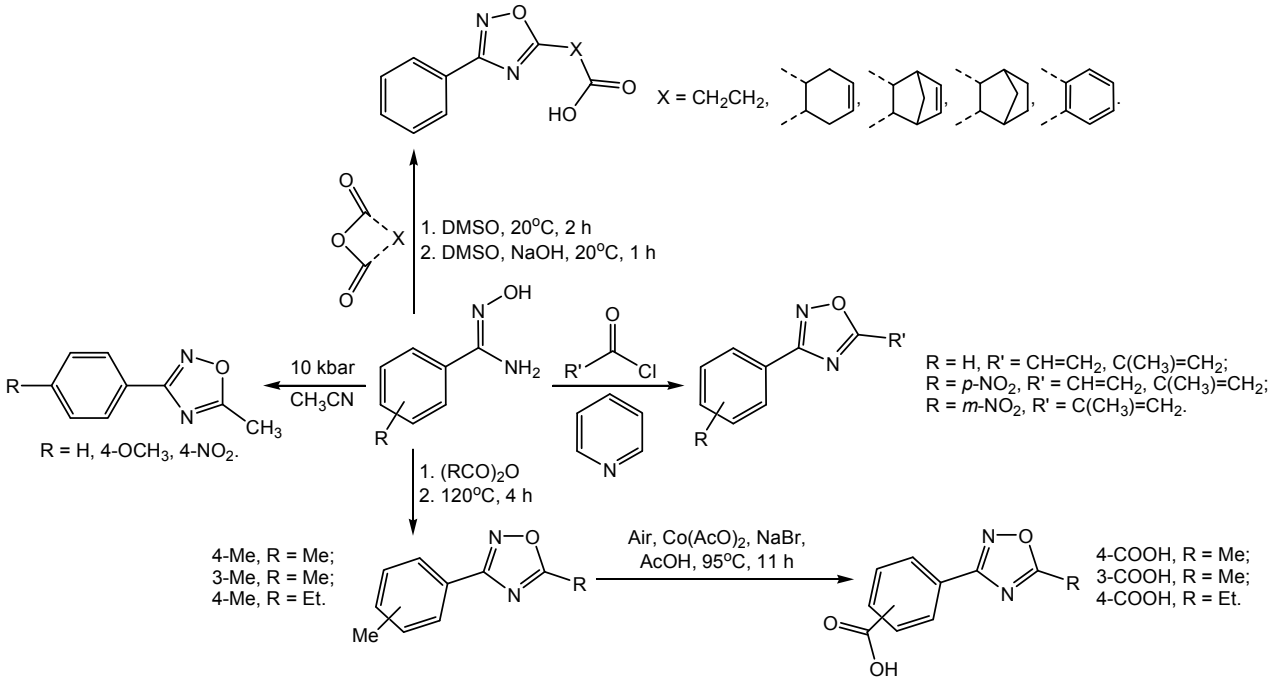
The possibility was demonstrated to build up dihydropyridines of symmetric and unsymmetrical structure in a modified four component version of reaction depending on chosen conditions: microwave activation or common heating, varying the order of reagents mixing (Scheme 14.2).

Features of acetoacetylchromen-2-one structure provide a possibility for a chain of cascade transformations to occur in Hantzsch reaction affording substituted hydrochromenoquinolineones or hydroid-

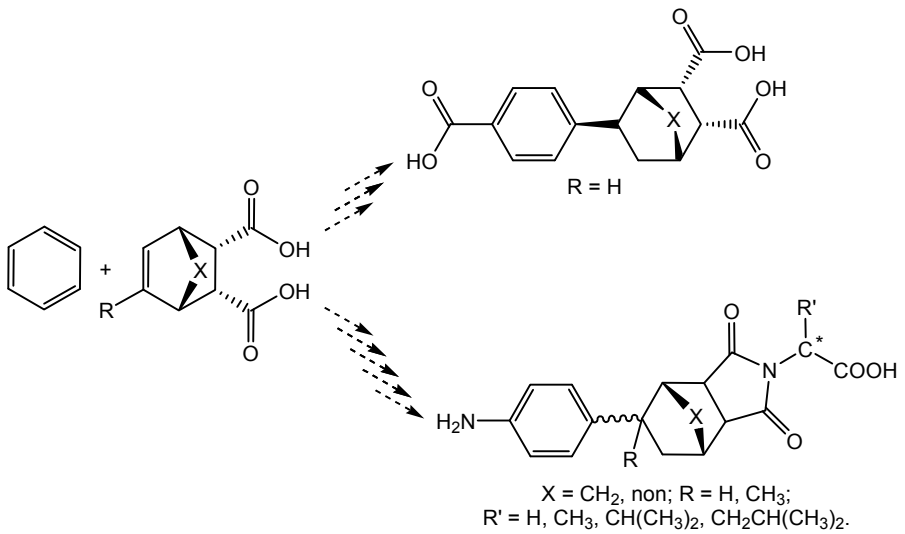
Scheme 13.2.



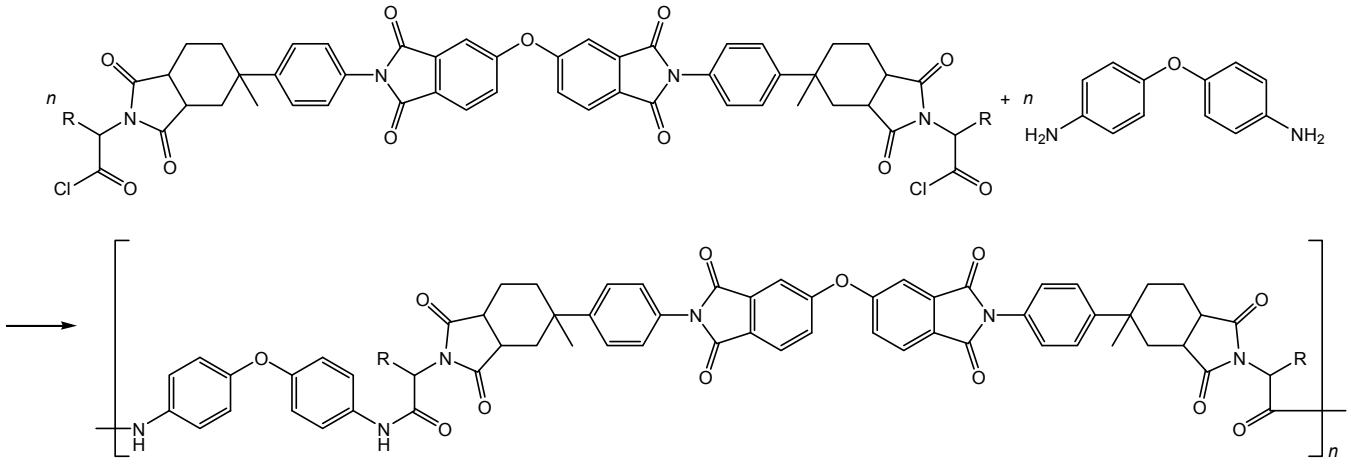
Scheme 13.3.



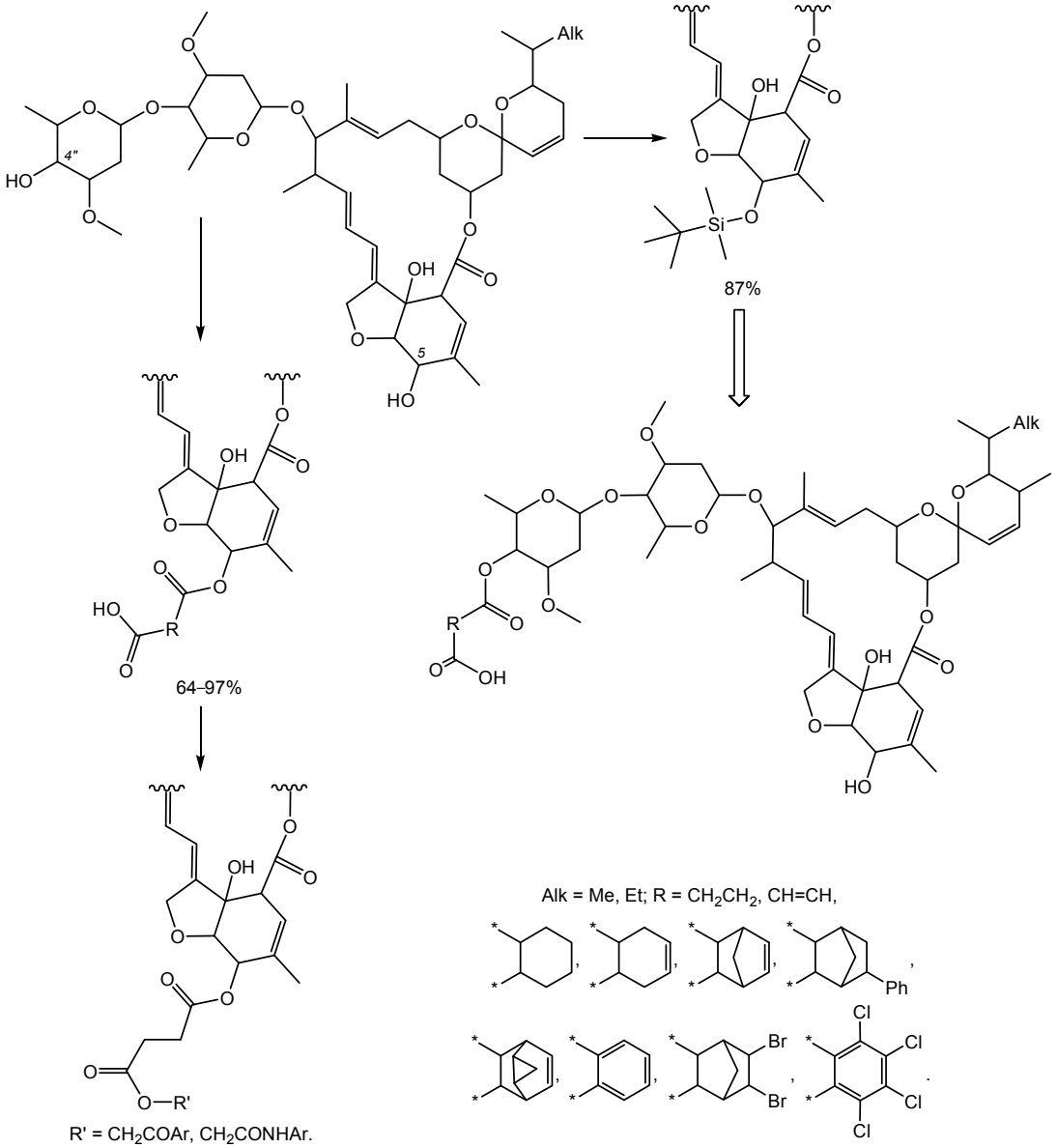
Scheme 13.4.



Scheme 13.5.



Scheme 13.6.



chromeno-acridinediones respectively in the presence or in the absence of acetoacetic ester (Scheme 14.3).

The 3-substituted 2*H*-chromen-2-ones were found to be prone to heterocyclization giving new di- and tetrahydropyridine systems and products of their aromatization, chromenopyridines; for the first time nucleophilic transformations afforded oxazepine and diazepine systems fused with chromen-2-one pharmacophoric fragment (Scheme 14.4) [727, 728].

A synthesis was carried out of new 3-hetaryl-substituted and condensed 2*H*-chromen-2-one with application of acyclic and heterocyclic aza(thio)reagents, including a one-pot process under microwave effect. Series of linearly bound hybrid systems were obtained containing two or more pharmacophore fragments including along with 2*H*-chromen-2-ones C–C-linked benzimidazole, benzothiazole, thiadiazole, and other cycles.

New data were obtained in the chemistry of furan-2-ones, their *S*,*N*-heteroanalogs of different grade of substitution containing one or several ethylene bonds, enone fragment, arylmethylene, allylidene, ethylene derivatives of the mentioned heterocycles; investigations were performed of the stereochemistry, relative reactivity, intermolecular reactions, tautomerism, reactions of cyclddition, azocoupling, multicomponent transformations.

A selective reactivity was revealed at investigation of the reaction of multicenter substrates of the above mentioned type with nucleophilic reagents of diverse strength, differing by the number and the nature of nucleophilic centers. Their chemical behavior was studied in reactions of Michael, Mannich, Vilsmeier–Haak, condensations with fatty-aromatic ketones, aldehydes, ethers, hetaryldiazonium salts, pericyclic rearrangements (Scheme 14.5) [729, 730].

The structural features of the objects of investigations and their accessibility allow their utilization as synthons for fused, bridged, spirocyclic, polynuclear (diaza- and oxabicyclo[3.3.0]octan-8-ones, pyridazinones, substituted oxazoles, pyrazoles, furapyrans, diazaspirononadienes).

Investigations were carried out in the field of chemistry of spiro compounds of complex structure, where the nitrogen atom of a pyrrolinone(furan) and pyrrolidine, and also of pyrazoline ring was located in the β-position, like in natural compounds; effective methods were developed of the synthesis of polynuclear fused and spiro joined ensembles basing on cycloaddition reactions that were a powerful instrument in building up various heterosystems (Scheme 14.6).

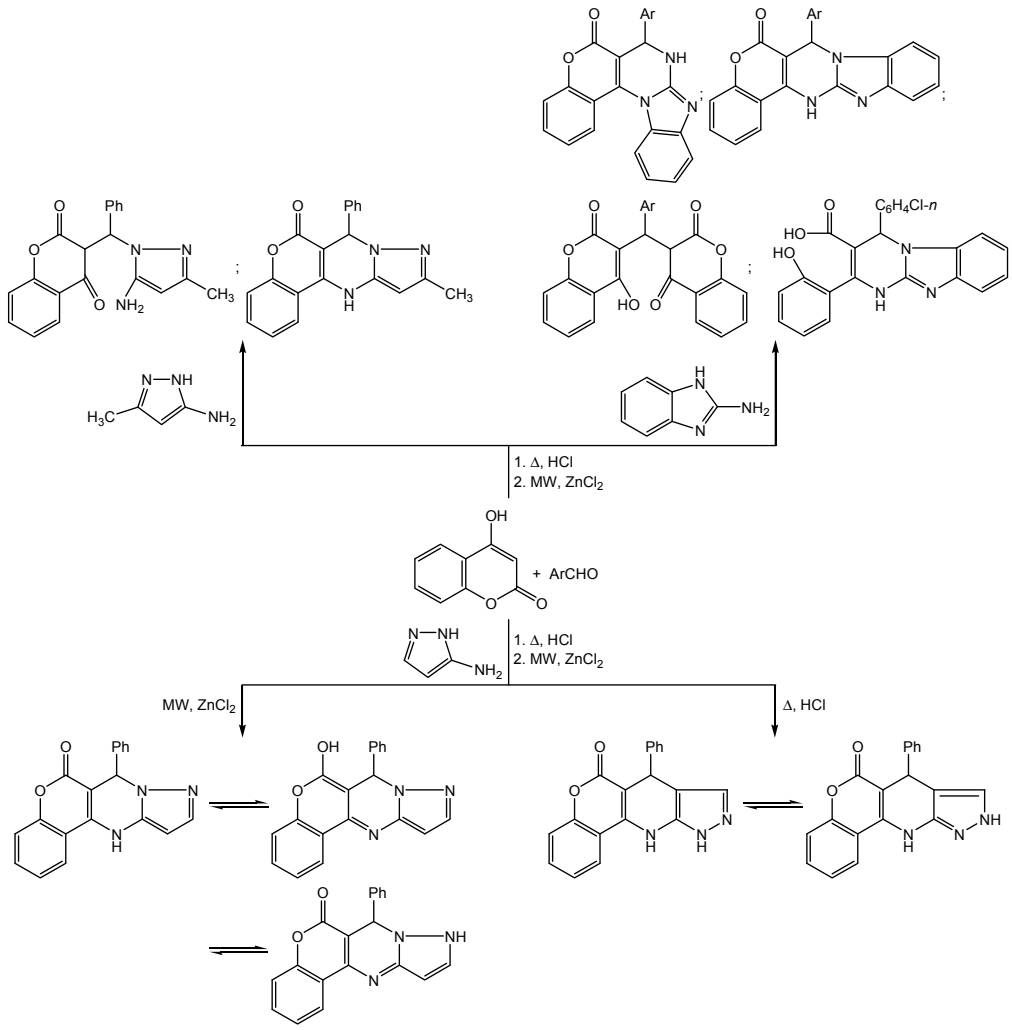
Sequences of reactions were explored including the generation of unstable 1,3-dipoles, their participation in effective assembly of more complex heterocyclic molecules, occurring at a high regio- and stereocontrol; a series of substances was obtained having in their structure molecular fragments possessing affinity to large number of receptors that are synthetic analogs of natural alkaloids. The use as dipoles substituted azides, azomethine imines, nitrile oxides, also those containing pharmacophore fragments, amino acids makes it possible to realize *click*-strategy for the preparation of a wide number of heterocycles, including peptidomimetics.

Synthetic opportunities were investigated of 3a-substituted 2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo-[1,2-*a*]imidazol-1-ones and 2,3,3a,4-tetrahydropyrrolo-[2,1-*b*]quinazolin-1(9*H*)-ones in reactions with electrophilic reagents (nitrosation, alkylation, and acylation) and diazonium cations. Using azomethine ylides it is possible to perform a one-pot process to obtain oxiindoles with several stereogenic sites with a high diastereomeric excess (Scheme 14.7) [731–733].

Synthetic approaches were developed to azolocyclanopyrimidines with a nitrogen nodal atom and possessing diverse saturation. At application of principles of "green chemistry" (modern methodologies of multicomponent reactions) both in thermal and microwave versions azolocyclano-pyrimidines were obtained, distinguished by the type of azole fragment (triazole, tetrazole, thiazole), by substituting groups (aryl, hetaryl), rings junction (linear, angular), size of fused alicycle (C_6–C_8).

The regularities and features of reactions were revealed depending on the structures of amine and carbonyl components. The application of aminoazoles of various types results in the formation of azolocyclanopyrimidines with different structure of pyrimidine fragment (enamine in the case of 3-amino-1,2,4-triazole and *C*-aminotetrazole, imine in the case of 2-amino-1,3-thiazole). A scheme was assumed of the formation of azolocyclanopyrimidines involving a sequence of transformations: azomethine, amino-ketone, hydroxylated azolocyclanopyrimidine of angular structure, its isomerization and dehydrogenation. The scheme was experimentally confirmed by the isolation of intermediates, experiments on

Scheme 14.1.



isomerization of positional isomers, by an authentic synthesis (Scheme 14.8) [734–738].

The complete aromatization was observed under rigid conditions (S, 170°C) and only for aryl-substituted tetrazolohexahydroquinazolines (due to the possibility of the formation of a stable benzene ring) (Scheme 14.9).

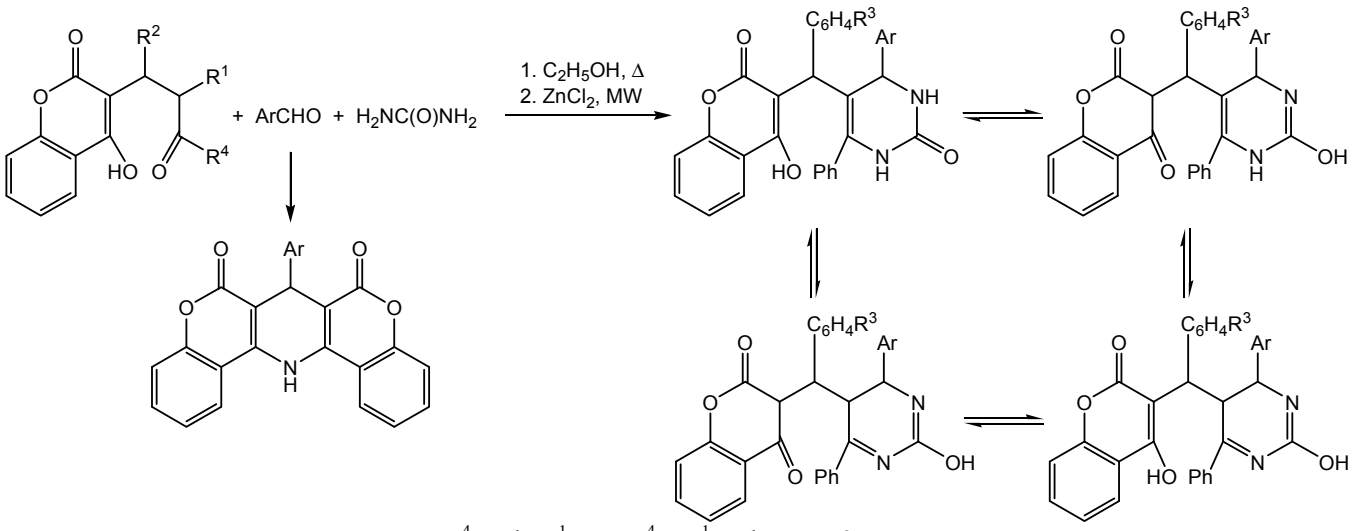
The utilization of multicomponent reactions, cascade processes, tandem transformations basing on multicenter substrates and polynucleophilic reagents one-stage procedures were developed for the preparation of difficultly accessible functionalized compounds of thiazole, thiadiazoline, pyrazoline, pyrrolidine, pyrrolizidine, dihydropyrimidine, hexahydroquinazoline, hydrothiadiazine, and other series.

The carbocyclization of conjugated dienones under the effect of *C*-nucleophiles proceeds regiospecifically and stereoselectively providing the 1,3-*cis*-isomer of spiro-fused carbo- and heterocyclic systems with diequatorial position of aromatic substituents in the alicycle (Scheme 14.10) [739–741].

The stereoselectivity and regiodirection of reactions of monoaryl(hetaryl)methylidenealkanones with dipoles of azomethine type [742], occurring as tandem simultaneous process of 1,3-dipolar *endo*-cycloaddition with the formation of *trans*-isomer of spirooxoindolopyrrolizidines and spirooxoindolopyrrolidines with diaxial position of substituents was proved. Features of heterocyclization of unsaturated and conjugated β-aminoketones of different series were reveled leading to the formation of pyrimidine-2-thiones and spiropyrans [743].

By modified method of basic hydrolysis [744] unsaturated 1,5-diketones of different series were obtained

Scheme 14.2.



R^4 = Ph, R^1 = H; R^4 + R^1 = chromen-2-one.

that thus became available: acyclic fatty-aromatic tri- and tetra-substituted 1,5-diketones, and also condensed analogs of cyclohexane and tetrahydronaphtalene series, distinguished by the number, the nature of substituents, the position of the multiple bond and the character of oxo groups, conjugated with the multiple bond, aryl substituent, or free of conjugation.

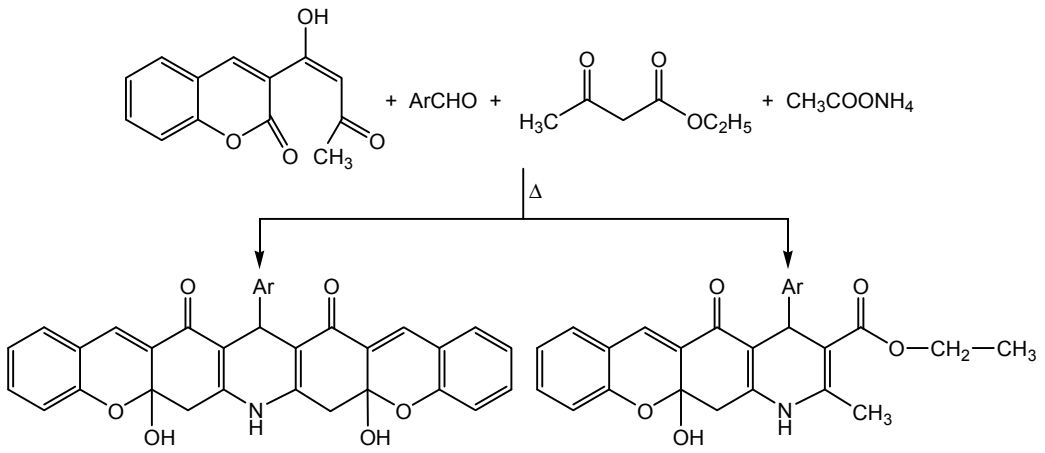
A preparatively simple method was advanced of the synthesis of 3-benzoyl-1,5-diphenyl-2-pentene-1,5-dione. The method consists in a three component one-pot condensation of acetophenone, phenylglyoxal in the presence of boron trifluoride etherate followed by the hydrolysis of 4-benzoyl-2,6-diphenylpyrylium fluoroborate under the effect of sodium acetate.

The behavior of tetrahydrochromenilium salts at alkaline hydrolysis is distinguished by the formation of 2-(3-oxo-1-Ar1-2-Ar-propylidene)cyclohexanones and 2,4-diarylbicyclo[3.3.1]non-3-en-2-ol-9-ones [745].

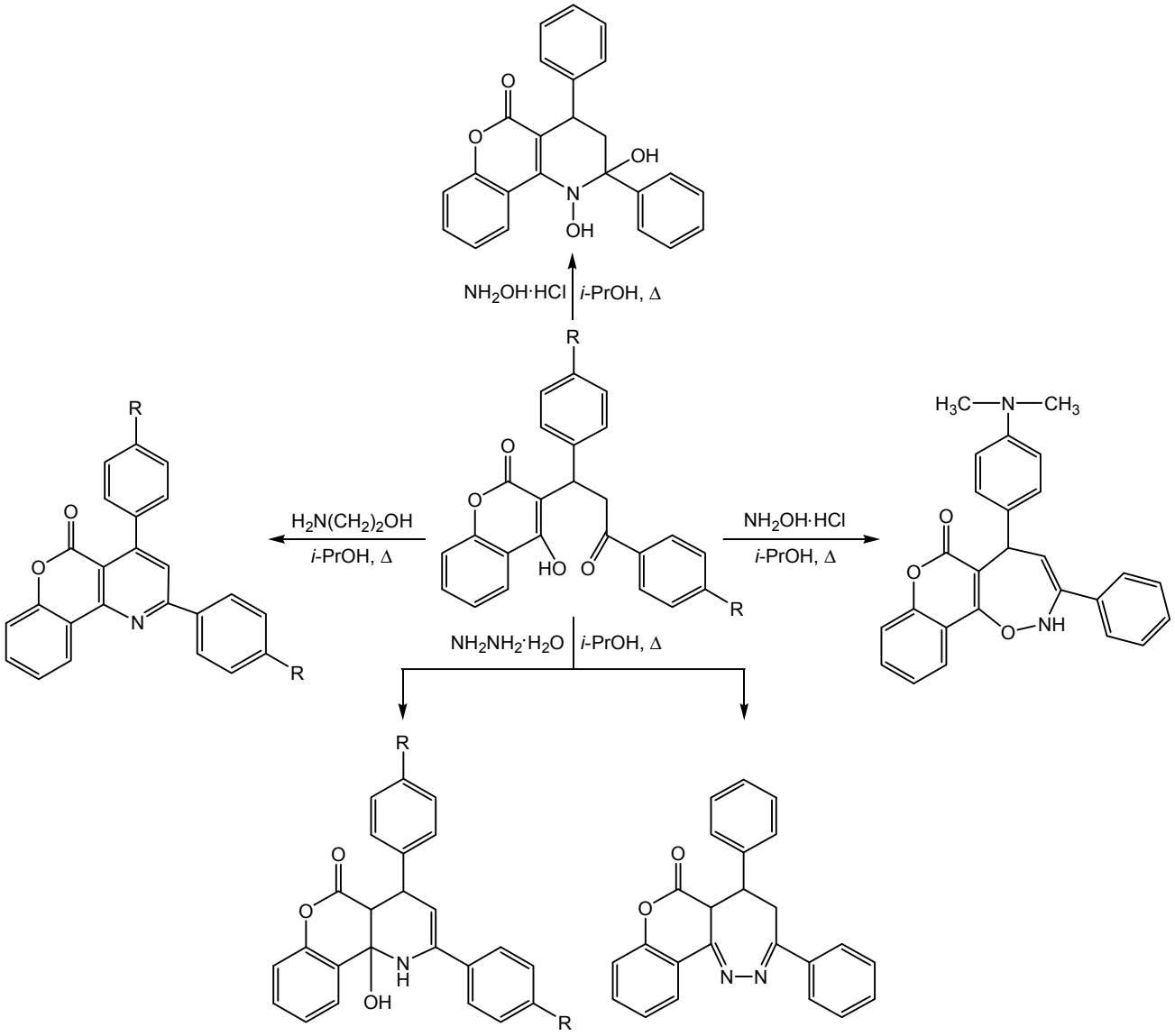
New approaches to the synthesis of aryl-substituted 2-penten-1,5-diones were developed basing on the corresponding pentanediones. A method of multiple bond introduction into the structure of pentane-1,5-diones through the halogenation of the latter and the dehydrohalogenation of monohalo-substituted diketones was developed furnishing *N*,*N*,*N*-triethyl-1,5-dioxo-1,3,5-triarylpentan-2-ylammonium bromide subjected further to decomposition.

Significantly stronger interest is attracted nowadays to the synthesis and transformations of α-haloketones, synthons for various heterocyclic compounds. In this connection new methods and reactions were developed, allowing the preparation of a-halopentane-

Scheme 14.3.



Scheme 14.4.

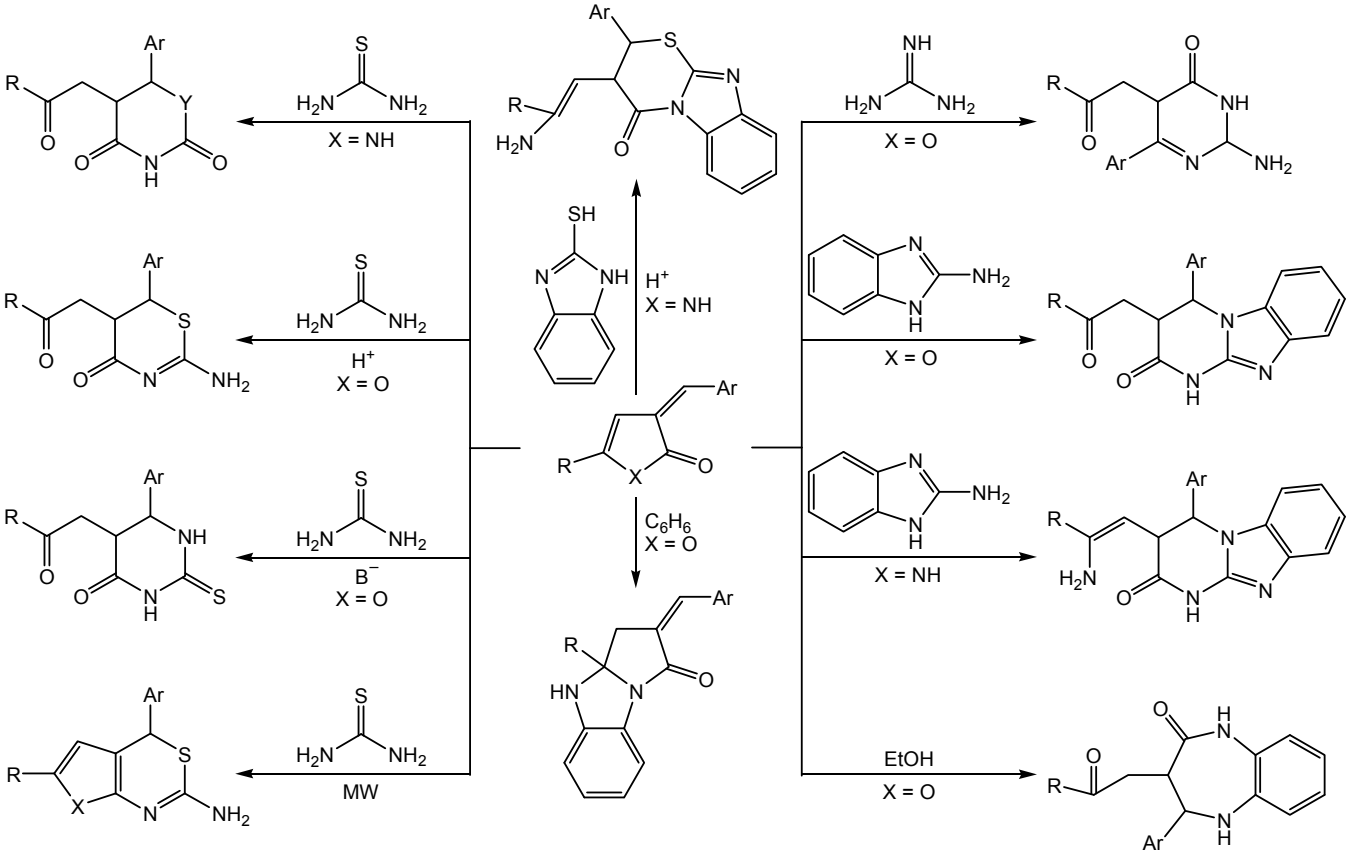


1,5-diones; halogenating agents were found (systems *N*-haloimide–*p*-TsOH–CH_3CN, bromine–diacetoxyiodobenzene–AcOH–CH_3CN, $CuBr_2$–DMF), which made easier the halogen introduction into the structure of ketone, and a-haloketones became accessible for purposeful investigations. A direct transition was performed to pseudohalo-substituted 1,5-diketones, 2-thio-cyano-1,3,5-triarylpentane-1,5-diones by treating 1,3,5-triarylpentane-1,5-diones with NH_4SCN in the presence of $FeCl_3$ in dichloromethane.

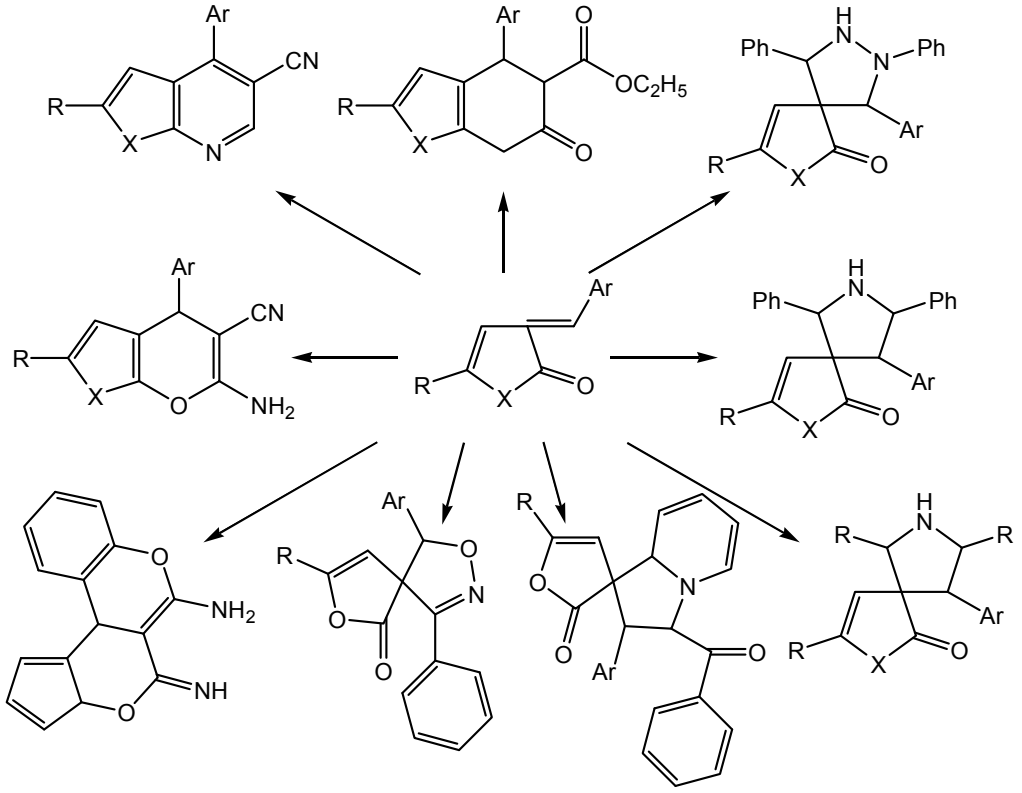
Among realized investigations a significant number of preparative methods is present of syntheses of three-, five-, seven-membered N,O,S-containing heterocyclic compounds underlain by 2-pentene-, pentane-1,5-diones, their mono- and dihalo-substituted derivatives. The cyclization of 1,3,5-triaryl-2-pentene-1,5-diones with hydroxylamine, thiosemicarbazide, thioacetamide under basic catalysis occurs involving the propenonyl fragment to afford functionalized aziridines, dihydropyrazoles, thiazoles, in acid medium, triazolethiones (Scheme 14.11).

In a series of heterocyclization reactions of halo-substituted 1,5-diketones processes involving *N*,(*N*,*O*,*S*)-bi(tri)nucleophilic reagents take special place, allowing the preparation of bi(tri)heteroatomic cyclic compounds of series of dihydroquinoxaline, benzo-

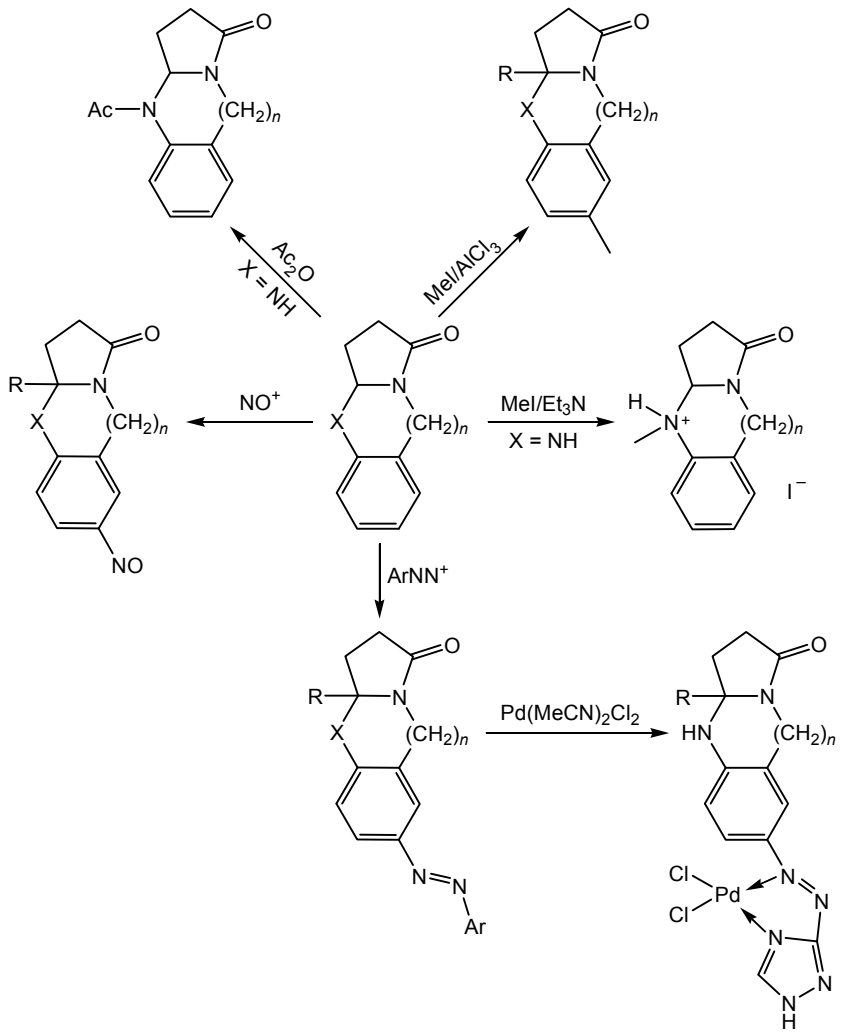
Scheme 14.5.



Scheme 14.6.



Scheme 14.7.

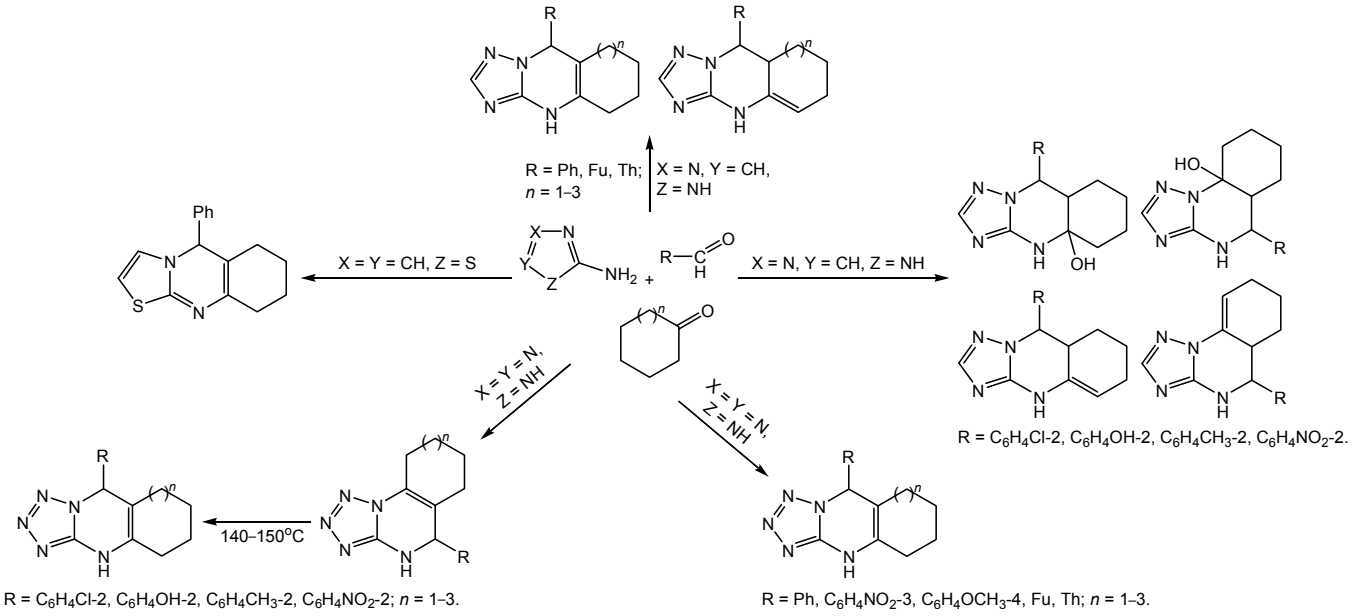


xazine, thiazole, thiadiazine. One of directions of the department's studies is the chemistry of polyfunctionally-substituted and unsubstituted cycloalkanones, the investigation of their reactions with *N*- and *C*-nucleophiles and transformations under peroxide oxidation (Scheme 14.12).

Basing on the reaction of acetyl- and ethoxycarbonyl-substituted cyclohexanones with *C*- and *N*-aminothiazoles functionally substituted quinazolines were obtained fused with triazole or thiazole ring, or systems, containing linearly bound aminotriazole and cyclohexane fragments (triazolyliminocyclohexanes). The presence of functional groups in products creates the opportunity of their further modification. The structure and basicity of the amine component (*C*-aminotriazole, benzimidazole, *C*-aminothiazole) determines the position of multiple bonds in the formed partially hydrogenated triazole-, thiazole-, benzimidazole-quinazolinecarboxylates [746]. At the replacement of *C*-aminotriazole for *N*-aminotriazole the reaction proceeds as a selective nucleophilic substitution of carbonyl group in the alicycle and due to the location of reactive centers unfavorable for further cyclization it stops on the stage of the formation of substituted *N*-triazolylcyclohexane imines. An alternative enhydrazine form is not realized due to the high mobility of the NH proton.

Polysubstituted benzimidazolohexahydroquinazolines and spiropyrazolocarbonitriles were obtained by multicomponent one-pot condensation of carbonyl methylene-active compounds and binucleophilic aminating agents [747]. The special feature of the

Scheme 14.8.



reaction of aldehydes, cycloalkanes, and aminoazoles is the formation of benzimidazolohexahydroquinazoline with angular joint of the rings, a rarely found structure in condensed azoloazines.

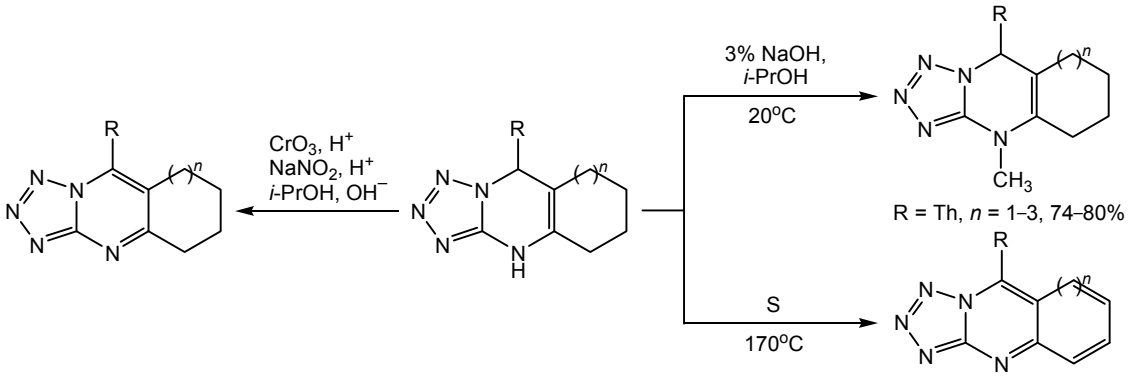
The oxidation was investigated of (diacetyl)diethoxycarbonyl-substituted hydroxycyclohexanones in the conditions of Bayer–Billiger reaction. Unlike the known reactions of cycloalkanones, where the ring expansion is observed, the investigated substrates reacted with the ring contraction and the formation of ethyl 4-aryl-2-carboxymethyl-2-methyl-5-oxodihydrofuran-3-carboxylates and 4-acetyl-5-carboxymethyl-5-methyl-2-oxo-3-aryloxolanes, close by the scaffold to the molecule of vitamin C, difficultly available otherwise [748, 749].

New substances and materials for medicine and veterinary were obtained. Biological activity of obtained substances (antimicrobial, antitumor, antioxidant, antiphage, growth regulating) was investigated. Analytic possibilities were tested and the creation of functionally oriented catalytic systems basing on complex compounds was studied.

