National Academy of Sciences of Ukraine

State Scientific Institution "Institute for Single Crystals"

ABSTRACT OF WORK

HIGH-SELECTIVE DESIGN OF BIOACTIVE HETEROCYCLIC SYSTEMS

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Relevance of work. Organic synthesis plays a key role in the development of innovative drugs. During the 20th century up to its last decade, organic synthesis of new biologically active compounds has significantly outstripped the potential of pharmacology to evaluate their activity. Screening has been a limiting stage in the detection of active pharmaceutical substances for a long time, and biological tests were conducted mainly in *in vivo* experiments, which required significant amounts of compounds and did not require molecular diversity. Progress in science has made radical changes in the process of selecting of potential drug candidates, therefore, screening capabilities have become dominant in the 1990s. An urgent need for highly efficient synthesis to provide a variety of compounds for the pharmacology has arisen, which led to revolutionary changes in the creation of medicines.

The chemical space available for today includes more than 100 million of organic compounds, mainly related to a limited set of classes and types. At the same time, modern trends in the creation of innovative drugs require introduction of original and highly effective synthetic approaches for equal and multi-vector filling of the chemical space as the primary source of the drug-like structures. Therefore, new strategies for the chemical synthesis had appeared, such as combinatorial chemistry, medicinal and biologically oriented synthesis, chemistry of molecular diversity. Alternative methods of chemical processes activation had spread: ultrasound, microwave irradiation, photo and mechanochemical methods. The interest in multicomponent reactions had increased.

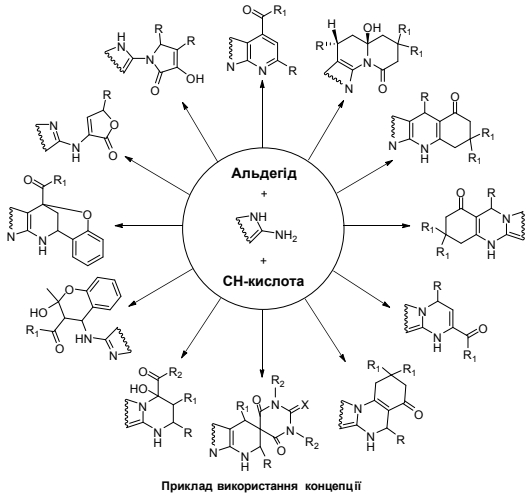
To a great extent these innovations have affected the chemistry of heterocyclic compounds as the main "supplier" of the drug-like molecules (near 80% of modern drugs contain heterocyclic fragments) which stipulates strict requirements both to the bioactive molecules as well as to the methods of their synthesis. In particular, patentable substances with certain physical and chemical properties, high level of specific action in combination with low toxicity became needed. In turn, methods of their synthesis should provide a diversity of molecular architectonics, high selectivity (chemo-, regio-, and stereo-) and atomic efficiency, be ecologically and economically justified. However, the simultaneous implementation of these requirements is rather difficult task, while research aimed at achieving a certain balance between them is relevant.

The main goal of this work is the development and progress of modern highly selective methods of structurally diverse functional heterocyclic systems constructing with powerful synthetic and pharmacological potential.

Scientific novelty of work:

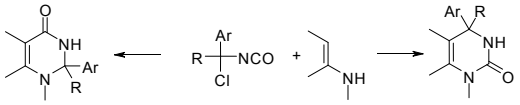
✓ synthetic possibilities of the heterocyclic compounds chemistry in the directions of search for fundamentally new methods of synthesis and organic reactions; convenient and affordable reagents and catalysts; structure-activity relathionship; ways of the purposeful design of the drug-like molecules had been substantially developed;

✓ a new concept for control of chemo- and regioselectivity of the heterocyclic reactions has been proposed:

