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CHEMISTRY OF THE HETEROCYCLIC COMPOUNDS IN V.N.KARAZIN UNIVERSITY AND IN KHARKIV

Imperial Kharkiv (then State and, finally, National) University was opened in January 1805, in these days Organic Chemistry was just originated as a Science. But already in 1842 Prof. P.Eynbort has studied some properties of xanthine. However, the systematic studies were initiated by Prof. A.Khodnev in the field of natural organic acids; he also developed the first course of Organic Chemistry, later published as a textbook. Natural carbon acids became for many years the main objects of study of our university chemists.

Department of Organic Chemistry as a self-funded structure was formed in 1894. Highly systematic synthetic and spectrographic researches in the chemistry of pyrrole were made by one of this department first head – Prof. Yu.Korshun. K.Krassuky and his students studied a variety of amines focused on piperidine and piperazine. In the 1930s, at the Institute of Chemistry, established at the University, it was opened Laboratory of heterocyclic compounds, where it were continued the study of pyrrole chemistry and related systems. This trend has been actively developed at the Department of Organic Chemistry at the head of Prof. E.Khotinskii (which became widely known thanks to his repeatedly reprinted textbooks in organic chemistry). Since then, the heterocycles formed the basis of the majority of research in the department. For example, they formed the basis of great series of works of Prof. B.Krasovitskii dedicated chemistry of dyes and fluorescent materials.

Since 1959 the department was headed by Prof. V.Lavrushin, whose range of scientific interests included first of all triaryl methanes halohromy. However, seeking to expand this range, he has set the task of synthesis of heterocyclic unsaturated alcohols (with a pronounced halohromy), which is clearly the way to go through the recovery enough available unsaturated ketones – heterocyclic analogues of chalcones. With this task successfully coped Prof. S.Zuckerman with his disciples, who includes the author of these lines have been able to reveal the ability of unsaturated ketones act as bielektrophiles in the synthesis of a variety of nitrogen-containing heterocycles: pirazolines, partially hydrogenated pyridine and pyrimidine, benzodiazepine and polycyclic aziridinilaniles, and so on.

And these studies have always attracted the support, development, deepening and the search for new directions in the SSI “Institute for Single Crystals”, in National University of Pharmacy and that was the reason for organizing and conducting on our database systematically International Conference "Chemistry Nitrogen Containing Heterocycles" Today – VII – seventh - "CNCH-2015" !!!

Prof. V.D. Orlov

ORAL REPORTS

Development of Novel Building Blocks to Accelerate Drug Discovery

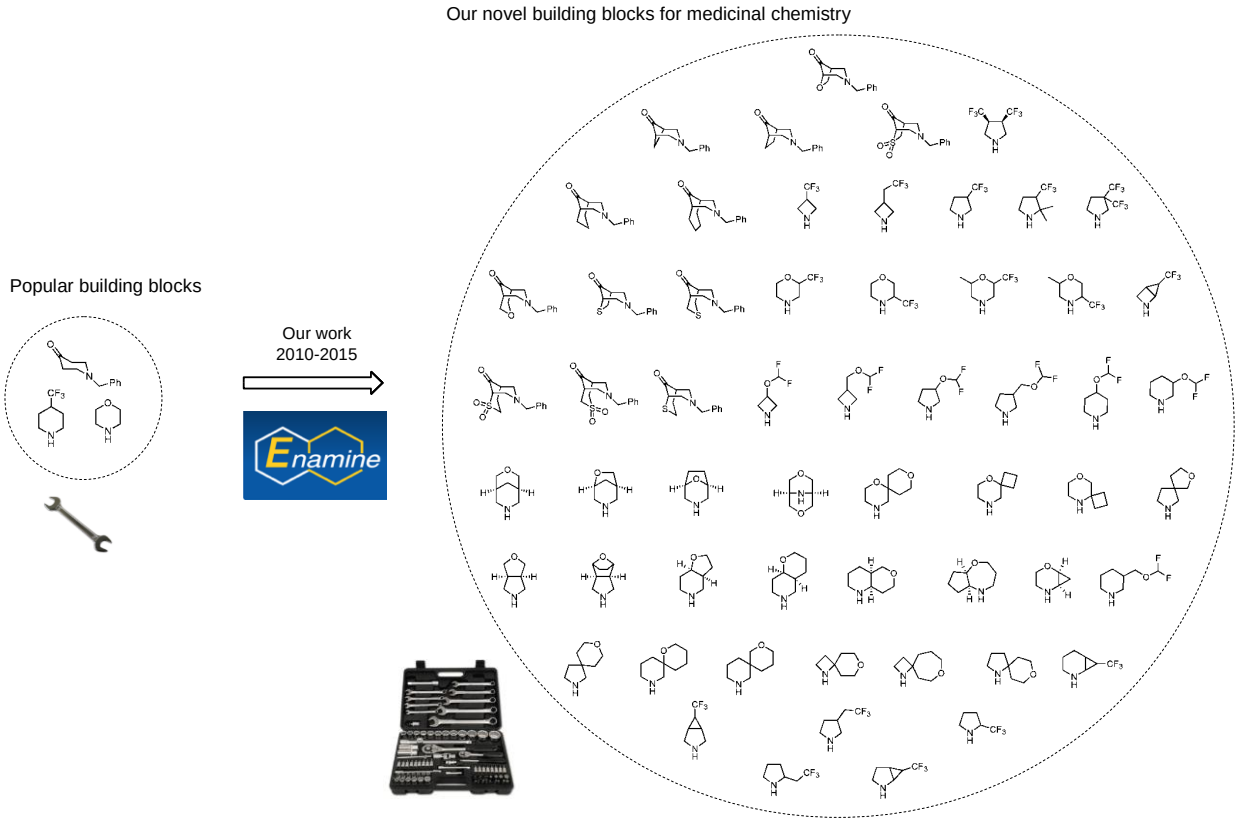
O-1

Andrei A. Tolmachev

Enamine Ltd., 78 Chervonotkatska str., 02094, Kyiv, Ukraine

>96% of medicinal chemistry projects fail. Often, medicinal chemists can not fine-tune the chemical structure of lead-candidates, because of low availability of the corresponding building blocks: many tiny molecules with 4-6 carbon atoms still remain unknown.