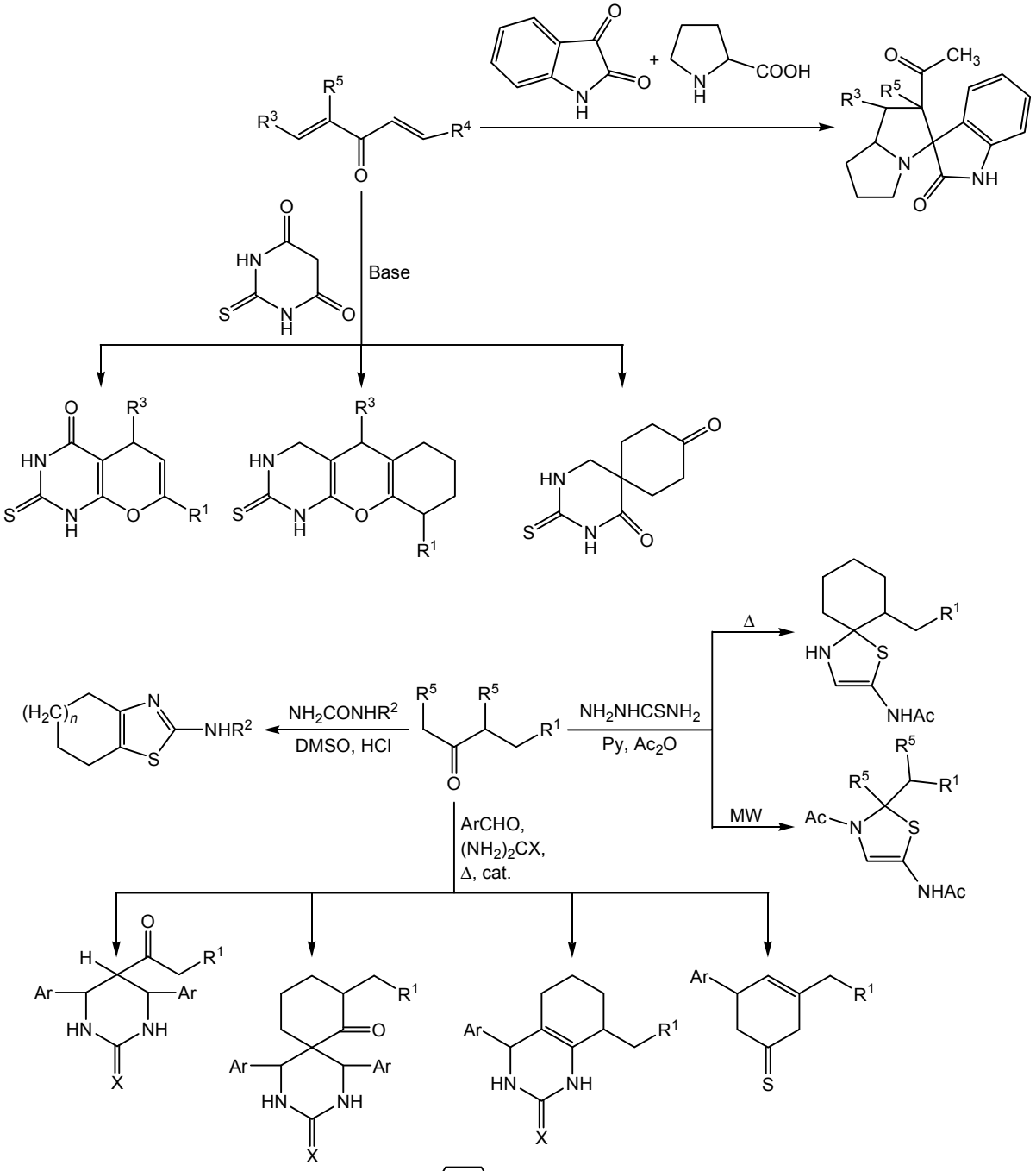
15. DEPARTMENT OF ORGANIC AND BIOMOLECULAR CHEMISTRY AT URAL FEDERAL UNIVERSITY

This department is one of the oldest of those founded in Soviet era. In 2014 it celebrated 90 years of existence, and since 2015 it was renamed into

Scheme 14.9.



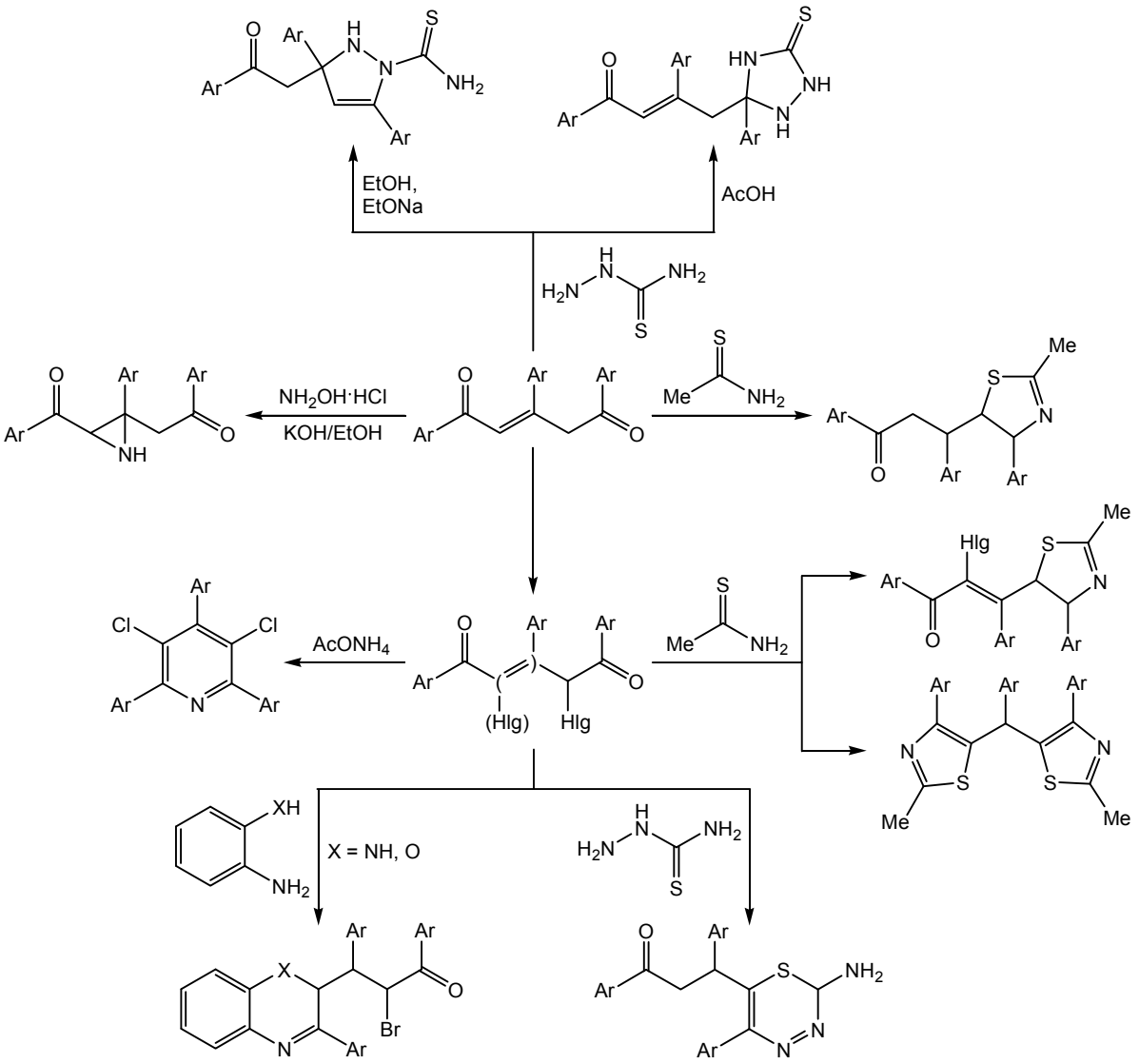
Scheme 14.10.



department of organic and biomolecular chemistry. Today in the staff of department work 2 Academicians of Russian Academy of Sciences, 1 Corresponding Member of Russian Academy of Sciences, 3 Professors, and 6 Assistant-Professors.

Dominating and combining the most part of research is the chemistry of heterocyclic compounds. In general, these investigations concern the reactivity, structures, and properties of heterocycles, mainly aromatic. Second important part of topics is those concerning

Scheme 14.11.



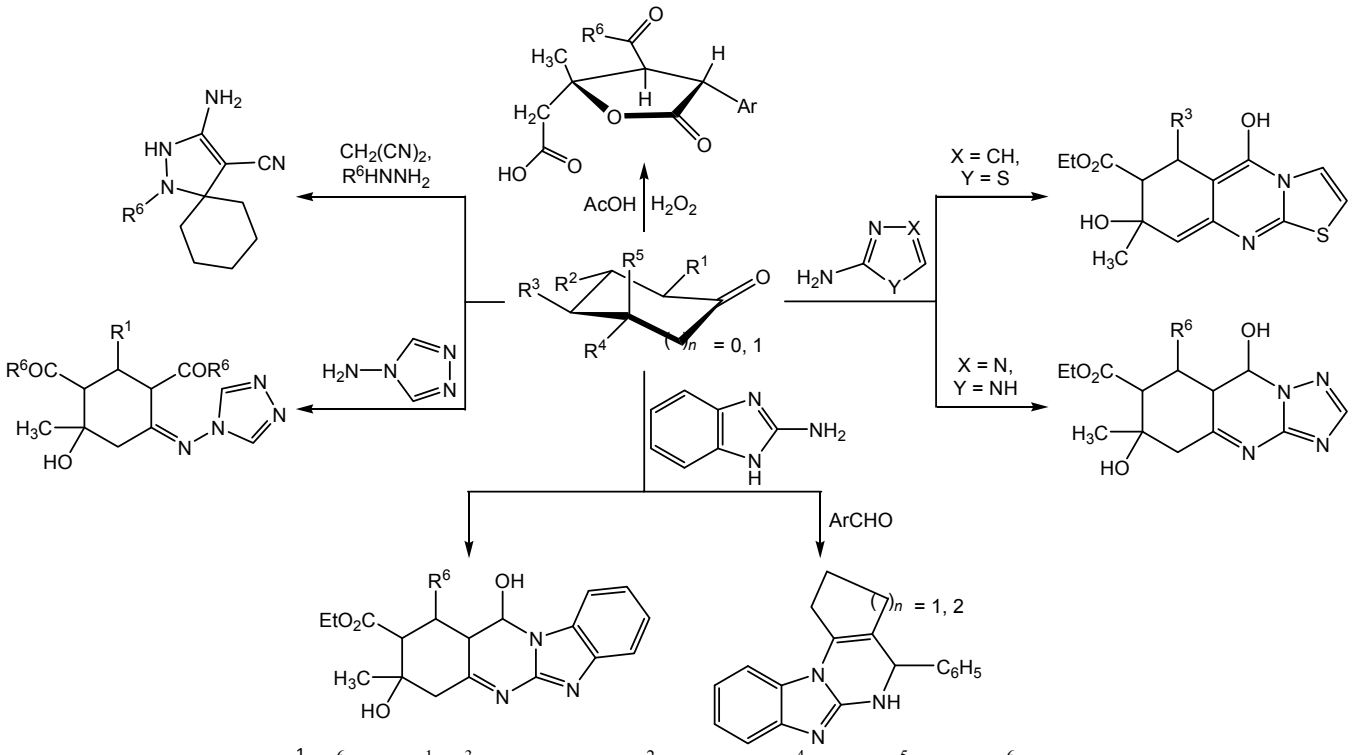
biomolecular chemistry establishing dependences between the structure and biological activity.

The department became pioneering in a new scientific direction, the nucleophilic aromatic substitution of hydrogen (S_N^H reaction), which was internationally recognized and Professor M. Mąkosza called "a new chapter in chemistry of arenes". This direction is being successfully developed nowadays, along with the chemistry of fluorinated heterocycles, polynitrogen heteroarenes, aryne chemistry, chemistry of polycyclic arenes.

Biomolecular direction combines fundamental and application character. In traditions of the department not only the search for new pharmaceutical substances should be performed, but it should be brought to the the development of technological methods for the synthesis of organic compounds and creation of substances for practical medicine. Pioneers of this trend were Academician I.Ya. Postovsky, Professor Z.V. Pushkareva, Professor N.P. Bednyagina, later Professors R.O. Matevosyan, S.V. Sokolov, through the last decade **Professors O.N. Chupakhin**, **V.N. Charushin**, **G.N. Lipunova**, **V.L. Rusinov**, **E.N. Ulomskiy**, **G.V. Zyryanov**, and **E.V. Nosova**, they all graduated as engineers. That naturally influenced their work leading to the request for practical realization of research activities, to creation of medicines and new organic materials for curing people.

Department of organic chemistry at the Ural State Polytechnic Institute was among the departments

Scheme 14.12.



R^1–R^6 = H; R^1, R^3 = Ac, CO_2Et, R^2 = Alk, Ar, R^4 = Me, R^5 = OH, R^6 = Ar.

where no students prepared their graduation works, and it provided a general training in the fundamental organic chemistry for not only students of chemical engineering faculty, but also for the other faculties (technology of silicates, metallurgy, physicotechnical, etc). At the neighbouring department of technology of organic synthesis where students prepared their graduate works investigations on similar topic were realized. These departments were cooperating within joined Problematic laboratory for the synthesis of pharmaceutical substances.

Ural Federal University can be proud of such preparations, created at the department of organic chemistry, as the first produced in Russia sulfonamide "sulfidine", antitubesculosis medicine "larusan", detoxicating substance "succimer", fluorine-containing "lubricant UPI" for Rosatom, antiviral preparation "triazavirine", achievement of the last years. The development of chemistry and technology of fluoroquinolone should be specially mentioned. In this field the department is the leader both in Russia and on all the Post-Soviet territory.

Within last decades at the department a research on developing new processes of organic compounds synthesis is successfully realized. Special place among these studies belongs to investigations on the theory and practice of nucleophile aromatic substitution of hydrogen (S_N^H reaction), initiated by Academician O.N. Chupahin (Scheme 15.1).

The article describing the nucleophilic attack on C–H bond has world-wide priority, is cited in textbooks on organic and heterocyclic chemistry [750], it is the first attempt in the world literature to systematize results in this field, and the book "Nucleophilic Aromatic Substitution of Hydrogen" [751] is the first monograph where questions of theory and practice of nucleophilic substitution of hydrogen in arenes and hetarenes are generalized.

As a result of systematic investigations performed at the department throughout several decades a wide range of chemical transformations was explored resulting from the nucleophilic attack on the non-substituted carbon atom in diverse by structure azaaromatic and other π-deficient systems (Scheme 15.2) [751–758]. Wide fundamental investigations of the mechanism of S_N^H reactions were realized using methods of computer simulation, electrochemistry, NMR, electron spin resonance that allowed discovering the role of oxidant, in particular, air

oxygen, registering the elemental acts of electron transfer, to understand the way of side products formation and anomalous routes of S_N^H reactions [751–758]. For these studies O.N. Chupakhin and V.N. Charushin in 2012 were awarded State Prize of Russian Federation in the field of science and technics.

New methods were developed of a direct and atom-economic C–H-functionalization of aromatic and heteroaromatic compounds, which were based on environmentally friendly processes of direct nucleophile aromatic substitution of hydrogen atom in arenes, azines, azoles, and their activated forms under the action of various *N*-, *O*-, *S*-, *P*-, and *C*-nucleophiles, including lithium salts of metallocenes, carboranes, calixarenes, imidazolyl oxide radicals, and other substances [751–758]. Basing on application of S_N^H methodology new approaches were developed to the synthesis of chiral ligands underlain by metallocenes. Their high activity in reactions of asymmetrical synthesis was demonstrated that might be applied to the preparation of biologically important structures and drugs (Scheme 15.3) [759, 760].

Great possibilities were demonstrated in the application of S_N^H reactions for production of biologically active substances, catalysts for asymmetric synthesis, molecular magnetics, supramolecular sensors, color sensitizers for solar batteries, and other organic materials. The effect was established of donor and acceptor substituents, leaving groups, fusion, methods of activation of substrate, and also the nature of nucleophile on competitive S_N^{ipso} and S_N^H-processes, oxidative and non-oxidative transfor-mations of s^H-adducts [751–760].

One more direction of application of S_N^H methodology is the development of methods of synthesis based on natural and renewable raw materials, and also modification of natural compounds. For example, derivatives of natural 5,7-dihydroxy-coumarins and their analogs may be modified by various heterocyclic compounds (Scheme 15.4) [761].

The same approach underlies the reaction of pyrimidines with 5,7-dihydroxycoumarins which in one stage results in the formation of complex alkaloid-like structures. Another example of modification of benzopyrones is the functionalization of quercetin with derivatives of azolopyrimidines (Scheme 15.5).

The procedure of direct nucleophilic functionalization of the C(sp^2)–H bond was successfully applied to the modification of azine *N*-oxide fragment of 1,2-*closo*-carborane. As a result of non-catalyzed by transition metals cross-coupling of azine *N*-oxides with lithium derivative of carborane for the first time new *C*-modified carboranes were obtained, and also their metallocomplexes of diverse structures (Scheme 15.6) [762, 763].

At the department fundamental and applied investigations on chemistry of fluoroquinolones were carried out. Together with researchers of the Postovsky Institute of Organic Synthesis of Ural Branch of Russian Academy of Sciences broad cycle of studies was realized at the department on the synthesis of antibacterial preparations of fluoroquinolone series, and also their heteroanalogs of the series of bi-, tri- and polycyclic fluorocontaining heterocycles [764–766].

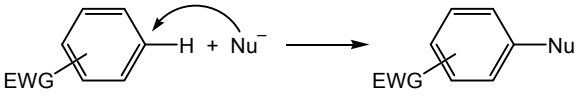
Unified R&D project on the synthesis of fluoroquinolones was developed, technologies were created for the preparation of pefloxacin, levofloxacin and other antibacterial preparations of fluoroquinolone series basing on fluoroanilines, fluorinated benzoic acids, and other fluoroarenes. New method was suggested of for the preparation of levofloxacin substance, based on the original method of synthesis of enantiomerically pure substances via kinetic separation of optical antipodes of partly hydrogenated methyl-benzoxazine in reactions with chiral acylating agent, naproxen chloride (Scheme 15.7).

Methods of synthesis were developed of fluoroquinolones and their heteroanalogs from the series of quinazolines and benzothiazines, dozens of new fluoroquinolones were synthesized, and also condensed systems on their basis were prepared as promising substances to create antibacterial, antituber-culosis, antiviral and antitumor drugs (Scheme 15.8) [767, 768].

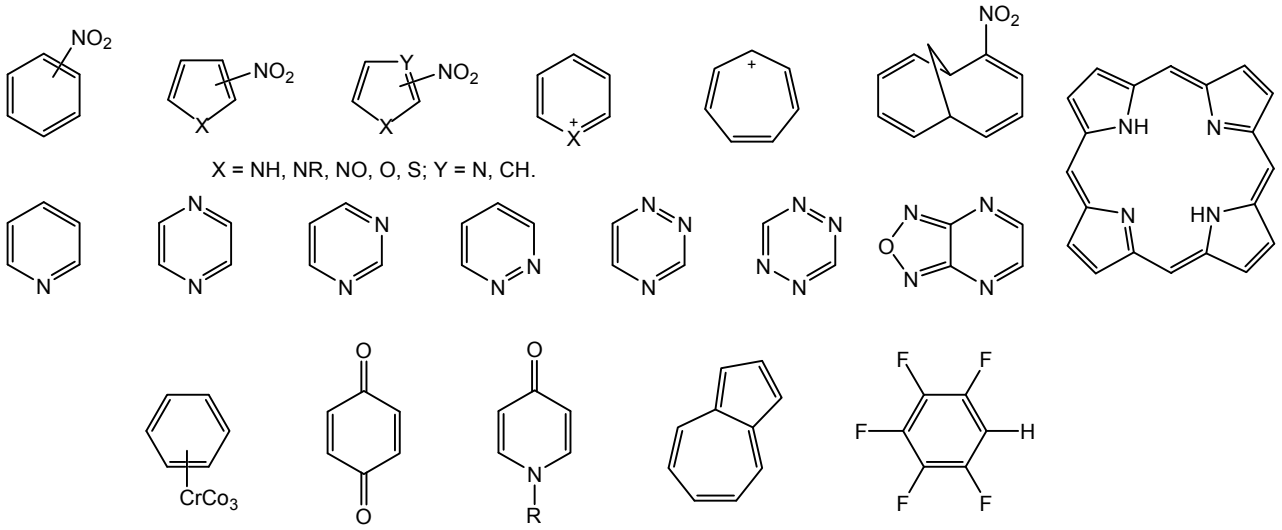
New classes were obtained of fluorinated nitrogen-, sulfur-, and oxygen-containing ligands that coordinate a wide range of transition metals thus making them promising for the application in modern technique as analytic reagents, molecular magnetics, light-sensitive materials, elements for supramolecular devices (Scheme 15.9) [769].

Nitrogen heterocycles, first of all, azoles, azines and azoloazines, were always in the center of attention of researchers at the department of organic and biomolecular chemistry considering that many substances of this series are analogs of vital structures

Scheme 15.1.



Scheme 15.2.



in DNA and RNA (Scheme 15.10) [770, 771]. Cycle of studies in this area was in 1990 awarded a prize of the Cabinet of Ministers of USSR (O.N. Chupakhin, V.L. Rusinov, Yu.A. Azev, T.L. Pilicheva). Later (in 2005) O.N. Chupakhin, V.L. Rusinov, G.L. Rusinov were aworded N.D. Zelinskii prize of Russian Academy of Sciences for the investigation of azole-fuzed nitroazines.

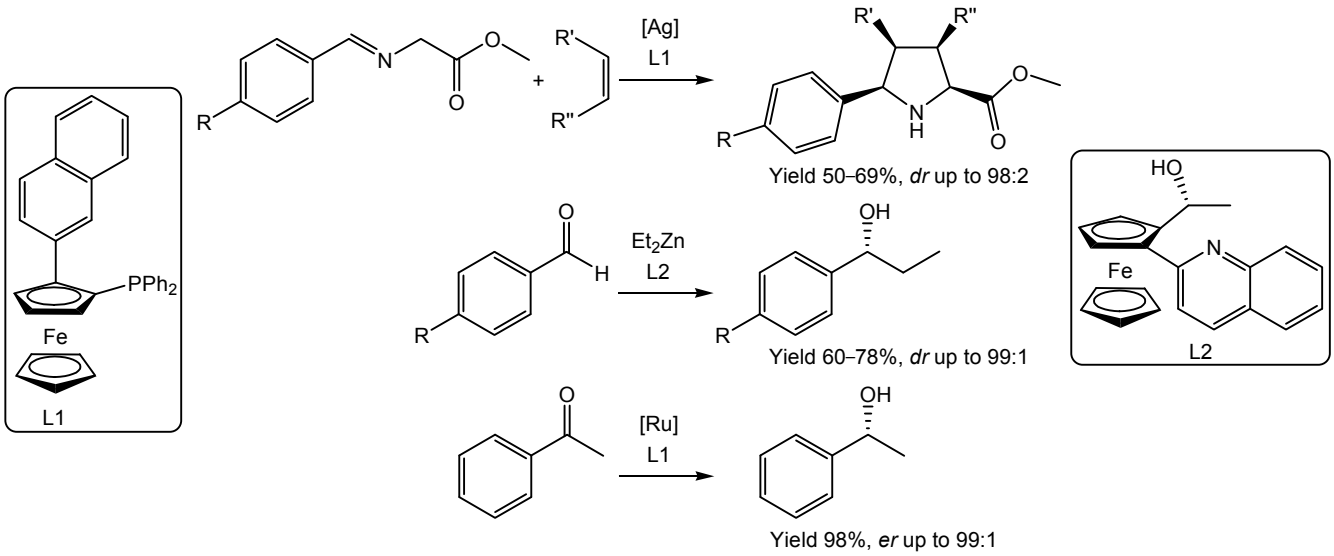
Researchers of the department together with Postovskii Institute of Organic Synthesis of Ural branch of Russian Academy of Sciences carried out a cycle of studies on production of an original family of antiviral preparations of azoloazine series, isosteres to purine bases. Together with Institute of Grippe of Russian Ministry of Health (Saint-Petersburg), Virological Center of Russian Ministry of Education (Sergiev Posad) and Institute of Military Medicine (Saint-Petersburg) a new family of Rusian antiviral pharmaceuticals was created. For investigations of specific features of metabolisms and pharmacokinetics methods were developed of introducing stable isotopes into the structure of 1,2,4-triazolo[5,1-*c*]-1,2,4-triazinones [772, 773]. As an example the synthesis is shown of the sodium salt of 2-methyl[$^{2}H_{3}$]thio-6-nitro-[^{15}N]-1,2,4-triazolo[5,1-*c*]-1,2,4-triazine[1,5-^{15}N]-7-one (Scheme 15.11).

The first preparation created basing on this class of compounds, triazavirine (sodium salt of 2-methylthio-6-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-7-one dihydrate), was subjected to a full cycle of clinical tests as anti-influenza drug and was included on 28.08.2014 into the register of pharmaceutic drugs of Russian Federation (no. LP-002604). The plant "Medsynthesis" and Ural Center of biopharmaceutical technologies organized its mass production and spreading since 2015 through network of pharmacies. The administration of the pharmaceutical in influenza therapy decreases duration of basic symptoms of the disease (intoxication, fever, catarrhal symptoms), promotes fast normalization of temperature in therapeutic groups and lowering the level of repeated secretion of influenza viruses. By series of parameters triazavirine exceed known foreign drug tamiflu.

The preparation triazide (arginine salt of 5-methyl-6-nitro-1,2,4-tri-azolo[1,5-*a*]pyrimidine-7-one) is in the stage of clinical study. Works on creation of antiviral preparations of azoloazine series were awarded in 2008 V.N. Tatitshchev and G.V. De Genine prize in the field of science, technics and medicine, and also international Prix Gallien Russia in 2016 as the best investigation in Russia in pharmaceutics (Academicians O.N. Chupakhin, V.N. Charushin, Corresponding Member of Russian Academy of Sciences V.L. Rusinov).

Nucleosides modified by a heterocyclic base or a carbohydrate fragment are very interesting for biology and medicine. Since azolo[5,1-*c*]-1,2,4-trizines and

Scheme 15.3.



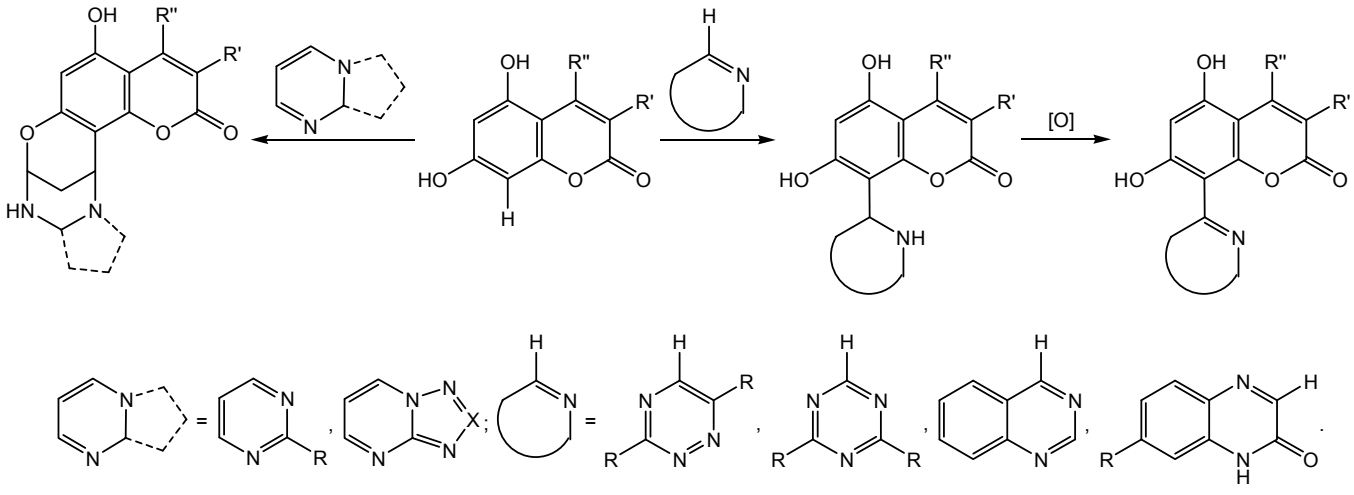
azolo[1,5-*a*]pyrimidines are regarded as isosteres of biogenic purines, the synthesis of a series of analogs of natural nucleosides was performed at the department (Scheme 15.12) [774, 775].

Along with the development of chemical methods of synthesis of nucleosides there are good prospects for investigations realized together with Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry of Russian Academy of Sciences (Academician A.I. Miroshnikov) on development of enzymatic methods of nucleosides synthesis through *trans*-glycolysis of azaheterocycles. Basing on enzymatic *trans* -glycolysis of fluorocontaining benzimidazoles effective methods were developed of nucleosides synthesis that demonstrated significant level of activity with respect to herpes viruses (Scheme 15.13) [776, 777].

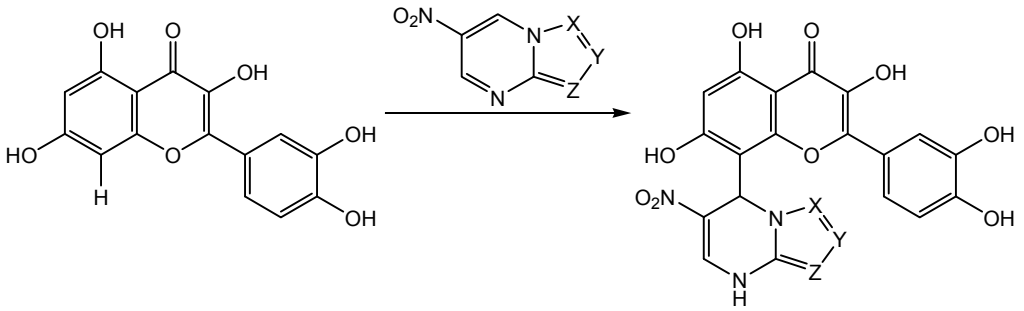
In the last decade works on application of highly reactive intermediates generated *in situ* (aryllithium salts, arynes, etc.) for the preparation of poly(aza)-cyclic compounds were in progress at the department. For example, the reaction of 1,2,4-triazines with arynes results in products of Diels–Alder reaction with reverse electron demands, isoquinolines or 2-azaanthracenes, and also in products of previously unknown transformation of 1,2,4-triazine cycle, 10-(1*H*-1,2,3-triazol-1-yl)pyrido- or 10-(1*H*-1,2,3-triazol-1-yl)pyrimido[1,2-*a*]indoles (Scheme 15.14) [778, 779].

By Diels–Alder reaction of anthracene with arynes generated from substituted pyrenes supramolecular chemosensors were obtained, ipticenes, applied for photoluminescence detection of nitro group contained in explosive substances (Scheme 15.15). The obtained

Scheme 15.4.



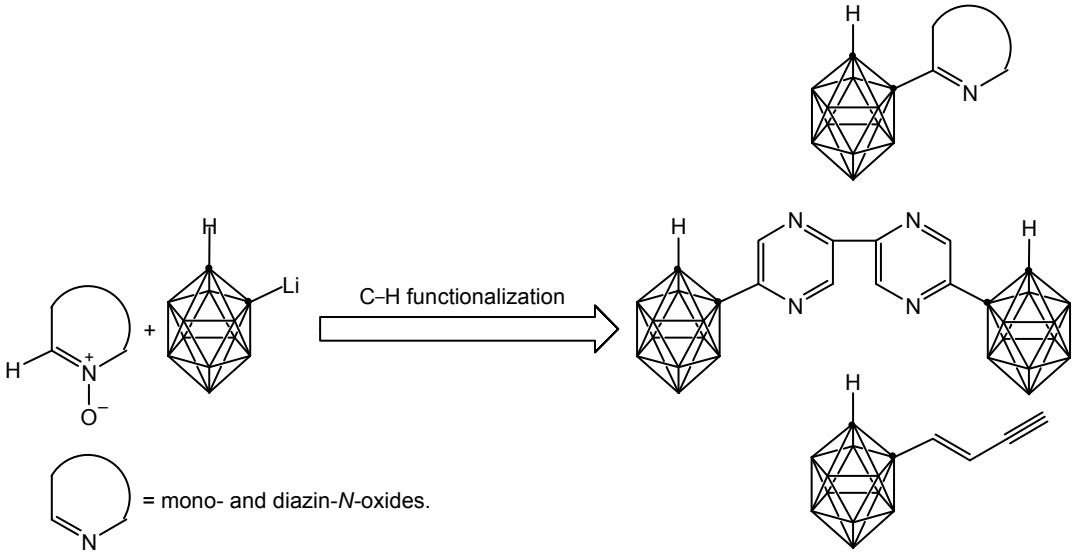
Scheme 15.5.



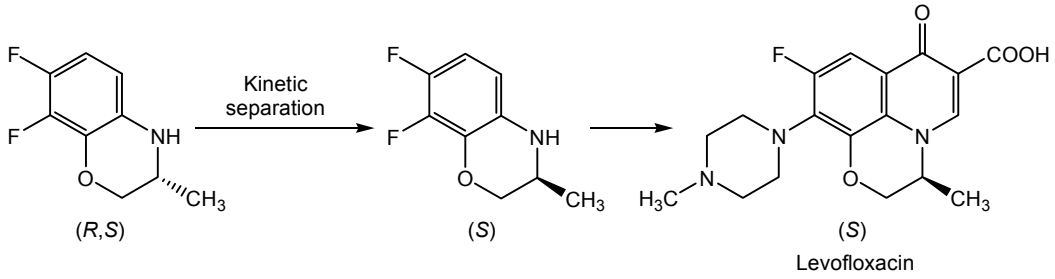
compounds demonstrated high selectivity and effectivity at the detection of nitro group containing explosives (2,4-DNT, 2,4,6-TNT, etc.), in particular, difficult to detect ones (hexogen) [780]. The obtained results were applied for development of prototype of portable explosives detector. Surface-active chromophores were synthesized basing on pyrene derivatives that in aqueous solutions form fluorescent micelles which may be used for detection of nitroaromatic compounds (2,4-DNT, TNT, dinitrocresol, etc.) in concentrations 5×10^{-8} [781].

In the last years at the department in tight cooperation with Postovskii Institute of Organic Synthesis of Ural branch of Russian Academy of Sciences and Rostov chemists (Academician V.I. Minikin) works on creation of organic color sensitizers for solar batteries and organic transistors are in progress. This work is based on creation of new heterocyclic π-electron systems of push-pull type and heteroacene compounds. For example, convenient methods were developed for obtaining thienoquina-zolines and azapyrenes derivatives underlain by reactions sequence

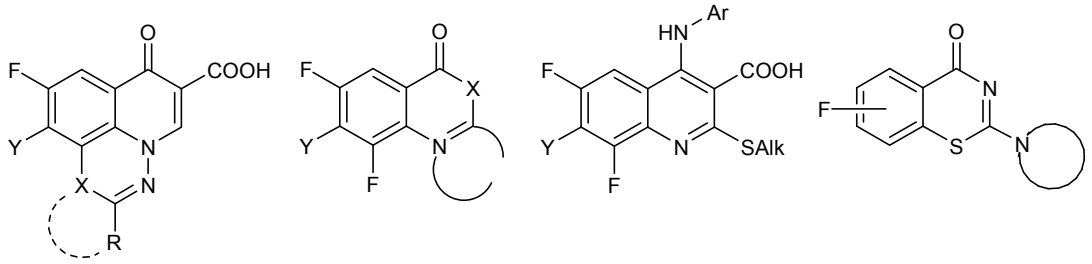
Scheme 15.6.



Scheme 15.7.

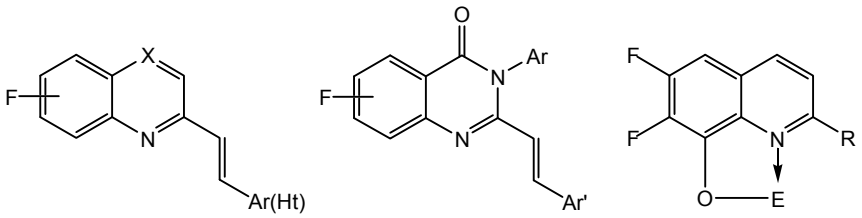


Scheme 15.8.



X = CCN, N.

Scheme 15.9.

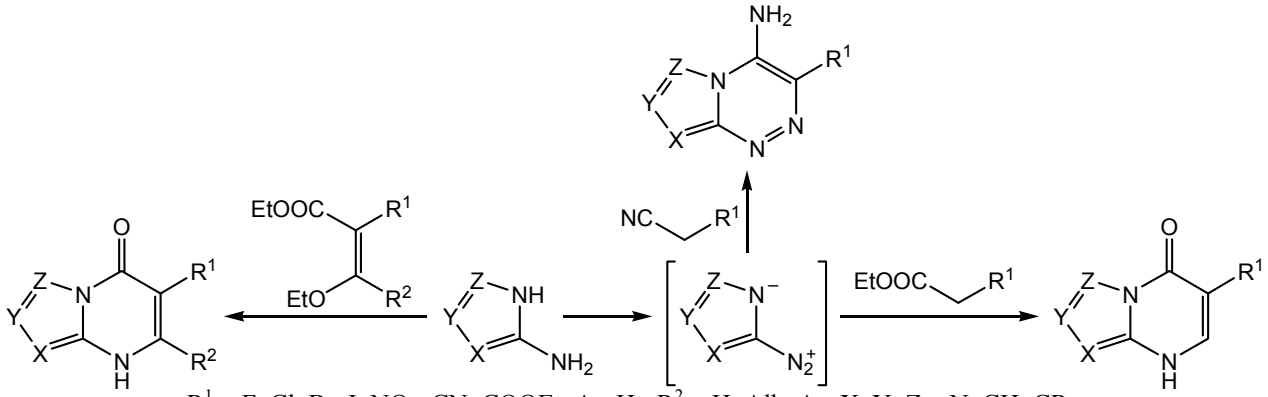


X = CH, N, C–COOH. E = Zn/2, BF_2, BPh_2.

of nucleophile aromatic substitution of hydrogen, cross -coupling, and photocyclization of 4,5-di(het)-aryl- and 4,5,6-tri(het)aryl-pyrimidines. The obtained data of photophysical and electrochemical inves-tigations point to possibilities of application of these compounds as transistor materials (Scheme 15.16) [782].

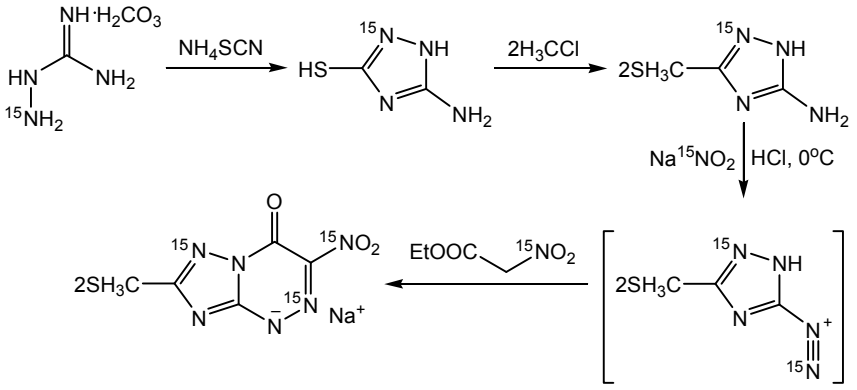
Preserving the traditions of Ural school of organic chemists the staff of the department successfully works in the field of fine organic synthesis, with noticeable focus on the development of medical and heterocyclic chemistry and the creation of new methodolodies for the synthesis of organic compounds, including the prepartion of biologically active substances and new organic materials. These studies were awarded in 2007 by Demidov scientific prize (Academician O.M. Chupakhin). Studies of department researchers were awarded in 2011 by the State Prize of Russian Federation in the field of science and technics formulated as "for significant contribution into development of organic synthesis, development of innovational technologies of production of pharmaceutical substances and materials, including ones for special tasks" (O.N. Chupakhin and V.N. Charushin), and in 2015, a Prize of the President of Russian Federation in the field of science and innovations for young scientists (D.N. Kopchuk) for development of new luminescent andfunctional materials for molecular devices of various purposes.

Scheme 15.10.

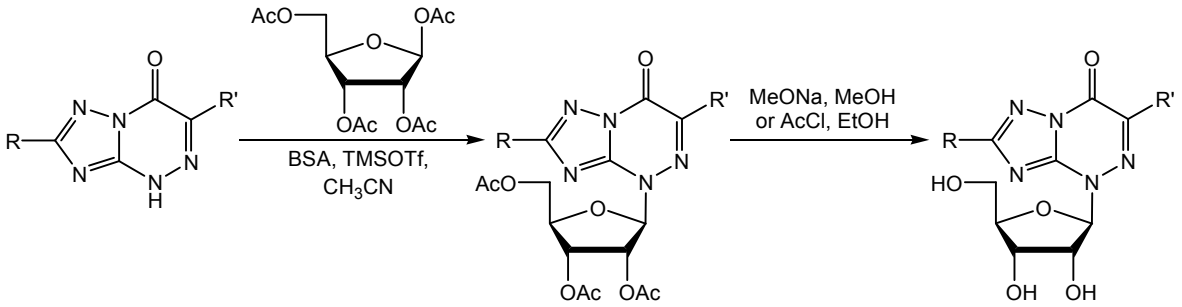


R^1 = F, Cl, Br, I, NO_2, CN, COOEt, Ar, Ht; R^2 = H, Alk, Ar; X, Y, Z = N, CH, CR_3.

Scheme 15.11.



Scheme 15.12.



16. DEPARTMENT OF ORGANIC CHEMISTRY AT SAMARA STATE TECHNICAL UNIVERSITY

Scientific school historically established at the department (**head of department Professor Yu.N. Klimochkin**) explores the chemistry of scaffold compounds. The studies performed now are related to the new approaches to mono- and polyfunctional derivatives of polyhedron structure aiming at the search for new biologically active molecules, design of promising materials, and development of original methods of the preparation of practically important substituted adamantanes.

A one-pot method was suggested for the preparation of amines directly from scaffold hydrocarbons by the reaction of adamantane, its homologues and adamantoid hydrocarbons with a mixture of nitric acid-acetic acid followed by urea addition and heating of the reaction mass (Scheme 16.1) [783].

This procedure was used in a promising one-pot method for the industrial production of 3,5-dimethyl-1-aminoadamantane hydrochloride ("memantine" drug for the treatment of Alzheimer's disease) in a yield of 87% directly from 1,3-dimethyladamantane, consisting in successive stages of nitroxylation in nitric acid medium, the amidation with acetone cyanohydrin, and hydrolysis to the amino derivative (Scheme 16.2).

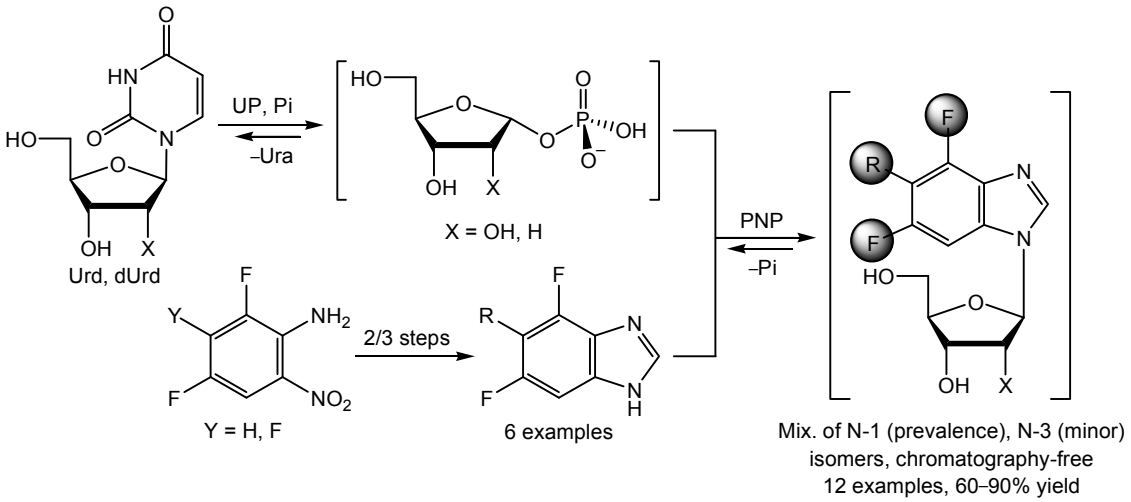
Tri- and tetrafunctionally substituted adamantanes are attractive structural blocks for the chemistry of modern materials and biomedical applications. However, a significant deactivation of the tricyclic scaffold in the presence in it of several electron-acceptor groups substantially limits the possibility of the subsequent functionalization.

Basing on the carbocation transformations of dicarboxylic acids of the adamantane series methods have been developed for the synthesis of adamantanes tri- and tetra-substituted at the bridgehead positions which contain up to four carboxy groups as well as various combinations of amino, acetamino, nitroxy and hydroxy groups with several carboxy or carboxymethyl groups (Scheme 16.3) [785].

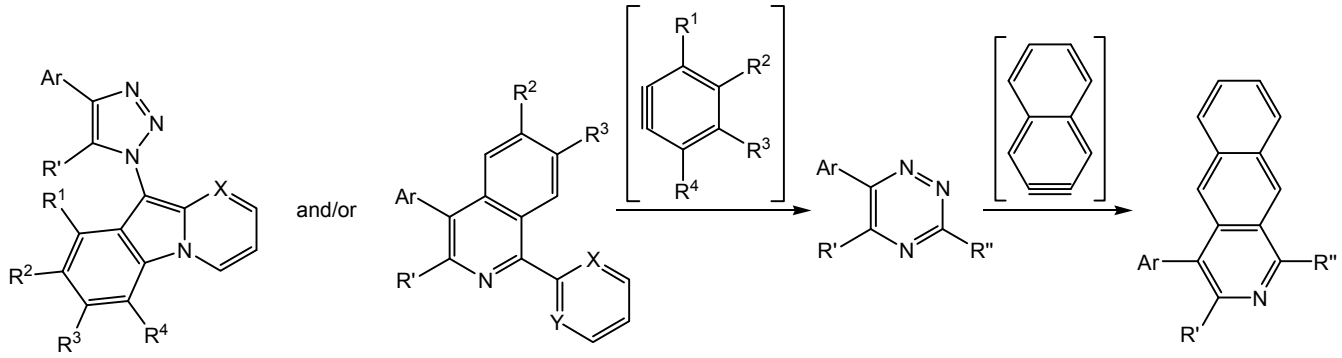
The screening effect of the adamantane scaffold on a double bond causes a steric strain in the molecule and often leads to structural deformations, which affect the chemical behavior of such spatially hindered substrates.

Depending on the conditions the allylic bromination of olefins of the adamantane series is accompanied by the formation of unsaturated polybrominated derivatives and vinyl bromides containing the adamantane fragment. The Ritter reaction of the resulting allyl bromides of the adamantane series leads both to the "classical"

Scheme 15.13.



Scheme 15.14.

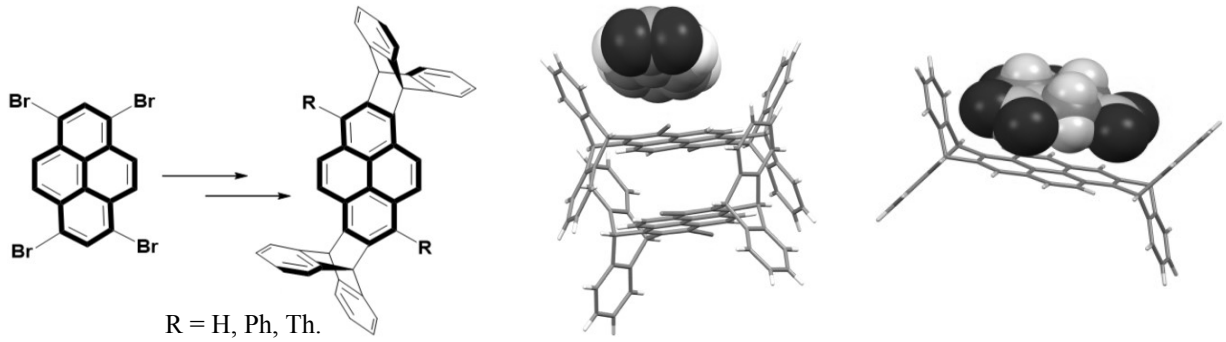


acetylamine derivatives and to the products of heterocyclization or skeletal rearrangement of the 4-(adamantane-1-yl)-2,4-dimethyl-4,5-dihydrooxazole and γ-sultones of the homoadamantane structure (Scheme 16.4) [786].