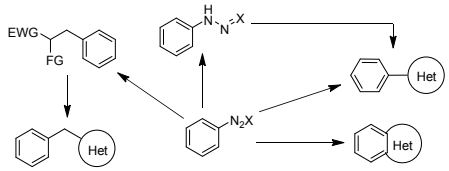


Приклад використання концепції

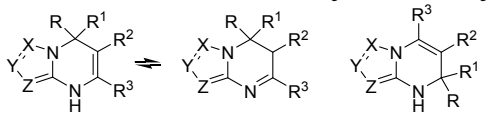
✓ a substantially new methodology for the synthesis of partially hydrogenated azine compounds using the enamine types of substrates has been developed:



✓ methods for the construction of heterosystems in new variants of highly selective reactions based on arenediazonium salts have been introduced in the organic synthesis:



✓ a new class of heterocyclic systems - dihydroazolopyrimidines with bridgehead nitrogen atom was discovered and made synthetically accessible:



✓ the opportunities for filling hard-to-reach segments of the chemical space in order to ensure the diversity of organic compounds have been increased.

14 New organic reactions had been discovered:

- heterocyclization of 5-aminopyrazoles, cyclic 1,3-diketones and aldehydes with the formation of new class of heterocyclic compounds – pyrazolo[4,3-*c*]quinolizin-9-ones that are analogs of natural alkaloids;
- multicomponent reaction of α,β-unsaturated ketones, carbonyl compounds and ammonia that yields substituted 1,2,5,6-tetrahydropyrimidines and 1,5,9-triazaspiro[5.5]undec-1-enes;
- domino reaction of 3-amino-1,2,4-triazoles, *o*-hydroxyacetophenone and two moles of aromatic aldehyde that leads to formation of triazolopyrimidobenzopyran systems;
- pseudo four-component reaction of 3-amino-1,2,4-triazoles, aldehydes and pyruvic acid with formation of 7-(4*H*-1,2,4-triazol-3-ylamino)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids;

- pseudo four-component reaction of aminoazoles, cyclohexane-1,3-diones and glyoxal with the formation of new indolo[1,2-*c*]azolo[1,5-*a*]quinazoline-8,10-dione system;

- sigmatropic rearrangement that follows transformation of 2'-benzoyl-2-oxohexahydrospiro[indoline-3,3'-pyrollizine]-1'-carboxylic acids into the 3-[5-aryl-2,3-dihydro-1*H*-pyrrolizin-6-yl]indolin-2-ones;

- synthesis of partially hydrogenated 1,2,4-triazolo[5,1-*b*]quinazolines in the reaction of alkylation of 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines by α,β-unsaturated ketones and their derivatives;

- rearrangement of 5,7-diaryldihydrotriazolo[1,5-*a*]pyrimidines in the Vilsmeier–Haack reaction with the opening of pyrimidine cycle and further recyclization;

- reaction of selective cyclocondensation of deactivated enamines, their enol and thiol analogues with α-chloroalkyl isocyanates and structurally related derivatives;

- domino Knoevenagel-*hetero*-Diels-Alder reaction of 4-thiazolidinethiones and dienophile aldehydes that opens synthetic routs for the obtaining of original isothiochromeno[4a,4-*d*]thiazoles and chromeno[4',3':4,5]thiopyrano[2,3-*d*] thiazoles;

- synthesis of 3-substituted isocoumarines and 3,4-dihydroisocoumarines based on intramolecular cyclization under arylation of unsaturated substances by *o*-alkoxycarbonilarene diazonium bromides;

- opening of tetrazole cycle under the action of N-nucleophiles that suggests convenient synthetic approach to substituted thieno[2,3-*d*]pyrimidines;

- one-stage synthesis of 1,2,4-triazoles by recyclization in the reaction of alkyl chloro-(2-arylhydrazynilidene)-ethanoates with thiazolidin-2,4-dione;

- domino reaction of 3-(furyl)allylamines with α,β-unsaturated carboxylic acids anhydrides, which includes N-acylation, intramolecular diene synthesis and aromatization with the formation of furo[2,3-*f*]isoindoles.