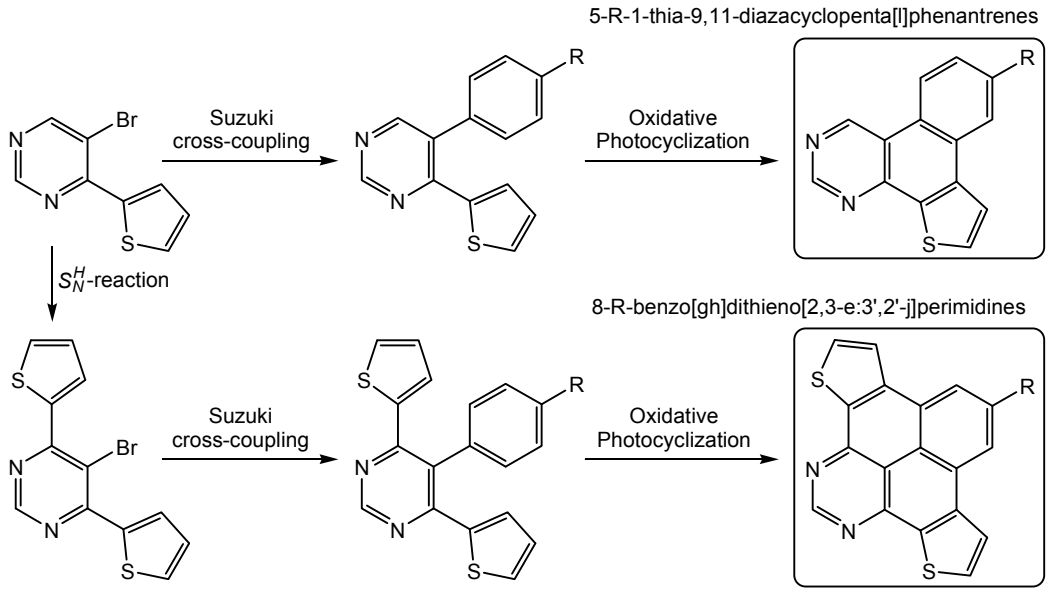
Reactions of tetracyclic γ-sultones with nucleophiles, depending on the structure of the initial γ-sultone and basicity of the reaction medium, can proceed with the formation of sulfonic acid derivatives of both homoadamantane and adamantane structures. In the presence of a base the reactions of γ-sultones containing a substituent in the α-position to the sulfo group occur with a reversal of the configuration at the carbon atom bound to sulfur [787].

The rearrangement of 1-[(*E*)-3-thiocyanatoprop-1-en-1-yl]adamantane in 1-(1-isothiocyanatoprop-2-en-1-yl)adamantane proceeds according to the [3,3]-sigmatropic rearrangement (Scheme 16.5) [788].

Scheme 15.15.



Scheme 15.16.



The reaction of 2-alkylidene adamantanes with nitrosyl chloride was studied; the reaction products are dimeric nitrosyl chlorides of 2-alkylidene adamantanes, and at the presence of significant steric hindrances and/or electron-acceptor substituents in the 2-alkylideneadamanthane molecule, monomeric α-chloroisonitroso compounds are formed in the reaction with nitrosyl chloride. The addition of dinitrogen tetroxide to 2-alkylideneadamantanes proceeds along the heterolytic pathway to form the corresponding nitrosonitrates in a dimeric form (Scheme 16.6).

The reactions were studied of nitrosyl chlorides of 2-alkylidene adamantanes with *O*-, *C*- and *N*-nucleophilic reagents. The substitution of chlorine atom takes place through the intermediate formation of conjugated nitrosoalkenes followed by the addition of nucleophiles by Michael reaction [789].

The features of alkylation of pyridine bases with halides of the adamantane series have been studied. In the reaction of 2-pyridone, 3-hydroxypyridine, and 4-pyridone with 1-bromoadamantane products of *C*-alkylation are formed along with *O*- and *N*-adamantylation compounds. The hydroarylation of the 1,2,3,6-tetrahydropyridine series performed by the reduction of quaternary pyridinium salts leads to the formation of piperidines with the equatorial position of the aryl substituent (Scheme 16.7) [790].

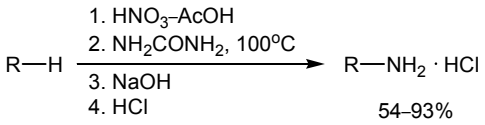
The existence in the structure of tetrahydropyridines, synthesized by the reduction with $NaBH_4$ of 1-adamantanoylmethylpyridinium bromides, of two reaction centers which are capable to participate in electrophilic reactions, makes it possible to obtain structures of increased molecular complexity. The reaction of 1-[2-(adamantan-1-yl)-2-hydroxyethyl]-1,2,3,6-tetrahydropyridine with TfOH leads to the product of intramolecular cyclization, the 1-azabicyclo-[3.3.1]nonene fused with the homoadamantane scaffold (Scheme 16.8) [791].

The mechanism of the reaction consists in the formation of a dicationic intermediate of a nonclassical nature, which is converted into a 3-homoadamantyl cation attacking the multiple bond of the tetrahydropyridine fragment. Elimination of a proton from the dication leads to a pentacyclic product.

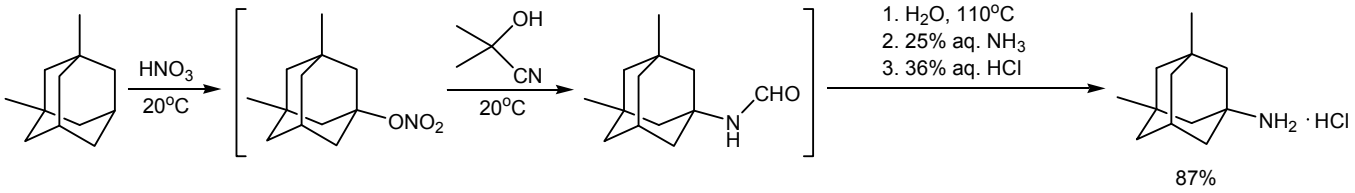
The vast majority of synthesized scaffold compounds have been tested for the manifestation of antiviral action and a significant amount of substances with pronounced activity has been found [792].

Together with the staff of the Department of Medical Chemistry of the Lomonosov Moscow State University we have substantiated the ways of searching for new blockers of the M2 channel of the influenza virus as promising medicinal candidates. As a result of the docking of over 1000 generated structures we have succeeded in identifying 20 leader structures that have the best predicted characteristics of binding with the mutant ion channels S31N and V27A and with the non-mutant M2 channel simultaneously [793].

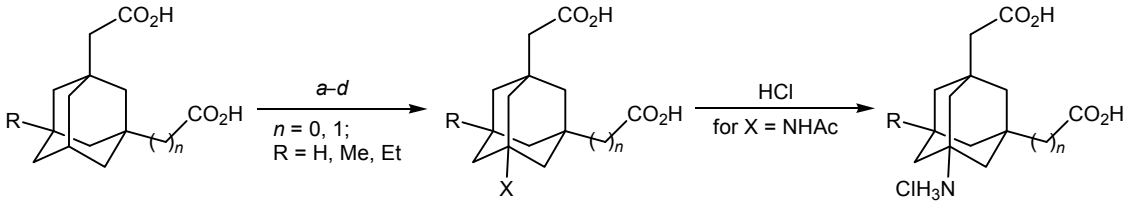
Scheme 16.1.



Scheme 16.2.



Scheme 16.3.



Reagents and conditions: *a* – HNO_3, X = ONO_2; *b* – H_2SO_4–HNO_3, X = OH; *c* – H_2SO_4–HNO_3, HCO_2H, X = CO_2H; *d* – H_2SO_4–HNO_3, CH_3CN, X = NHAc.

Another research area at the department is the search for new synthons for the purposeful synthesis of heterocyclic compounds. In this connection a very promising direction is associated with the use of reactive compounds, *ortho*-quinone methides (*o*-QM), for building up and functionalization of heterocycles [13, 14]. Since most of *o*-QM-compounds are unstable, the choice of the precursor and the generation conditions play a key role in the success of further reaction with their participation. Most often, *o*-QM are generated by thermolysis of salicylic alcohols from Mannich phenolic bases and their iodomethylates, Mannich bases of the naphthalene series, and some other precursors.

The high activity of *o*-QM with respect to various dienophiles and nucleophiles are primarily due to the formation from them of stable aromatic products.

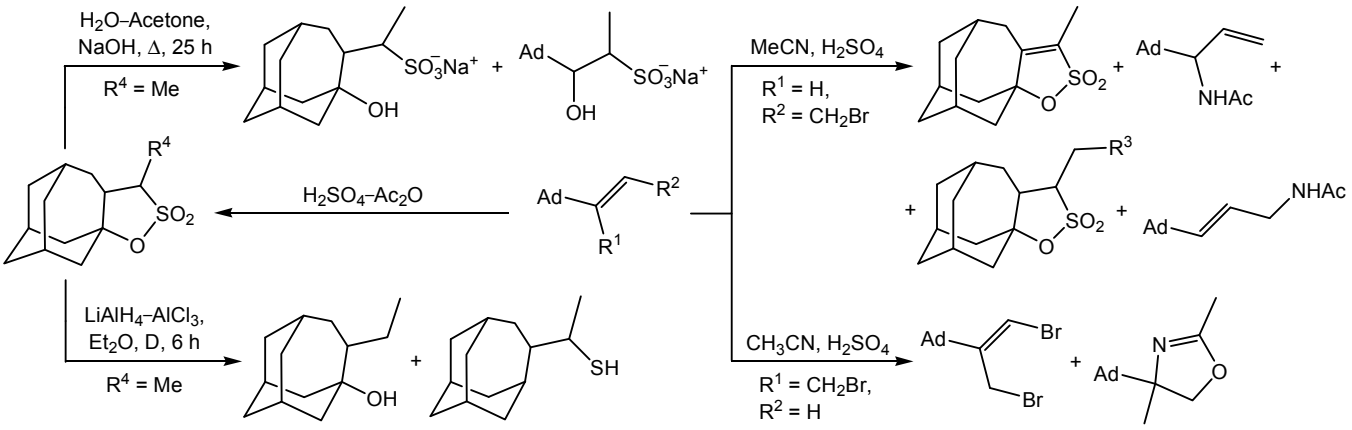
o-QM are extensively used as effective alkylating agents for introducing a hydroxybenzyl group into various *N*-, *S*-, *O*-, and *C*-nucleophiles, including aromatic compounds. The possibility of the functio-nalization of NH-azoles (imidazoles, benzimidazoles, pyrazoles, 1,2,4-triazoles, benzotriazoles, tetrazoles) at a nitrogen atom has been demonstrated (Scheme 16.9) [794].

o-QM can alkylate indoles in the position at C^3, and if it is occupied, then at the C^2 position. This reaction was used in the synthesis of alkaloid uvarindol A (Scheme 16.10) [794].

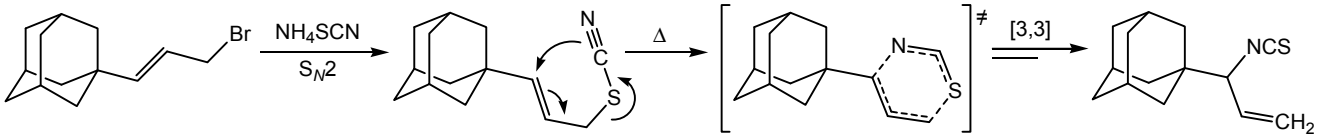
The developed non-catalytic methods of hydroxybenzylation of azoles and indoles due to a sufficiently high regioselectivity and to the use of available starting materials as well as to good yields, easy processing and high atomic economy may be applied in the synthesis of more complex compounds including those used as intermediates in the synthesis of drugs. The presence of a good leaving group (a halogen atom or a methylsulfanyl group in the α-position to the NH fragment) in the structure of the nucleophilic reagent has made it possible to develop a new cascade reaction in a sequence of *o*-QM, Michael aza-reaction, an intramolecular nucleophilic substitution that underlies a method for the preparation of azolo-fused 1,3-oxazines [794–796]. Molecular ensembles containing a combination of several nitrogen- and oxygen-containing heterocycles have been obtained: arene-fused 1,2,4-triazolo-, pyrazolo-, imidazo-, benzimidazo-1,3-oxazines, 12*H*-pyrido[2', 3'; 5,6][1,3]oxazino[3,2-a]benzimidazoles, and 9*H*-pyrazolo[5,1-*b*]pyrido-[2,3-*e*][1,3]oxazines (Scheme 16.11).

All the above methods for the preparation of condensed 1,3-oxazines are based on the reactions of conjugated addition to *o*-QM followed by cyclization. A fundamentally different way of constructing this type of system can be the cycloaddition between *o*-QM and iminodienophiles (Scheme 16.12) [794, 795].

Scheme 16.4.



Scheme 16.5.



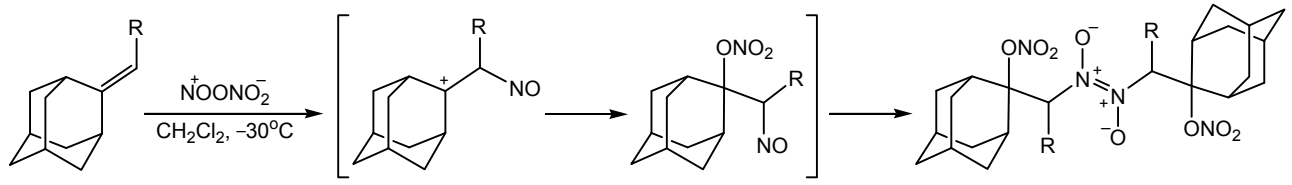
This method has been used in obtaining of a number of dihydro-7a*H*,15*H*-naphtho[1',2':5,6][1,3]-oxazino[2,3-*a*]isoquinolines which are of interest as structural analogs of some isoquinoline alkaloids [794]. A series of arene-fused 1,3-oxazines has been synthesized from arylimidates and precursors of the *o*-QM of benzene, naphthalene, and heterocyclic series. An 1,1,3,3-Tetramethylguanidine widely used as a strong non-nucleophilic base can also be chosen as an iminodienophile (Scheme 16.13), [794, 795].

One of the directions of *o*-QM stabilization in the presence of olefins is the [4+2]-cycloaddition with reversed electronic requirements, which is a convenient and general method for the synthesis of chromene and chroman systems. Moreover, these heterocycles can be obtained by combining Michael reaction and nucleophilic addition (Scheme 16.14).

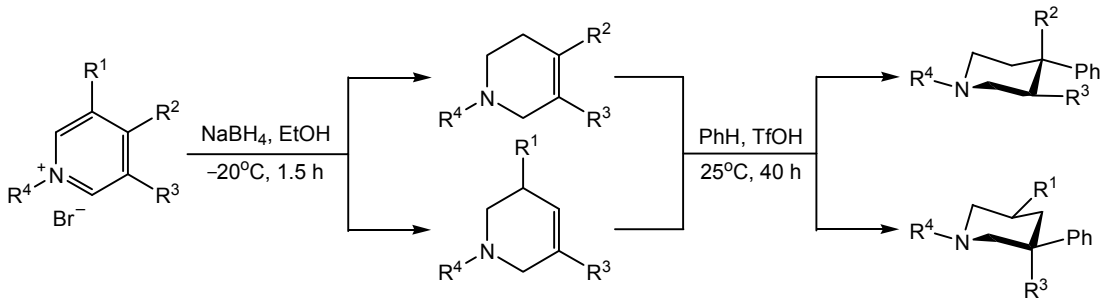
The efficiency of the approach based on the combination of two complementary ambiphilic synthons for the production of condensed pyrans has been demonstrated by an example of reactions of push-pull olefins with *o*-QM. Methods have been developed for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthenes and 4*H*-chromenes containing an acceptor group in the β-position of the pyran ring [794, 797]. The possibility to use 3-dimethylamino-5,5-dimethyl-2-cyclohexen-1-one as a universal "trap" for various *o*-QM has been shown (Scheme 16.15).

The developed method for the preparation of electron-deficient 4*H*-chromenes proved to be valuable for the synthesis of various functionalized heterocycles, which is due to the existence of two unequal electrophilic centers in the chromene structure. For example, the reaction of chromenes with amidines as 1,3-binucleophiles allows the preparation of a wide spectrum of *ortho*-hydroxybenzylated pyrimidines. In the case of aminouracils, a series of pyrido[2,3-d]pyrimidines has been synthesized. The reaction with hydrazine hydrate or hydroxylamine leads, respectively, to substituted pyrazoles and isoxazoles. At the same time, the presence of a trifluoroacetyl group in the chromene structure can

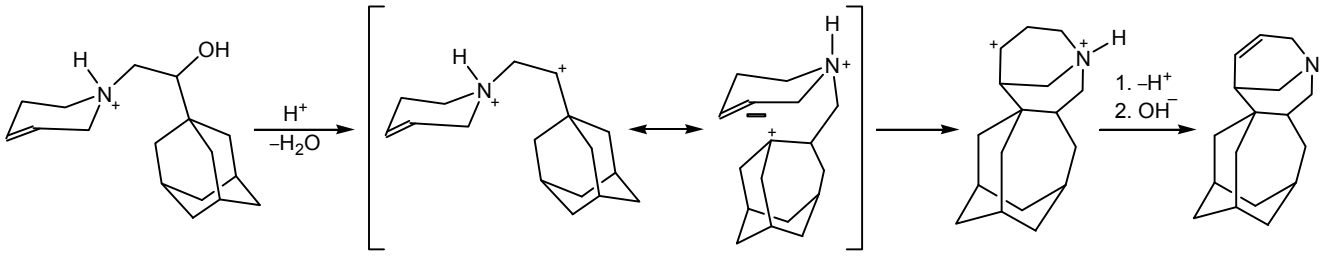
Scheme 16.6.



Scheme 16.7.



Scheme 16.8.



strongly affect its reactivity. For example, the reaction with *o*-phenylenediamine leads to 2-trifluoromethylchroman-2-ols as a result of the Michael aza-reaction and the Mannich retro-reaction. Reaction with 2-naphthols is accompanied by intramolecular haloform cleavage, which leads to substituted benzocoumarins [798]. Reaction of chromenes with malononitrile or cyanothioacetamide provides an approach to pyridine derivatives (Scheme 16.16) [797].

Most heterocyclization reactions involving *o*-QM lead to six-membered heterocycles, but there are examples of their application to the synthesis of benzofurans and 2,3-dihydroarenofurans. For example, in the reaction of *o*-QM with potassium trinitromethanide a series of 2-nitrobenzofurans was obtained. Reaction of *o*-QM with pyridinium ylides provides access to a wide range of 2,3-dihydroarenofurans (Scheme 16.17) [794, 795].

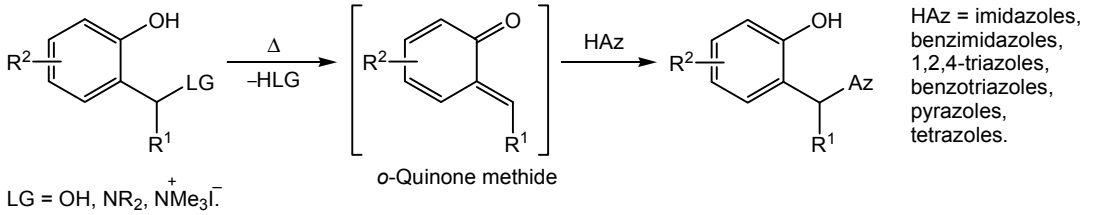
Within the framework of the department investigations on the asymmetric synthesis of biologically active compounds an effective procedure was developed based on the catalytic activation of carbonyl compounds by the chiral Lewis acids. 1,3-Dicarbonyl compounds added to nitro-alkenes in the presence of nickel complexes with chiral vicinal diamines (Scheme 16.18) [799-801].

The addition of β-ketophosphonates to nitroalkenes in the presence of Ni(II) complexes occurs with a high enantioselectivity to the position *3* and leads to the formation of (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers whose ratio is determined by the nature of the solvent in which the reaction is carried out. The reaction in toluene leads to the formation of predominantly (2*R*,3*S*)-isomers with an enantiomeric excess over 99% (Scheme 16.19) [802].

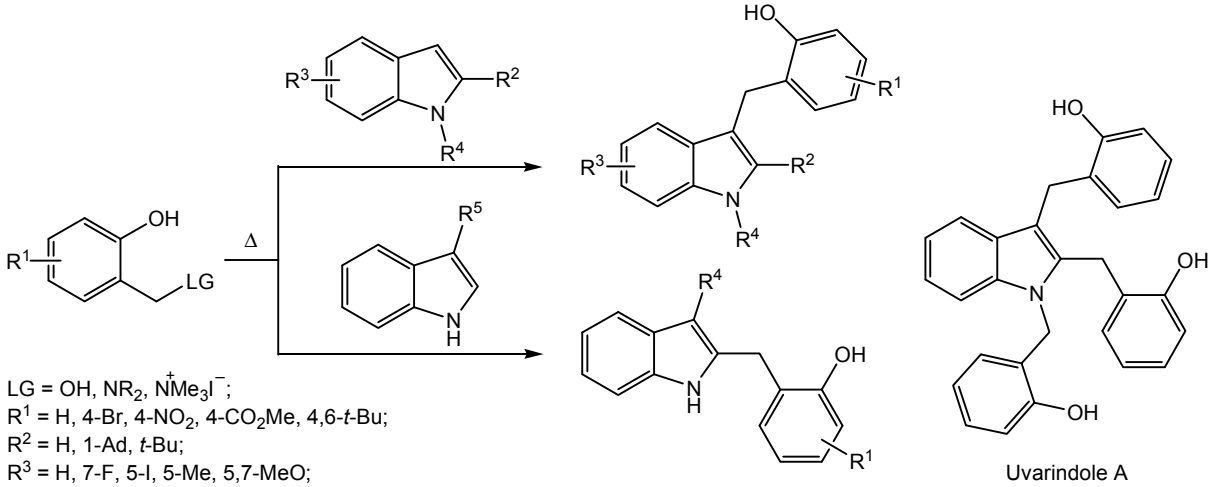
The reaction of racemic β-ketophosphinate with nitrostyrene leads to the formation of three diastereomers. By the recrystallization from methanol the individual (*S*,2*R*,3*S*)-isomer was isolated (Scheme 16.20) [803].

The reaction of β-ketosulfoxides with nitroalkenes followed by the oxidation of the sulfinyl group of adducts was used in the synthesis of non-racemic ketonitrosulfones (Scheme 16.21) [804].

Scheme 16.9.



Scheme 16.10.

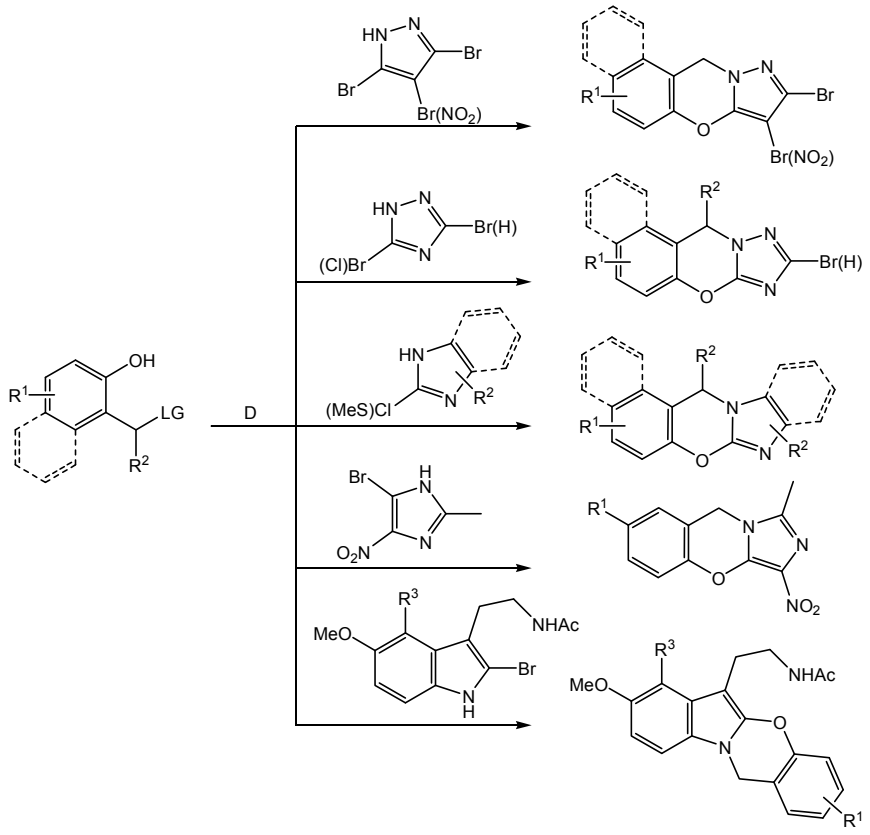


The presence of several functional groups in the chiral Michael adducts opens wide possibilities for their use in the processes of the reductive cyclization and cascade transformations. The first approach was used for the asymmetric synthesis of pyrrolidin-2-one derivatives and 3-substituted derivatives of γ-aminobutyric acid [800], since only one of the enantiomers of these compounds exhibits a neurotropic activity (Scheme 16.22).

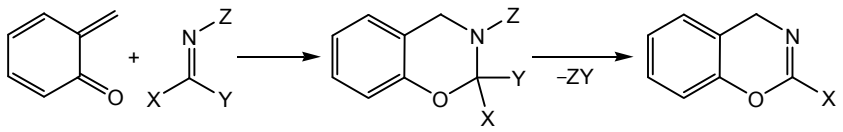
Adducts of the acetoacetic ester and nitroalkenes were used in cascade transformations of the Michael reaction/aldol condensation involving cinnamaldehyde (Scheme 16.23) [801].

The addition of imines generated *in situ* from the corresponding aldehydes to the α-position with respect to the nitro group of the Michael adducts followed by a

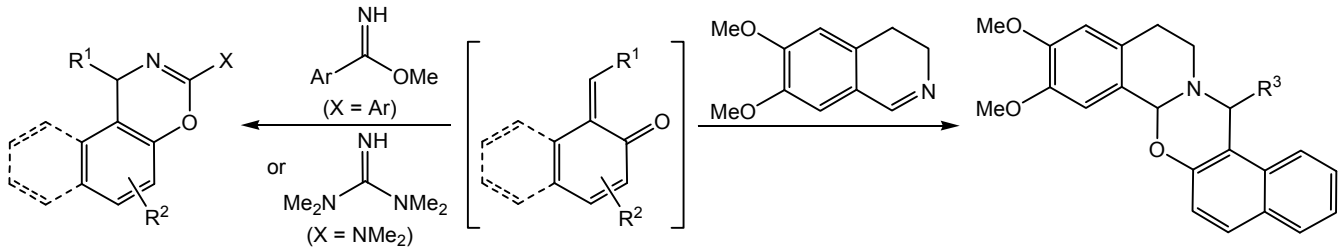
Scheme 16.11.



Scheme 16.12.



Scheme 16.13.



nucleophilic attack on the ester group results in chiral 5-nitro-2-oxo-4,6-diarylpiperidine-3-carboxylates (Scheme 16.24) [805].

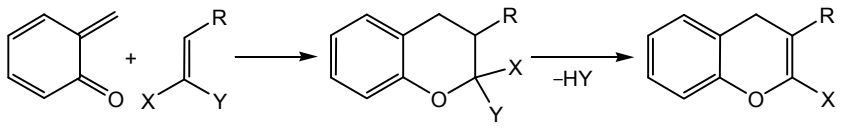
Thus, the asymmetric addition of carbonyl-containing reagents to nitroalkenes does not only open the way to chiral 3-substituted derivatives of γ-amino-butyric acid, which possess a wide spectrum of the neurotropic activity, but also allows the preparation of polysubstituted alicyclic and heterocyclic structures containing several chiral centers of a desired configuration.

17. DEPARTMENT OF ORGANIC CHEMISTRY AT DOSTOEVSKY OMSK STATE UNIVERSITY

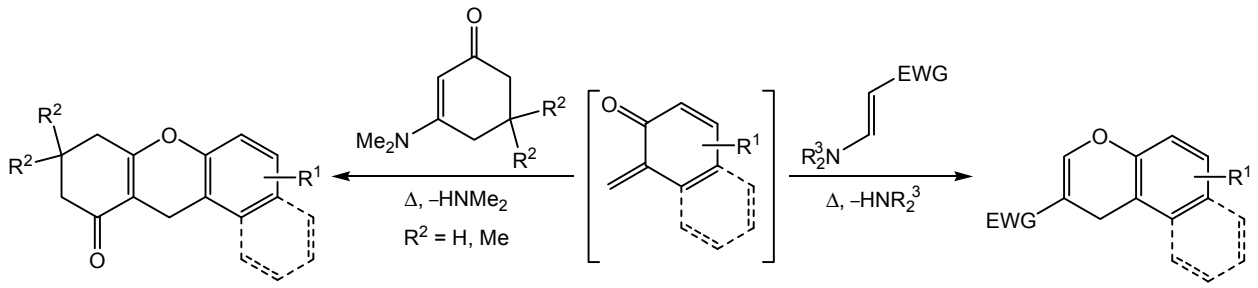
Department of organic chemistry (**head of the department Professor A.S. Fisyuk**) was organized in 1975. In 1981 **Doctor of chemical sciences R.S. Sagitullin** from Lomonosov Moscow State University) was invited to be the head of the department. The basic scientific direction of the department becomes the study of synthetic possibilities of a new reaction, registered in 1978 as scientific discovery no. 205 "Event of isomerisation recyclization of nitrogen heteroaromatic compounds". These reactions are a family of rearrangements of aromatic nitrogen heterocycles which result in the opening of aromatic rings and the formation of another heterocycle or carbocycle. The discovered transformations are referred to in the scientific literature as "Kost-Sagitullin rearrangement" [806, 807] (Scheme 17.1). In 1983 A.N. Kost (posthumously) and R.S. Sagitullin were awarded a Butlerov Prize by Russian Academy of Sciences for the cycle of studies "New rearrangements of nitrogen heteroaromatic compounds".

Approximately at the same time under the guidance of A.S. Fisyuk one more direction of investigations formed connected with intramolecular cyclization of bifunctional compounds containing in the molecule carbonyl and amide groups. Among such compounds are *N*-(3-oxoalkyl)amides and

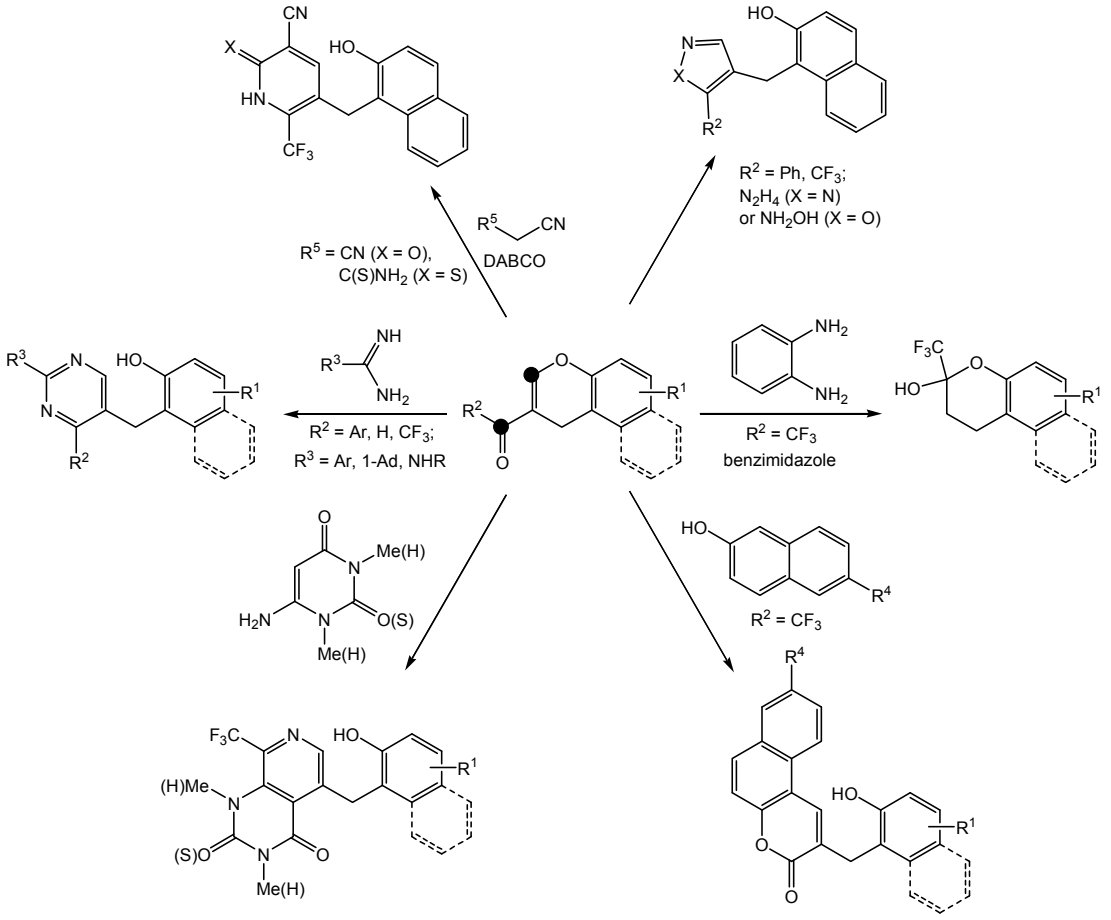
Scheme 16.14.



Scheme 16.15.



Scheme 16.16.



-thioamides, *N*-(3-oxoalkenyl)amides, *N*-(2-oxoalkyl) amides (Scheme 17.2).

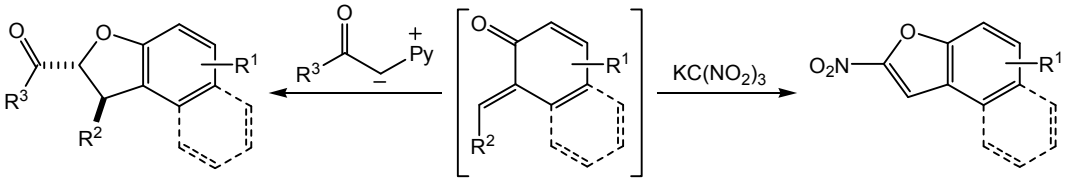
This direction appeared as a result of investigation of cyclization of analogs of intermediate compounds forming during Kost-Sagitullin rearrangement of pyrimidinium salts, and also of some oxygen-containing heterocycles. Lately many forces of the department were concentrated on the development of electro- and photoactive compounds, interesting as materials for organic electronics. The scientific direction based by Professor R.S. Sagitullin at the beginning of 1980-ies is continued at present as the development of new methods of synthesis and investigation of rearrangements of electron-deficient nitrogen heterocycles. Products of such rearrangements are as a rule polyfunctional compounds that are not obtainable by other methods. Basing on quaternary salts of nitropyridinium methods were developed of the synthesis of functionally substituted biphenyles and *m*-terphenyles interesting as bioligically active compounds (Scheme 17.3) [808, 809].

By reaction of 3,5-dinitropyridone-2 with cyclic ketones 3-nitropyridines were obtained, fused at the position C^5–C^6 with a carbocycle containing from 6 to 10 methylene units. Their alkylation and subsequent rearrangement led to the corresponding *meta*-cyclophanes. This approach turned out to be effective even for the synthesis of strained cyclophanes possessing 6–8 methylene units with distorted planarity of the benzene ring (Scheme 17.4) [810].

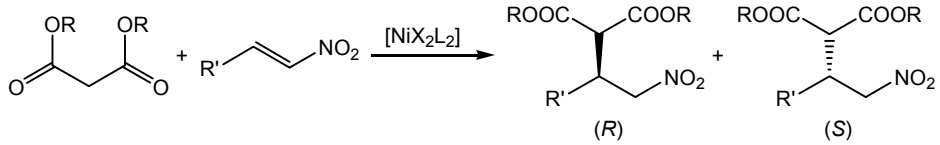
Polyfunctional compounds obtained as a result of rearrangement were used for building new heterocycles. So 3,5-diarylanilines formed as a result of a rearrangement of quaternary salts obtained from Hantzsch pyridines were utilized in the synthesis of previously unknown indazole derivatives (Scheme 17.5) [811].

Benzimidazoles are the end products of anionic domino-process occurring under the treatment with aqueous-alcoholic NaOH solution of the 3-benzoylamino-1,2-dimethyl-5-nitropyridinium salt (Scheme 17.6) [812].

Scheme 16.17.

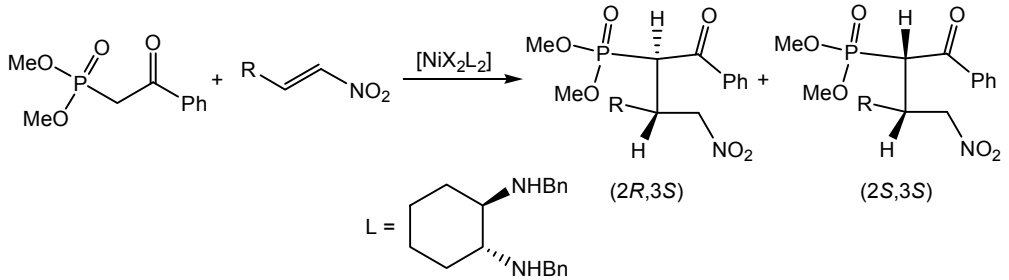


Scheme 16.18.



R = Me, Et; R' = Me, *i*-Bu, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-MeO-3-$CpOC_6H_3$.

Scheme 16.19.

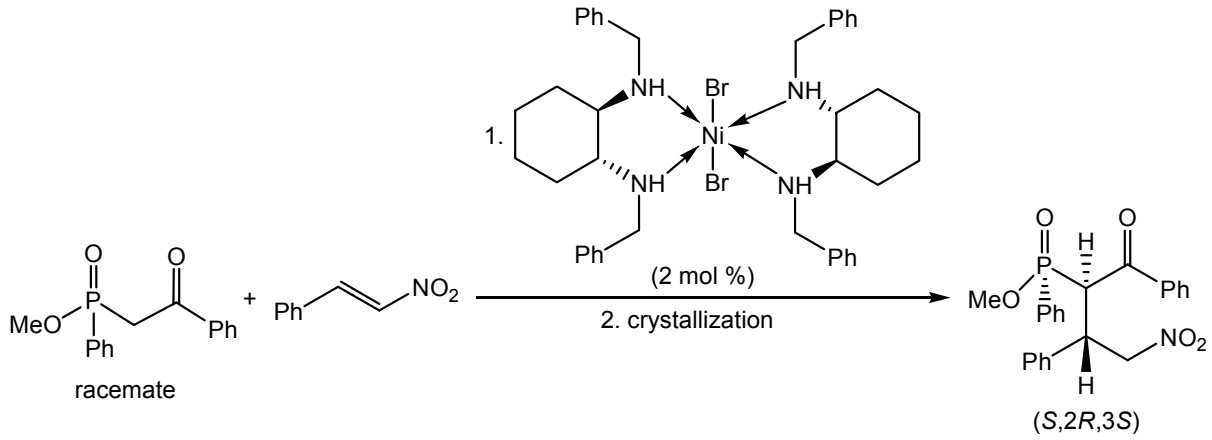


R = Ph, 4-ClC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$.

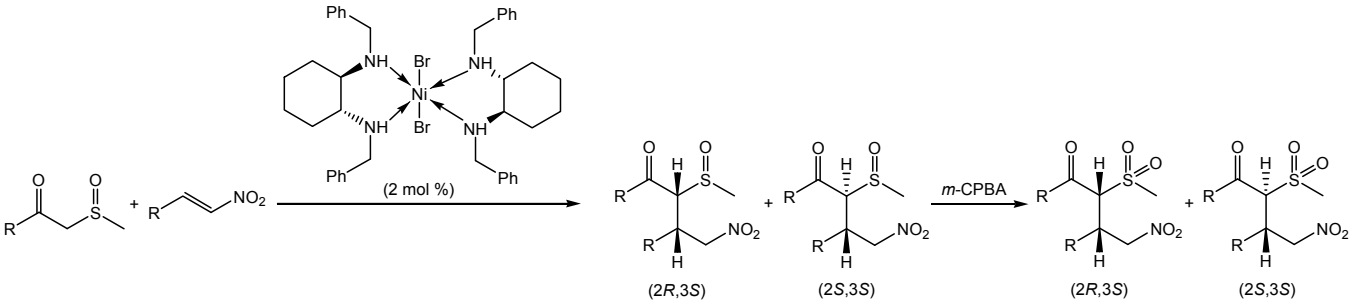
The action of alcoholic solution of methylamine on 3-benzoylamino-5-nitropyridinium salts gave a principally different result: due to the cycle contraction main products of reaction were 2-acyl-4-nitro-pyrroles (Scheme 17.7) [813].

Base-catalyzed intramolecular cyclization of bifunctional compounds containing a carbonyl and an amide group in the molecule was investigated by an example of *ortho*-aminoacylacetophenones [814]. It is known as Camps quinoline synthesis. At the same time the cyclizations of analogs of these compounds, *N*-(3-oxoalkyl)amides and *N*-(3-oxoalkenyl)amides, were practically unknown. The researchers and post-graduate students of the department studied in detail the cyclization of *N*-(3-oxoalkyl)amides and -thioamides; regularities of this process were found, methods of the synthesis of series of hydrogenated derivatives of pyridin-2(1*H*)-ones were developed [815, 816]. The base-catalyzed cyclization of *N*-(3-oxoalkenyl)amides was investigated, new approaches to the synthesis of 3-arylpyridin-2(1*H*)-ones [817] and 3-tozylpyridin-2(1*H*)-

Scheme 16.20.



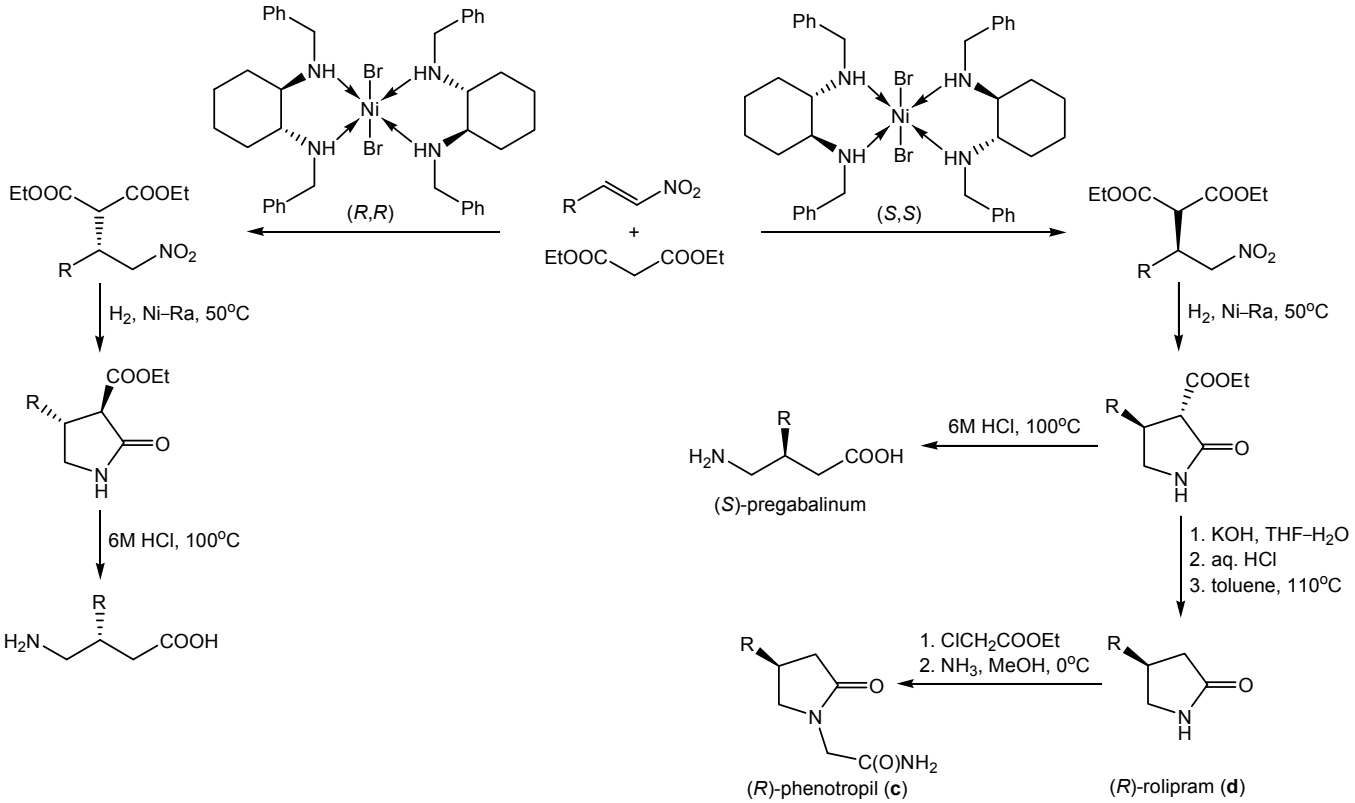
Scheme 16.21.



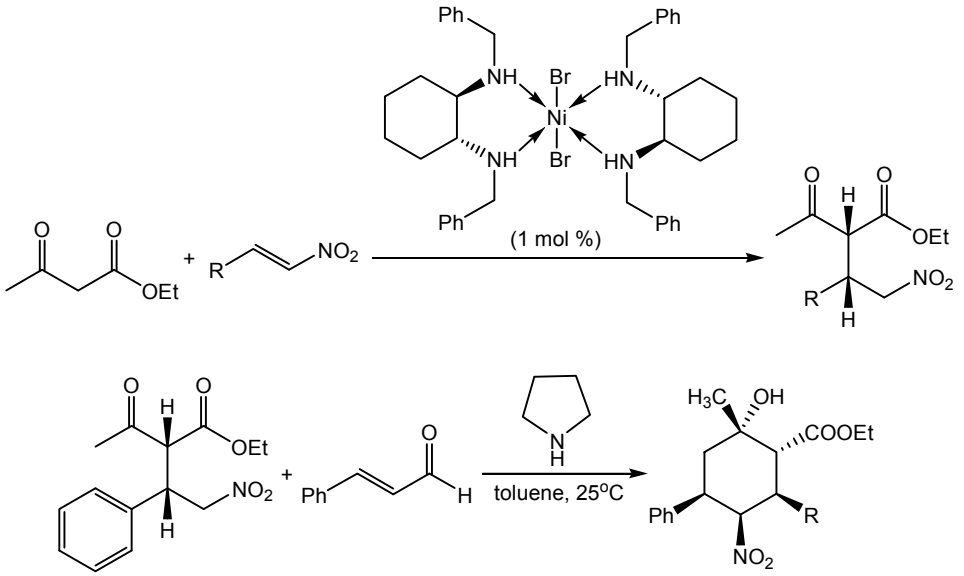
ones were developed [818]. Pyridin-2(1*H*)-ones were obtained containing a pyridinium nucleus [819] in the position *3* or an atom of bivalent sulfur bound with the heterocycle [820]. The effect of electronic and structural factors on this process was investigated, the yield and structure of reaction products were explored [817]. At the decomposition of pyridinium salts by hydrazine hydrate new 4-aryl(hetaryl)-substituted 3-aminopyridin-2(1*H*)-ones were synthesized that demonstrated high antiradical activity with respect to ABTS and DPPH radicals and that possessed luminescent properties [821]. These compounds were used for the synthesis of previously unknown 6-arylbenzo[*c*][1,7]naphthyridin-4(3*H*)-ones [822], 8-aryl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2(3*H*)-ones [821, 823], and other heterocyclic systems (Scheme 17.8) [824].

A similar ring closure in *N*-hydroxy-*N*-(2-oxoalkyl)-amides resulted in the formation of cyclic hydroxamic acids. The main cyclization product of *N*-hydroxy-*N*-(2-oxoalkyl)arylacetamides in the presence of 3 equiv of potassium *tert*-butoxide are 1-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones. Decreasing the amount of base to 1.5 equiv or less resulted in the prevailing formation of 1-hydroxy-3-phenyl-1,6-dihydropyridine-2,5-diones due

Scheme 16.22.

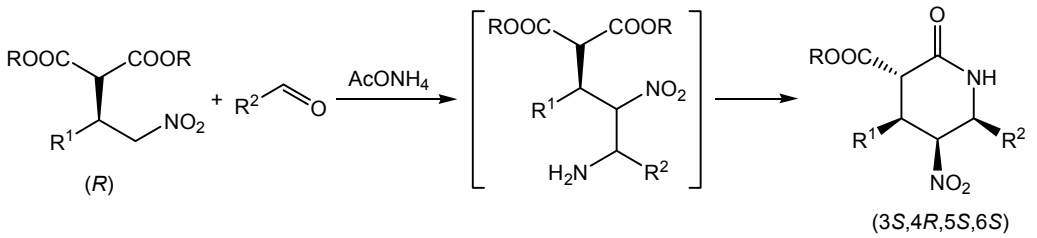


Scheme 16.23.



R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$.

Scheme 16.24.

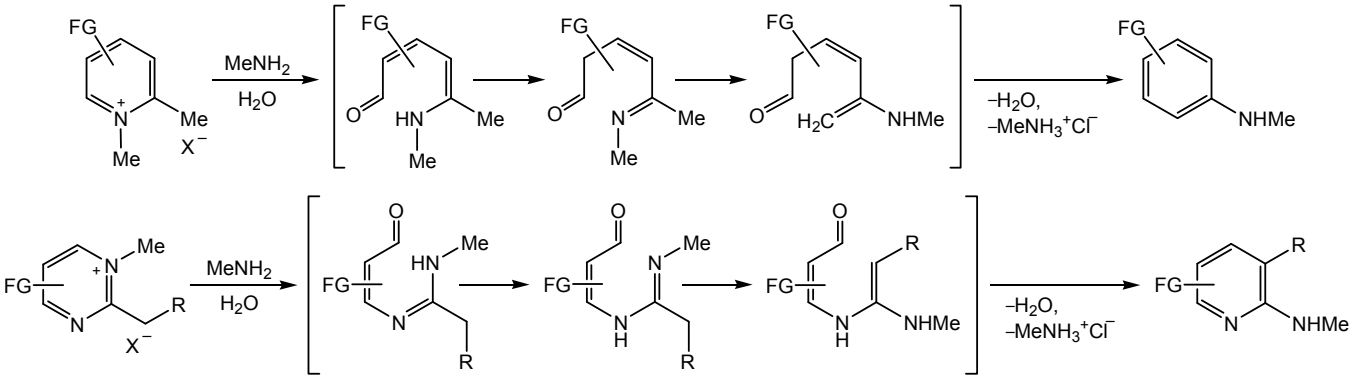


to the oxidation of initial compounds with air oxygen and their subsequent cyclization (Scheme 17.9) [825].

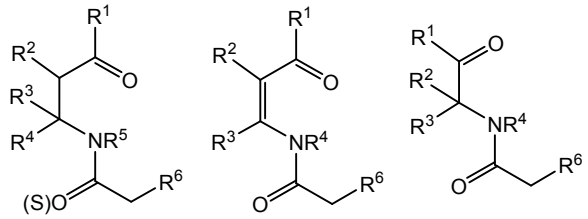
Heating of arylethylamines or tryptamine with isothiocyanatocarbonyl compounds in acid medium results in 6-hydroxyhexahydropyrimidine-2(1*H*)-thiones that undergo intramolecular amidoalkylation (to be more exact, thioureidoalkylation) transforming into 1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-thiones and 2,3,6,7,12,12b-hexahydropyrimido[6,1-*a*]-β-carbolin-4(1*H*)-thiones in good yields [826]. Instead of unstable 1,3-isothiocyanatocarbonyl compounds 1,3-isothiocyanatoacetal may be applied that has been obtained for the first time at our department [827]. Similar cascade cyclizations also occurs at heating of a,b-unsaturated compounds with 1-[2-(1*H*-indol-3-yl)-ethyl]urea or *N*-arylethylureas in alcohol in the presence of acids [828]. An effect of electronic and structural factors on the course of this cyclization was investigated [829], the limits of the reaction, and also the information was systematized concerning similar domino-reactions [830]. The properties of obtained compounds were investigated (Scheme 17.10) [831].

Important advantage of organic semiconductors is the possibility of fine tuning of their electronic and optical properties by molecular engineering. One of possible paths allowing the tuning of these properties is the synthesis of donor-acceptor-donor (D-A-D) molecules. Such conjugated molecules are often difficultly soluble due to strong intermolecular interactions. Long alkyl chains allow enhancing the solubility. Among such molecules are thiophene-substituted 1,3,4-thiadiazoles, 1,3,4-oxadiazoles, and 1,2,4-triazoles. By changing amount and nature of donor and acceptor fragments in the conjugated chain it is possible to affect levels of frontier orbitals, the energy gaps width, and optical properties. Convenient structural blocks for the synthesis of such semiconductors are functionally substituted bi-, ter- and quaterthiophenes containing long alkyl chains. Unfortunately, methods of synthesis of such compounds were until recently very difficult. Simple method was

Scheme 17.1.



Scheme 17.2.



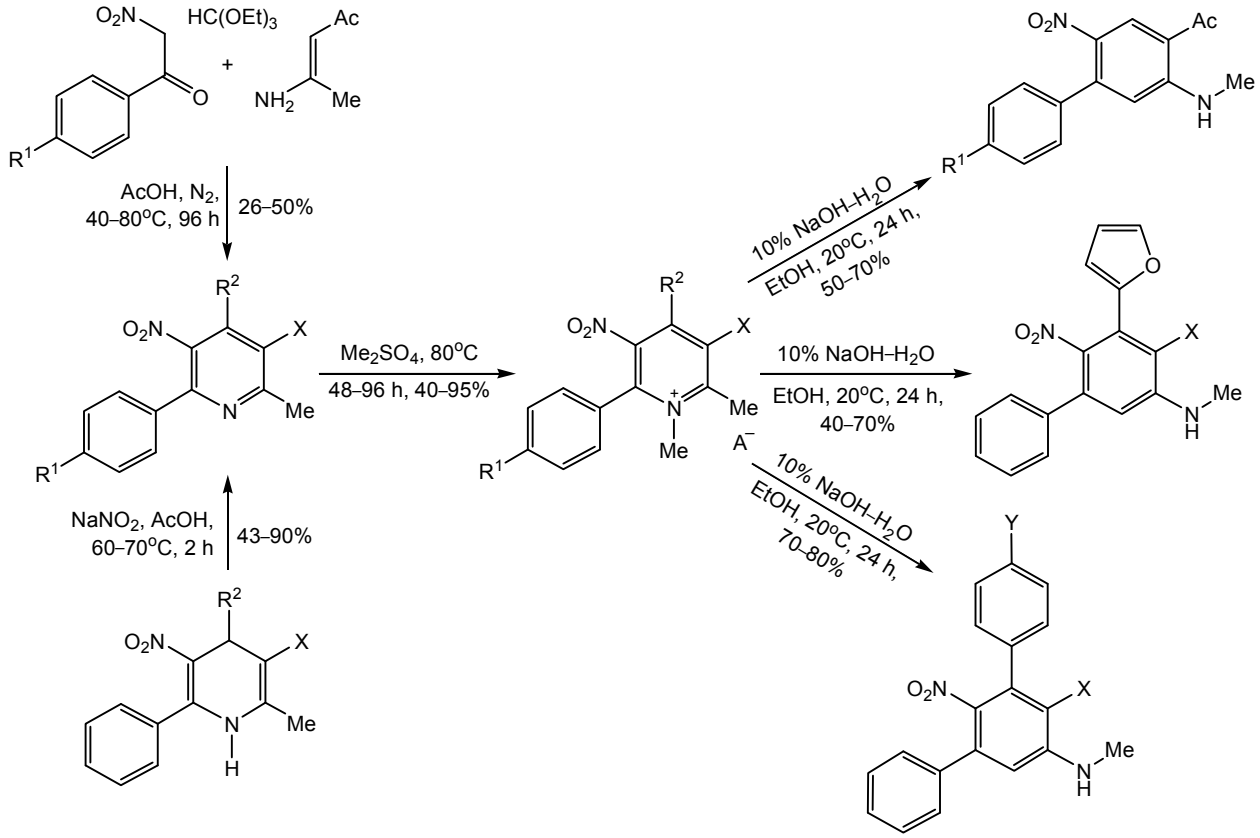
developed of preparing esters of (2,2'-bithiophen)-, (2,2':5',2"-terthiophen)-, (2,2':5',2":5",2"'-quarterthiophen)-5-carboxylic acids containing long alkyl chains or aryl substituents, based on thiophene ring closure by Fisselman reaction (Scheme 17.11) [832, 833].

Palladium-catalyzed cross-coupling was investigated of the ester of 2,2'-bithiophen-5-carboxylic acid with iodobenzene, 1-bromonaphtalene, 9-bromoanthracenone, and 1-bromoperilene [834], and also of the ester of 5'-bromo-3-decyl-2,2'-bithiophene-5-carboxylic acid with bithiophene [835]. Reactions occur in the presence of tetrakis(triphenylphosphine)palladium and result in the formation of the corresponding 5'-aryl-(hetaryl)-substituted esters of 2,2'-bithiophen-5-carboxylic acids (Scheme 17.12).

Based on derivatives of 3-alkyl-2,2'-bithiophen-5-carboxylic acids a flexible method was developed of the preparation of soluble luminescent organic semiconductors of linear and star-shaped architecture, containing conjugated thiophene chains linked to 1,3,4-oxadiazole, 1,3,4-thiadiazole, *N*-phenyl-4*H*-1,2,4-triazole, 2,2'-bi(1,3,4-oxadiazole), 2,2'-bi(1,3,4-thiadiazole), 2,2':5',2":5",2"'-quater-1,3,4-thiadiazole (Scheme 17.13). By the method of cyclic voltammetry the position of frontier orbitals (HOMO, LUMO) of these compounds was established. Their optical properties were investigated. The regularities of substituent effects, the nature of heteroatom of the acceptor heterocycle, the expanding of conjugation system on the position of frontier orbitals, the energy gaps width, quantum yield of luminescence of synthesized semiconductors were established [836–840]. The obtained organic semiconductors were used as active materials for fabrication of effective organic light emitting diodes [841, 842].

By the reaction of 4-chloromethylthiophene-2-carbaldehyde or its iodo derivative with phenoles or *N*-tozyl-, *N*-alkoxycarbonyl-, *N*-acetyl-substituted anilines a synthesis was performed of previously unknown 4-(aryloxymethyl)- and 4-(arylaminomethyl)thiophene-2-carbaldehydes. Methods were developed of the preparation of 4,5-dihydrothieno[3,2-*c*]-quinoline-2-carbaldehydes and 4*H*-thieno[3,2-*c*]chro-mene-2-carbaldehydes underlain by palladium catalyzed intramolecular arylation of iodo(bromo) derivatives of 4-(aryloxymethyl)- and 4-(arylamino-methyl)thiophene-2-carbaldehydes in conditions of homogeneous and heterogenic catalysis (Scheme 17.14) [843]. Transformations were investigated of 4*H*-thieno[3,2-*c*]-chromenes and 4,5-dihydrothieno[3,2-*c*]quinolines at the functional groups, methylene bridge, benzene ring [844]. Conditions were found allowing the removal of protection group from the nitrogen atom in *N*-substituted 4,5-dihydrothieno[3,2-*c*]quinolines. General regularities and specific features of the

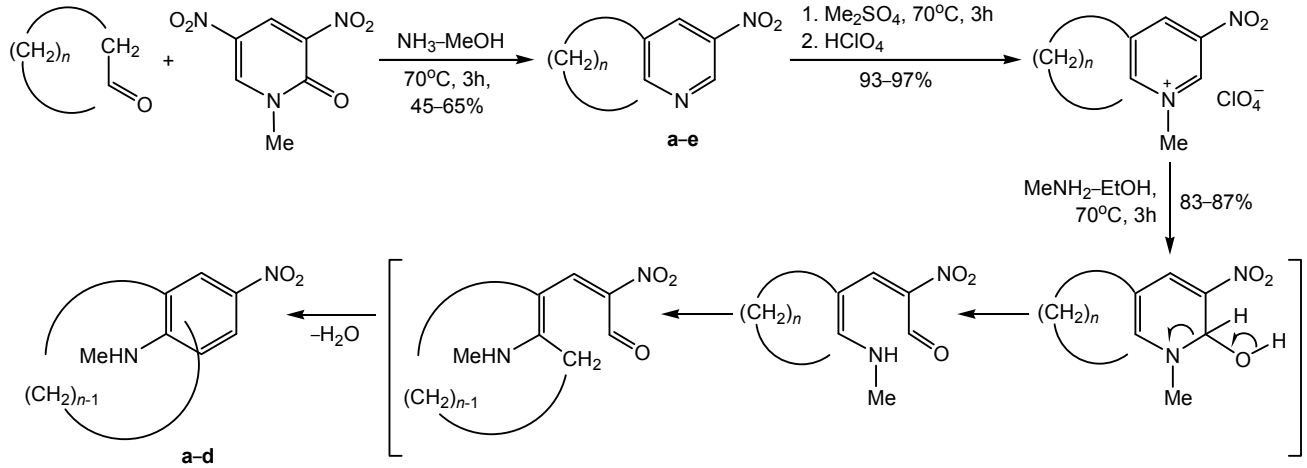
Scheme 17.3.



X = Ac, CN, NO_2, COOEt, CO-*c*-Pr, COPh, COC_6H_4Me-4, COC_6H_4OMe-4, COC_6H_4Cl-4, COC_6H_4Br-4, CO-napthyl-2, NHCOPh; R^1 = H, Me, MeO, Cl, Br; R^2 = H, furyl-2, C_6H_4Y-4 (Y = H, OMe).

structure influence of 2-functionally substituted derivatives of 4*H*-thieno[3,2-*c*]chromenes and 4,5-dihydrothieno[3,2-*c*]quinolines on their absorption and luminescence spectra in UV and visible ranges were found. A high antiulcer activity was established of 4-methoxy-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde [845]. Among these compounds luminophores were found possessing a high quantum yield (up to 0.9) and anomalously high Stokes shift (up to 160 nm).

Scheme 17.4.

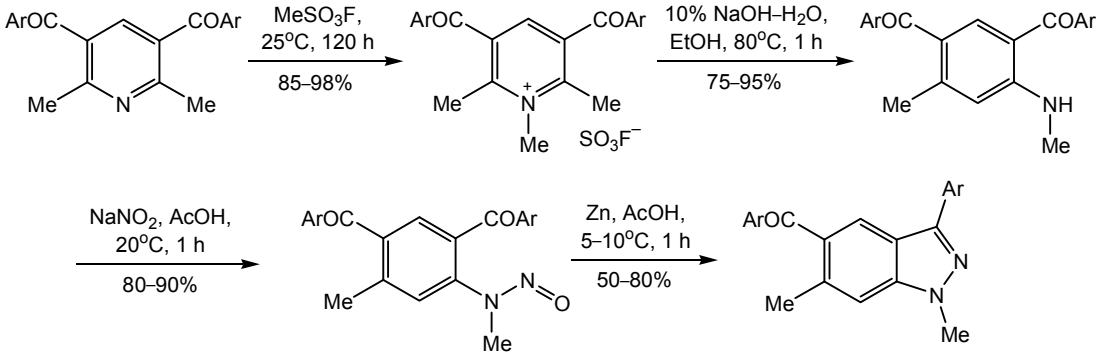


a–e

a–d

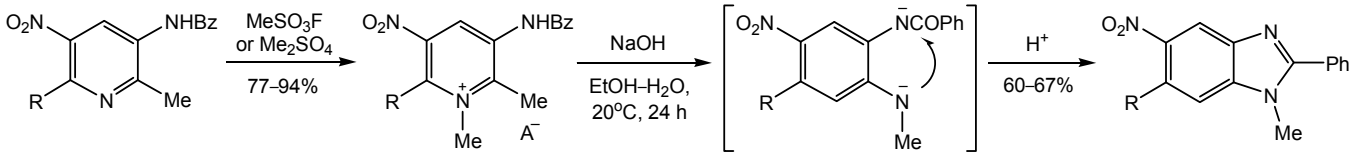
n = 10 (**a**), 9 (**b**), 8 (**c**), 7 (**d**), 6 (**e**).

Scheme 17.5.



Ar = Ph, C_6H_4Me-4, C_6H_4OMe-3, C_6H_4OMe-4, C_6H_4Cl-4, C_6H_4Br-4, 1-napthyl, 2-napthyl.

Scheme 17.6.



R = H, Me, Ph.

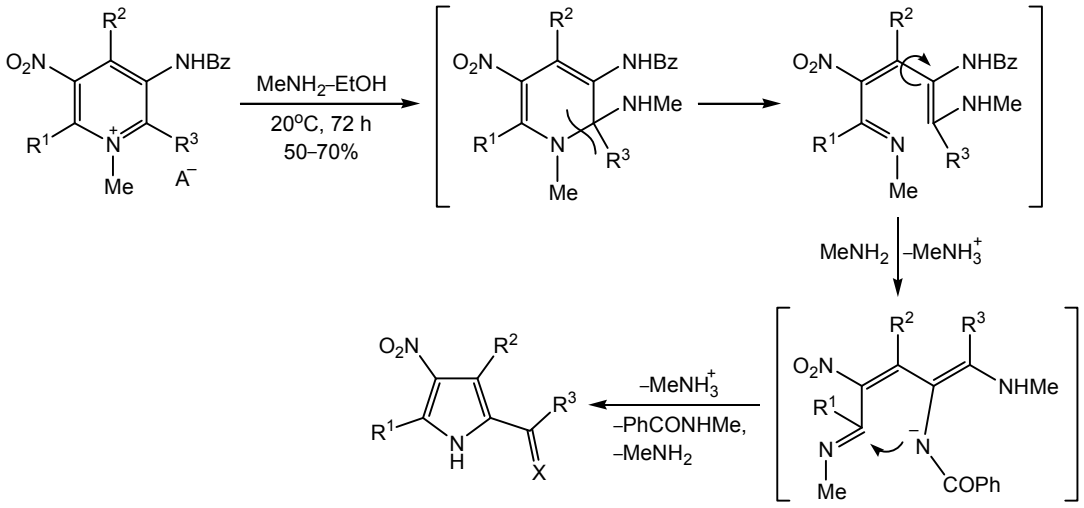
18. DEPARTMENT OF CHEMISTRY AT NORTH-CAUCASIAN FEDERAL UNIVERSITY

During the last 8 years organic chemists of Stavropol under the guidance of **Professor A.V. Aksenov** investigate the possibility to monitor the cascade transformations, utilizing the properties of reaction environment, modifying reaction conditions, introducing modifiers. This approach got a name of "smart" reaction media. Such media were underlain by polyphosphoric acid (PPA).

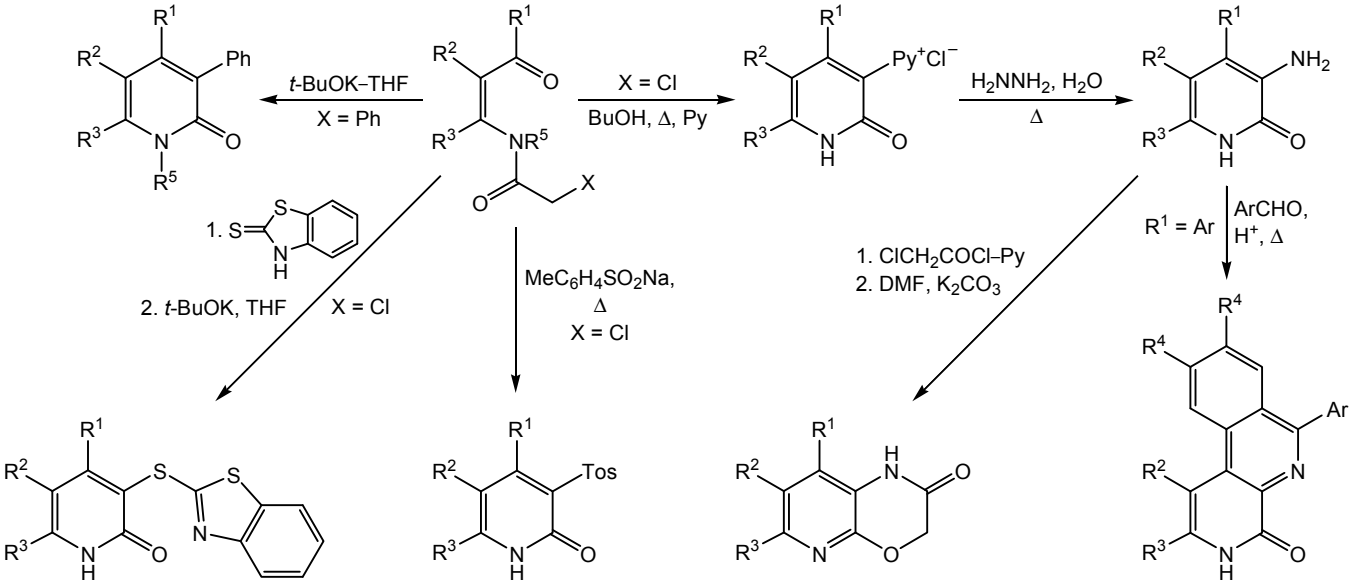
Among the first processes performed applying this approach were reactions of nitroalkanes with arenes in polyphosphoric acid [846–853]. Depending on the structure of nitro compounds and arenes different products were formed. So, reactions of arenes with nitromethane in PPA resulted in primary arylamides (Scheme 18.1) [846].

Reaction includes the following sequence of stages: the formation of phosphorylated derivatives of nitromethane, the alkylation of arene along Vilsmeier

Scheme 17.7.



Scheme 17.8.



R^1 = Me, Ph, C_6H_4-4-Cl, C_6H_4-4-Me, C_6H_3-3,4-$(OMe)_2$, Naphthyl-1, Naphthyl-2; $R^1+R^2 = (CH_2)_3$; $R^2+R^3 = (CH_2)_4$;

reaction, the dehydration of resulting oxime to afford the corresponding nitrile (Scheme 18.2).

Nitriles in PPA are easily hydrolyzed to primary amides. The amides formed in the course of the reaction may be easily hydrolyzed to the corresponding acids by adding into the reaction mixture after treating with water a small excess of sodium nitrite [846] (Scheme 18.3).

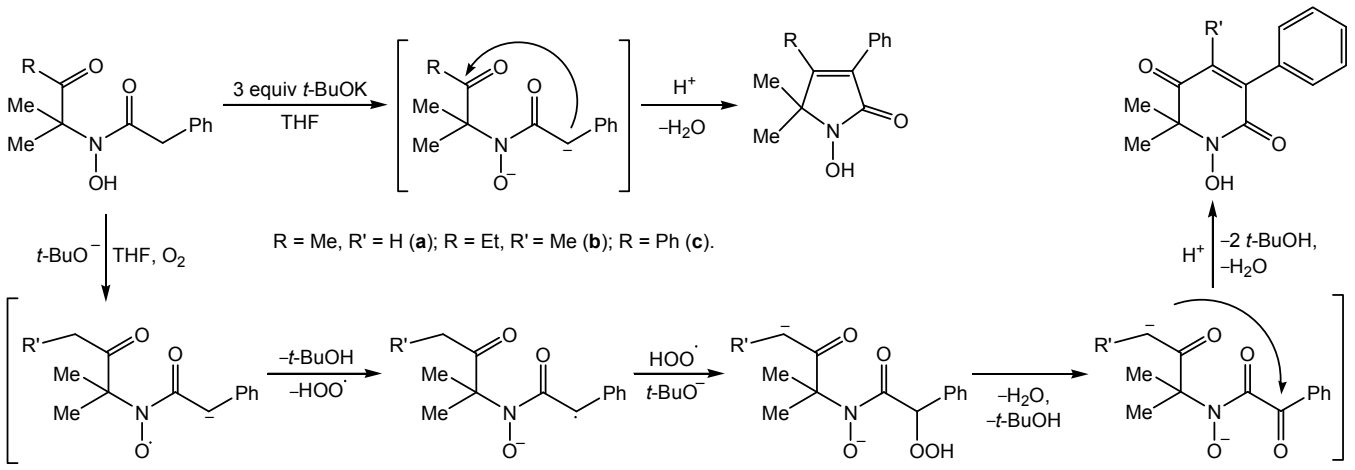
The reaction of arenes with primary nitro compounds occurs in PPA otherwise: main products are acetanilides [847–849] (Scheme 18.4). Ketoximes undergo Beckmann rearrangement, and initial stages of the mechanism are the same (Scheme 18.5).

Secondary nitro compounds cannot form an oxime, so after successive alkylation and 1,2-shifts the hydrolysis of the reaction products affords the corresponding diarylamines (Scheme 18.6) [850].

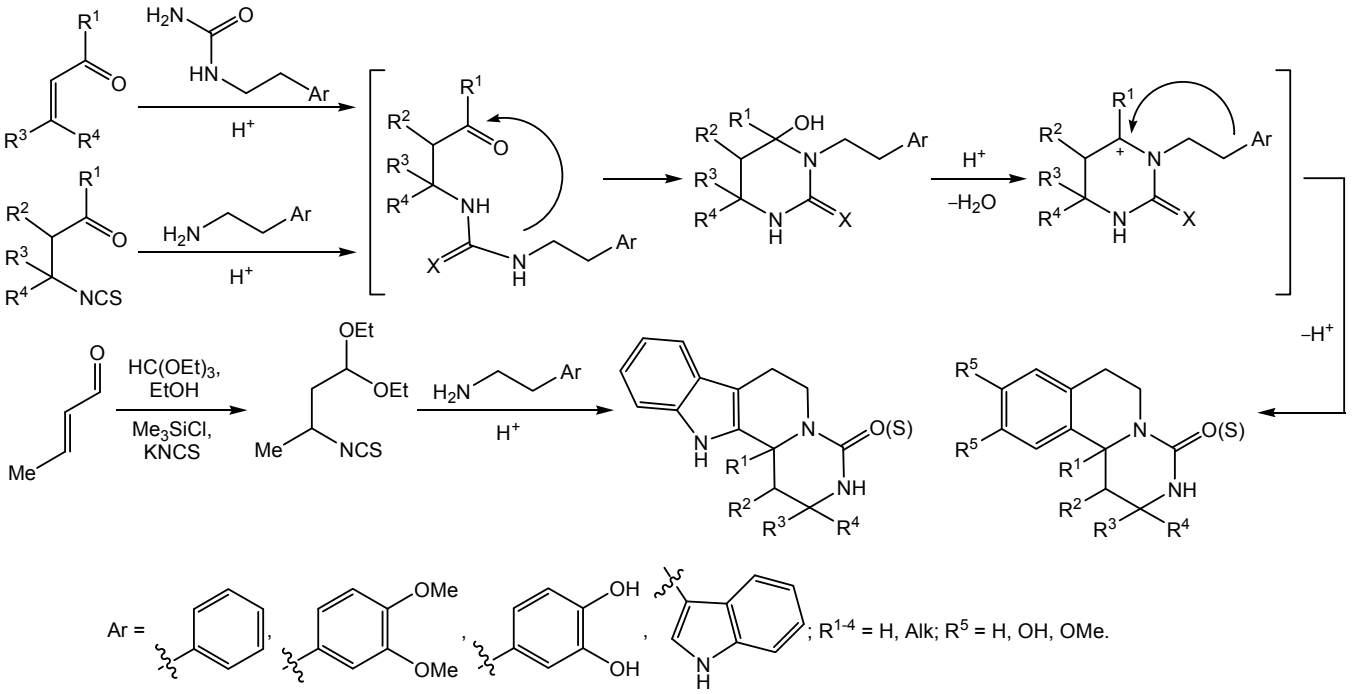
Only arenes with several donor substituents or anisole may be used as substrates, while the yield of reaction product reaches 72%. As side products the corresponding anilines are formed [850] (Scheme 18.7). Key stages are two 1,2-shifts of aryl group. As a side process 1,3-rearrangement occurs.

Anilines by reactivity and regioselectivity in the reactions are distinguished from the other donor arenes. They are either unreactive, like for example

Scheme 17.9.



Scheme 17.10.



N,*N*-dimethylaniline, or operate as *N*-nucleophiles (Scheme 18.8) [851].

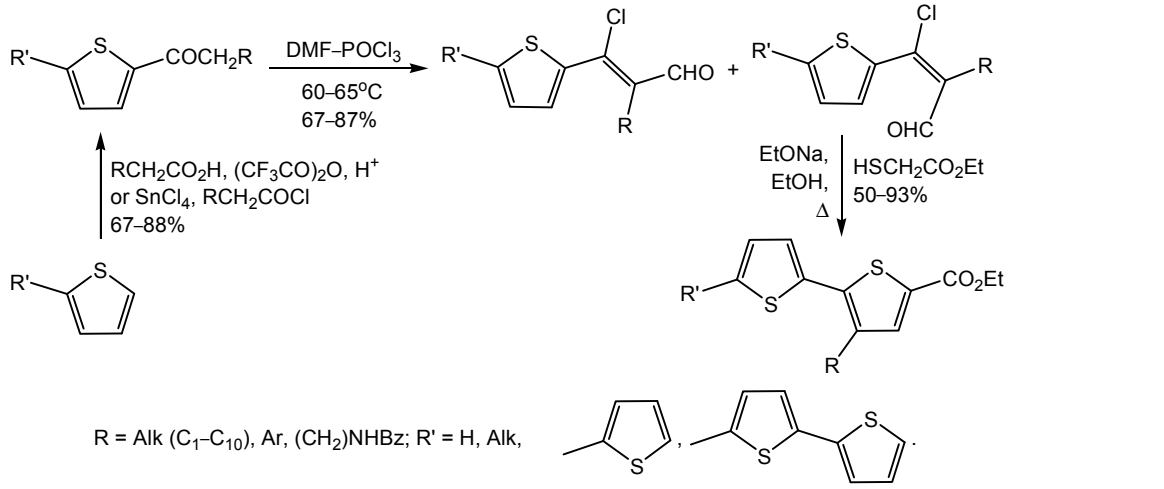
This reaction was applied to the synthesis of benzoxazoles and benzimidazoles [851]. In this case nitro compounds in PPA act as equivalents of carboxylic acids, but in a number of cases with respect to *o*-aminophenol and *o*-phenylenediamines their reactivity is significantly higher than that of carboxylic acids (Scheme 18.9).

Phenoles that are incapable to react at the *para*-position either due to the orientation of a substituent, or because this position is occupied, form benzoxazoles with primary nitro compounds [852] (Scheme 18.10). By this method may be fused either one oxazole ring, or two, and they may be similar or different.

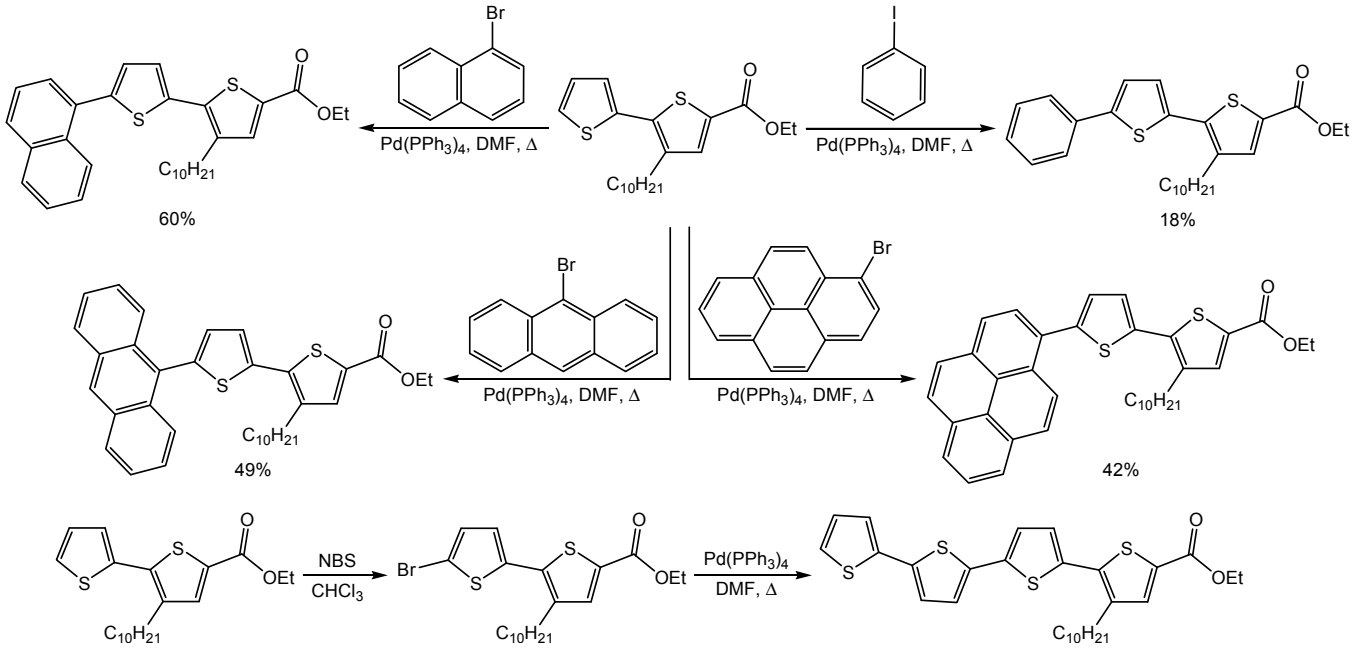
Nitro compounds containing an additional functional group may react with the participation of the latter. Thus, derivatives of nitroacetic acid in reactions with arenes are capable to form isatins (Scheme 18.11) [853].

According to the above it could be expected that in reactions with unsaturated nitro compounds these transformations would be supplemented with the addition by Michael reaction. This behavior of

Scheme 17.11.



Scheme 17.12.

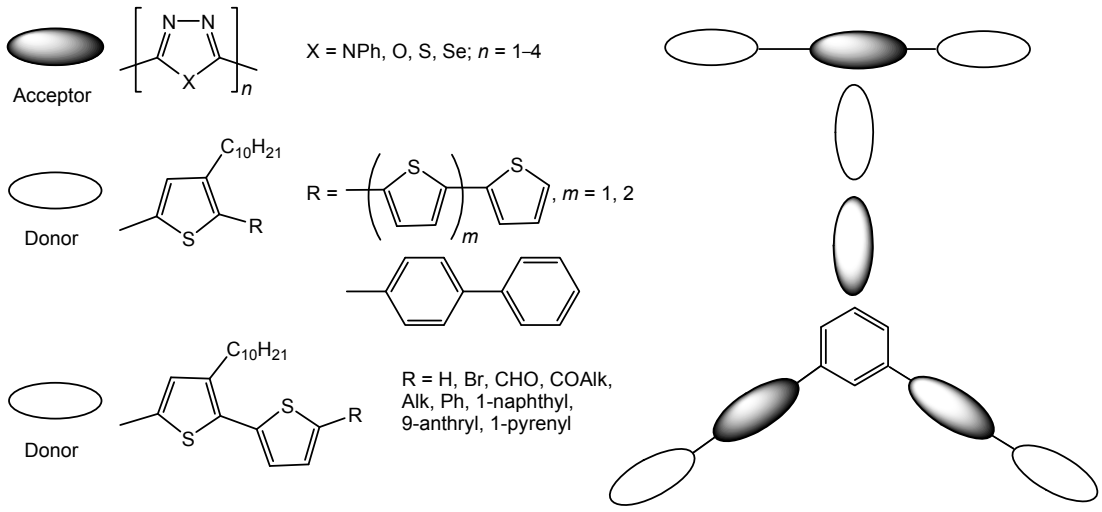


unsaturated nitro compounds was observed in reactions with azaphenalenes in PPA [854, 855]. For instance, the reaction of perimidines with unsaturated nitro compounds results in arylation products, and further the intramolecular acylation and Beckmann rearrangement occur (Scheme 18.12). Specimens of previously unknown heterocyclic systems, 1,3,6-triazapyrene and 1,2,3,6-tetraazapyrene, were thus obtained.

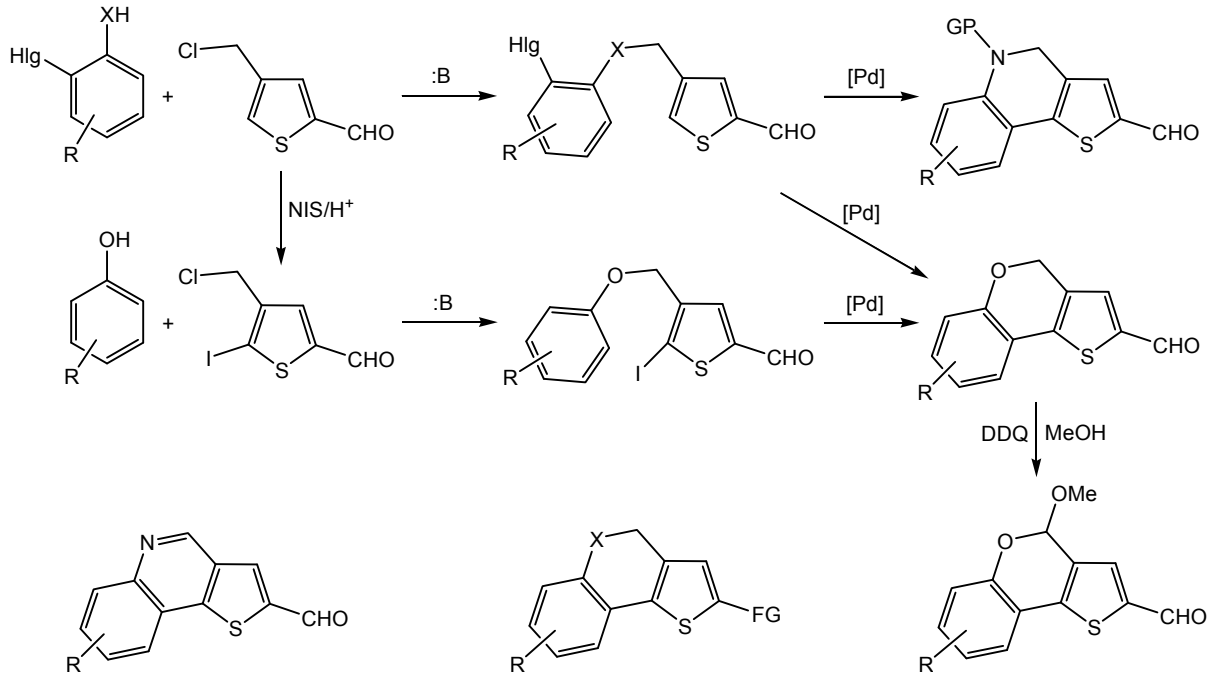
Indoles differently react with unsaturated nitro compounds in polyphosphoric acid. Under mild conditions at temperatures up to 75°C 2-aryl-2-(3-indolyl)acetohydroxamic acids were formed [856] (Scheme 18.13). As a result of alkylation by β-nitrostyrene of 2-arylindole in the position *3* nitronic acid is formed that transforms into anhydride of hydroxamic acid giving hydroxamic acid after the decomposition of the reaction mixture with water.

These hydroxamic acids possess high antitumor activity, some of them are able to cause a reverse differentiation of neurons affected by glioblastoma. The necessity to synthesize various indoles of definite structure for the systematic investigation of correlation structure–biological activity (SAR) demanded a development of simpler alternative procedures, for example, basing on the synthesis of indoles by Fischer method with the application of arylhydrazines and methyl ketones [856].

Scheme 17.13.



Scheme 17.14.



X = O, NPG (PG = Tos, Boc, CO_2Me, Ac); R = H, Me, F, Cl, OMe; Hlg = I, Br; FG = CO_2H, CO_2Me, CN, CH_2OH, $CONH_2$, CONHOH.

Thus the existence of two mutually supplementary approaches to 2-aryl-2-(3-indolyl)acetohydroxamic acids provides a possibility to synthesize analogs of a desired nature and the position of substituents in the scaffold and to explore these compounds as probable drugs.

Unexpectedly [857, 858] the reaction of 2-substituted indoles with nitrostyrenes at higher temperature proceeds as *trans*-fusion with the forming of 2-quinolones (Scheme 18.14). The nature of substituent in the position *2* of indole scaffold does not affect the product yield, therefore it is more convenient to apply isoscatole as precursor, for as a side product acetamide forms, easily removable with water [857, 858].

Reaction of scatole with β-nitrostyrene results in 3-phenyl-2-quinolone in a low yield (12%) only at 140°C. Good yields (62–92%) were obtained by reaction with nitrostyrenes containing either electron-acceptor or, electron-donor substituents. A mechanism was suggested of these multistage transformations.

This method can be extended to a direct synthesis of quinolines from easily accessible arylhydrazines by combination in a one-pot process of Fischer synthesis of indoles and the procedure described above (Scheme 18.15).

The alkylation of the other electron-rich arenes (*o*-xylene, veratrole, [1,3]benzodioxane, phenetole, and *tert*-butylbenzene) also furnishes 3-arylsubstituted 2-quinolones in good yields. The application of this method for one-stage introduction of important quinolone chromophore into complex aromatic structures was also investigated. The reaction of nitrovinylindole and dibenzo-18-crown-6 ether in PPA in standard conditions afforded the desired object in 34% yield, and also small amounts of a mixture of two alkylation products of both benzene rings (Scheme 18.16) [858].

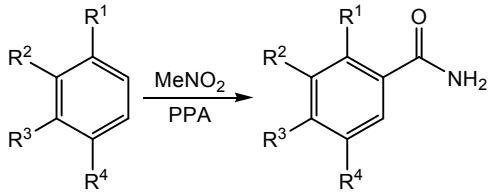
An effective module approach was developed to 2-quinolones unsubstituted at the C^4 atom [859]. This strategy includes Fischer synthesis of indoles based on 4-nitroketones and arylhydrazines, and ANRORC ring expansion (Scheme 18.17).

Hydroxamic acids can be reduced into amides under treatment with different reductive reagents: thionyl chloride, phosphorus trichloride, etc. By combining phosphorus trichloride [860] with polyphosphoric acid an effective method was developed of amides synthesis (Scheme 18.18).

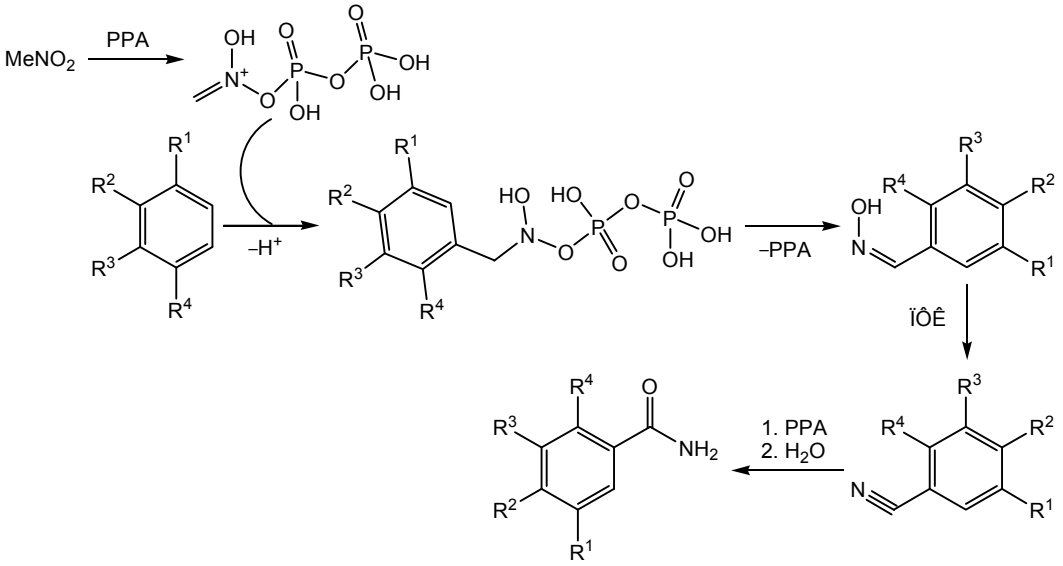
19. DEPARTMENT OF ORGANIC CHEMISTRY AT MOSCOW PEDAGOGIC STATE UNIVERSITY

Head of department of organic chemistry since April 2013 is **Professor M.K. Grachev**. At the department three topics of research and development

Scheme 18.1.



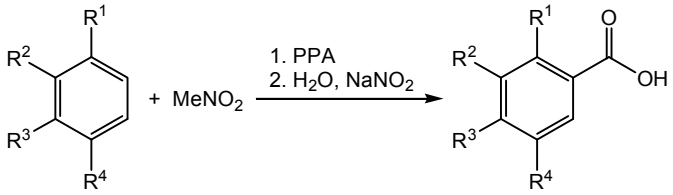
Scheme 18.2.



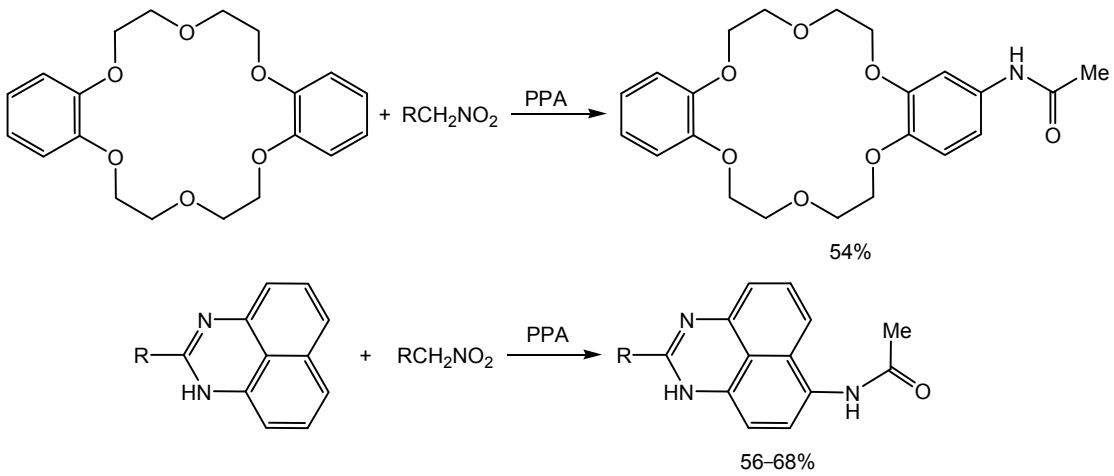
are performed (supported by 3 grants of the Russian Foundation for Basic Research) and it occupies the leading position in three educational programs.