Content of the work. Reactions of cyclocondensation of α,β-unsaturated carbonyl compounds, their synthetic equivalents and precursors with mono- and diaminoazoles were studied for the first time. Synthetic approaches to dihydro derivatives of azolopyrimidines with bridgehead nitrogen atom were proposed, that allow obtaining compounds both of 1,2- and 1,4-dihydro types. It was established that cyclocondensations of aminoazoles with α,β-unsaturated carbonyl compounds and their synthetic precursors may have independent character of the pyrimidime cycle's formation mechanism.

A strategy, called Conditions-based Divergence Strategy in the world literature, for controlling chemo- and regio-orientation of multi-component heterocyclizations was developed. Multicomponent reactions of polynucleophiles and carbonyl compounds are proposed on its base. These reactions allow controlling the direction of interactions and to selectively synthesize above five different heterocyclic systems from the same starting chemotypes by changing the temperature, acidity of the medium, type of catalytic system or structure of the reagents. In particular, these multicomponent reactions target the following main directions:

✓ *involving the aminoazole component:*

- involving exocyclic amino group and CH-group with the formation of pyrimidine cycle;
- involving exo- and endocyclic amino groups with the formation of pyrimidine fragment;
- involving exocyclic amino group only with the formation of pyrrolone, furanone, chromane and acridinedione;
- involving CH-group only with the formation of xanthenone;

✓ *involving the α-carbonyl CH acid:*

- involving active methylene center and carbonyl group with the formation of pyridine or pyrimidine cycles;
- involving active methylene center and carboxylic group with the formation of pyrrolone or furanone derivatives;
- involving active methylene center only with the formation of spiro-heterocycles;
- involving active methylene center and carbonyl group with the opening of diketone fragment, rearrangement and formation of quinolizines;

✓ *involving the aldehyde moiety:*

- if in the aryl cycle *o*-hydroxy group is present – post-cyclization with the formation of oxygen containing bridge heterocyclic systems.

Complex research of the chemical features of dihydroazolopyrimidine systems with bridgehead nitrogen atom had been carried out. A powerful synthetic potential of partially hydrogenated azolopyrimidines as the base for drug-like substances synthesis had been identified. A fundamental difference between chemical behavior of dihydroazolopyrimidines and their non-annealed analogues was established, which lies in related decrease of ability to be oxidized comparing with the substitution reactions when interacting with electrophilic reagents (“chemical quazi aromaticity”).

Imine-enamine tautomerism in the rows of annealed dihydropyrimidines had been established as well as systematic analysis of its factors had been conducted. For the first time in the chemistry of heterocycles both individual tautomeric forms of compounds were isolated and characterized that experimentally illustrates the relativity of “tautomers” and “isomers” separation.

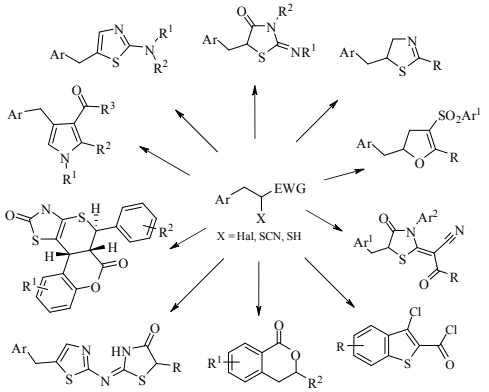
Based on the microwave and ultrasound irradiation, an efficient tool of flexible and wide variation of reaction’s conditions had been proposed for preparative organic synthesis. The possibility of multicomponent reactions of heterocyclization of aminoazoles, aldehydes and cyclic or non-cyclic α-carbonyl active methylene compounds under kinetic or thermodynamic control was shown, that allows to selectively manage their direction by changing the temperature, including non-classic methods of activation.

General approach to the reactions of arenediazonium salts with unsaturated compounds had been developed, which allowed to suggest methods of polyfunctional compounds synthesis – reagents for cyclization. It was shown that such reactions may proceed through different mechanisms depending: on the variants of one-electron transfer in the system and stability of corresponding intermediates; on the possibility of complex formation; on nucleophilicity and ability of exo-nucleophiles to take part in the reactions of one-electron transfer. Formation of the arylalkyl radical adduct at the last stage of the majority of anionarylation reactions occurs as intra-sphere oxidation

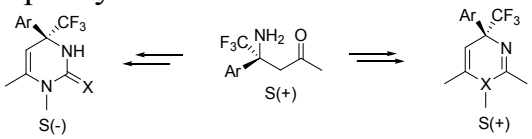
with the ligand transferring. Regularities of three-component reaction of non-saturated compounds with diazonium salts and SO_2 were established.

Arylation of the functionalized pyrrols, thiophens, furans and a series of six-membered heterocycles by aryldiazonium salts had been performed for the first time, as well as its region-orientation had been established. Methodology of synthetic usage of 2-functionalized 5-arylfurans (-pyrrols, -thiophens) in biologically active substances design was developed. A series of new multi-component reactions for the synthesis of polysubstituted derivatives of pyridine, pyrimidine, imidazo[1,2-a]-pyrimidine, imidazole and partially hydrogenated acridines had been developed.

Efficient modifications of Meerwein and Sandmeyer reactions based on the usage of arenediazonium tetrachlorocuprates (II) were found. Conditions of new catalyst – iron chloride (II) effective usage in the reaction of chloroarylation of unsaturated substances had been developed. It was shown that arylation and anionarylation of unsaturated compounds by arenediazonium salts is convenient method for the synthesis of polyfunctional reagents used in heterocycles design:



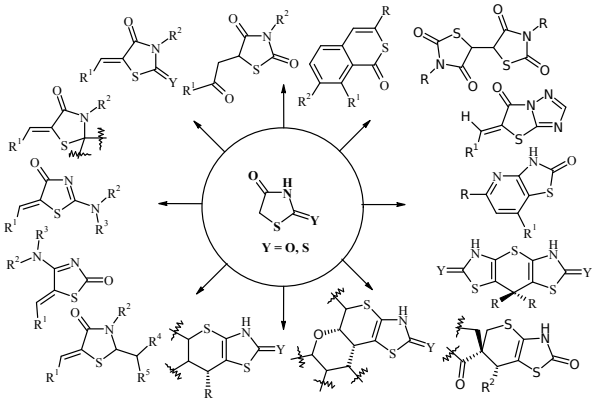
The principles of the design of optically active azine systems with trifluoromethyl group were developed. An effective organocatalytic method of new chiral β-trifluoromethyl-β-aminoketones obtaining was proposed. Synthetic potential of the latter as important bifunctional synthetic blocks for implementation of preparative convenient approaches to a row of partially hydrogenated azine structures of high optical purity was discovered:



New methodology for highly electrophilic 4-trifluoromethyl-2-oxo-1,2-dihydropyrimidine-5-carboxylates synthesis was developed, which is based on regioselective cyclocondensation of β-aminoesters and N-(1-chloro-2,2,2-trifluoroethylidene)-carbamates. They were shown to be original electrophilic systems with endocyclic alkenyl and iminoacyl fragments that allowed to treat them as efficient substrates in the reactions of C-C bond formation.

A new approach to regio- and enantioselective carbo-functionalization of 4-trifluoromethylpyrimidine-2-ones was developed, which is based on the reactions of the latter with C-nucleophilic reagents in the conditions of organocatalysis, including assymetric organocatalysis.

Efficient regio- and stereoselective methods of polyfunctional 5-ene-4-thiazolidinones, thiopyrano[2,3-*d*]thiazoles, thiazolo[4,5-*b*]pyridines and related heterosystems synthesis had been developed in a detailed study of structural modifications of «4-thiazolidinone matrix»:



The rows of new 4-thiazolidinones were obtained, for the first time, as a result of systematic research of [2+3]-cylocondensation reaction of different S,N-binucleophiles with the equivalents of dielectrophilic synthone $[C_2]^{2+}$. Investigation of their behaviour in the Knoevenagel, *N*-alkilation, acylation and aminolysis reactions allowed to synthesize biologically active 2- and 3-substituted 5-ene-4-thiazolidinones.