The main direction of scientific research in the team of **Professor M.P. Koroteev** is the investigation of phosphorylation, acylation, and aminomethylation

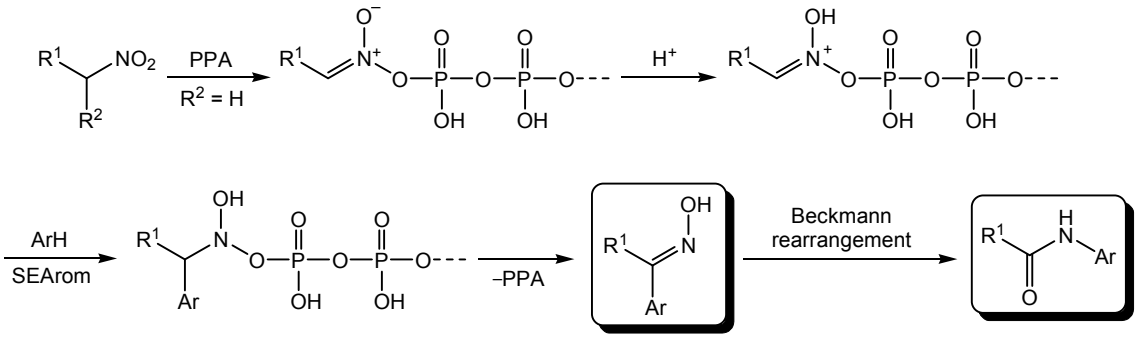
Scheme 18.3.



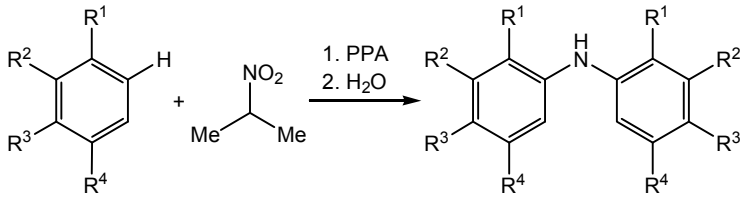
Scheme 18.4.



Scheme 18.5.



Scheme 18.6.



of dihydroquercetin (taxifolin) and catechin [861–870]. Phosphorylation of partially protected taxifolin (DHQ) was realized with different hexaalkyltriamides of phosphoric acid. Structure of the reaction product was very unusual, it contained a four-membered phostone cycle (Scheme 19.1).

The specific feature of DHQ phosphorylation consist in a selective phosphorylation in this flavonoid at the seventh hydroxy group that is the only one not involved in internal hydrogen bonds (Scheme 19.2).

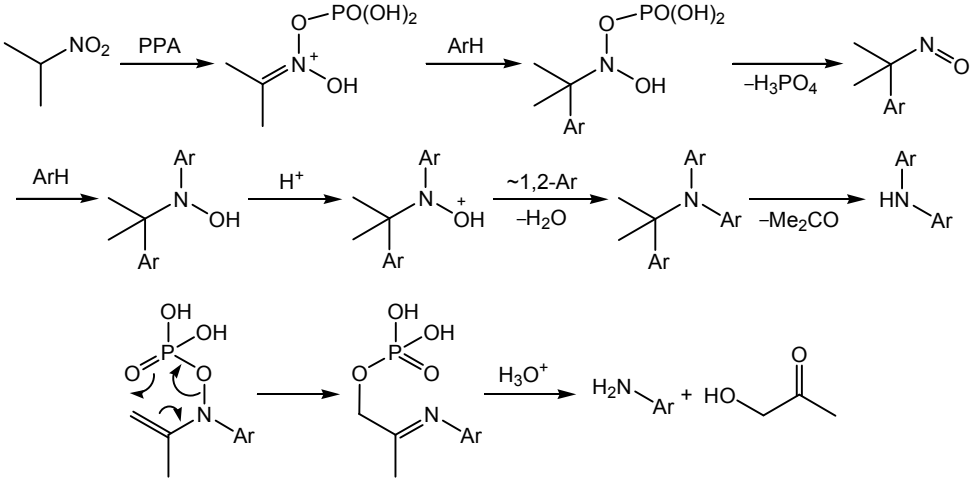
Acylation of catechin with chlorides of heterocyclic carboxylic acids was performed in two stages along Scheme 19.3.

Taxifolin reacts well in Mannich reaction involving formaldehyde and amines. Products of reaction of mono- and bisaminomethylation of DHQ in good yields are isolated from the reaction mixture (Scheme 19.4).

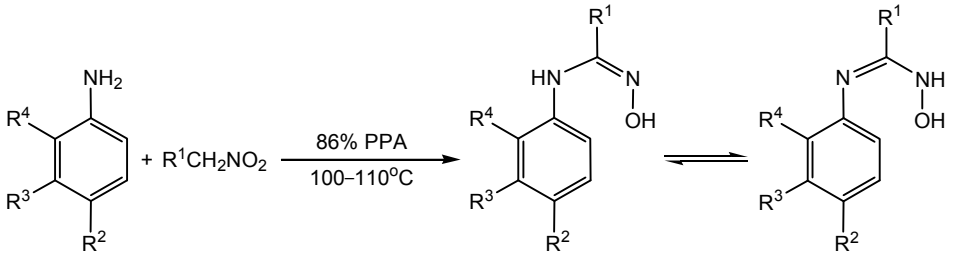
A selective bisaminomethylation of DHQ was also realized applying amino acids of diverse structures as amino component: α-glycine, β-alanine, γ-amino-butyric acid, α-phenylalanine, etc. (Scheme 19.5).

Aminomethylation with excess of formaldehyde, amines and amino acids does not result in electrophilic substitution in the ring B of dihydroquercetin. This fragment of flavonoid molecule in this process is inert. At present flavonoid-containing drugs are studied at the Blokhin Oncology Center and at the department of

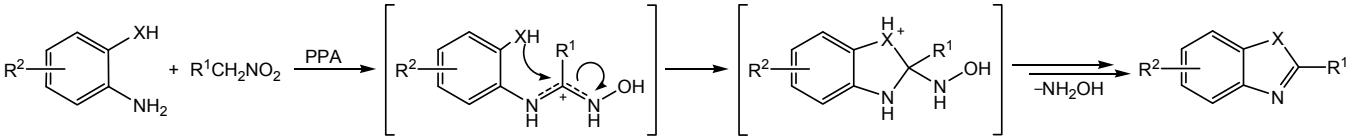
Scheme 18.7.



Scheme 18.8.

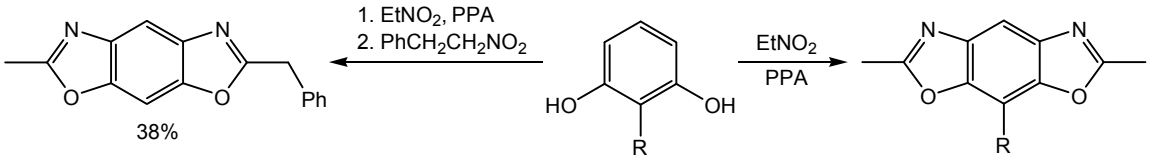


Scheme 18.9.



R^1 = H, Me, Ph, CH_2Ph; X = O, R^2 = H, 4-Me; X = NH, R^2 = H, 4-NO_2; X = NMe, R^2 = H; X = NCH_2Ph, R^2 = H.

Scheme 18.10.



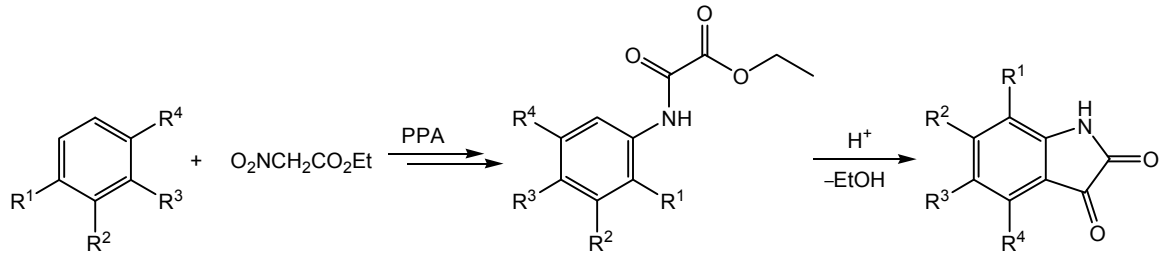
biotechnology and radiobiology of Pirogov Russian National Research Medical University.

Work of scientific group under the guidance of **Professor V.I. Maslennikova** [871–880] is connected with designing nano-dimensional polyfunctional macrocyclic molecules possessing receptor properties and high selectivity to transition metals, ions, and biologically significant organic molecules.

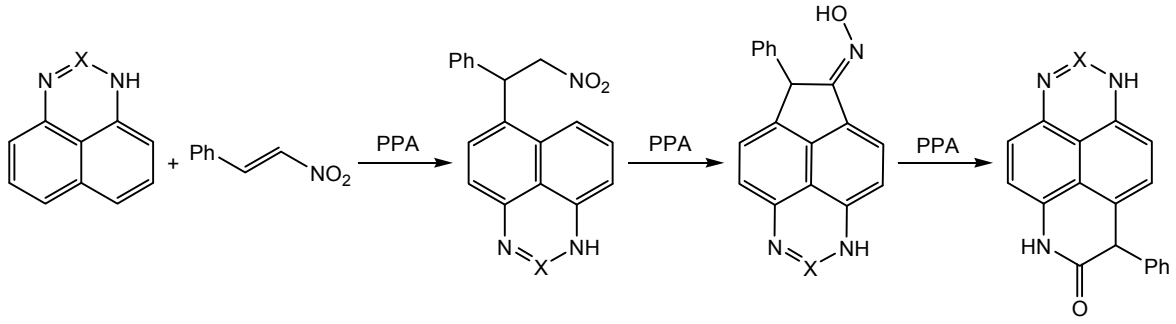
As "structural blocks" for the design of such supramolecular systems are applied 2,2'-dihydroxy- and 2,2',7,7'-tetrahydroxydinaphtylmethanes, *rccc* and rctt-calix[4]rezorcinarenes, existing in conformations *crown* and *chair* with alkyl and aromatic substituents in methylidene bridges.

Effective methods were developed of total and selective modification of calix[4]resorcinarenes,

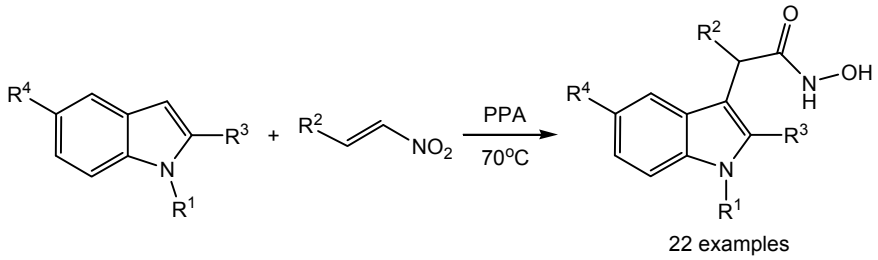
Scheme 18.11.

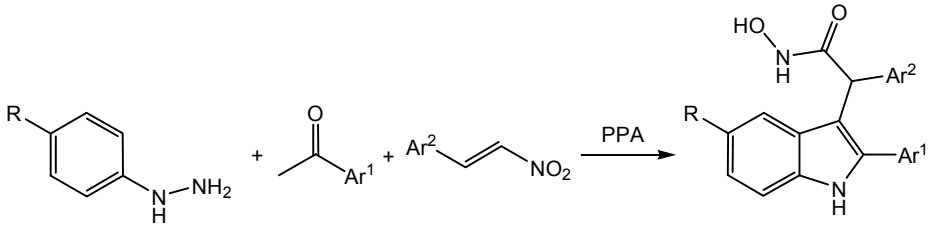


Scheme 18.12.

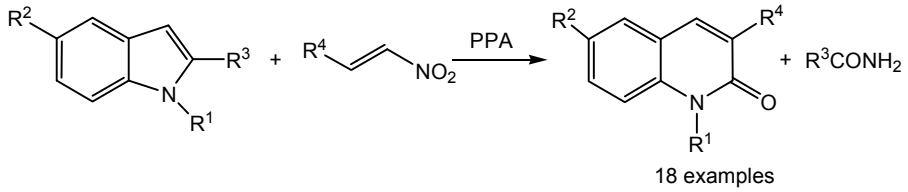


Scheme 18.13.





Scheme 18.14.



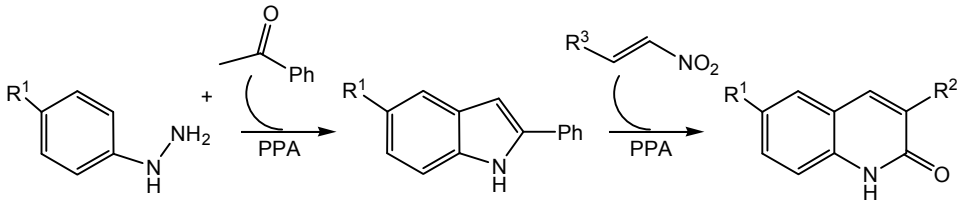
preorganized receptor systems were obtained, differing by the number, nature, and mutual orientation of functional groups fixed on resorcinarene platform (Scheme 19.6).

Methods of introducing functional groups into the structure of 2,2'-dihydroxy- and 2,2',7,7'-tetrahydroxy-dinaphtylmethanes were advanced with subsequent transformation of obtained derivatives (Scheme 19.7).

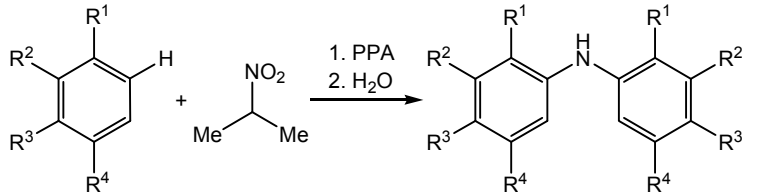
High efficiency and selectivity was demonstrated in extraction of cations Cd^{2+}, Ag^{+}, Hg^{2+}, and Nd^{3+}. The ability was demonstrated of phosphorus-containing resorcinarenes to form coordination structures with salts of transition metals and lanthanoids [Pd(II), Rh(III), Nd(III), Tb(III), and Yb(III)] and supramolecular systems of different structure and architecture of tetraphosphatotetraacetylresorcinarene with organic amines (hexyl-amine, aniline, benzylamine, phenethylamine, tryptamine, and tyramine) (Scheme 19.8).

Work of the scientific group under the guidance of **Professor M.K. Grachev** consists in the investigation of synthetic opportunities of chemical binding

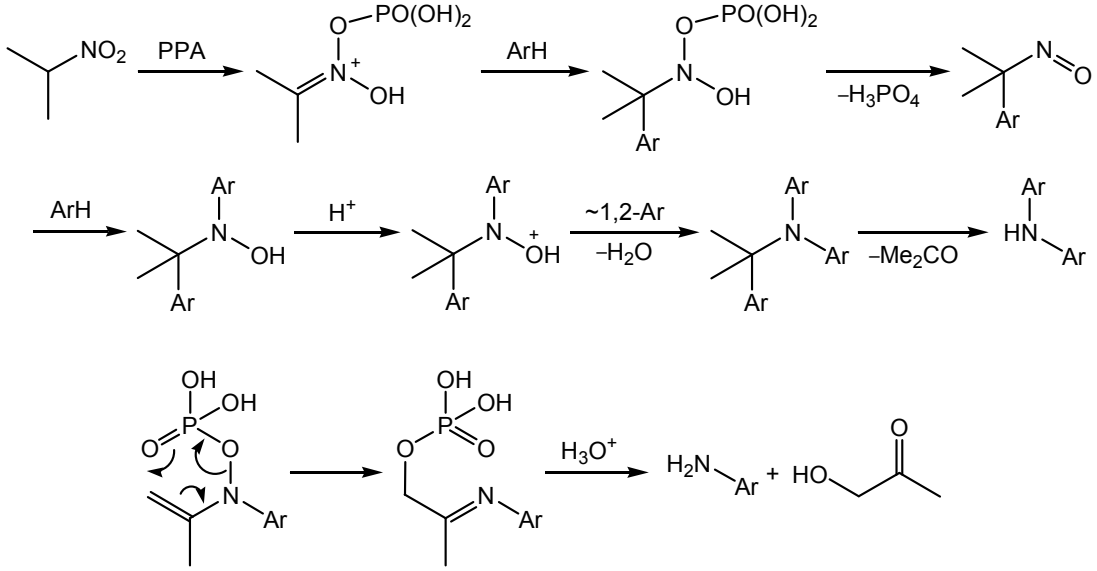
Scheme 18.15.



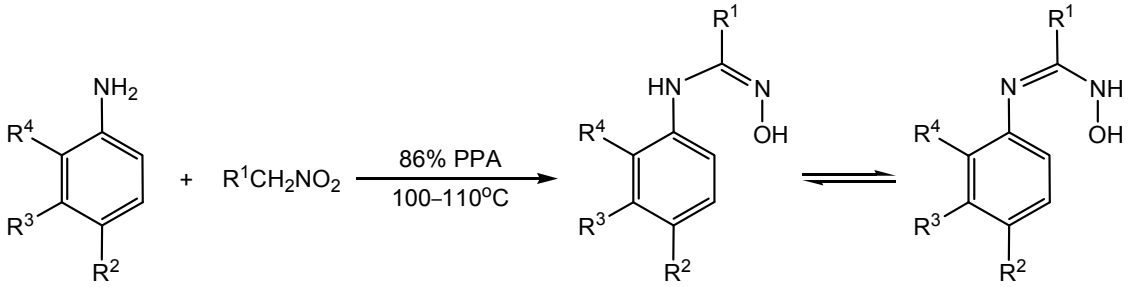
Scheme 18.6.



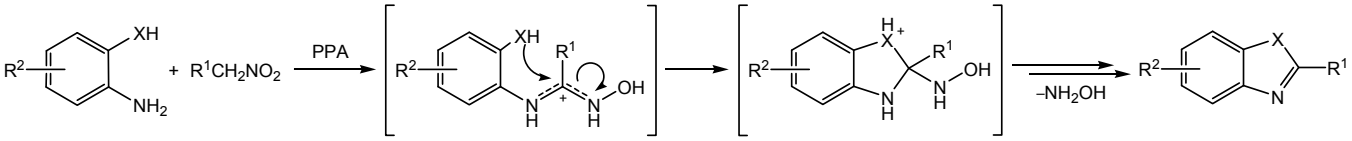
Scheme 18.7.



Scheme 18.8.

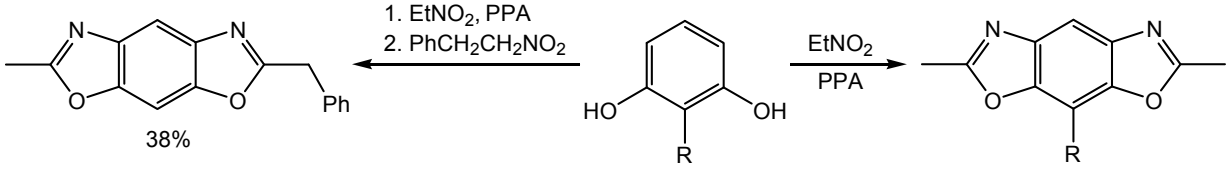


Scheme 18.9.



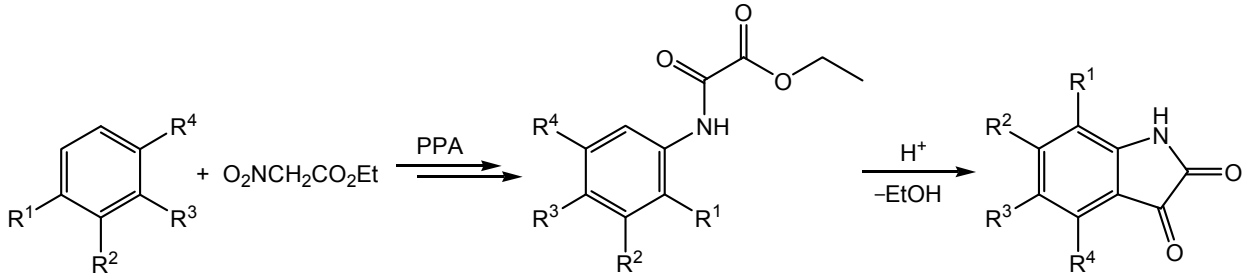
R^1 = H, Me, Ph, CH_2Ph; X = O, R^2 = H, 4-Me; X = NH, R^2 = H, 4-NO_2; X = NMe, R^2 = H; X = NCH_2Ph, R^2 = H.

Scheme 18.10.

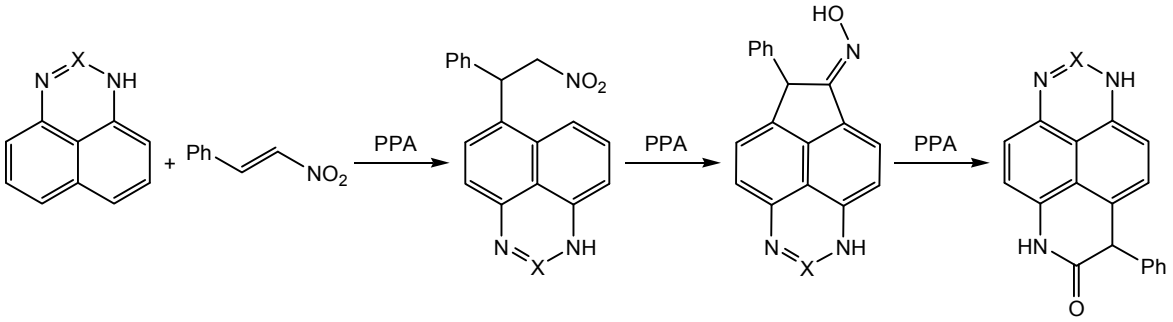


R = H (23%), Me (40%)

Scheme 18.11.



Scheme 18.12.

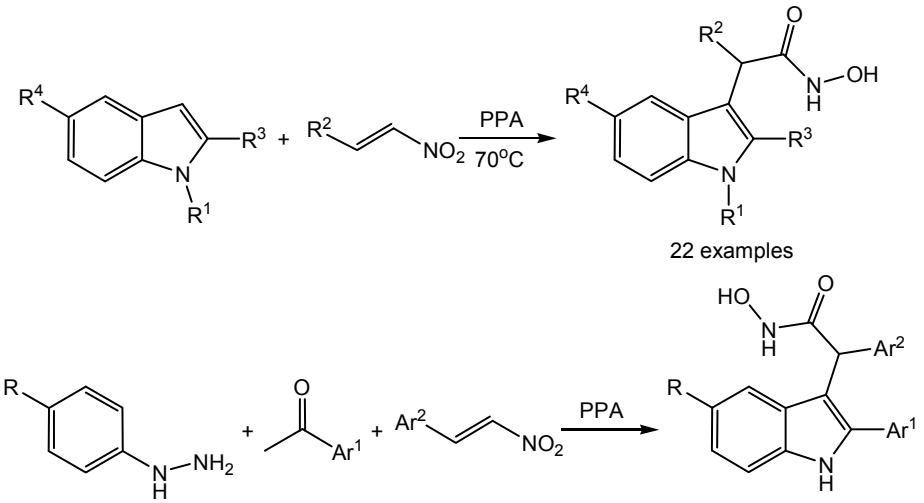


X = N, CH, CMe, CPh.

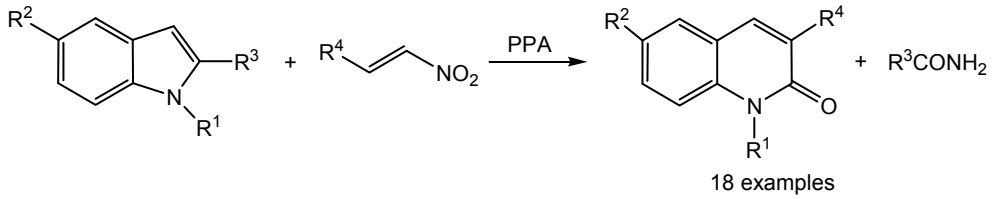
(conjugation) of a number of drugs with β-cyclodextrin and its derivatives aiming at the preparation of compounds, distinguished by the position and amount of fragments conjugated to the cyclodextrin matrix [881–890] (Scheme 19.9).

The possibility of direct esterification of non-protected β-cyclodextrin was studied by pharmacologically important aromatic acids, and also non-steroid antiphlogistic drugs: 2-(4-isobutyl-phenyl)-propionic (active substance ibuprofen), 2-(3-benzoyl-

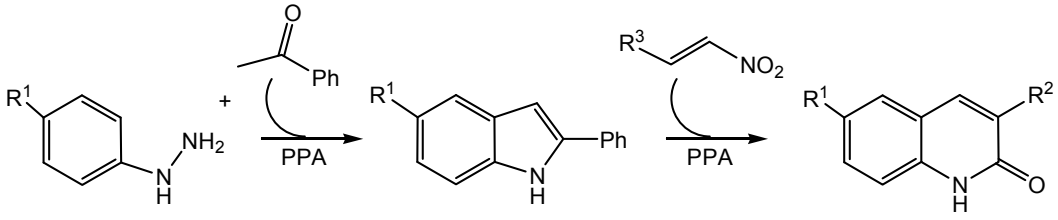
Scheme 18.13.



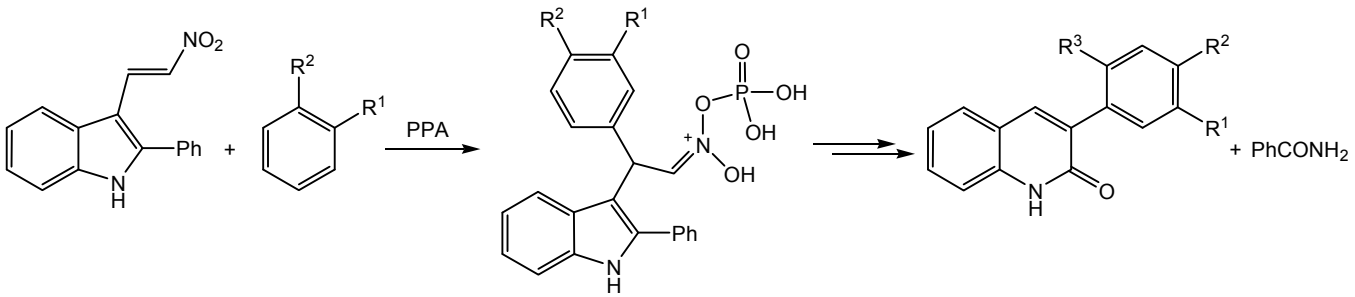
Scheme 18.14.



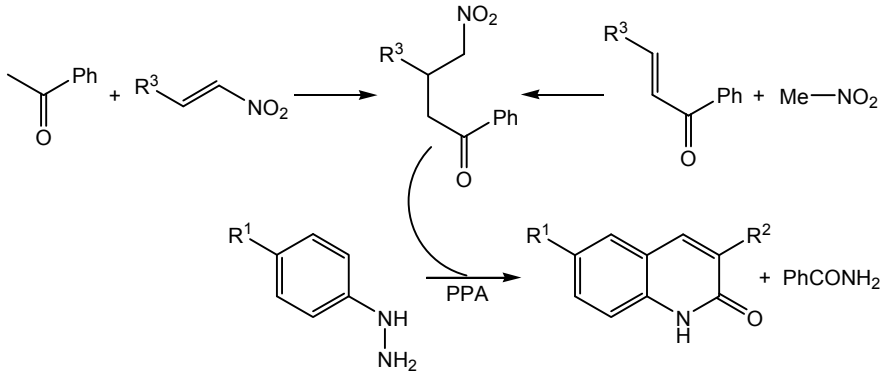
Scheme 18.15.



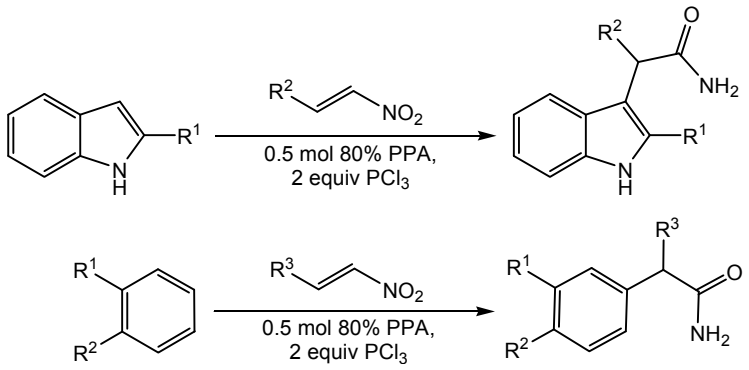
Scheme 18.16.



Scheme 18.17.



Scheme 18.18.



phenyl)propionic (ketoprofen), and 2-(6-methoxy-naphtalen-2-yl)propionic (naproxen) acids.

The possibility was investigated of regiodirected synthesis of monocation derivatives from halo derivatives of β-cyclodextrin and the corresponding amine. The synthesis of haloderivatives was carried out basing on monotosyl derivative of β-cyclodextrin. Another approach consists in application of 6-mono-aldehyde of β-cyclodextrine and imino derivatives obtained from it, for the preparation of cation derivatives of β-cyclodextrin.

The obtained monocation derivatives of β-cyclodextrine are interesting as potential carriers (inclusion compounds and conjugates) of drugs for multidirectional pharmacological investigations. Due to the ability to encapsulate hydrophobic substances β-cyclodextrin found an important application in pharmacology as "container" of medicinal compounds that, besides protection of included "guest" from biodecomposition and raising the solubility in water, in a number of cases provides effective and selective drug delivery to a desired site (targeting site delivery). Practical ways were suggested for the preparation of stable at storage and application inclusion compounds of cyclodextrins with some mono- and dicarboxylic acids of aromatic and aliphatic structure. The effect of cavity size, nature of solvent, character and number of substituents in the cyclodextrin structure was estimated on the possibility to isolate the complexes in an individual state (Scheme 19.10).

20. DEPARTMENT OF CHEMISTRY AT VOLGOGRAD STATE MEDICAL UNIVERSITY

Work of finding new effective methods of synthesis and investigation of biological activity of new compounds containing pharmacophore groups is performed at the department for approximately 20 years. Introducing pharmacophore molecular fragments (amino acids, hydroxybenzoic acids, heterocyclic compounds) into known biologically active structures makes it possible not only to extend their spectrum of pharmacological activity but also to lower their toxicity [891, 892]. The synthesis of such compounds is underlain by accessible initial compounds that presumes its industrial realization.

Previously new synthetic approaches were developed to the preparation of organophosphorus compounds by the reaction of homolytic addition with the application of different peroxides. Chemical properties were investigated of phosphorus-containing compounds synthesized by such reactions: dialkylphosphonalcanols and their acetates, organophosphorus derivatives of uracil, cytosine, and thymine, the extent was established of the influence of phosphoryl group on the activity of other functional groups. For the first time a series was synthesized of new phosphorylated derivatives of neuroactive amino acids (Scheme 20.1), demonstrating cardiovascular activity and exceeding several times unsubstituted amino acids by this kind of activity. Compositions were developed based on functional organophosphorus compounds as fixing and conserving solutions for histologic and anatomic preparations.

Among multiple kinds of activity of derivatives of hydroxybenzoic acids of certain interest are analgetic, pyretic, antitumor, neurotropic, vasodilator, antiviral actions. One of directions of investigations was the modification of esters of 2-hydroxybenzoic (salicylic) acid with dialkylphosphonalcanol (Scheme 20.2) and investigation of the relation structure–activity in a series of synthesized compounds. The introduction of phosphoryl fragment into the structure results in a broadening of the spectrum of pharmacologic properties and lowering of toxicity. Hence, the modification of salicylates with organophosphorus alcohols is an effective path both to increasing their activity and to reducing their toxicity.

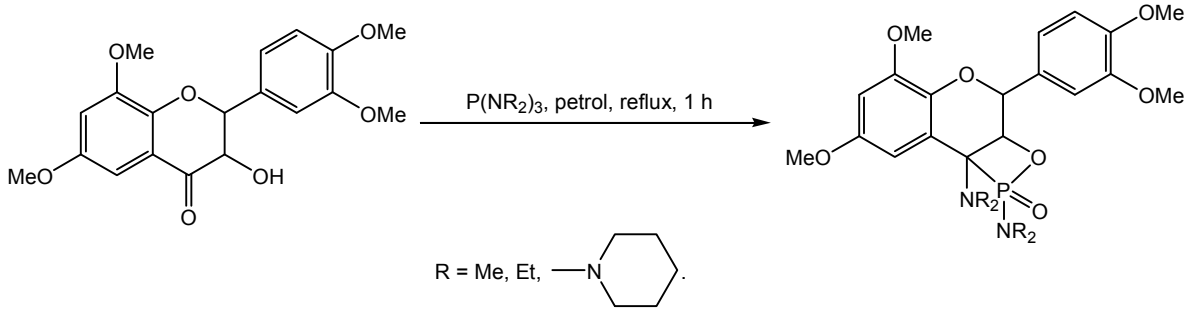
Careful choice of synthesis conditions for the preparation of esters of salicylic and acetylsalicylic acids by etherification with aliphatic, organophosphorus alcohols allowed the improvement of technologically accessible method of their preparation.

The kinetics of alkylation of salicylic acid salts with alkenyl halides (by an example of allyl bromide) was experimentally studied for the first time aiming at determining the optimal conditions of the process. The reaction proceeds by the pseudo-first order (the ratio of metal salicylate to alkyl halide is 1 : 60) (Scheme 20.3) [893].

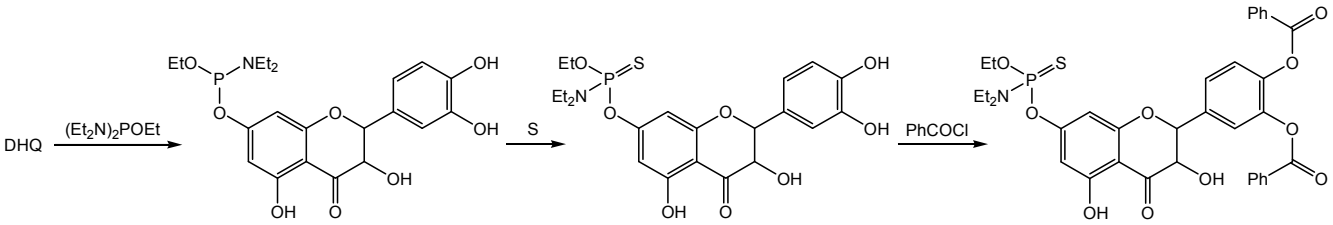
The obtained alkyl salicylates possess a pronounced prolonged antipyretic effect. Investigations of antipyretic activity of new phosphorus-containing salicylates demonstrated that dialkyl-β-(O-salicyloyl)-ethylphosphonates had a noticeable antipyretic effect, and the most significant effect was demonstrated by dimethyl-β-(O-salicyloyl)ethylphosphonate. By harmfulness classification the derivatives of salicylic acid at endogastric administration to mice were classed as low-toxic compounds [894, 895].

Hence the synthesized phosphorus-containing salicylates, and also aliphatic butylsalicylate, allylacetylsalicylate are of considerable interest as technologically accessible potential antipyretic drugs. Their application as antipyretics will allow decreasing the therapeutical dose of widely applied aspirin and

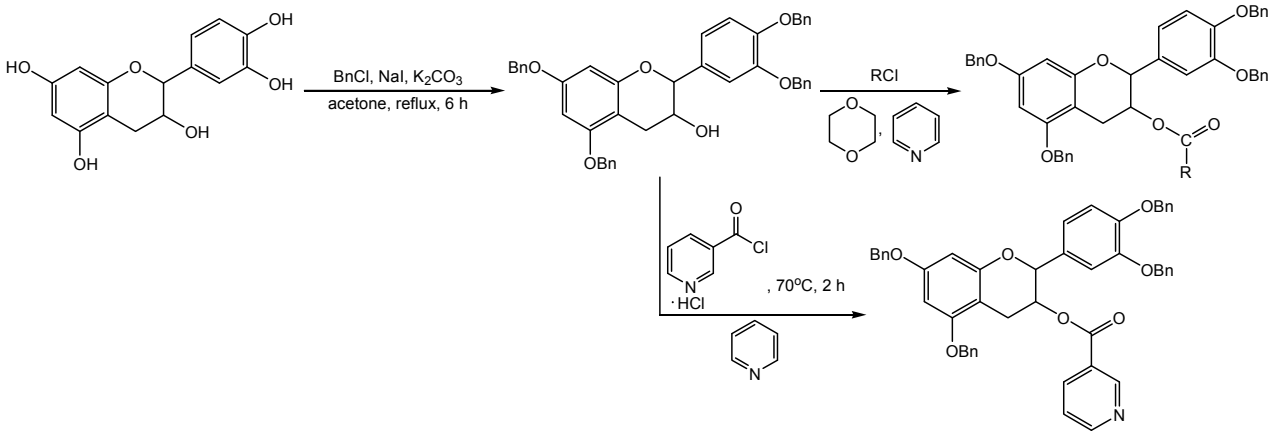
Scheme 19.1.

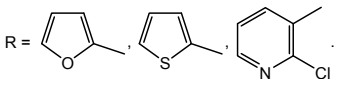


Scheme 19.2.

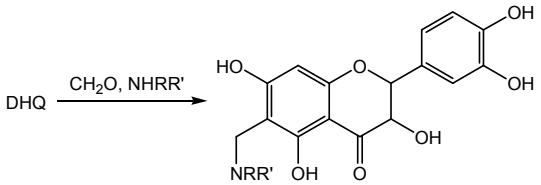


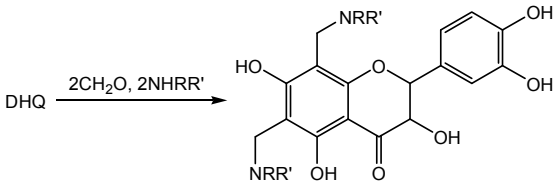
Scheme 19.3.



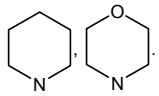


Scheme 19.4.

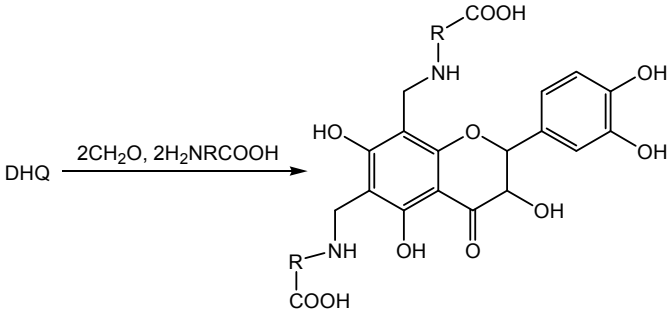




R' = R = Et, *i*-Pr; R = Me, R' = $CH_2C_6H_5$; NRR' =

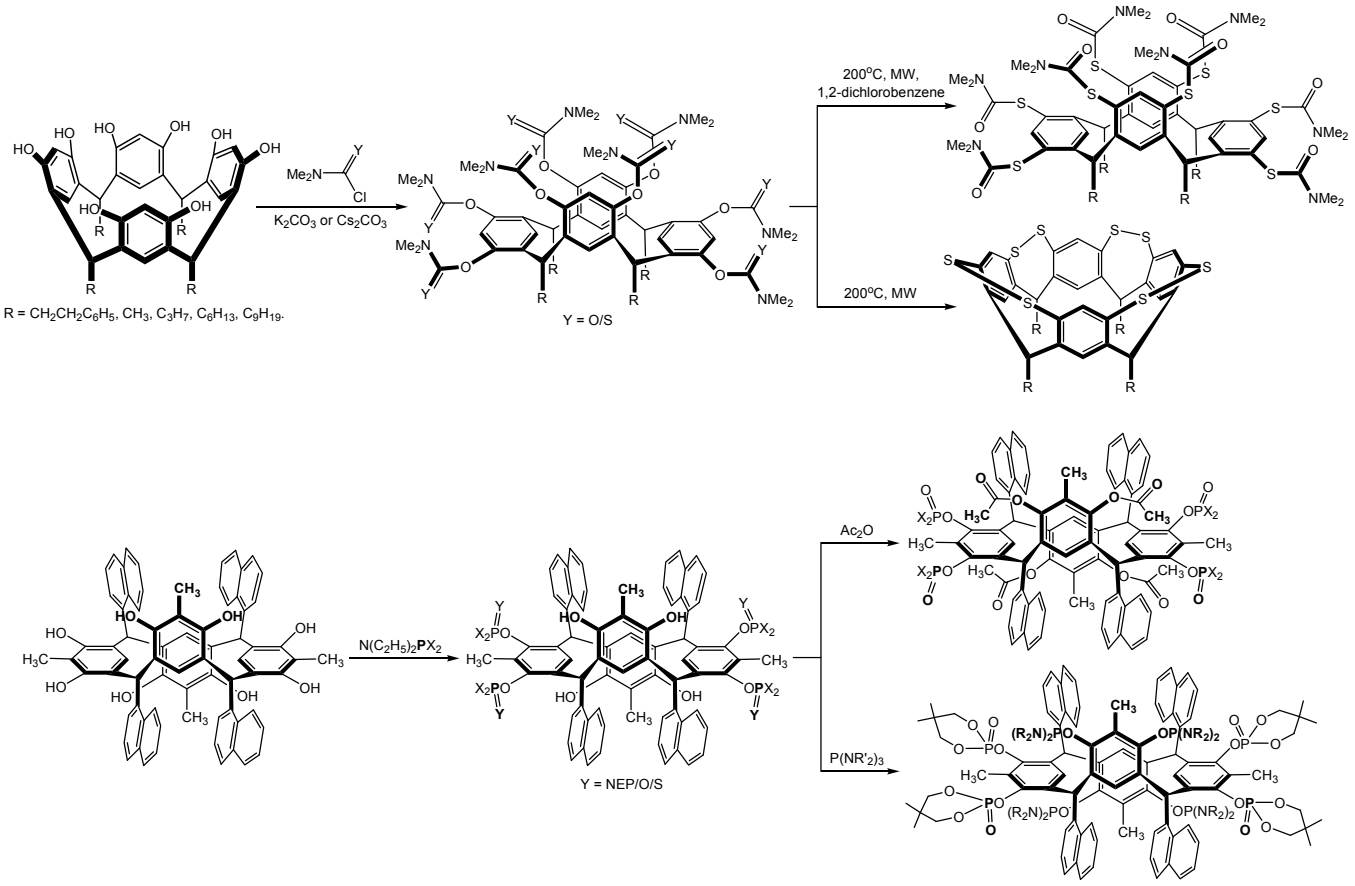


Scheme 19.5.



R = CH_2, $(CH_2)_2$, $(CH_2)_3$, $CH(CH_2)Ph$.

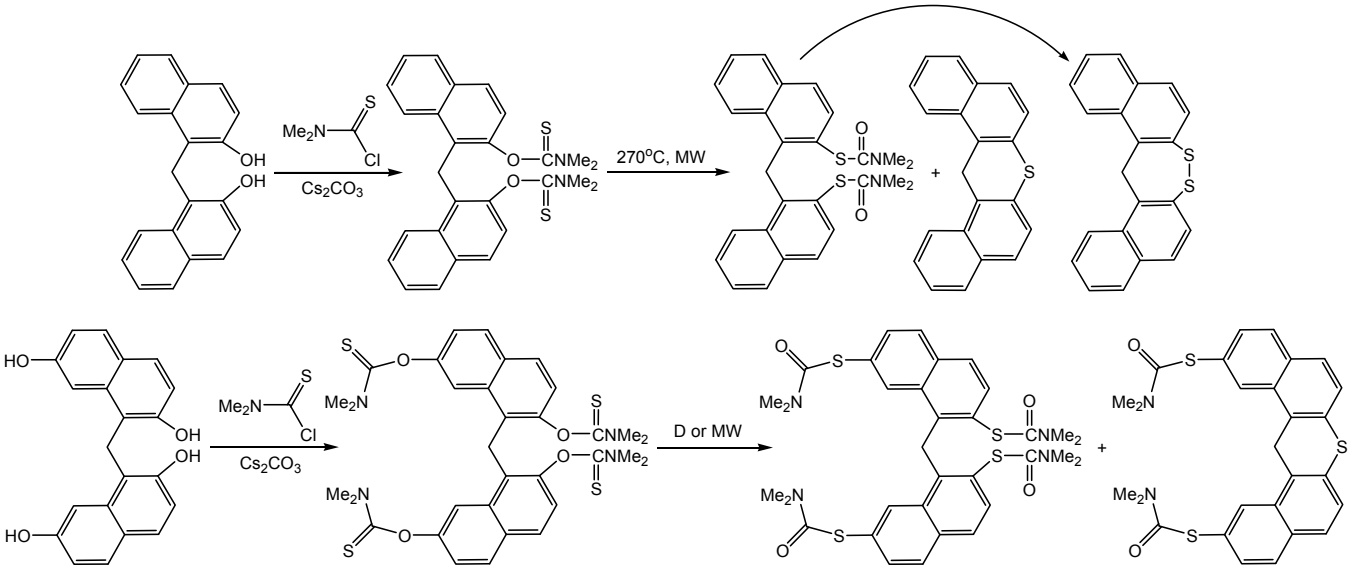
Scheme 19.6.



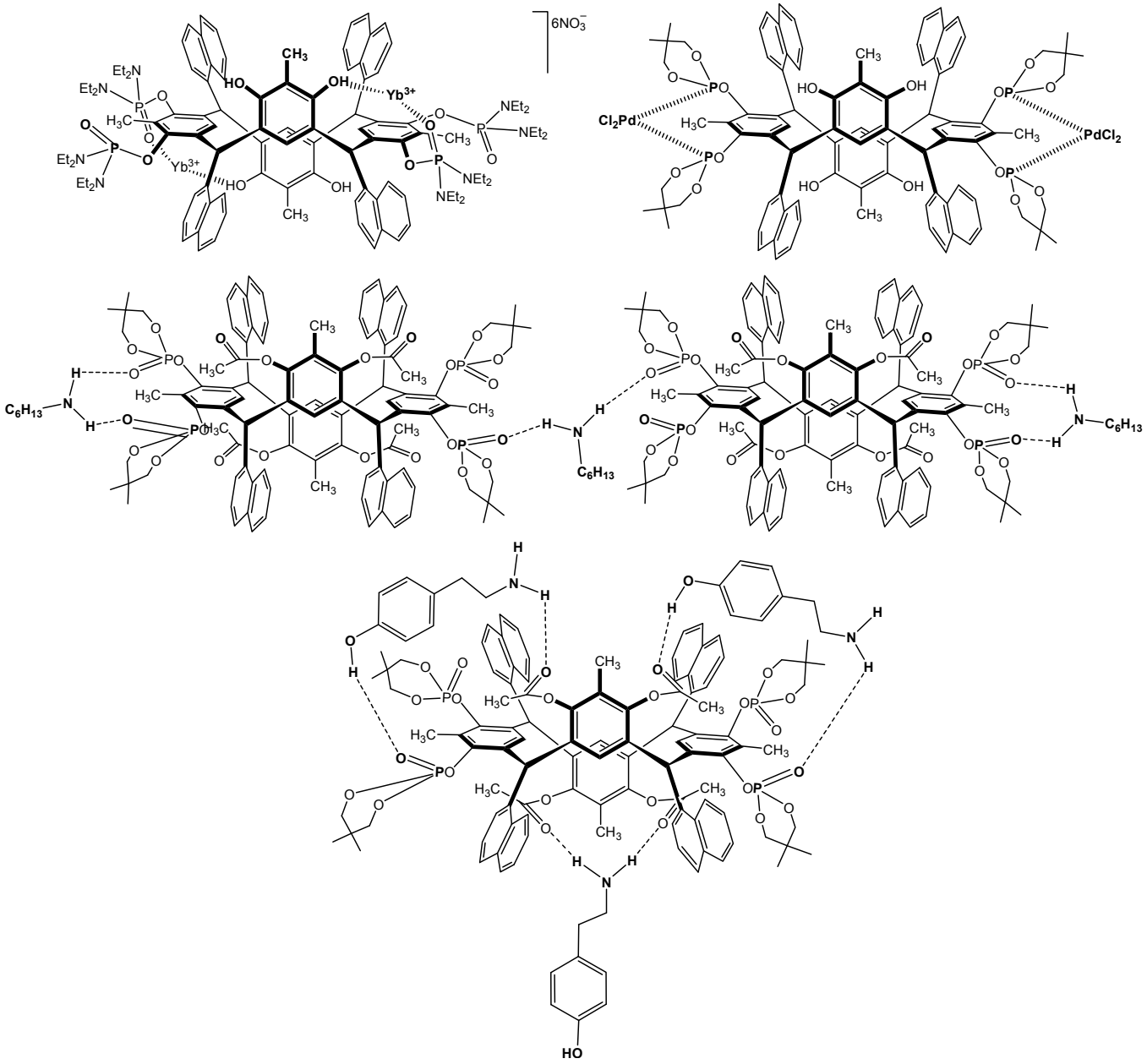
lower the risk of side effects connected with medical application of salicylates [891].

Amides of hydroxybenzoic acids may be obtained by reaction of hydroxybenzoyl chlorides with amines by the method of mixed anhydrides and by carbodiimide method. However a long reaction time (method of mixed anhydrides) and a small yield of the final product (carbodiimide method) call for a search of new and improvement of existing paths of synthesis

Scheme 19.7.



Scheme 19.8.

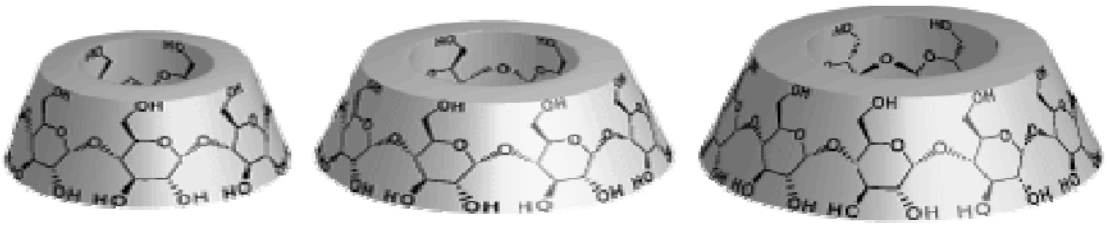


of hydroxybenzoic acids amides. An improved method was suggested for the preparation of hydroxybenzoic acids chlorides [896], distinguished by the use of oxalyl chloride as chlorinating agent and the performance of the process at boiling the reaction mixture at molar ratio acid–oxalylchloride–dimethylformamide 1 : 1.1 : 0.07. The chlorides of hydroxybenzoic acids were obtained in yields up to 91% with a high grade of purity. Further the acylation of amino group in the molecule of amino acid (glycine, γ-aminobutyric acid, β-alanine) was done by Schotten-Baumann reaction in water-alkaline solution and in a mixture water–DMF in the presence of NaOH (Scheme 20.4).

Taking into account the greatest bioacessibility of water soluble salt forms, and also the possible effect of metal cation on biological action we prepared sodium, potassium, and lithium salts of synthesized amides [897].

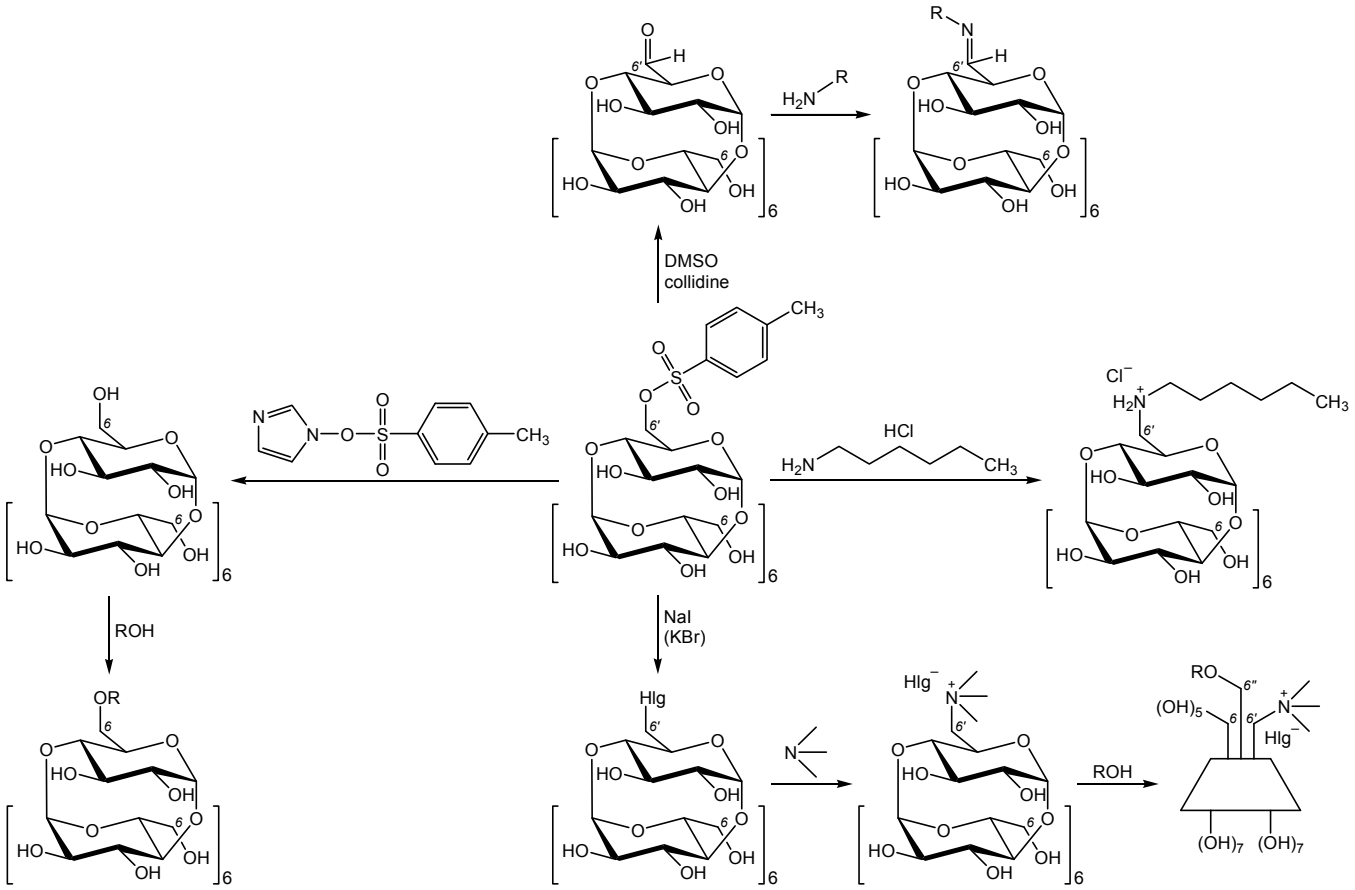
Studied compounds demonstrate psychotropic, tranquilizer, anamnestic, and antidepressant activity. While studying the effect of the metal nature on the

Scheme 19.9.



α-cyclodextrin β-cyclodextrin γ-cyclodextrin

Scheme 19.10.



biologic activity it was discovered that lithium salts of hydroxybenzoic acids derivatives with aminoacids demonstrated higher psychotropic activity compared to sodium salts, and potassium salts possess antihypoxic and antiischemic effect exceeding these of reference preparations [898].

Chlorides of obtained *N*-hydroxybenzoylamino acids were applied to the synthesis of diamides (Scheme 20.5). Synthesis of diamide was realized by modified Schotten-Baumann reaction in pyridine (Eichhorn method).

For broadening the spectrum of biological effect synthesis was realized of amides of hydroxybenzoic acids with heterocyclic compounds: five-membered imidazole (Scheme 20.6) and pyrazole, and also with heterocyclic bases of pyrimidine series, uracil and thymine (Scheme 20.7).

The application of Schotten–Baumann reaction (6 N NaOH) to the preparation of *N*-salicyloylimidazole and *N*-acetylsalicyloylimidazole results in decyclization of imidazole by Bamberger reaction giving the final reaction products in over 70% yield (Scheme 20.6) [899]. Several of newly obtained imidazole derivatives demonstrated high nootropic, cerebroprotective, and analgesic activity.

N^1-derivatives of uracil and thymine are obtained by acylation of the corresponding nitrogen bases with acyl chloride at the ratio 1 : 1, N^1,N^3-derivatives, at the 1 : 2 in pyridine at room temperature. N^1,N^3-Substituted pyrimidine bases are unstable in alkaline medium: at treating with 0.25 M KOH solution N^3-derivatives are formed (Scheme 20.7).

Screening of biologic activity of new derivatives of *N*-hydroxybenzoyluracil and -thymine demonstrated that some of them possess ability to break crosslinks of glycosylated proteins [900].

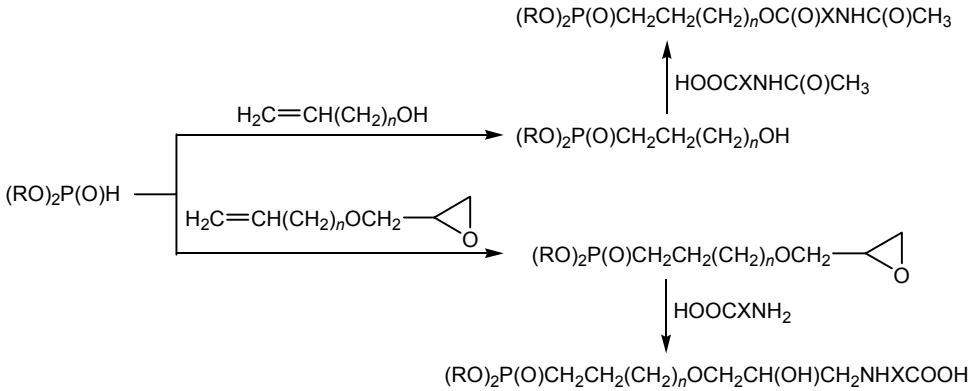
21. DEPARTMENT OF ORGANIC CHEMISTRY AT VORONEZH STATE UNIVERSITY

Research directions at the department (**head of department Professor Kh.S. Shikhaliev**) are fairly versatile, yet the center of fundamental studies is the development of highly selective synthesis procedures and investigation of functional derivatives of mono- and polynuclear azaheterocycles and their analogs possessing a wide spectrum of practically useful characteristics.In this survey we report on results of the department work in this direction obtained within the last decade.

In the molecular design of versatile heterocyclic matrices both linearly bound and fused maleic acid derivatives are extensively utilized. In reactions with various 1,4-binucleophiles *N*-arylmaleimides play the role of C^3-electrophile leading to the formation of six-membered heterocyclic systems: piperidinones, hydrogenated thiazinones, oxazinones. At the same time with 1,3-binucleophiles the behavior of arylmaleimides is not so unambiguous, and they may act as both C^3-electrophile and C^4-electrophile forming five-membered heterocyclic systems (pyrrolidines, imidazolinones, thiazolinones) and six-memebered heterocycles respectively. Often a mixture is formed of five- and six-membered heterosystems. Substituted imidazolinones and thiazolinones exhibit a wide range of biologic activity, and at the same time they have in the structure several reactive functional groups and are interesting as substrates for the preparation of new heterocyclic compounds. In this connection recyclization was carried out of *N*-arylmaleimides under the action of *N*,*N*- and *N*,*S*-polynucleophiles like *N*-carboximidamide, *N*-substituted biguanides, and amidinothiourea. The reactions proceed regioselectively even with polynucleophilic biguanides and amidinothiourea, and the latter acts as S^1/N^3-binucleophile. As a result 4-oxo-4,5-dihydro-1*H*-imidazoles (X = NH) and 4-oxo-4,5-dihydro-1,3-thiazoles substituted in the positions *2* and *5* were obtained (X = S) (Scheme 21.1) [901, 902].

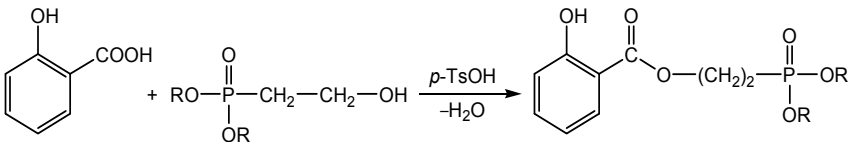
The recyclization reactions were also performed with maleic anhydride. The reaction of aminopyrazoles

Scheme 20.1.



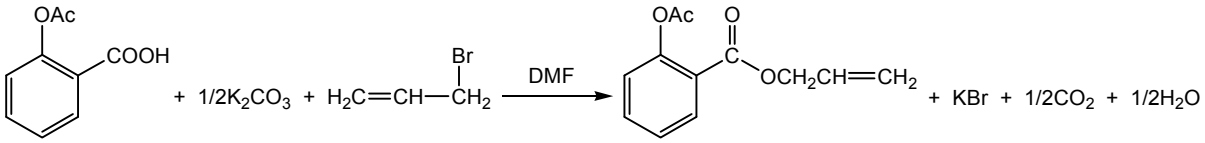
X = glycine, β-alanine, γ-aminobutyric acid, L-leucine; n = 0, 1, 2.

Scheme 20.2.

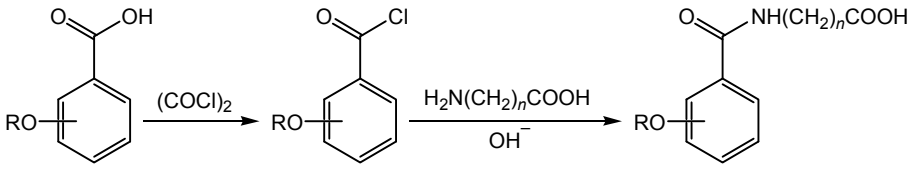


RO = CH_3O, C_2H_5O, $(CH_3)_2CHO$.

Scheme 20.3.



Scheme 20.4.



n = 1, 2, 3.

with maleic anhydride proceeds in several stages including aminopyrazole acylation followed by cyclization leading instead of expected substituted imides to the formation of fused systems, 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazoles that via a rearrangement transform in pyrazolopyrimidines [903]. Exclusion was found at the condensation of aminopyrazoles with an electron-acceptor trifluoromethyl substituent: here an imide was obtained (Scheme 21.2).

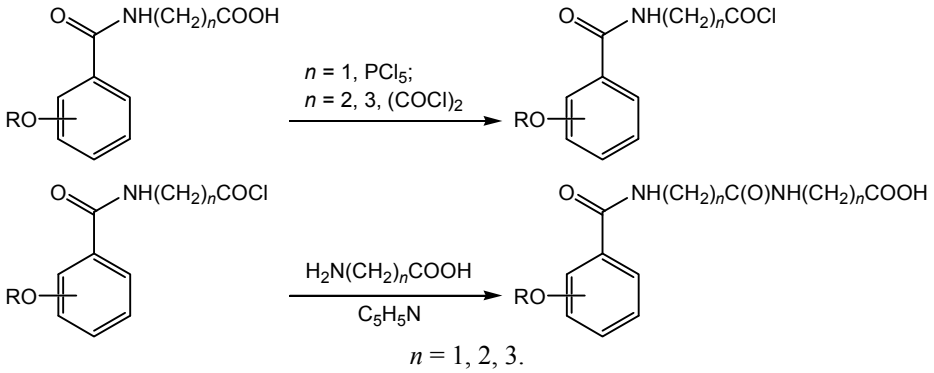
The reaction of *N*-arylarylmaleimides with 1,2-diamino-4-phenylimidazole that may act as *N*,*N*- and *C*,*N*-binucleophile proceeds regioselectively: It starts with the addition of diaminoimidazole to the activated bond of maleimide owing to the nucleophilic carbon atom of the imidazole ring, further the succinimide fragment of the addition product undergoes recyclization under the effect of the amino group in the position *1* of the imidazole ring with the closure of a six-membered ring and the formation of tetrahydroimidazo[1,5-*b*]pyridazin-2-ones (Scheme 21.3) [904].

From the viewpoint of creation of combinatorial libraries for productive biologic screening the synthesis of new heterocyclic compounds by multicomponent procedures is considered nowadays as the most promising. The additional advantage of the three component syntheses is the reduced number of stages and as a result the increased yield of target products and cheaper technology of the process.

For the preparation of imidazopyridazines the use of polynucleophilic 1,2-diaminoimidazole in multicomponent condensations is very attractive. The reaction of diaminoimidazole with methylene-active compounds like acetylacetone (R = CH_3) and ethyl acetoacetate (R = OC_2H_5), and also with some 1,3-cyclohexanediones in combination with triethyl orthoformate or dimethylformamide dimethyacetal afforded new substituted imidazo[1,5-*b*]pyridazines and fused imidazo[1,5-*b*]pyridazines respectively (Scheme 21.4) [905].

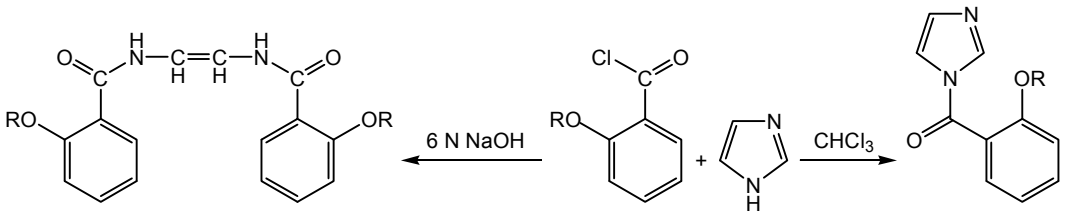
Moreover, a four component condensation was performed of 1,2-diaminoimidazoles with primary amines and excess formaldehyde that resulted in the formation of 5-phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*]-[1,2,4]-triazin-7-amines whose acylation at the free amino group provided a series of derivatives (Scheme 21.5) [906].

Scheme 20.5.

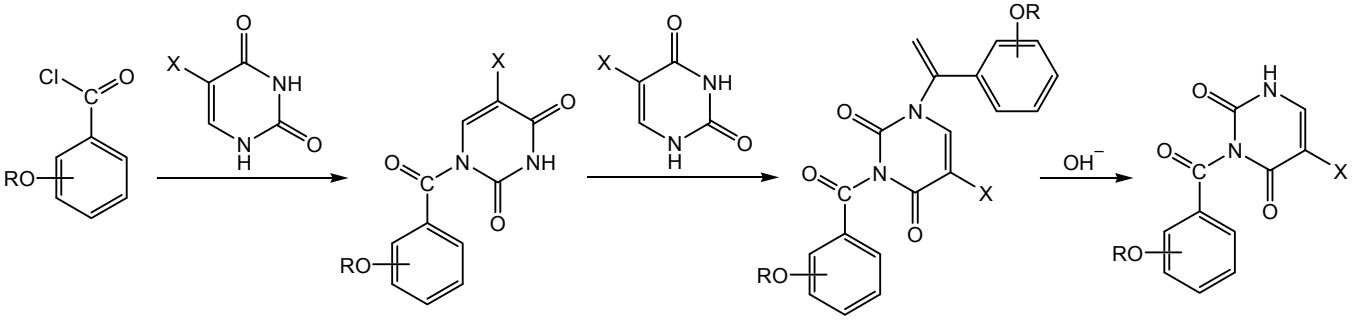


n = 1, 2, 3.

Scheme 20.6.



Scheme 20.7.



Similar condensation of aminobenzimidazoles with formaldehyde and primary amines led to the formation of substituted 1,2,3,4-tetrahydro[1,3,5]triazino[1,2-*a*]-benzimidazoles; in case of unsubstituted aminobenzimidazole side products were formed by Mannich condensation via reaction of appropriate compounds with equimolar amount of formaldehyde (Scheme 21.6) [907].

One more approach to building up the fused diazolotriazine derivatives consisted in [4+2]-fusion of 1,2,4-triazine to a pyrazole ring utilizing salts of pyrazole-3(5)-diazonium (in some cases of 3-diazopyrazoles) as initial substrates [908].

The choice of this procedure is due firstly to the preparative and commercial availability of initial reagents, secondly, to a large variability of substituents both in the pyrazole and in *as*-triazine ring providing an opportunity to obtain large libraries of new substances, and triply, to the possibility to use the derivaties of bicyclic systems as semiproducts in the synthesis of more complex molecules.

As a synthetic realization of this block-synthon approach the reaction should be mentioned of pyrazole-3(5)-diazonium salts with aliphatic CH-acids that afforded a series of 3,4,7,8-substituted pyrazolo[5,1-*c*]-[1,2,4]-triazines. The opportunity to vary substituents in the positions *3* and *4* of the triazine ring was achieved owing to the application as the azo components of 1,3-diketones, β-ketoesters [909], acetonedicarboxylic esters [910], β-ketosulfones [911], malonic acid derivatives (Scheme 21.7).

The developed method of building up fused pyrazolo[5,1-*c*][1,2,4]triazines proceeding from pyrazole-3(5)-diazonium and CH-active heterocycles opens wide opportunities for the synthesis of new polycyclic ensembles. In such reactions *N*-, *O*-, *S*-containing five- and six-membered (also fused) heterocyclic azo components were brought, like hydantoin, rhodamine, derivatives of pyrazolone, pyridine-2,4-dione, pyran-2,4-dione, pyrimidine-2,4-dione, barbituric and thiobarbituric acids [912], 4-hydroxycoumarin, homophthalic anhydride [913].

At the presence of diverse functional groups in pyrazolo[5,1-*c*][1,2,4]triazines an opportunity appears of building on their basis of inaccessible fused and linearly linked polyheterocyclic systems. In the search for potential drugs tricyclic azoloazines attract much interest. Attractive substrates for designing this kind systems are pyrazolo[5,1-*c*][1,2,4]triazines containing reactive groups in the positions *3* and *4*. Their modification can be purposefully carried out using *N*,*N*-dimethylformamide dimethylacetal (DMF DMA) which on the one hand is a source of electrophilic one-carbon synthon, and on the other hand is a nucleophilic base. CH_3 and NH_2 groups in the position *4* of pyrazolo[5,1-*c*][1,2,4]triazines are able to react with the solvent: at a short heating in DMF the corresponding enamines and formamidines are formed. The latter operate as 1,5-bielectrophilic agents in heterocyclization reactions resulting in fused systems [914]. The reaction of *ortho*-(dimethylaminovinyl)-ethoxycarbonylpyrazolo-*as*-triazines with hydrazine

leads to 1,3-exocyclic CC exchange involving the atoms of the side chain, proceeding according ANRORC-mechanism and resulting in the formation of the linearly linked system [915].

A convenient method was developed for the synthesis of thiazolylpyrazolo[5,1-*c*][1,2,4]triazines underlain by a reaction of aminopyrazolo[5,1-*c*][1,2,4]-triazine-3-carbothioamides with phenacyl bromides at short heating in DMF (Scheme 21.8) [916].

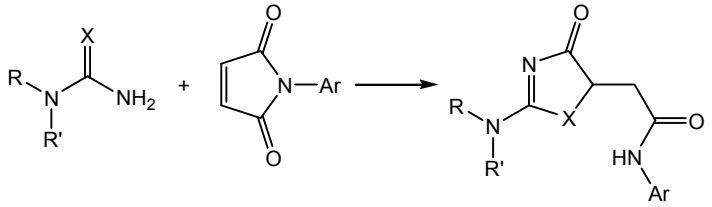
The most interesting systems among fused azaheterocycles are the quinolone derivatives. The hydroquinoline fragment is a structural moiety present in versatile alkaloids and pharmaceuticals with a wide range of biologic activity. One of the strategic approaches to designing new linearly linked or fused heterocyclic systems is the preparation of formyl derivatives of 2,2,4-trimethylhydroquinolines and their further functionalization. Under the action of Vilsmeier-Haack complex the 7-substituted *N*-alkyl-2,2,4-trimethylhydroquinolines reacted at the most electron-excessive position *6* of the hydroquinoline ring, same as the 8-substituted substances, and they were converted in *N*-alkyl-6-formyl-2,2,4-trimethyl-hydroquinolines, and the hydroquinolines containing a substituent in the position *6* formed 8-formyl derivatives (Scheme 21.9) [917].

In Willgerodt–Kindler reaction 6-formyl-2,2,4-trimethyl-1,2-dihydroquinolines depending on the quantity of sulfur participating in the reaction form along with the linearly connected 6-hydroquinol-ylthiocarboxamides thioxocarbamides of the class of 4,5-dihydro-4,4-dimethyl-1*H*-1,2-dithiolo[3,4-*c*]qui-noline-1-thiones (Scheme 21.10) [918].

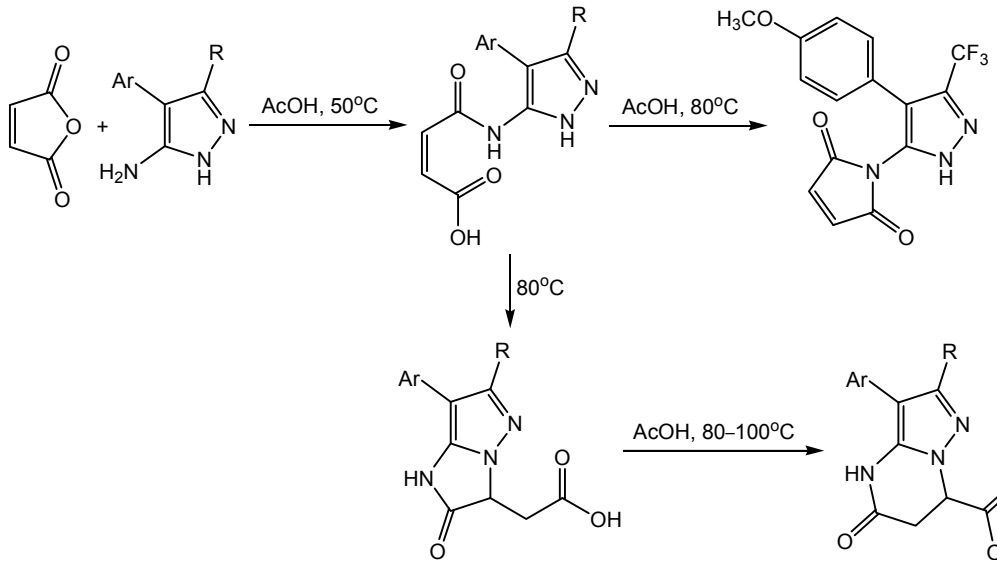
The next approach to hydroquinolines functionalize-tion consists in the fusion of the pyrroledione fragment using the modified Stolle procedure. The reaction of 2,2,4-trimethyl-1,2-dihydroquinolines and their hydrogenated analogs with oxalyl chloride afforded substituted pyrrolo[3,2,1-*ij*]quinoline-1,2-diones (Scheme 21.11) [919–921].

The selective activity of the β-carbonyl (with respect to nitrogen) group in the obtained pyrrole-1,2-diones made it possible to bring them into various condensations with a number of 1,2- and 1,3-dinucleophiles (*N*,*N*′-dibenzyl-1,2-ethylenediamine, ethylene glycol, *o*-aminothiophenol, some tryptamines, 2-aminobenzyl alcohol, anthranylamide), in three

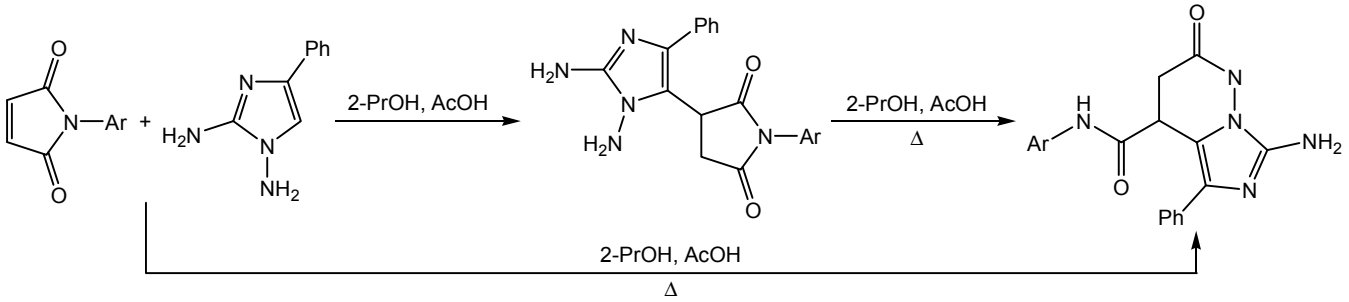
Scheme 21.1.



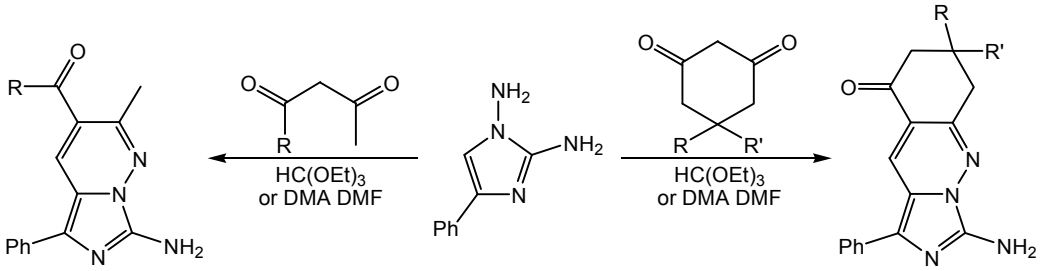
Scheme 21.2.



Scheme 21.3.



Scheme 21.4.



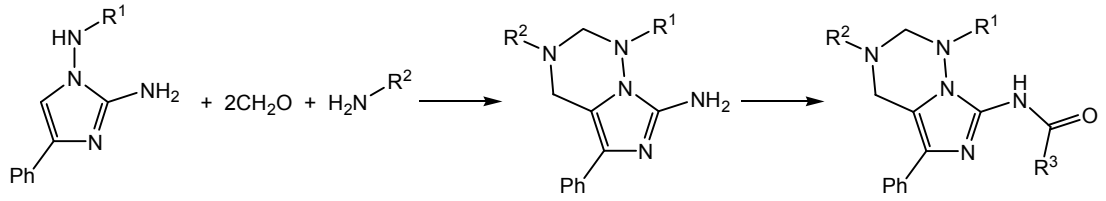
component cyclocondensations with malononitrile and various methylene-active carbonyl components (ethyl acetoacetate, some cyclic 1,3-dicarbonyl compounds, resorcinol, and diverse methylene-active heterocycles containing a carbonyl group), as well as in a three component reaction with arylamines and mercaptoacetic acid. Spiro derivatives were prepared where the pyrroloquinoline fragment was spiro attached to five-membered (X = Y = O, NCH_2Ph; X = S; Y = NR'') and six-membered (X = C, O, NR''; Y = NR'') heterocycles and to versatile 2-aminopyrans (Scheme 21.12) [920, 921].

One more way to functionalize the hydroquinoline ring consists in the introduction of a carboxy group. At the oxidation of pyrrolo[3,2,1-*ij*]quinoline-1,2-diones with hydrogen peroxide in alkaline medium the pyrroledione fragment suffers opening and subsequent decarboxylation. As a result 2,2,4-trimethylhydroquinoline-8-carboxylic acids are formed [922]. The obtained quinolinecarboxylic acids are not only the structural analogs of a natural antibiotic *Helquinoline* [(2*R*,4*S*)-4-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline-8-carboxylic acid], but also good building blocks for the synthesis of new hydroquinoline derivatives (Scheme 21.13).

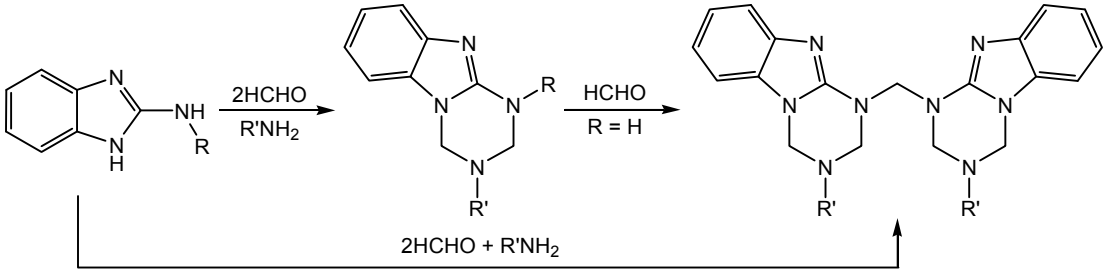
Apart from quinolone derivatives with partially hydrogenated heterocycle also fused 5,6,7,8-tetrahydroquinolines are of interest. A new three component reaction of methyl(3-oxopiperazin-2-ylidene)acetate with aromatic aldehydes and cyclohexane-1,3-diones furnished derivatives of polyhydrogenated heterocyclic system of 2,3,4,6,7,8,9,10-octahydropyrazino[1,2-*a*]quinoline. The sequence of the reactions cascade forming the multicomponent process (condensation of 1,3-diketones with aldehydes "*C*-nucleophilic addition of the heterocyclic enaminone" intramolecular heterocyclization) was confirmed by the HPLC-MS method [923]. This approach may be used in the synthesis of the other fused heterocyclic compounds containing a piperazine fragment (Scheme 21.14).

One more *one-pot* approach to the synthesis of tricyclic piperazine derivatives was developed: The

Scheme 21.5.



Scheme 21.6.



reaction of 1,3-dipolar cycloaddition of *N*-arylmaleimides to azomethine ylides obtained at the action of aromatic aldehydes on alkyl(3-oxopiperazin-2-yl)acetates led to the formation of a new heterocyclic system, decahydro-3b*H*-pyrrolo[3',4':3,4]pyrrolo[1,2-*a*]pyrazine (Scheme 21.15) [924].

An efficient means of attaining chemical diversity is the alkylation of derivatives of six-membered azaheterocycles fused with carbo- and heterocycles, and also their analogs. In the presence of *N*- and *S*-alkylation centers the latter are preferable. Alkylation occurs highly hemoselectively exclusively at S atom in thiol form with substituted in the position *3* (R = Alk, Ar) 2-thioxopyrimidin-4-ones (X = NH, Y = S) leading to the formation of thioalkyl derivatives (Scheme 21.16) [925, 926].

Alkylation of unsubstituted 2-thioxothiazin-4-ones (R = H, X = Y = S) proceeds less selectively. In this case under the same conditions a mixture is formed of the products of *S*- and *N*-alkylation with the sulfur derivative prevailing. Yet in milder basic conditions (using trimethylamine instead of sodium methylate) a selective S-alkylation succeeded [927]. In the presence of the single *N*-alkylation site the corresponding alkyl derivatives form in good yields from benzothiazine-dione (R = H, X = Y = O) [927], substituted quinazolinediones (R = Alk, X = NH, Y = O) [928], and thienopyrimidinediones (R = Alk, X = NH, Y = O) (Scheme 21.17) [925].

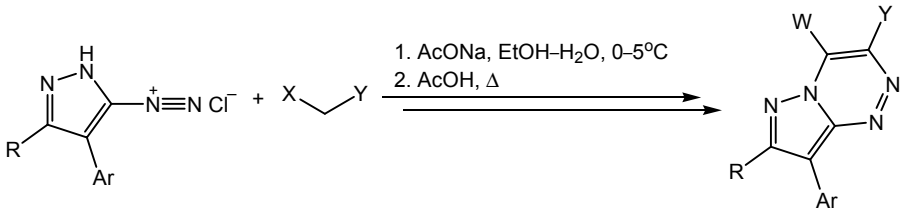
In the presence of a secondary amino group in the fused fragment the alkylation of 5*H*-pyrimido[5,4-*b*]-indoles (R = Ar, X = NH, Y = O) with equimolar quantity of alkyl halide provides a mixture of mono- and dialkyl derivatives and the initial substrate. At the use of 4-fold excess of alkyl halide the corresponding dialkyl derivatives were obtained [926]. In the case of a tautomeric form in compounds (R = H, X = S, Y = NAr) with an endocyclic double bond a mixture of alkylated products was obtained and only repeated recrystallization made it possible to isolate a pure regioisomer [927].

In some cases we succeeded to attain regioselectivity even in the presence of tautomerism. For instance, 4,6-dimethylpyrimidin-2-ylcyanamide was alkylated exclusively at the exocyclic nitrogen atom whereas *N*-(puridin-2-yl)cyanamide gave alkylation products at the endocyclic nitrogen atom (Scheme 21.18) [929].

With substituted dihydropyrimidin-2-ylcyanamides according to the data of quantum-chemical calculations the probability to be involved in alkylation for nitrogen atoms in the positions *1* and *3* is practically the same therefore at the treatment of their sodium salts with excess benzyl chloride dialkyl derivatives are formed (Scheme 21.19) [930].

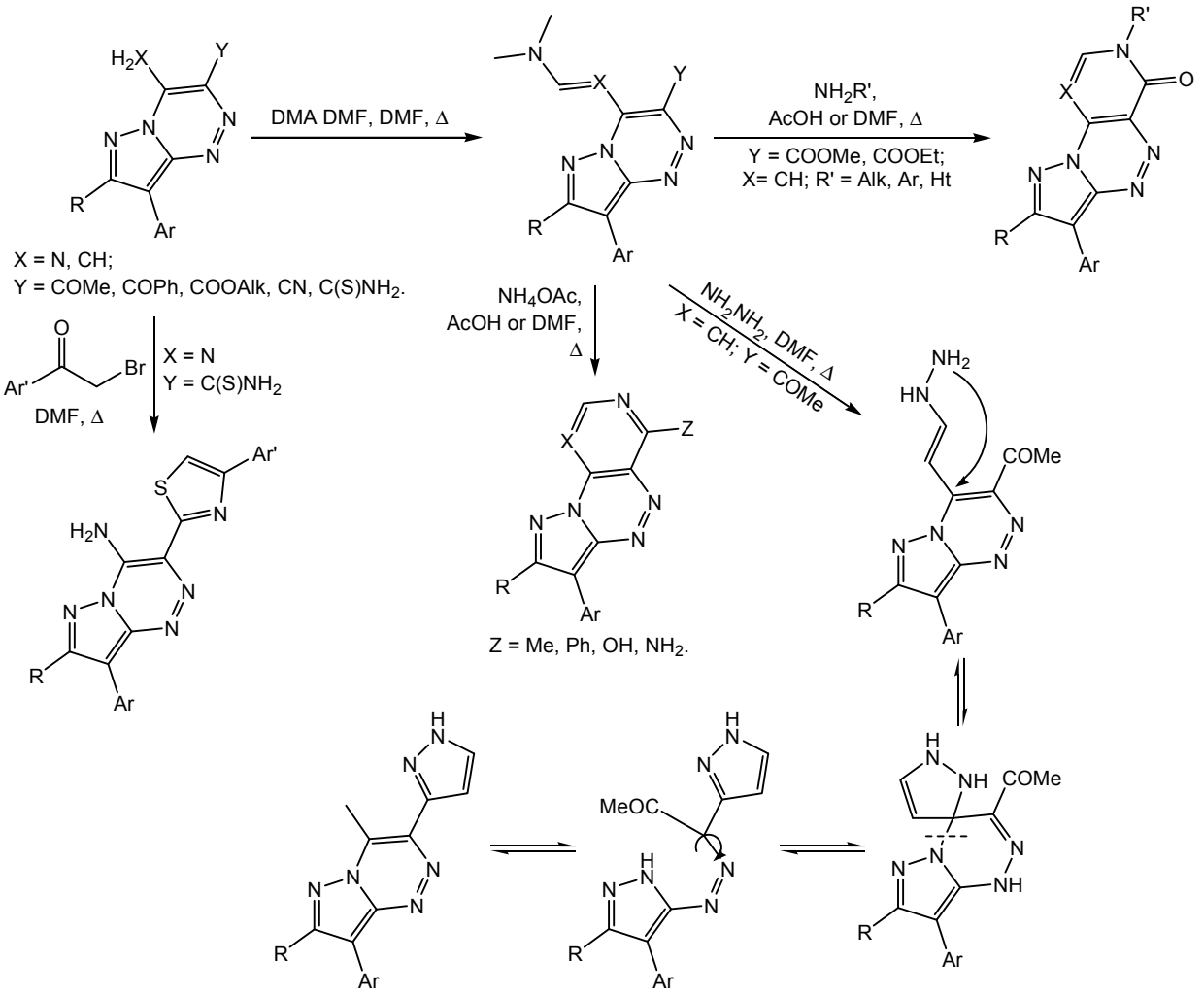
Therefore in the last decade at the department of organic chemistry new types of cascade reactions were developed including one-pot combinations of 2–4 processes, in some cases in multicomponent versions. Besides much attention was paid to the study of rearrangements of nitrogen heterocyclic compounds,

Scheme 21.7.



X = C(O)Me, C(O)Ph, CN, C(O)CH_2Cl; Y = C(O)Me, C(O)Ph, CN, COOMe, COOEt, C(S)NH_2, Ms, Tos;
W = Me, Ph, NH_2, CH_2Cl.

Scheme 21.8.



and of reaction mechanisms, in particular, involving the quantum-chemical calculations of the structure and properties of substances.

22. DEPARTMENT OF ORGANIC CHEMISTRY AND TECHNOLOGY OF ORGANIC COMPOUNDS AT RESHETNEV SIBERIAN STATE UNIVERSITY OF SCIENCE AND TECHNOLOGY

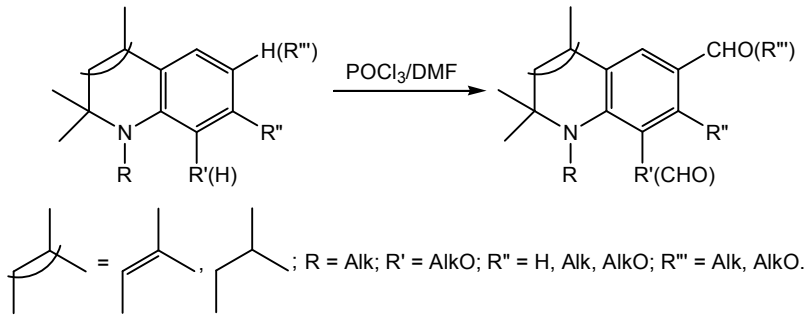
Since 1964 at the department of organic chemistry of the Siberian Technologic Institute (now Reshetnev Siberian State University of Science and Technology, **head of department Professor G.A. Suboch**) the main research direction was the study of synthesis methods and properties of aromatic nitroso compounds.

Since 1976 a method was under development underlain by the cyclocondensation of isonitroso-β-dicarbonyl compounds with ketones and enamines (Scheme 22.1).

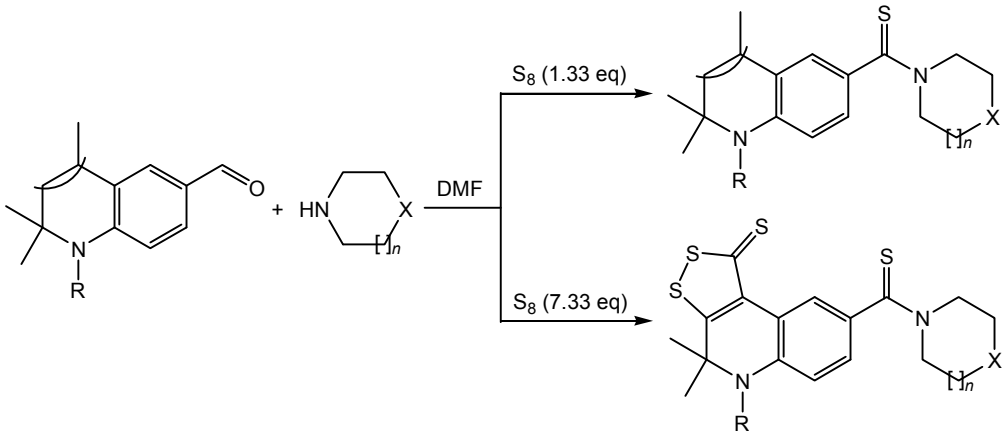
The advanced method essentially extends the preparative opportunities of the synthesis of nitrosophenols, nitrosoanilins, nitrosoheterocycles. We succeeded to synthesize whole series of previously unknown nitrosoarenes with alkyl, aryl, and heteryl substituents, and in its turn it opened wide opportunities for the preparation from nitrosocompounds of new products of reduction, diazotization, alkylation, acylation, etc. Within the last decade the developed method of cycloaromatization was further elaborated. For instance, alkyl esters of acetonedicarboxylic acid were brought into the reaction with isonitroso-β-diketones (Scheme 22.2) [931–933].

As a result a number of persubstituted *para*-nitrosophenols were obtained possessing unique properties. Unlike all known nitrosophenols they are dimerized in the solid state by the type of azo dioxides as has been confirmed by X-ray diffraction analysis. In

Scheme 21.9.



Scheme 21.10.



solution equilibrium is established between the dimeric and monomeric nitrosophenol (Scheme 22.3).

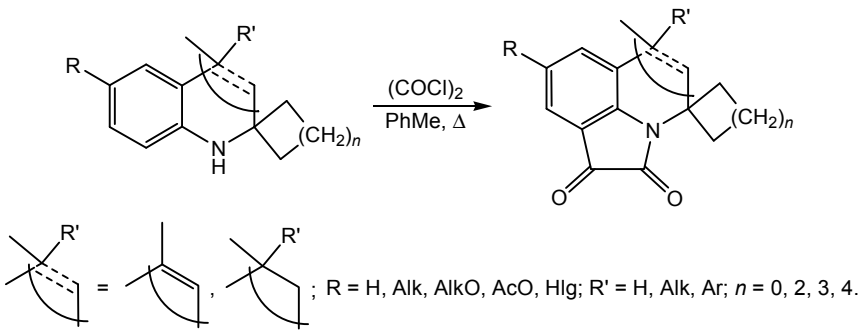
Two nucleophilic sites are present in the nitrosophenolate ion: oxygen atoms of hydroxyl and nitroso groups. The alkylation occurs exclusively at the oxygen atom of the nitroso group with the formation of alkyl ethers of *para*-benzoquinone monooximes [934]. Acylation of persubstituted nitrosophenols proceeds analogously [935] (Scheme 22.4).

Cyclocondensation of isonitroso-β-diketohes with acetonedicarboxylic acid arylamides was successfully carried out (Scheme 22.5). As a result we obtained a series of completely substituted nitrosophenols with arylamide groups in the ring [936]. These substances exist in two tautomeric forms, and in DMSO the equilibrium is totally shifted to quinone oxime tautomer.

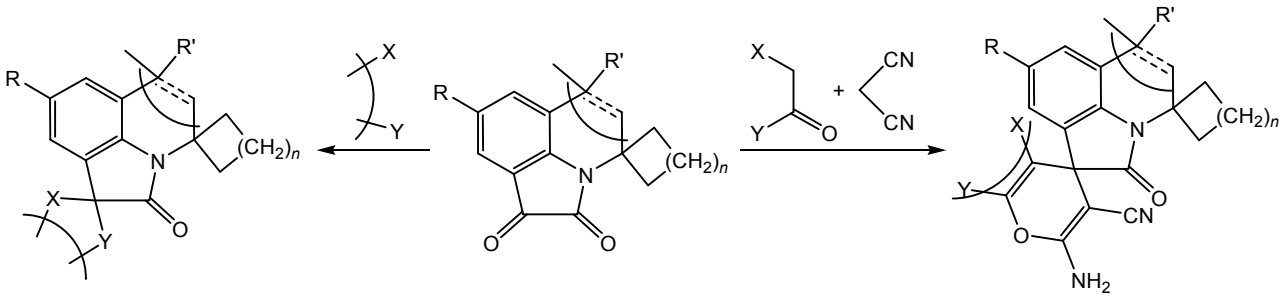
The reduction of hexa-substituted nitrosophenols with hydrogen (Pd/C catalyst) makes it possible to obtain the corresponding amines [937] (Scheme 22.6). Nitrosophenols with arylamide groups are reduced on the same catalyst with hydrazine hydrate [938].