It was shown that 5-ene-4-thiazolidinethiones are effective heterodienes in the [2+3]-cycloaddition reactions. This allowed proposing regio- and diastereoselective approaches, including numerous tandem acylation-*hetero*-Diels-Alder reactions and semiacetals formation, to the synthesis of new biologically active functional derivatives of thiopyrano[2,3-*d*]thiazole and chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazol-2-one.

For the first time, it was established that reaction of 2-thioxo-4-thiazolidinone and 4-amino-5*H*-thiazol-2-one with arylidene pyruvic acids goes as [3+3]-cycloaddition with the formation of 7-arylthiopyrano[2,3-*d*]thiazol-2-ones and 2,3-dihydrothiazolo[4,5-*b*]pyridines.

Based on unsaturated azlactones new phosphorylated enamides, phosphorylated azlaktone analogues, phosphorus-containing 2-aza-1,3-dienes as well as phosphonium ylides and betaines were obtained, that opens up wide opportunities for further synthesis of different acyclic and heterocyclic organic phosphorus compounds.

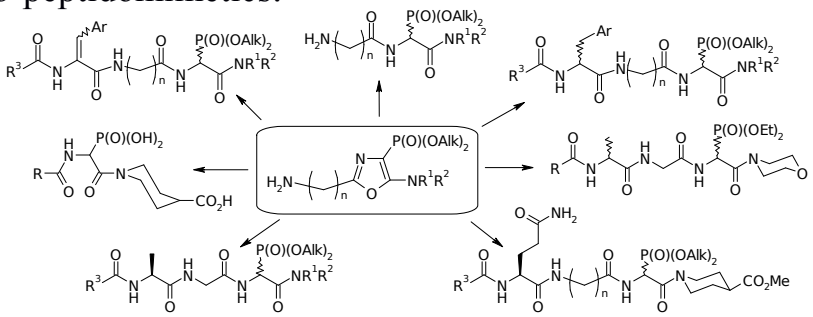
A unique reactivity of chloro-containing azlaktones was identified, which lies in regio-selective reaction of electrophilic centers of dichloromethylene group and carbonyl bond with «soft» and «hard» nucleophiles and formation of polycentric intermediates capable of transformations characteristic for unsaturated azlactones.

It was shown that available derivatives of 5-mercapto-, 5-amino- and 5-hydrazino-1,3-oxazoles are unique substrates for new types of potential bioregulators creation, in which oxazole ring remains or transforms into other azole systems.

It was established that condensation of tetrachloro-substituted 2-aza-1,3-dienes with 2-(aminoalkyl)benzimidazoles goes as regio-selective

annealing of benzimidazole system to seven-, eight- and nine-membered azaheterocycles with formation of triazepine, triazonine and triazocyne derivatives unknown before.

It was shown that 1,3-oxazol-4-ylphosphonic acids are unique reagents for synthesis of new derivatives of α-aminophosphonic acids, phosphorylated peptides and phosphono-peptidomimetics:



New reagents for the design of thiazoles, 4-thiazolidinones, 5*H*-[1,3]thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidin-4-one and polysubstituted pyrrols were proposed.

Regioselectivity of cyclizations of 2-aryl-1,4-benzoquinones with thiocarbamide, alkyl xanthogenates and dimercaptocarboxylic acids derivatives was clarified that allowed developing the method of 1,3-benzoxathiol and 1,3-benzodithiol derivatives synthesis. It was established that cyclization of 2-aryl-1,4-benzoquinones with CH-acids yields 7(6)-aryl-5-hydroxybenzo[*b*]furans and furobenzofurans.