The obtained *para*-aminophenol with R = CH_3 exhibited a significant biologic activity: the antiphlogistic and analgesic action was demonstrated on

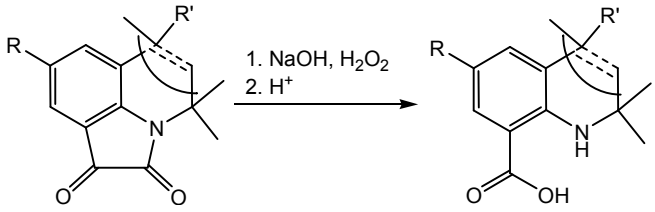
Scheme 21.11.



Scheme 21.12.



Scheme 21.13.



animals [939]. Chloroacetylation of amine with R = C_2H_5 followed by diethylamination provided in a high yield a compound with a strong antiarrhythmic action. This compound was first prepared in Germany but our synthetic route contained fewer stages and provided 4.5 times higher yield [940]. The obtained hexa-substituted *para*-aminophenols with arylamide groups showed a high biologic activity: bactericidal action *in vitro* with respect to *Staphylococcus aureus* stable to antibiotics [941]. In the test on animals *in vivo* the compounds demonstrated a powerful antiarrhythmic and antihypertensive action [942].

The cycloaromatization processes under study are not limited to the synthesis of nitrosocompounds of the benzene series. The investigation of heterocyclizations of isonitroso-β-dicarbonyl compounds made it possible to prepare previously unknown naphthyl-substituted nitrosopyrazoles (Scheme 22.7) [943, 944]. At the reduction of naphthyl-substituted alkylnitrosopyrazoles with hydrazine hydrate on the Pd/C new aminopyrazoles were isolated in a good yield [945, 946].

We recently demonstrated that in the cyclocondensation reactions may be involved not only the nitroso diketones, but also derivatives of isonitrosketoaldehydes (Scheme 22.8) [947].

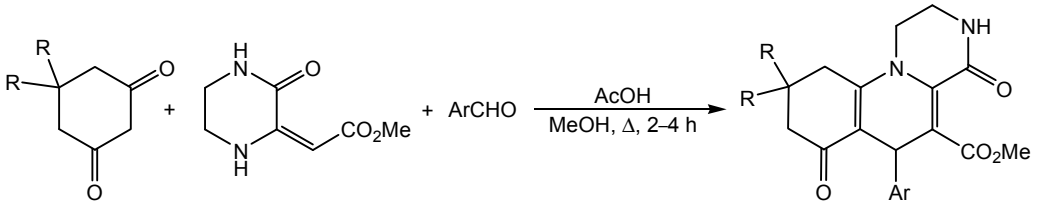
The attempt to use in heterocyclizations ketoaldehyde dimethylacetal as a more stable compound proved to be successful [948]. The introduction of a hydroxyimine group in the *meso*-position of 3-oxobutanal was performed after removing the dimethylacetal protection. The isonitrosoketoaldehyde without preliminary isolation underwent a cyclization with hydrazine or with arylhydrazine giving the corresponding 3-methyl-4-nitrosopyrazoles whose synthesis with known methods was impossible up till now (Scheme 22.9).

Department of organic chemistry and technology of organic compounds at Reshetnev Siberian State University continues successful studies in the field of the carbo- and heterocyclizations resulting in the preparation of new organic compounds possessing useful properties.

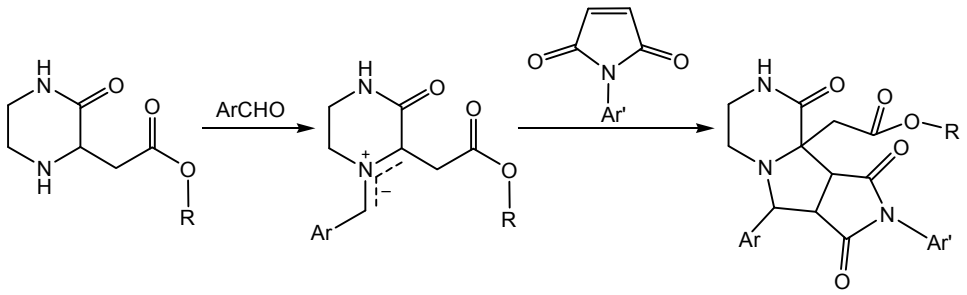
23. DEPARTMENT OF FUNDAMENTAL CHEMISTRY AND CHEMICAL ENGINEERING AT SOUTHWESTERN STATE UNIVERSITY

The department was founded in 1964. The first head of the department was Candidate of chemical

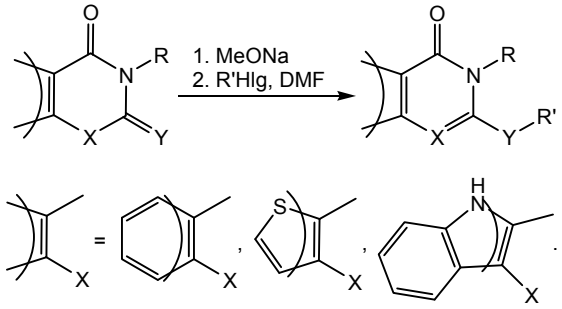
Scheme 21.14.



Scheme 21.15.



Scheme 21.16.



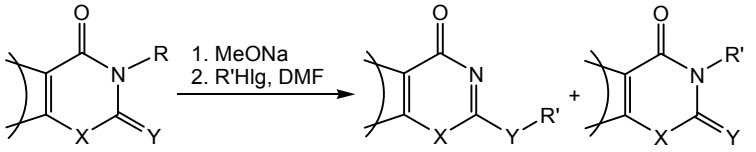
sciences, Assistant-Professor A.P. Momsenko, later heads of the department were Candidate of chemical sciences, Assistant-Professor V.N. Tamazina and A.K. Gabduvalieva. In 1985 A.M. Ivanov became the head of the department. In 2008 a Department of Organic and Analytic Chemistry separated that is training students before graduation, and Professor Yu.D. Markovich became its head. **The head of the department** of fundamental chemistry and chemical engineering since 2011 is **Professor L.M. Mironovich**. 3 Professors, Doctors of Chemical Sciences and 8 Assistant-Professors, Candidates of Chemical Sciences work at the department.

The department is specialized on the chemistry of heterocyclic compounds: synthesis, investigation of chemical properties and kinetic laws of reaction processes. Traditionally at the department new derivatives are synthesized of 1,2,4-triazine and their chemical properties are explored. The other direction of research on heterocyclic compounds is the search for new compounds in acridine series.

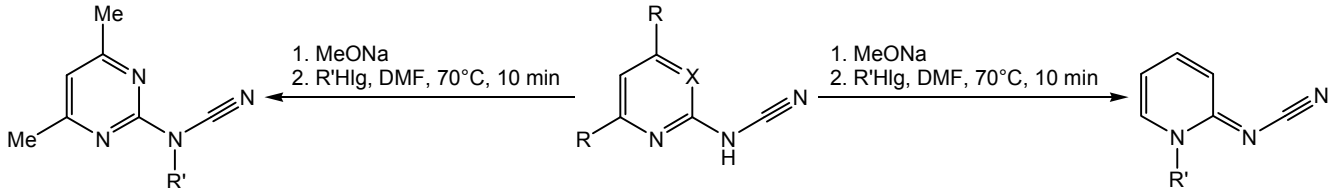
One of the general synthetic methods for diversely substituted pyrazolo[5,1-*c*][1,2,4]triazines are the successive reactions of azocoupling of pyrazolo-3(5)-diazonium salts and intramolecular cyclization (Scheme 23.1).

A multitude of new heterocyclic systems was produced in this manner (Scheme 23.2) [949]. The intermediately formed hydrazones are unstable and undergo cyclization when subjected to chromatog-

Scheme 21.17.

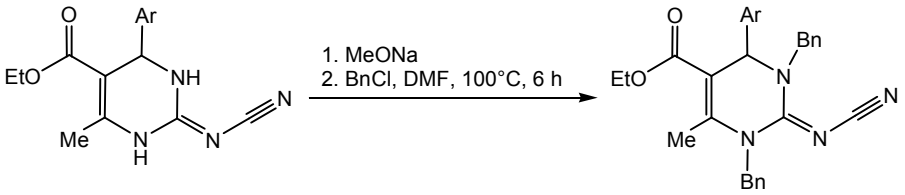


Scheme 21.18.



R = H, Me; X = CH, N.

Scheme 21.19.



raphy [950], at heating in weakly acidic or basic media. The variation of reaction conditions affects the regioselectivity of the process. Many heterocycles were obtained analogously proceeding from 3(5)-hydrazinopyrazoles and α-dicarbonyl compounds.

Some pyrazolo[5,1-*c*][1,2,4]triazin-4-ones unavailable by other methods were prepared from 4-amino-3-mercapto-6-R-1,2,4-triazin-5(4*H*)-ones or from the products of their S-alkylation and methylene-active compounds by the sequence S_NAr reaction intramolecular cyclization (Thorpe reaction). The reaction was applied to the syntheses of 8-cyano-, 8-alkylsulfonyl- and 8-carboethoxy-7-amino-3-R-pyrazolo[5,1-*c*][1,2,4]triazin-4-ones (Scheme 23.3). Also *N*-methyl-2-benzoyl-thioamides were involved in the reaction [951].

The reaction with 1,1,3-tricyano-2-aminopropene results in the formation of 8,10-diamino-3-(*tert*-butyl)-4-oxo-4,6-dihydropyrido[2',3':3,4]pyrazolo[5,1-*c*]-[1,2,4]triazine-9-carbonitrile due to the domino-sequence S_NAr" double Thorpe reaction; this is the only published example of the reaction between 1,2,4-triazines and malononitrile dimer (Scheme 23.4) [952].

The heating of products of 4-amino-3-mercapto-6-R-1,2,4-triazin-5(4*H*)-ones alkylation with phenacyl halides leads to the formation of triazinothiadiazinone derivatives whose pyrolysis affords the corresponding 3-R-7-R'-pyrazolo[5,1-*c*][1,2,4]triazin-4-ones (Scheme 23.5). The desulfurization occurs at heating in an inert atmosphere or at boiling in acetic anhydride.

The reactivity of the aromatic ring of the 1,2,4-triazine depends strongly on the nature and the position of the substituents in the ring. For instance, unsubstituted 1,2,4-triazine and 3-alkyl-substituted analogs suffer fact decomposition in 0.5 N NaOH at room temperature, but the majority of 1,2,4-triazine are stable against the acid action [953]. Yet the triazine ring in a fused system 7-R-[1,2,4]triazolo[5,1-*c*][1,2,4]triazin-4(1*H*)-one is completely destroyed under the effect of trifluoroacetic acid already at 20°C with the formation of hydrazinotriazoles. The skeleton of 1,2,4-triazine having a *tert*-butyl group in the composition of pyrazolo[5,1-*c*][1,2,4]-triazin-4-ones possesses a low reactivity and a high resistance to the treatment with conc. acids and bases as well as diverse oxidants and reducers. It provides a possibility to examine selectively the reactivity of the pyrazole part of this heterocyclic system.

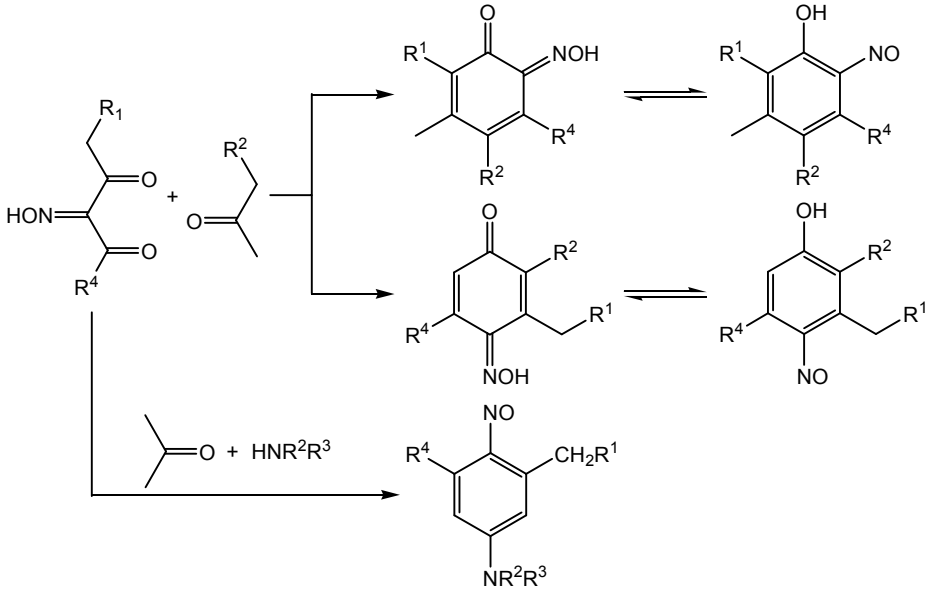
The regioselectivity of alkylation in azolo[5,1-*c*]-[1,2,4]triazines was investigated using X-ray diffraction analysis and NMR spectroscopy. Unlike 1,2,4-triazolo[5,1-*c*][1,2,4]triazines, the reaction of pyrazolo-[5,1-*c*][1,2,4]triazin-4-one salts with various electrophiles (haloalkanes, alkyl tosylates) led to the formation of the products alkylated at the N^1 atom (Scheme 23.6).

7-Amino-3-(*tert*-butyl)-4-oxo-4,6-dihydropyrazolo-[5,1-*c*][1,2,4]triazine-8-carbonitrile was used as an available precursor for the synthesis of many heterocyclic systems. The diazotization of the carbonitrile with $NaNO_2$ provides 3-*tert*-butyl[1,2,4]-triazino[4',3':1,5]pyrazolo[3,4-*d*][1,2,3]triazine-4,8-(3*H*,9*H*)-dione that after treating with P_2S_5 affords the thioanalog, and on acylation gives *N*-acylation products. The action on the compound of sodium azide made it possible to close the tetrazole ring (Scheme 23.7) [954, 955].

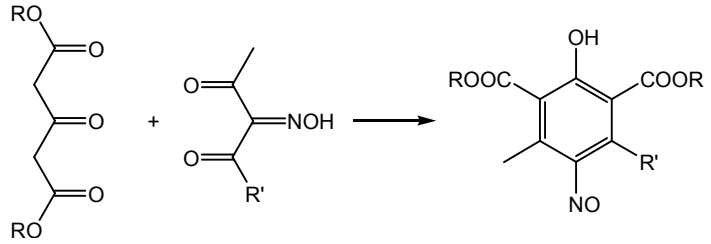
Boiling of carboxylic acids derivatives with 7-amino-3-(*tert*-butyl)-4-oxo-4,6-dihydropyrazolo[5,1-*c*]-[1,2,4]triazine-8-carbonitrile furnished derivatives of pyrimido[4',5':3,4]pyrazolo[5,1-*c*][1,2,4]triazinediones that at the treatment with P_2S_5 suffered the replacement of oxo groups for thioxo groups, the hydrazine action led to the hydrazinolisis of the C^{11}=S group and the separation of hydrazine derivatives. 3-(*tert*-butyl)-10-hydrazono-9,10-dihydropyrimido[4',5':3,4]pyrazolo-[5,1-*c*][1,2,4]triazin-4(6*H*)-one when treated with sodium nitrite in phosphoric or polyphosphoric acid affords an azide or tetrazole derivative respectively (Scheme 23.8) [956].

Proceeding from substituted pyrazolotriazines other heterocyclic compounds were also obtained. For

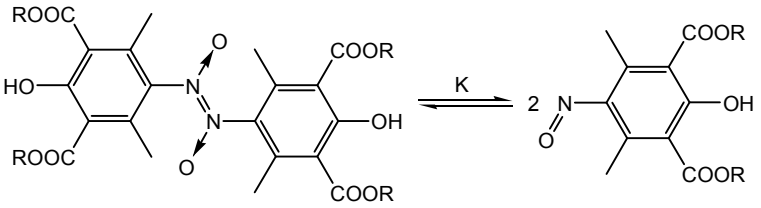
Scheme 22.1.



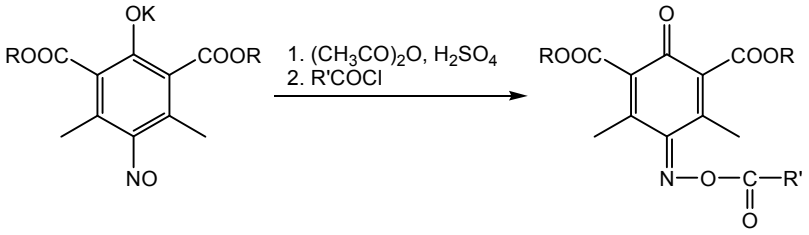
Scheme 22.2.



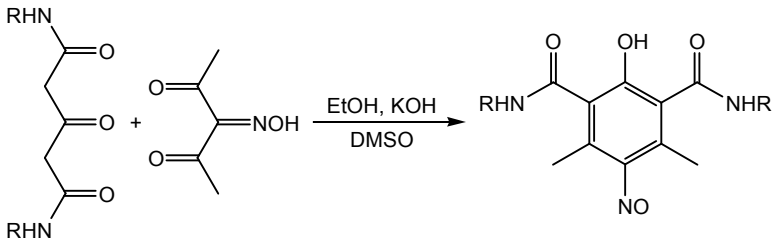
Scheme 22.3.



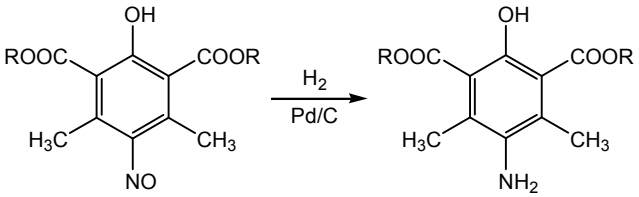
Scheme 22.4.



Scheme 22.5.

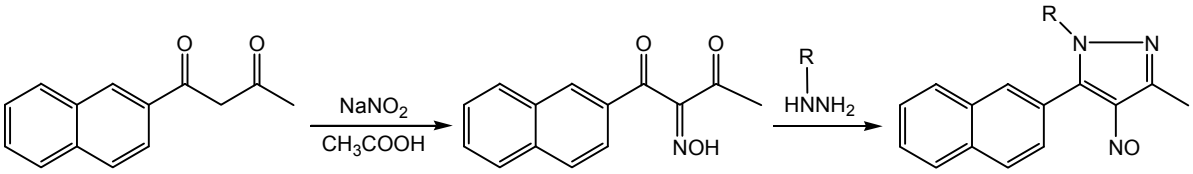


Scheme 22.6.



R = Me, Et, Pr, Bu, *i*-Bu.

Scheme 22.7.



R = H, CH_3, C_2H_5, C_3H_7, *i*-C_3H_7.

instance, the reaction of 7-amino-3-(*tert*-butyl)pyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one with α-diketones results in the closure of a new pyrazole ring with the isolation of 3-(*tert*-butyl)-7-*R*-8-*R'*-imidazo[1',2':2,3]-pyrazolo[5,1-*c*][1,2,4]triazin-4(9*H*)-ones, and heating with benzalacetone makes it possible to obtain pyrimido derivatives.

Condensation with benzaldehyde leads to imines. The phosphorylation of the amino group with the simultaneous replacement of the oxo and cyano groups for thioxo group occurs at heating the compounds with phosphorus pentasulfide; presumably an amide of metadithiophosphoric acid has been isolated (Scheme 23.9) [957].

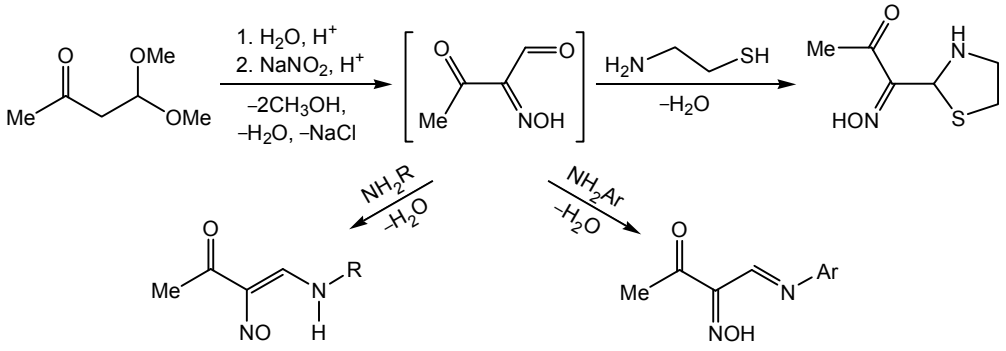
The reaction of hydroxylamine with 8-acyl-3,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-4-ones leds to the formation of the corresponding oximes which were brought in the reaction with PhCOCl [958]. The reaction with hydrazine derivatives afforded hydrazones and azines (Scheme 23.10). The reaction occurred with the formation of intermediate stable hydrazinium 8-acyl-3,7-dimethyl-4-oxo-4*H*-pyrazolo-[5,1-*c*][1,2,4]triazin-6-ides which were isolated [958].

Pyrazolo[5,1-*c*][1,2,4]triazines are intensively studied with respect to the biologic activity, development is in progress for their application as practically useful compounds. Therefore the exploration of reactivity and search for new synthesis methods of these compounds is a topical issue.

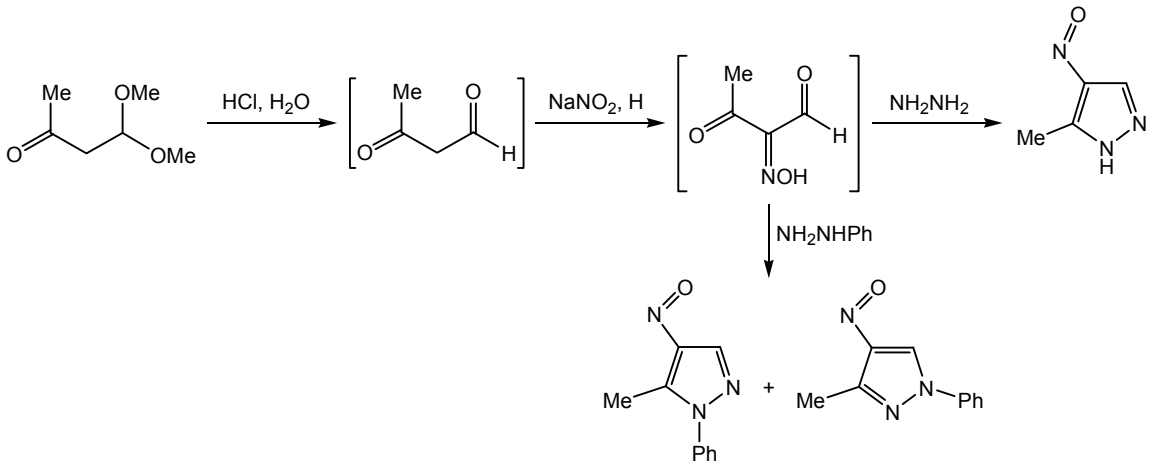
24. DEPARTMENT OF CHEMISTRY OF NATURAL AND HIGH MOLECULAR COMPOUNDS OF THE CHEMICAL FACULTY AT THE SOUTHERN FEDERAL UNIVERSITY

The priority direction of researches at the department is the synthesis, study of the structure and reactivity of nitrobenzoxadiazoles derivatives. Superelectrophilic properties of such system appear in their ability to take

Scheme 22.8.



Scheme 22.9.



part in S_NAr–S_EAr reactions even with weak electroneutral *C*-nucleophiles (of dihydroberberine type) and in unusual reactions of (4+2)- and (3+2)-cycloaddition. Using direct methods of NO detection *in vitro* and *in vivo* that were confirmed by quantum-chemical calculations *in silico* the promising application of nitrobenzoxadiazoles derivatives in medicinal chemistry as exogenous source of nitrogen(II) oxide was demonstrated.

Electroneutral aromatic superelectrophiles form a large class of fused π-deficient carbo- and heterocycles, possessing a unique, versatile reactivity in the processes of nucleophilic substitution and addition. The central position among 10π-electronic superelectrophiles belongs to the derivatives of dinitrobenzofuroxan (DNBF), and among the 14π-electronic compounds, to the derivatives of nitrobenzodifuroxan (NBDF) [959] (Scheme 24.1).

The quantitative estimation of the reactivity of DNBF and related compounds using the universal Mayr electrophilicity scale [960] showed that the electroneutral DNBF molecule is a stronger electrophile than the 2,4-dinitrophenyldiazonium cation. Just this fact permits to use the term *superelectrophile* with respect to DNBF [961, 962]. The superelectrophilicity of DNBF is due to the electron acceptor effect of nitro groups and the furoxan ring (equivalent approximately to 1,5-nitro groups) and to abnormally low aromaticity of the six-memebered carbocycle facilitating the Meisenheimer complex formation which is the key intermediate of S_NAr reactions.

A quantitative increase in electrophilicity leads to the appearance of a qualitatively different reactivity, compared with nitroaryls or nitroazines, namely: the capability to participate in the S_NAr–S_EAr reactions with weak neutral *C*-nucleophiles, in the reactions of polar (2+4)-, (4+2)- and (3+2)-cycloaddition; and the ability to generate NO *in vivo* and *in vitro*.

The reactivity of nitrobenzofuroxans goes far beyond the processes of σ-complexation with *O*-, *N*-, *S*-nucleophiles and extends to S_NAr reactions even with weak neutral *C*-nucleophiles [963]. While only very strong bases with $pK_a \geq 9$ react satisfactorily with 1,3,5-trinitro-2-chlorobenzene, the *Cl*-substituted derivatives of dinitrobenzofurazan and -furoxan (DNBZ-Cl and DNBF-Cl) are able easily at room temperature in ethanol to enter in S_NAr reactions with weak carbocyclic and heterocyclic bases like *N*-methylindole (pK_a –2.32), azulene (pK_a –1.76), and 1,2,5-trimethylpyrrole (pK_a –0.49) leading to substitution products [964] (Scheme 24.2).

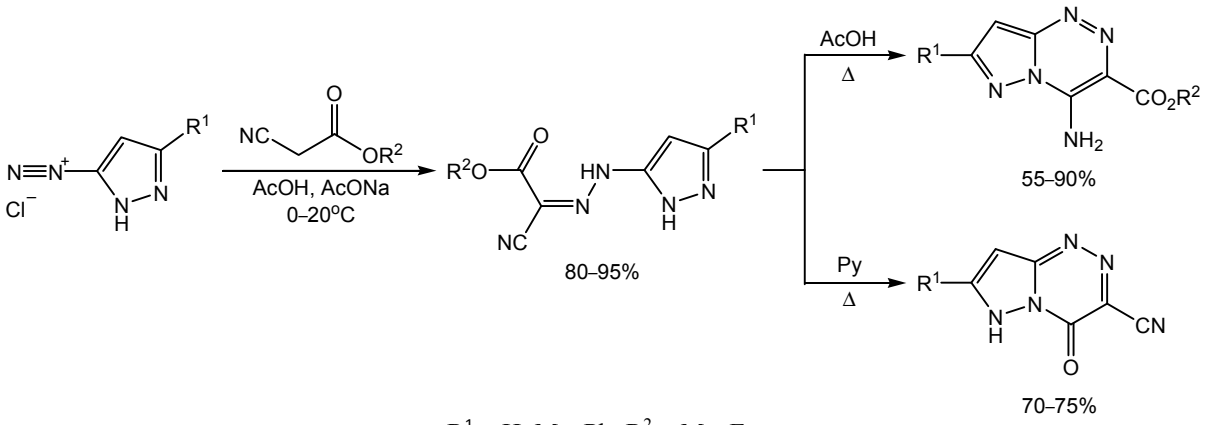
The latter are deeply colored stable substances that are well soluble in most organic solvents and exhibit appreciable solvatochromism (Scheme 24.3).

The significant intramolecular charge transfer shown in these resonance structures has been confirmed by UV and NMR spectroscopy.

Similar S_NAr–S_EAr reactions are quite rare in organic chemistry processes occurring through the zwitterion complex of Meisenheimer-Whelland (Scheme 24.4). We succeeded in bringing in reactions of this type a wide series of π-excessive carbo- and heterocycles, for example, julolidine, trimethoxybenzene [965], benzofulvene [966], and chromeno-indolizine [967].

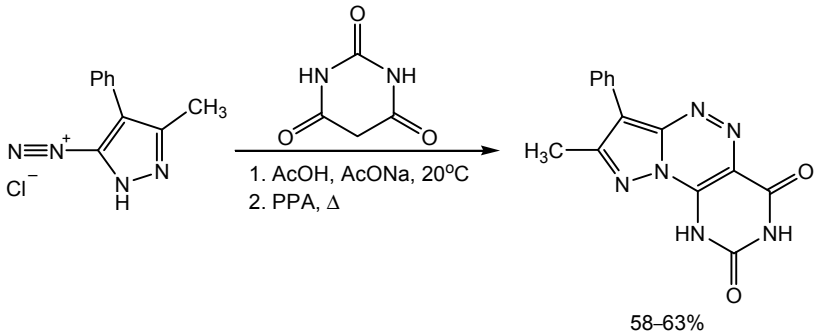
The DNBZ-Cl and DNBF-Cl, closely related by the structure, react with indolizines in different ways: in the first case, the expected diaryl of DNBZ-Ind is formed,

Scheme 23.1.



R^1 = H, Me, Ph; R^2 = Me, Et.

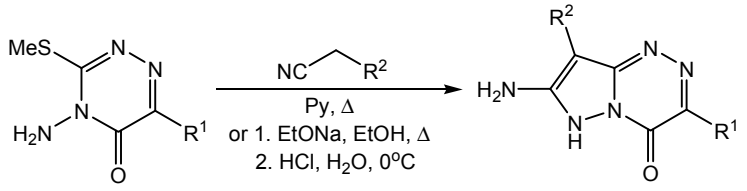
Scheme 23.2.

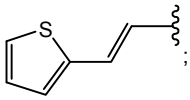


and in the second case, quinolizinium betaine (spiro-DNBF-Qui), bipolar spirocyclic σ-complex arises (Scheme 24.5).

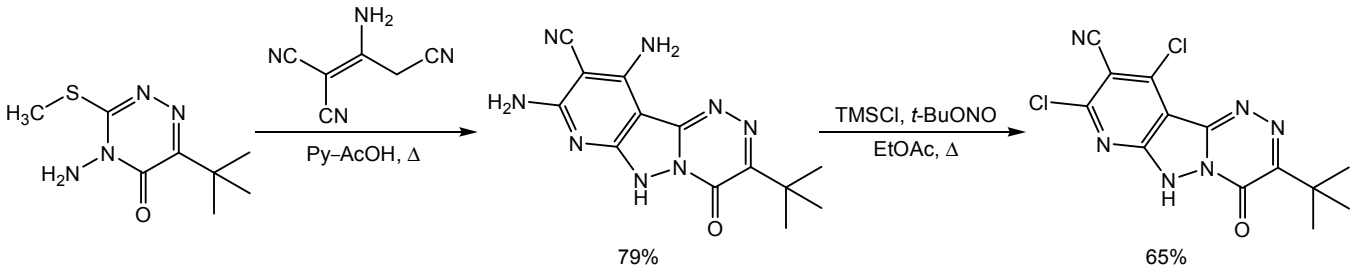
Intramolecular charge transfer is the key factor determining the rearrangement of the initially formed diaryls into spiroadducts (Scheme 24.6).

Scheme 23.3.

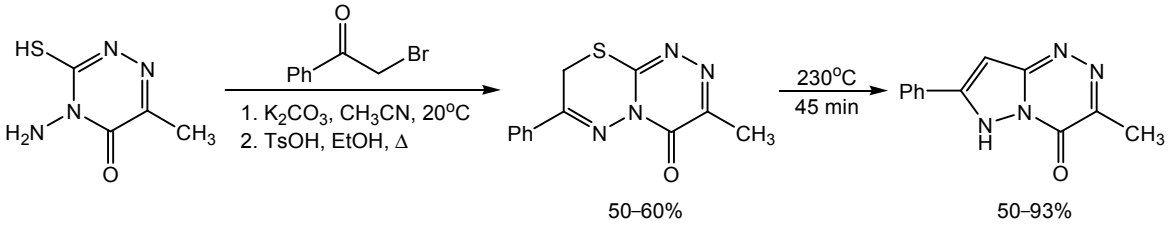


R^1 = Me, Ph, *t*-Bu,  ; R^2 = CN, CO_2Et, SO_2R^3.

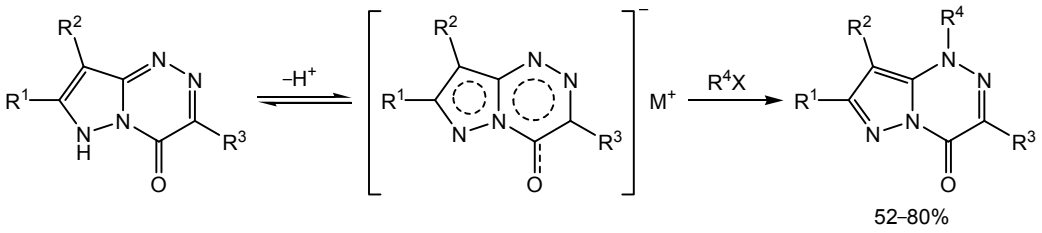
Scheme 23.4.



Scheme 23.5.



Scheme 23.6.



R^1 = H, Me, NH_2; R^2 = H, CO_2Et, CN; R^3 = Ph, CO_2Et, *t*-Bu; R^4 = Alk, Bn; M^+ = Na^+, K^+, NBu_4^+; X = Hlg, TsO.

The existence of metastable diaryls in the reaction with DNBF-Cl and its recyclization were successfully observed by NMR [968].

The novelty and attractiveness of structures like spiro-DNBF-Qui is due at least to two facts. First, it is a previously unknown example of a bipolar spirocyclic σ-complex containing three carbon atoms at the spiro node. Secondly, the observed ring expansion and the transformation of indolizine into quinolizinium betaine is an earlier unknown transformation in the chemistry of indolizines. Such recyclizations may also be successfully carried out with dihydroindolizine derivatives [969].

For the formation of new carbon-carbon bonds involving superelectrophiles of the DNBF-Cl and DNBZ-Cl types any electrically neutral nucleophiles with C(sp^2) centers of attack, for example, dihydroberberine, can be used. Thus, when attacking the nucleophilic C^{13} atom of dihydroberberine with appropriate chlorodinitrobenzoxadiazole or 7-chloronitrobenzofurazan deeply colored crystals are formed rapidly and in a high yield. Despite a considerable interest in the chemistry of berberine derivatives only alkylation reactions at the C^{13} atom of dihydroberberine were previously known [970]. The synthesized systems can be represented by resonance structures, which are the first examples of betaine berberine derivatives with the charge transfer through a conjugated system of bonds (Scheme 24.7).

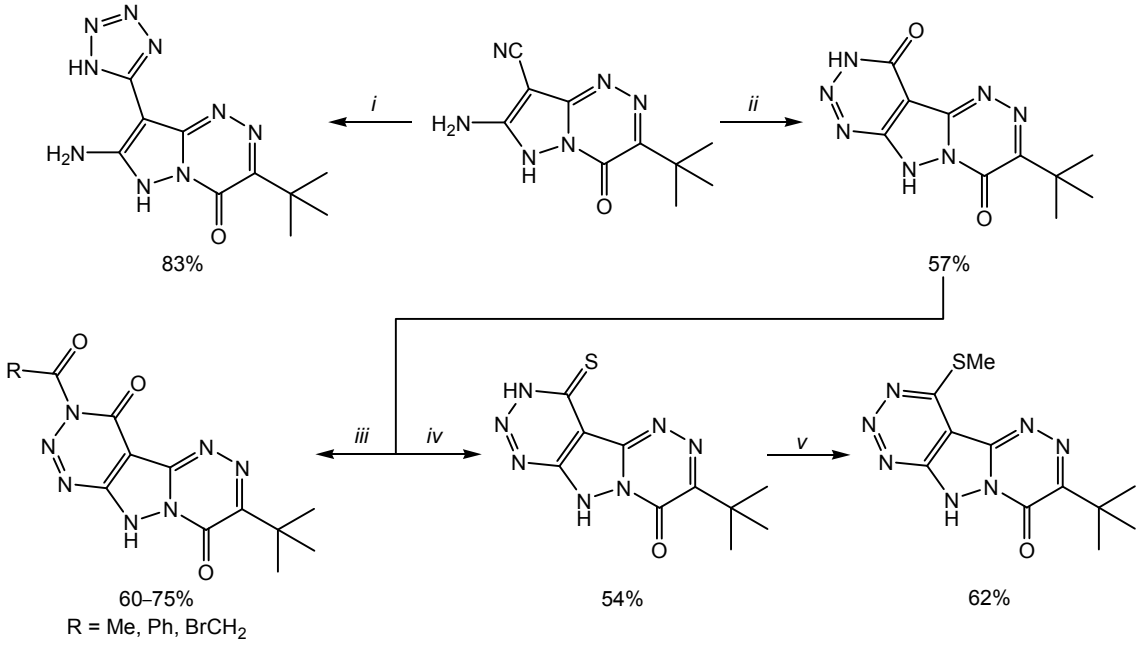
The charge transfer in nitrobenzoxadiazoles leads to the fact that they appear to be promising ligands for coordination with G-quadruplexes of telomeric DNA sections that control, among other things, the processes of apoptosis of cancer cells. According to the molecular docking in the G4LDB.ORG system [971] the strongest binding occurs with loose G-quadruplexes of telomeric parts formed by several strands of DNA (Fig. 24.1). In the oxadiazole series, the activity is directly dependent on the intramolecular charge transfer values. The strongest binding, according to the results of modeling, showed a derivative of berberine with dinitrobenzofuroxan (DNBF-Ber) with the sequence 3QSC.

As seen from fig. 24.1, the DNBF-Ber derivative forms an intercalation complex in which the berberine scaffold is located between two nucleic acid loops and is coordinated with four guanine fragments. The nitroaryl fragment in the associate is located at a significant angle to the berberine scaffold and forms two additional hydrogen bonds with thymine NH groups [970].

A low aromaticity of superelectrophiles, which is reflected in a significant alternation of the C-C bonds of the six-membered carbocycle, allows them to enter readily into a reaction of (2+4)-cycloaddition with direct electronic requirements as a dienophile at the C=C–NO_2 fragment, and also as a heterodiene C=C–N=O in the reaction of (4+2)-cycloaddition with reverse electronic requirements (Scheme 24.8).

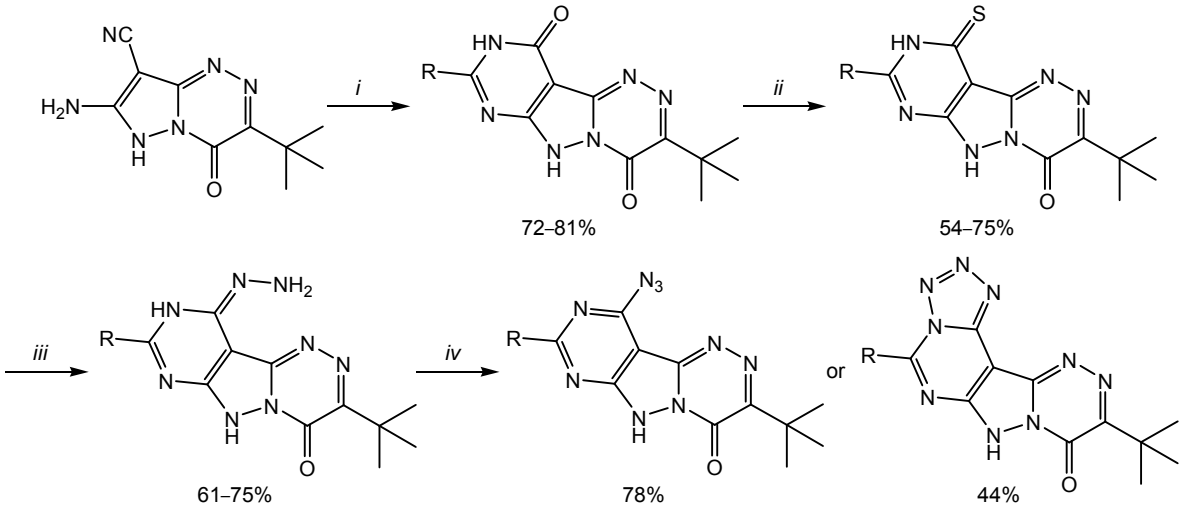
The most interesting results have been obtained when investigating the cycloaddition of cyclopenta-diene and cross-conjugated trienes([3]dendralenes) (Scheme 24.9).

Scheme 23.7.



i: NaN_3, NH_4Cl, DMF, Δ; *ii*: $NaNO_2$, HCl, H_2O; *iii*: RCOCl; *iv*: P_2S_5, Py, Δ; *v*: MeI, OH^-.

Scheme 23.8.



i: HCO_2H, Ac_2O or RCOCl, Δ; *ii*: P_2S_5, Py, Δ; *iii*: N_2H_4, *i*-PrOH, Δ; *iv*: $NaNO_2$, H^+.

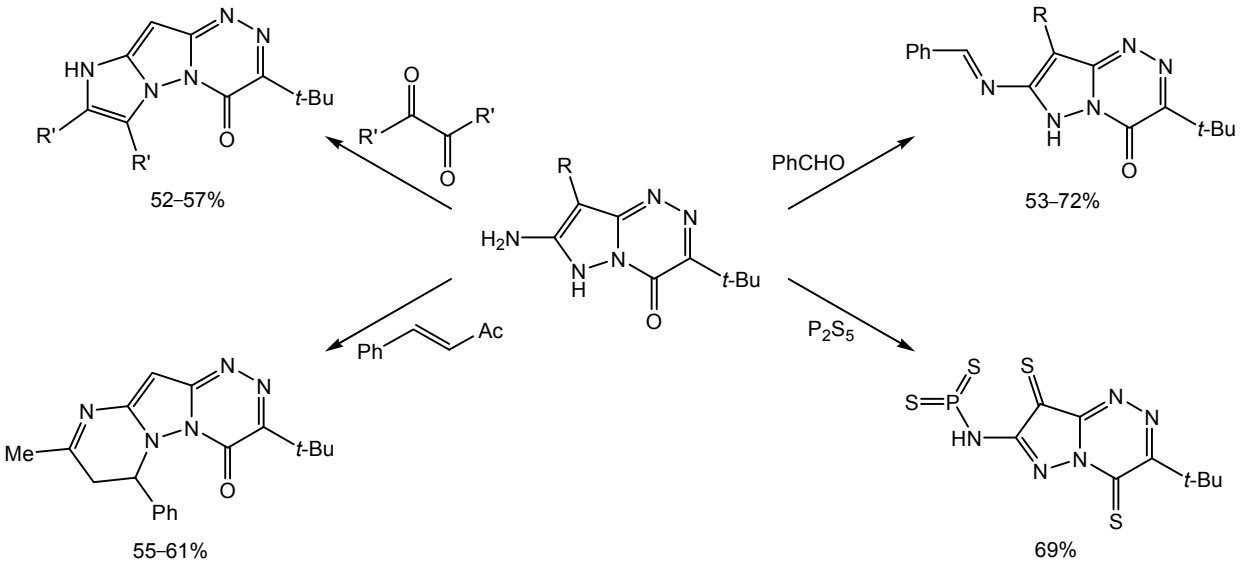
When a solution of nitrobenzodifuroxan NBDF and cyclopentadiene is mixed in dichloromethane an *endo*-[2+4]-cycloaddition product is formed, whose structure was confirmed by X-ray diffraction data (Scheme 24.10).

However, the quantum chemical DFT/B3LYP calculations in 6-31G* the basis set and *ab initio* MP2/6 -31G* for the gas phase and dichloromethane showed that this reaction occurred by a mechanism more complex than the concert (one-step) diene coupling to dienophile.

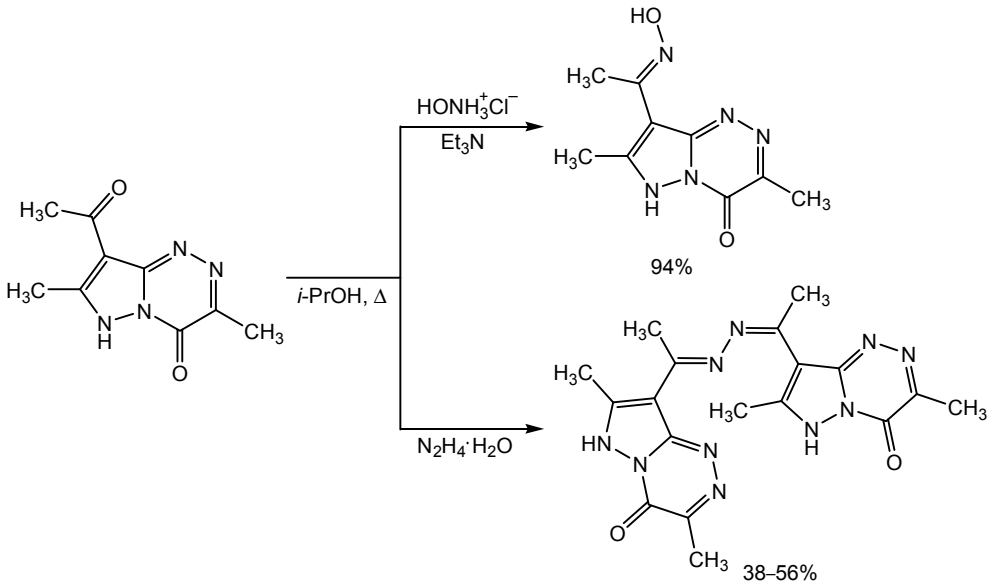
At the very beginning, a pre-reaction π-complex with an intermolecular charge transfer PRC1 is formed; it is stabilized by electron transfer from the binding molecular orbitals of the diene system to the corresponding antibonding molecular orbital of dienophile.

Further, the *endo*[4+2]-cycloadduct 16 is formed through the highly asynchronous transition state TS1

Scheme 23.9.



Scheme 23.10.



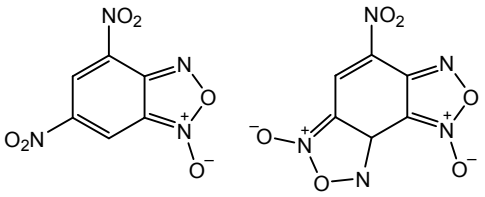
and, finally, the [3,3]-Claisen sigmatropic rearrangement into the *endo*[2+4]-cycloadduct 15 takes place through the transition state TS2 (Fig. 24.2). Theoretically possible direct [2+4]-cycloaddition (the left side of the Figure) would proceed, firstly, with a higher energy barrier of TS3 and, secondly, would lead not to the *endo*-, but to the *exo*-product of cycloaddition 15'.

We succeeded to obtain an experimental confirmation of the calculated mechanism, fixing the formation of intermediate product 16 during the reaction in the ampule of the NMR spectrometer. The NMR monitoring of the process showed that the 16→15 transformation is almost completely finished within 5 hours [972].

For non-polar and weakly polar reagents, Diels-Alder reactions are considered to be classic examples of pericyclic processes where the rupture/formation of bonds occurs by concerted process, and the stereochemical result of cycloaddition is determined by the Alder *endo*-rule. However, at very high values of the dienophile electrophilicity and the diene nucleophilicity a cycloaddition through a zwitterionic mechanism is possible that increases the probability of *exo*-addition.

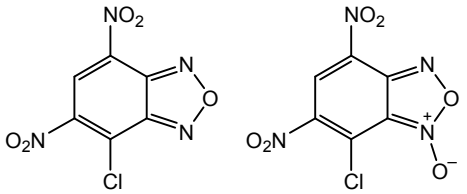
The mechanisms of electrophilic/nucleophilic interactions (including the reactions of polar cycload-

Scheme 24.1.



DNBF NBDF

Scheme 24.2



DNBZ-Cl DNBF-Cl

dition) can be predicted using the proposed by Parr [973] global electrophilicity indices (ω) of the reagents. For their calculation the energies of the highest occupied (ε_H) and lowest unoccupied (ε_L) molecular orbitals in the ground electronic state are used:

$$\omega = \mu^2/2\eta;\ \mu = (\varepsilon_H + \varepsilon_L)/2;\ \eta = \varepsilon_L - \varepsilon_H.$$

At that, the polarity of Diels-Alder reactions is estimated as the difference Δω between the diene and dienophile.

Let us consider the reaction of DNBF with dendralene. The stereochemical results of two successive stages of cycloaddition have been determined by X-ray diffraction analysis of the hydrolysis product. They differ significantly: the first stage (addition *via* the more active C^6–C^7 bond) leads to the *exo*-adduct, and the second (via the C^4–C^5 bond) results in the *endo*-adduct (Scheme 24.11).

To comprehend the reasons for these differences, DFT calculations of the process mechanism in the B3LYP/6-31G* basis were carried out. The first addition of ethoxydendralene to DNBF proceeds not according to concerted, but according to the zwitterionic mechanism. In this case, the obtained σ-complex is a sufficiently deep local minimum of PES (Scheme 24.12).

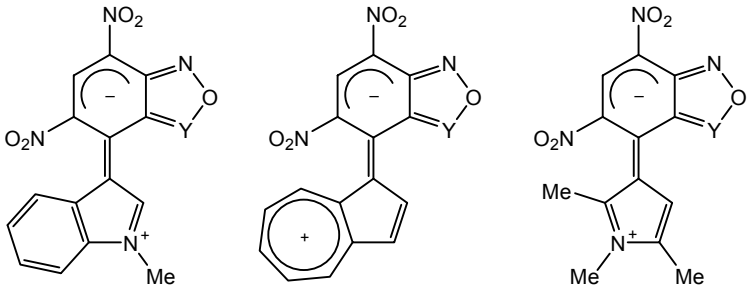
Further, the zwitterionic intermediate is cycled into the *exo*-cycloadduct with an energy gain of 6.5 kcal/mol. The formation of the *endo*-cycloadduct from the σ-complex is thermodynamically less favorable: the energy gain in this case is only 3.0 kcal/mol. So, the first molecule of ethoxytriene is attached to DNBF against to the Alder *endo*-rule by the zwitterionic mechanism [974].

Interacting ethoxydendralene and dinitrobenzofuroxane are highly polar systems with a large difference in global electrophilicity (Δω = 4.68 eV). The (4+2)-cycloaddition reaction of analogous in polarity systems, dinitrobenzofuroxan and the "Danishefsky diene", also occurs through a zwitterionic intermediate with the subsequent violation of Alder *endo*-rule [975].

The *exo*-cycloadduct formed in the first stage is obviously significantly less electrophilic due to the nitro group's withdrawal from the conjugation chain and the loss of aromaticity compared to the initial dinitrobenzofuroxan molecule (Δω = 3.00 eV). As a result, the second stage develops by the concerted mechanism as a classical cycloaddition and in accordance with Alder *endo*-rule.

Reactions of (3+2)-cycloaddition of unstabilized azomethane ylides were not possible with any of the superelectrophiles. The most probable reason for this is the excessive reactivity of both reagents, which invariably leads to tarring of the reaction mixture. However, the use of the C^7-arylation products as dipolarophiles allowed, firstly, to reduce the electrophilicity of the nitrobenzoxadiazole fragment of the molecule and, secondly, to block spatially the most reactive bond C^6–C^7 of DNBF. Scheme 24.13 shows the cycloaddition to indolyl derivatives of DNBF, although similar products of (3+2)-cycloaddition have been obtained for various 7-aryl- and hetaryl derivatives of nitrobenzoxadiazoles [965, 966]. The systems of subsequent elimination and aromatization were also preparatively obtained [976], and this was very valuable for subsequent bio-tests.

Scheme 24.3.



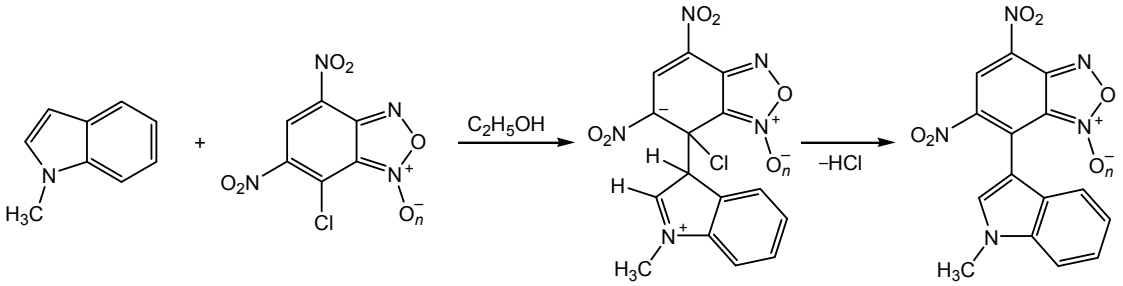
Y = N (Z), NO (F).

Derivatives of nitrobenzoxadiazoles, exogenous donors of nitrogen(II) oxide. It is well known that nitrogen(II) oxide is a multimodal regulator of a variety of physiological processes (vascular relaxation, platelet aggregation inhibition, immune and nervous system functioning), as well as pathological states of the organism (infectious, inflammatory, tumor diseases) [977]. In general, the creation of new exogenous NO donors is one of the priority tasks of medicinal chemistry, but the lack of adequate methods for measuring the amount of nitrogen monoxide hinders in many respects its solution: the lifetime of the NO radical *in vivo* is 10–20 s.

One of the most promising approaches to the primary estimation of the efficiency of new potential ntrogen monoxide donors is the use of biosensors that combine living organisms and electronic modules.

Together with V.A. Chistyakov (Southern Federal University), we have used a biosensor of *E. coli* MG 1655 (pSoxS-lux) to detect the ability of the test substances to induce the SOX operon. The biosensor was created by introducing a plasmid with the luxCDABE operon of the photobacterium *Photorhabdus luminescens* under the control of the pSoxS promoter. This genetic construction responds

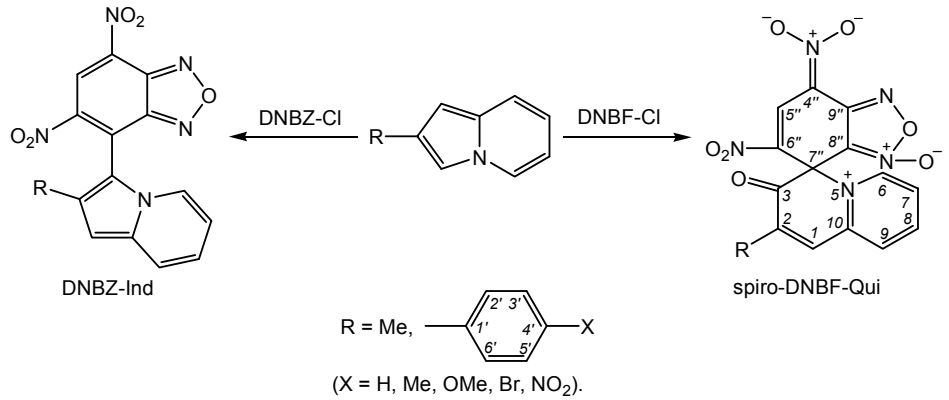
Scheme 24.4.



Meisenheimer-Welland σ-complex

n = 0, 1.

Scheme 24.5.

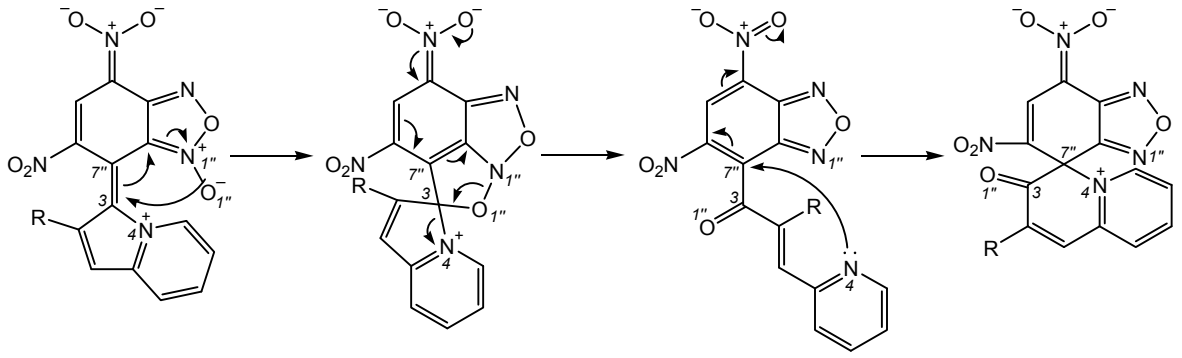


DNBZ-Ind

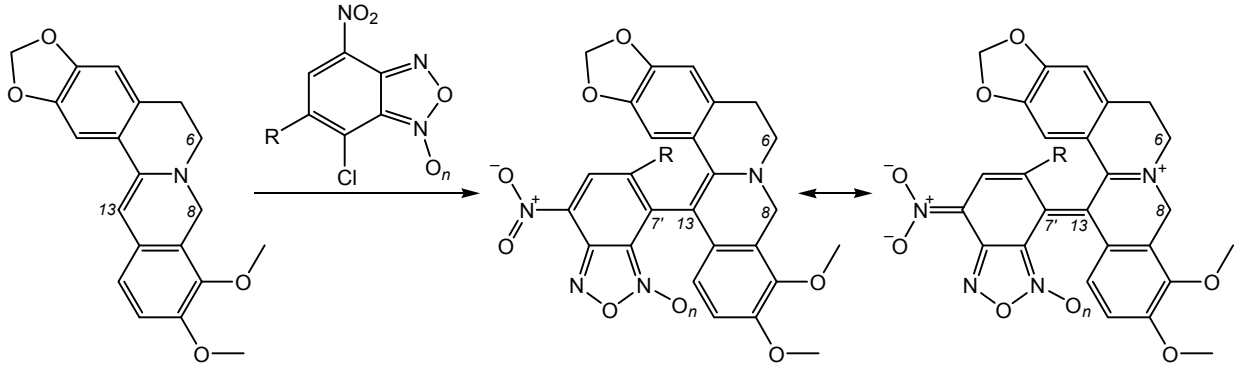
spiro-DNBF-Qui

(X = H, Me, OMe, Br, NO_2).

Scheme 24.6.



Scheme 24.7.



R = H, n = 0; R = NO_2, n = 0, 1.

by the enhancement of bioluminescence to the presence in the intracellular environment of compounds that generate nitrogen(II) oxide.

By the above described methods of nucleophilic aromatic substitution and cycloaddition, we have synthesized a number of nitrobenzoxadiazole derivatives. Their structure can be represented by a scaffold of type A having three points of diversification: 1, azine nitrogen atom or its *N*-oxide; 2, aromatic carbo- or heterocycle (for example, pyrrole, indole, indolizine); 3, pyrrol or dihydropyrrole ring fused as a result of (3+2)-cycloaddition of azomethine ylide (Scheme 24.14). In experiments *in vivo*, it has been found that the compounds obtained have an abnormally high NO-donor activity, far exceeding the activity of such reference agents as nitroglycerin and NOC-5 [978, 979].

Together with V.A. Serezhenkov (Institute of Chemical Physics of Russian Academy of Sciences) we have used for the direct confirmation of the NO-producing ability the ESR method with the participation of hydrophobic or hydrophilic NO spin traps: diethylthiocarbamate or *N*-methyl-D,L-glucamine dithiocarbamate with iron(II) salts (Scheme 24.15). The use of such traps has proved effective in assessing the NO level in liquids and animal tissues in the norm and in pathology [980].

When the cysteine or sodium sulfide is introduced into the reaction medium during the generation of NO from nitrobenzoxadiazoles, it is also possible to form dinitrosyl iron complexes existing in a dimeric diamagnetic form in equilibrium with a paramagnetic monomeric form [981].

Thus, experimental evidence was obtained that the use of *Lux*-biosensors was a correct method for determining NO donor activity *in vivo*. In addition, it has become evident that the yield of nitrogen(II) oxide increased in the presence of thiols [982]. The fixed formation of dinitrosyl iron complexes in the case of thiol dependent generation of nitrogen monoxide allows us to consider nitrobenzoxadiazole derivatives as promising NO donors for both direct and indirect effects.

As known, there are two main ways to increase NO level in the human body: stimulation of NO-synthase and the introduction of exogenous NO sources that enzymatically or non-enzymatically (e.g., when endogenous thiols are operating) release it in the body.

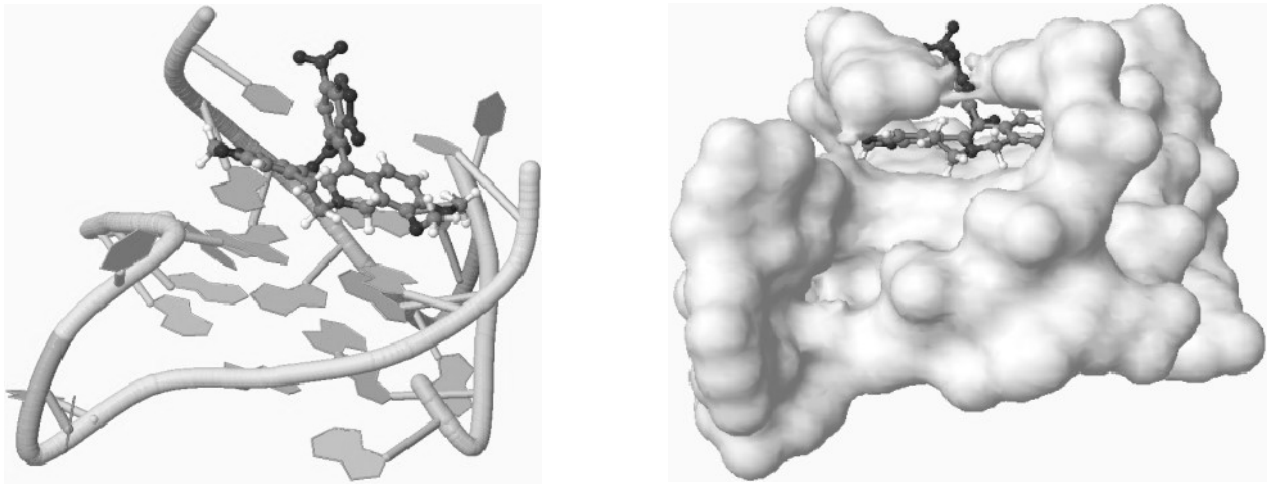


Fig. 24.1. The complex of DNBF-Ber with G-quadruplex 3QSC in tentative representation of DNA (left) with accounting for van der Waals radii in quadruplex (right) in keeping with results of simulation using program package G4LDB.ORG.

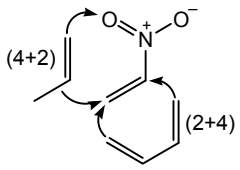
Since the thiol dependent NO generation was established experimentally, we performed quantum-chemical DFT calculations (UB3LYP functional in the 6-311++G** basis, taking into account solvation effects) of the mechanism of thiol induced nitrogen monoxide donation by furoxans and benzofuroxans [983] (Scheme 24.16).

The mechanism of attack of furoxans by thiolate anions previously considered as conventional has happened to be thermodynamically unacceptable not only for furoxans, but also for benzofuroxans, since it proceeds with a significant increase in the Gibbs free energy [983].

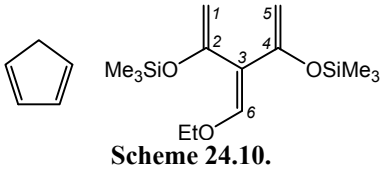
For the first time we have established that endogenous thiols can interact with furoxans not in the form of thiolate anions RS^-, but in the form of $RS^{\cdot}$ radicals (Scheme 24.17).

For all types of furoxans, thiol induced nitrogen monoxide donation begins with an attack by a sulfanyl radical on the carbon atom nearest to the *N*-oxide function [985].

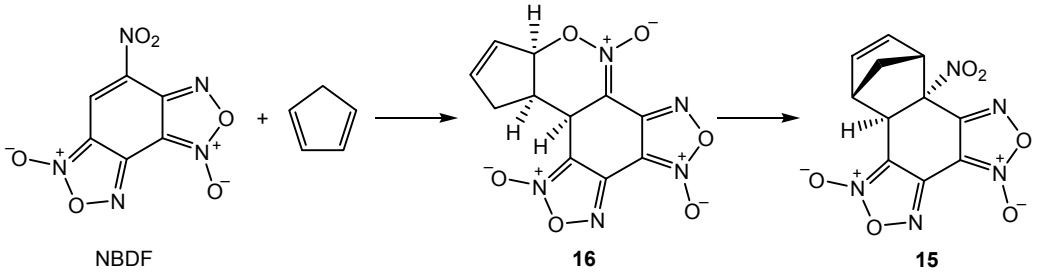
Scheme 24.8.



Scheme 24.9.



Scheme 24.10.



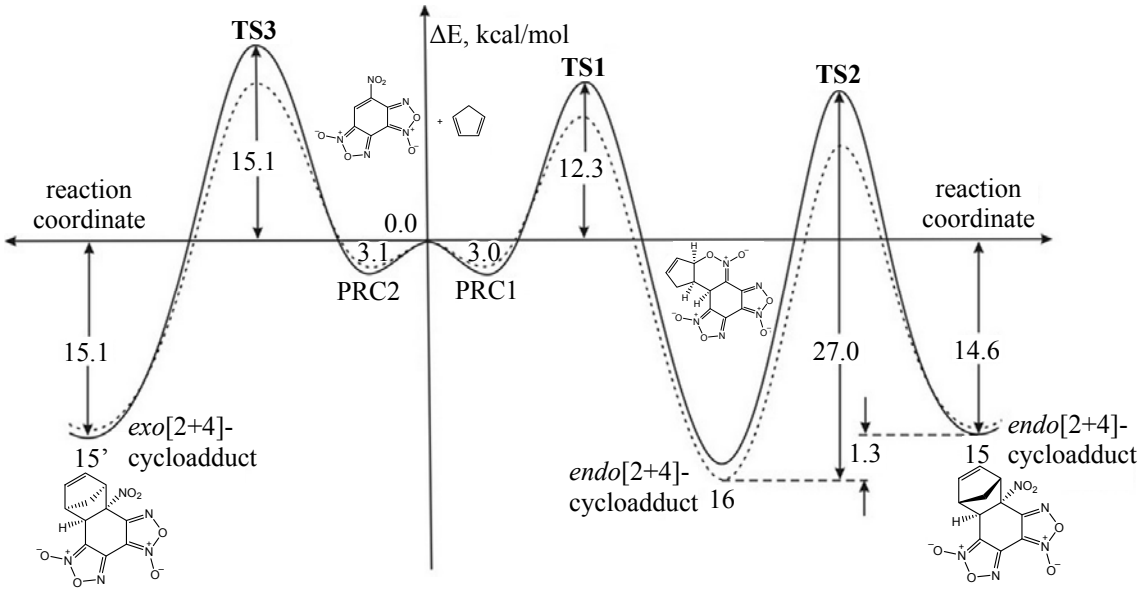


Fig. 24.2. Energy profile of reaction between NBDF and cyclopentadiene in the gas phase (dotted line) and dichloromethane (solid line).

In this case, it is the first stage (the addition of the model sulfanyl radical $HS^{\cdot}$ to furoxans and benzofuroxans) that is limiting, and the decrease in the electrophilicity of furoxans correlates with a decrease in the barriers of the limiting stages and, probably, with an increase in NO-induction.

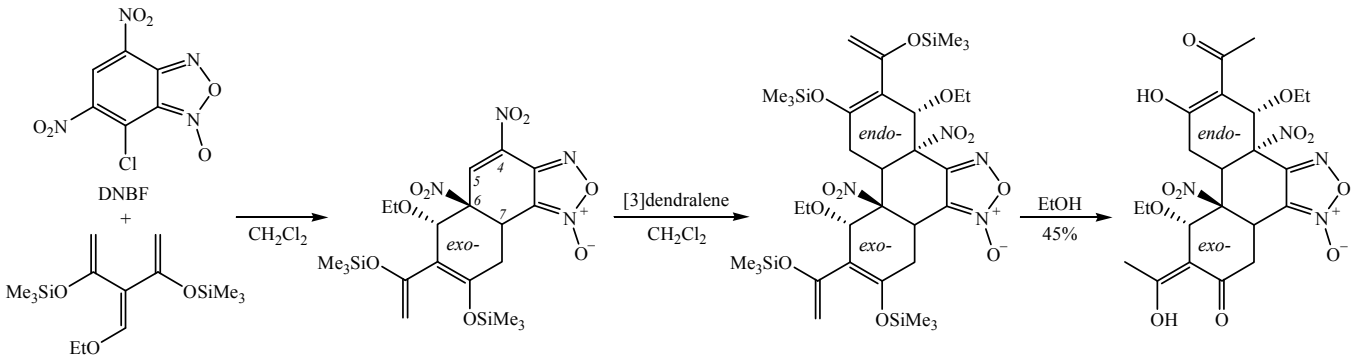
The investigation of superelectrophilic activation (that is, a quantitative increase in electrophilicity, which initiates the appearance of qualitatively new reaction paths in substitution, addition, cycloaddition, and recyclization processes) opens ways to the synthesis of compounds having structural motifs that allow *a priori* to generate NO by various means. This may be the elimination of HNO_2 in the products of (3+2)-cycloaddition, and/or an attack with endogenous thiols of the furoxan ring, or the formation of NO from nitroso groups in the intermediate states of 1,3-*N*-oxide tautomerism. Studies in this direction have a significant development potential and, obviously, require a comprehensive approach and attention of specialists of various profiles (chemists, biologists, pharmacologists), with whom our department is always ready to cooperate.

25. DEPARTMENT OF ORGANIC CHEMISTRY AT KOSYGIN RUSSIAN STATE UNIVERSITY

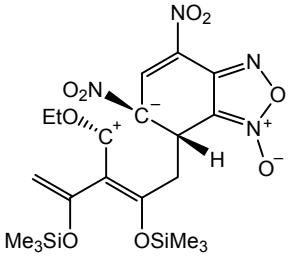
The department was founded in 2013 by joining the department of organic chemistry and chemistry of dyes of Kosygin Moscow State Textile University and the department of organic chemistry of Moscow State University of Design and Technology.

The traditional topics of research at the department are logically connected with the profile of the joint

Scheme 24.11.



Scheme 24.12.

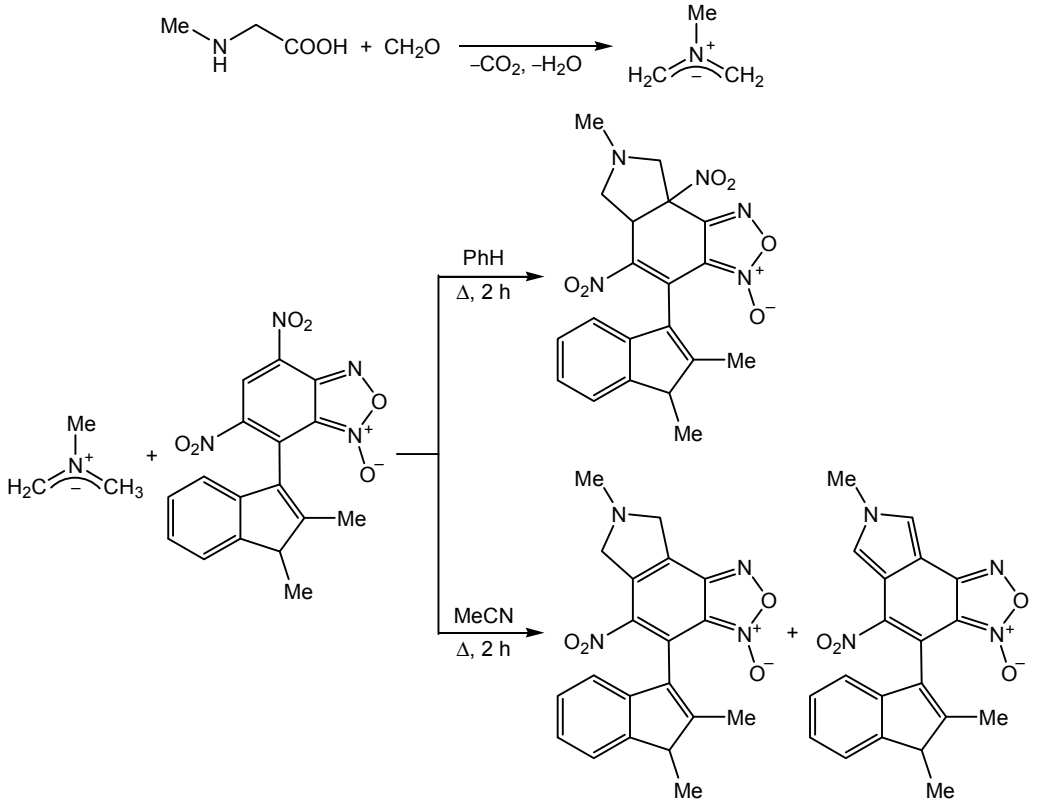


Universities and with the scientific interests of scientists supervising the joining departments since the moments of their foundation: Academicians of Russian Academy of Sciences M.M. Shemyakin and V.M. Rodionov, Corresponding Member of Russian Academy of Sciences D.N. Kursanov, Professors B.M. Bogoslavskii, E.A. Smirnov, Ya.Ya. Makarov-Zemlyanskii, Yu.A. Romanov, and A.G. Repin, honored worker of science and technics of the USSR G.A. Shvekhgeimer.

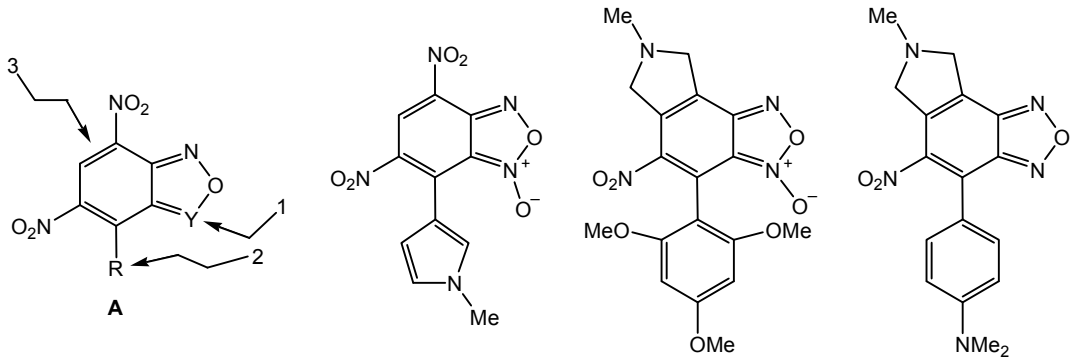
One of research directions regularly developed at the department is the synthesis and the study of properties of various classes of dyes capable of coloring textile and other materials providing high stability of color with respect to various physicochemical actions and simultaneously protecting the material from destruction by moldy fungi. The latter is especially important for materials used under elevated moisture and temperature, and also for those of special purposes (used in army, ministry of special situations etc.). The application of such dyes in industry provides a possibility to combine the processes of dying and biocidal finishing thus improving the technical and economical quality of the process.

Within last 8–10 years the researchers of the department synthesized over 200 new organic compounds, semiproducts for dye synthesis, and over 250 new azadyes from these semiproducts. A number of biophore fragments are revealed, as a rule, five- and six-membered nitrogen heterocycles, whose introduc-

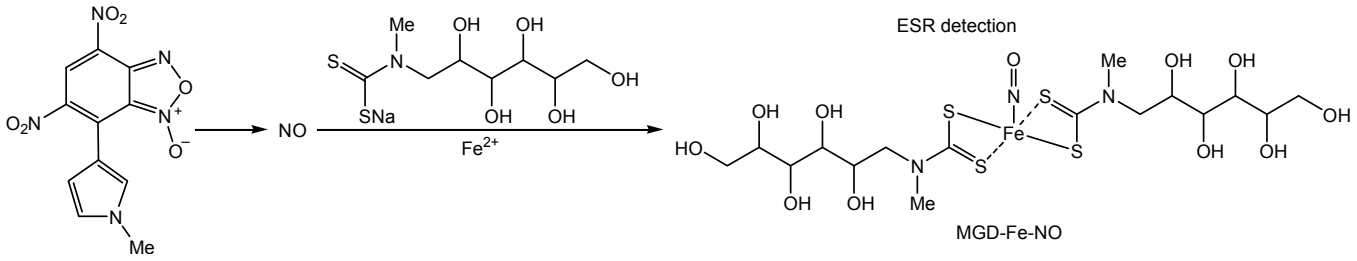
Scheme 24.13.



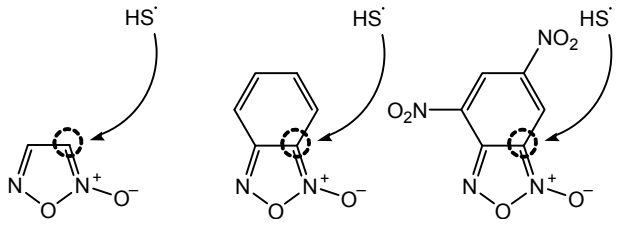
Scheme 24.14.



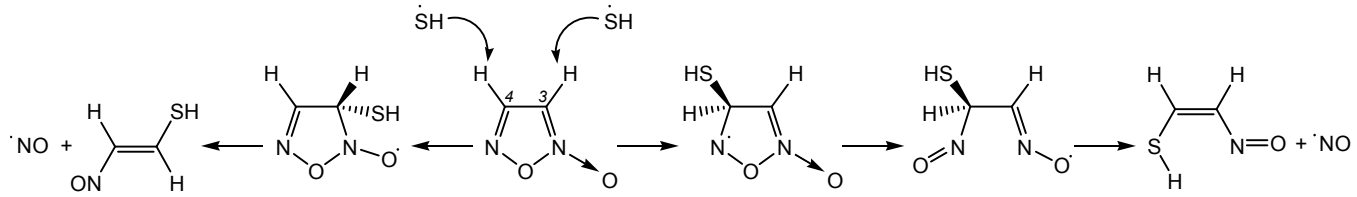
Scheme 24.15.



Scheme 24.16.



Scheme 24.17.

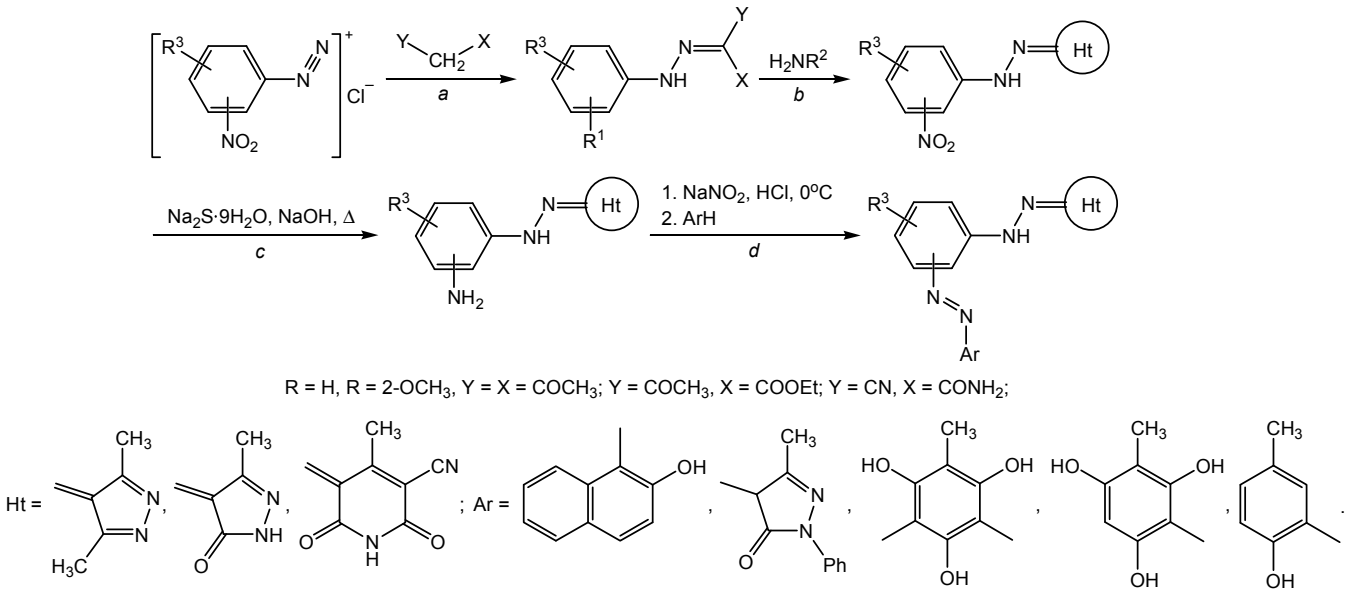


tion into the dye molecule makes it possible to obtain azo compounds with the desired properties. The synthesized compounds were subjected to testing by modified method in the Center of biologic control of the laboratory of microfilming and documents restoration of the Russian State Archive of Scientific and Technical Documentation [986]. The results obtained were the basis for the design and purposeful synthesis of dyes capable on the level of 90% from the reference show the biostability against the action of moldy fungi (*Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Ulocladium atrium*, *Chaetomium globosum* etc.) [987–989].

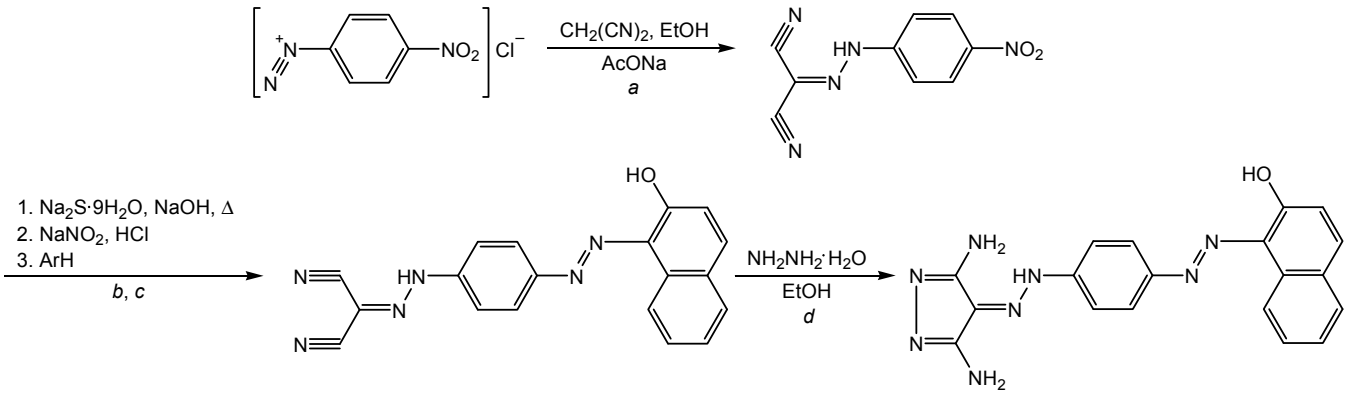
Synthetic procedure was developed at the department for the preparation of the target biocidal azo compounds consisting in a stage of formation in the molecule of the chromophore system (color) and biophore fragment (fungicidal property). The azo compounds prepared by the developed method are efficient dyes for fibers of various chemical nature and they are able to provide the dyed materials with a high fungicidal activity. This approach was performed along two schemes [990].

The first synthetic scheme included the following stages: azocoupling of diazocomponent containing a

Scheme 25.1.



Scheme 25.2.



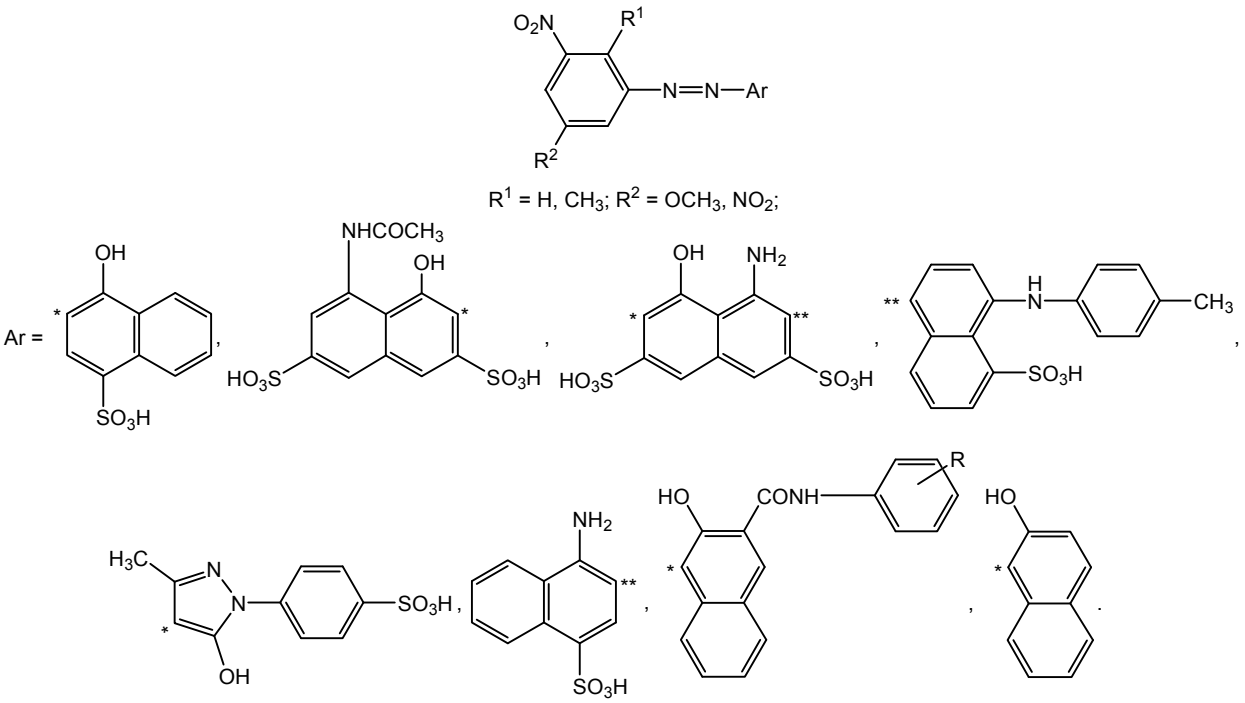
nitro group in the aryl fragment with versatile methylene active compounds (*a*); formation of biophore fragment (heterocycle synthesis) by cyclization involving the functional groups of hydrazonocompounds (*b*); reduction of the nitro group in the aryl fragment of the obtained azo compounds (*c*); formation of the chromophore system by successive diazotization and azocoupling reactions (*d*) (Scheme 25.1).

The alternative synthetic scheme includes the following stages: azocoupling of diazocomponent containing a nitro group in the aryl fragment with versatile methylene active compounds (*a*); reduction of the nitro group in the aryl fragment of the obtained azo compound (*b*); formation of the chromophore system by successive diazotization and azocoupling reactions (*c*); formation of biophore fragment (heterocycle synthesis) (*d*) (Scheme 25.2).

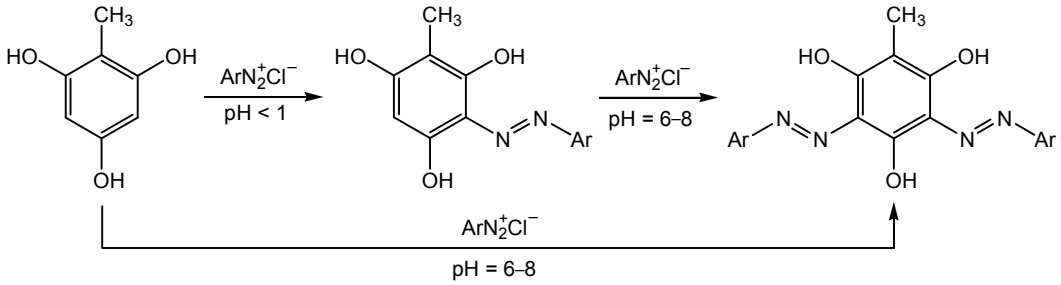
Lately at the department a direction is developing concerning the chemical transformation of 2,4,6-trinitrotoluene (TNT) in useful chemical products of common applications. The research is carried out in collaboration with the staff of laboratory no. 18 of Zelinskii Institute of Organic Chemistry of the Russian Academy of Sciences. These studies are aimed at the transformation of TNT into raw material “of double purpose” and at the utilization of “demilitarized” TNT taken from waste ammunition [991].

Proceeding from amines obtained by selective reduction of TNT and 1,3,5-trinitrobenzene a series of azodyes and azopigments was synthesized; among them some showed a high thermal stability (up to 350°C) (Scheme 25.3) [992].

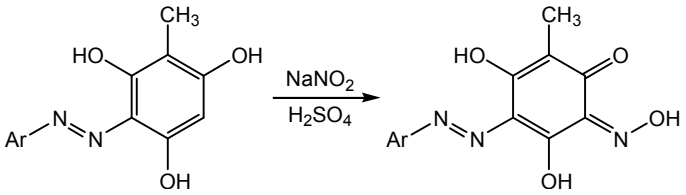
Scheme 25.3.



Scheme 25.4.



Scheme 25.5.

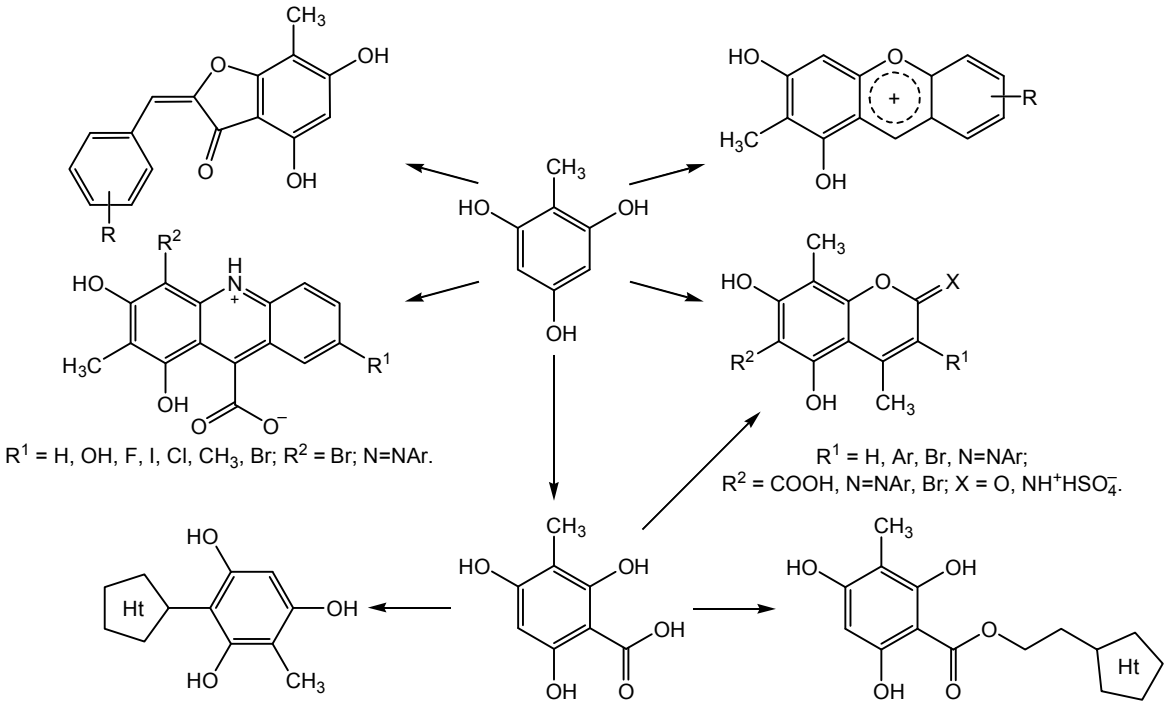


From another product of the chemical transformation of TNT, 2,4,6-trihydroxytoluene (methylphloroglucinol) possessing a high synthetic potential organic compounds of versatile structures were prepared.

Methods of selective synthesis were developed and samples of over 130 mono- and bisazo compounds were prepared and it was established that they all depending on the structure may by recommended for coloring textile materials from fibers of various origin and also for fur, wood, and plastics (Scheme 25.4) [993].

Proceeding from monoazoderivatives of methylphloroglucinol a series of its azo nitro derivatives was synthesized for the first time. These products are of interest as dyes and modifiers of polymer materials that provide the latter with sorption activity and sometimes also fungicidal properties (Scheme 25.5).

Scheme 25.6.



One more synthetic way of methylphloroglucinol utilization is the synthesis therefrom of six-membered fused *O*,*N*-heterocyclic compounds, synthetic analogs of natural substances [994, 995].

Due to the features of the structure methylphloroglucinol depending on the reagent type and reaction conditions can form regioisomers in the cyclocondensation. Conditions were found for the regioselective proceeding of necessary reactions (Scheme 25.6).

In the course of examination of physicochemical characteristics of the synthesized heterocyclic compounds a number among them exhibited pronounced luminescent properties and are of interest for developing new luminophores.

The results of computer screening of biophysical characteristics, biologic activity, and acute toxicity of synthesized polycyclic compounds permit a conclusion that it is purposeful to use these products as objects for testing as chemical pharmaceutical preparations in the schemes of fragmentary oriented design of promising drugs.

The study of the biologic activity of the synthesized polycyclic compounds *in vitro* showed a moderate inhibiting activity with respect to examined test-strains. The tested compounds showed a high activity with respect to fungi *Candida albicans*.

The results of mycological studies on the series of *O*-containing heterocyclic compounds allow a conclusion that a number of tested compounds are of interest as moderately active fungicides against certain fungi kinds living on textile materials. The synthesized dihydroxy-2*H*-1-benzopyran-2-one derivatives exhibit a pronounced antioxidant property.

The above results allow a conclusion that the synthetic potential of methylphloroglucinol provides a possibility to regard it as a promising compound platform in the small scale chemical industry.

At the department efficient work is in progress on the synthesis of organic compounds possessing specific ligand properties and used for modification of natural and synthetic fibers in order to obtain efficient chemosorption quality of materials and products. The long investigations on the interaction of dyes having chelating groups with metal ions and nanosized silver particles led to establishing a technology of the preparation of nanomodified fabrics implemented in some industrial enterprises. Using the developed technology stokings and socks, thermal underwear, top knitwear, military uniform with bactericidal properties are produced. The applied technology makes it

possible to conserve the biocidal action after many washings [996–998].

26. CONCLUSION

The main goal of this survey is establishing contacts between colleagues. We hope that the picture of the organic chemistry development in Russian Universities drawn in this review will be useful for all colleagues working in this most interesting part of sciences.

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