The possibilities of substituted aryl(heteryl)azides utilization in the reactions with functionalized CH-acids, including molecular design of 1,2,3-triazole and 1*H*-tetrazole, were identified.

Efficient methods of the ethyl 1*H*-pyrazol-3-carboxylates synthesis were developed that made them available reagents, including synthesis of heteryl-substituted 1-arylpyrazoles and 1-aryl-1,2,3-triazoles.

New one-step method of 1,2,4-triazoles synthesis based on the reaction of ethyl chloro-(2-arylhydraziniliden)-ethanoates with thiazolidin-2,4-dione was found. Convenient method of thiopyrano[3,4-*c*]pyrazoles synthesis is recyclization of products of ethyl 1-aryl-4-formyl-1*H*-pyrazol-3-carboxylates condensation with rhodanine under the action of alkali.

As the key reagents for the formation of functional azine cycles original bielectrophilic α-chloroalkylisocyanates and α-alkylidenecarbamates were proposed. This allowed putting into the practice of new equivalents of aza-allyl synthones and the development of new scheme of partially hydrogenated azine substances design, which implies C-C bond formation with the usage of various substrates of enamine type.

General character of the reaction of 1-chlorobenzylisocyanates with alkoxy-carbonilmethylenepiperazines (quinoxalines, morpholines, benzo[1,4]oxazines) was identified that opens the ways to original pyrazino[1,2-*c*]pyrimidines, pyrimido[1,6-*a*]quinoxalines and pyrimido[6,1-*c*][1,4]oxazines or benzoxazines.

An approach to isomeric pyrrolo[3,4-*d*]pyrimidime-2,5-diones synthesis was found, which lies in regioselective addition of nitromethane to 4-trifluoromethyl-pyrimidin-5-carboxylates with further reduction of nitro group and

thermal cyclization. Regioselective hydrocyanation of 5,6-unsubstituted 4-trifluoromethylpyrimidin-2(1*H*)-ones with further methanolysis of the obtained carbonitriles was developed as synthetic method for new trifluoromethylated analogues of 4,5-dihydroorotic acid and its esters in racemic as well as in enantiomeric pure forms.

Practical value of the work is in development and usage of new methods of original heterocyclic compounds, new heterocyclic systems and heterocyclic ensembles synthesis, which have a wide range of practical applications, primarily as reagents for fine organic synthesis and sources for biologically active substances. Using the developed methods, new libraries of organic compounds were created, their biological activity was investigated and lead-compounds that may be used for drugs design were identified.

Based on the available reagents, preparative methods for synthesis of «building blocks» for a series of azoles and azines, their annealed and hydrogenated derivatives were developed. More than 300 systematic series of heterocycles and more than 100 thousand of new compounds were obtained. The prognostic criteria for *de novo* design of drug-like moleculs were formulated.

For the obtained substances such kinds of activities were identified: antibacterial, anti-inflammatory, anticancer, anti-tuberculosis, antivirus, analgesic, antioxidant, antidiabetic, hypotensive, antitrypanosomal, cardiostimulating, membrane stabilizing, hemolytic and neuroleptic. There were discovered more than 30 drug candidates with high antitumor, antivirus, cardiostimulating and antidiabetic activities that along with low toxicity profiles are the reasons for their in-depth pre-clinical studies.

New small-scale method for the synthesis of chloramphenicole is proposed and laboratory regulations were developed.

New microwave one-pot method for the formation of alkaloid pyrazoloquinolisine core was developed, which has no analogues.

“Biological” and “chemical” solutions of the fundamental problem of Michael acceptors as potential “promiscuous inhibitors” were found based on 5-ene-4-thiazolidinones. “Biological” way was based on the optimization of polypharmacological properties of hit-compounds by the modification of positions C2, N3, C5 in “4-thiazolidine matrix” as well as on the synthesis of isosteric heterosystems and hybrid-pharmacophore approach implementation. “Chemical” way, in its turn, is based on the experimentally confirmed hypothesis about thiopyrano[2,3-*d*]thiazoles and thiazolo[4,5-*b*]pyridines being cyclic isoster mimetics of pharmacologically active 5-ene-4-thiazolidinones without “Michael acceptors” properties.

Linear and nonlinear correlations “structure-anticancer activity” for 4-thiazolidinones and related heterosystems are established for the first time. A model of anticancer pharmacophore was built that allowed implementation of *denovo* design of compounds with significant anticancer effect.

Based on the “double-drugs” concept, for the first time, original semisynthetic 4-thiazolidinone substituted oleanane derivatives containing natural triterpene scaffold, linker oxime group and heterocylic core were synthesized.

These derivatives showed highly selective antileukemic activity and good toxicity parameters in *in vivo* study.

It was established that molecular mechanisms of thiazolidinones and their analogues anticancer effect is implemented by the induction of cell apoptosis through tree possible molecular mechanisms: “classic apoptosis”, “mixed apoptosis” or “caspase-independent apoptosis”.

Some of the compounds are used in other fields of chemistry and material science: as dyes and complex compounds for analysis; for explants sterilization, as fungicides and herbicides; as components of compositions for organic electronics, including organic light-emitting diodes (OLEDs); as adhesive and sealing materials used in components of measuring equipment, microcircuits and semiconductor elements; for obtaining thin coatings with a wide temperature spectrum (–196 ÷ +250°C) and improved physical chemical properties.

Research results are used in implementation of various lecture courses, practical classes and laboratory works at leading Ukrainian Universities.

Conclusions

1. New concept of directed organic synthesis is proposed. Novel methods of synthesis are created as well as existing synthetic methods for highly selective construction of new types of heterocyclic systems with good synthetic and pharmacological potential have been substantially developed that is a reliable experimental basis for the creation of new materials and active substances for biomedical research.

2. A number of fundamental principles of organic chemistry on the structure of organic compounds and their reactivity have been developed. A phenomenon of imine-enamine tautomerism of dihydroazolopyrimidine systems was identified and analyzed and the relativity of “tautomers” and “isomers” separation was illustrated. The phenomenon of chemistry quazi-aromaticity for a particular class of partially hydrogenated heterocycles was identified and studied, for the first time. An essential contribution is made to solving the fundamental problem of directed functionalization of heterocyclic systems, in particular, the methodology for creating a new carbon-carbon bond with the use of classical organic reactions and the latest catalytic methods is worked out.

3. In the practice of organic synthesis, a number of new environmentally attractive, preparation-efficient and readily available reagents and catalysts for heterocyclic reactions and structural rearrangements have been introduced; 14 new organic reactions were discovered, their main regularities, mechanisms and limits of their application were studied.

4. Based on systematic combination of pharmacological screening methods, *in silico* research of structure-activity relationships (SAR) and biological tests *in vitro* and *in vivo* priority activity types for classes of studied heterocycles were outlined and experimentally established antibiotic, anti-inflammatory, anticancer, antituberculosis, antiviral, antioxidant, antidiabetic, antihypertensive, analgesic, antitrypanosomal and neuroleptic activity on the background of low toxicometric parameters. The hit- and lead compounds have been discovered for further optimization, in-depth research and

directed synthesis of new biologically active molecules as potential drugs.

The results of research carried out during 1991-2016 are published in 36 monographs and collective monographs, 47 scientific reviews and 666 original articles. According to the results of scientific research 118 patents were obtained. The h_{index} (Scopus) of all publications included in the work is 33, their index of citation is 5883. The total number of publications of applicants in the Scopus database is 936, and the number of their citation is 5945, the total h_{index} of scientific team members is 102 (Volodymyr Brovarets – 8, Mykhailo Vovk – 12, Sergiy Desenko – 20, Roman Lesyk – 23, Victoria Lipson – 10, Mykola Obushak – 13, Valentyn Chebanov – 16). 10 Doctoral (DSc) and 76 candidates thesis (PhD) have been defended on this subject.