Therefore, recently we started a project on developing novel structures for drug discovery. We first rationally designed each compound following the principles of "Conformational restriction," "Escape the Flatland"[2] and "Scaffold hopping."[3] Then, we synthesized diverse libraries of novel *morpholine surrogates* (Figure 1a), *unusual scaffolds*, and *fluorinated amines* (>500 structures).[4]



Indeed, after publishing the synthetic details,[4] and making the compounds commercially available, they found a huge practical application in drug discovery (Figure 1b). We do believe, that these structures will inevitably lead to discovery of novel drugs very soon.

Details of the compounds design, synthesis and application in drug discovery will be discussed.

[1] A. Mann In *The Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C. G., Ed.; Elsevier: Amsterdam, 2008; p. 363.
[2] F. Lovering *et al. J. Med. Chem.* **2009**, *52*, 6752.
[3] H.-J. Böhm *et al. Drug Discovery Today: Technol* **2004**, *1*, 217.

[4] We published >80 manuscripts on these topics. Please, see: www.enamine.net / Research / Publications http://www.enamine.net/index.php?option=com_content&task=view&id=180

O-2

Synthesis and Luminescent Properties of the Imidazole and Pyrimidine Derivatives and their Complexes with Lanthanides

A.A. Yavolovskii, N.V. Rusakova, G.L. Kamalov

A.V. Bogatsky Physico-Chemical Institute of NAS Ukraine,
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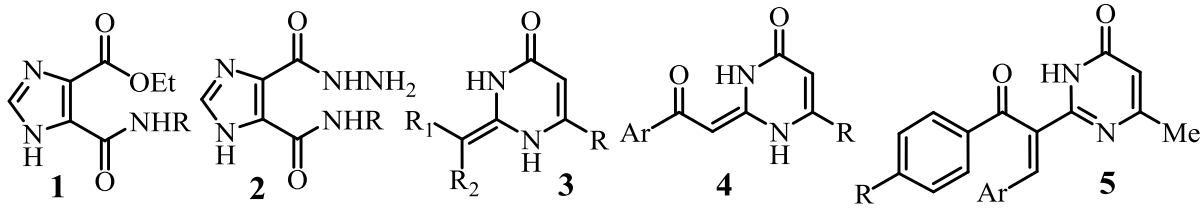
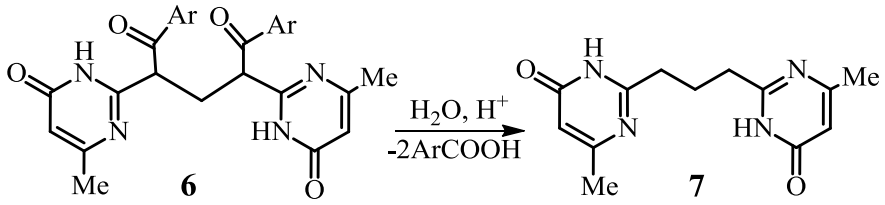
The peculiarities of synthesis of the imidazoles (**1** and **2**) and pyrimidines (**3**-**5**) – perspective as "building blocks" for obtaining of photometric and fluorescent chemosensors of cations, anions and biologically active molecules are considered.



It was revealed, for example, that compounds **5** are formed by interaction of pyrimidines **4** with aromatic and heteroaromatic aldehydes, whereas in reaction **4** with formaldehyde *bis*-compounds **6** are formed, which easily transformed to 1,3-disubsti-tuted propane **7**. A close correlation ($0{,}98 \geq R^2 \geq 0{,}94$) of the intensity ($\mathbf{I_{fl.}}$) and quantum yield ($\boldsymbol{\varphi_{fl.}}$) of fluorescence and values of lipophilicity descriptor CLogP for ketone and enol forms was disclosed. As for imidazoles (22 compounds) and pyrimidines(14 compounds) both relationships in the coordinates $\varphi_{fl.}$-CLogP are parabolic. In contrast to the **1** and **2**, the pyrimidines $\varphi_{fl.}$ values in DMF are higher than that in MeOH. At the same time, for compounds **3-6** containing in position "2" aromatic (heteroaromatic) fragments, bathochromic shifts of the fluorescence bands in the 10-40 nm were observed, which is qualitatively similar to "distribution" of studied pyrimidines on the respective "branches" of the parabola.



Based on the solvatochromic effects of fluorescence in a wide range of solvents and interpretation of spectral data taking into account parameters of the Kamlet-Taft correlation equation the conclusion is made that an increase of the solvent polarity and its basicity stabilizes the excited states of the studied compounds molecules.

The features of the 4f-luminescence of complexes **1-7** with Tb (III), Yb (III) and Eu (III) ions in the visible and infrared range of the spectrum due to the composition and structure of the ligands as well as the complex composition, which does not changes during the transition from the solid state to the solution are discussed.

This work was carried out in the frame of Comprehensive program of basic research of the NAS of Ukraine "Fundamental problems of the creation of new substances and materials of chemical production" (Project № 34-15).

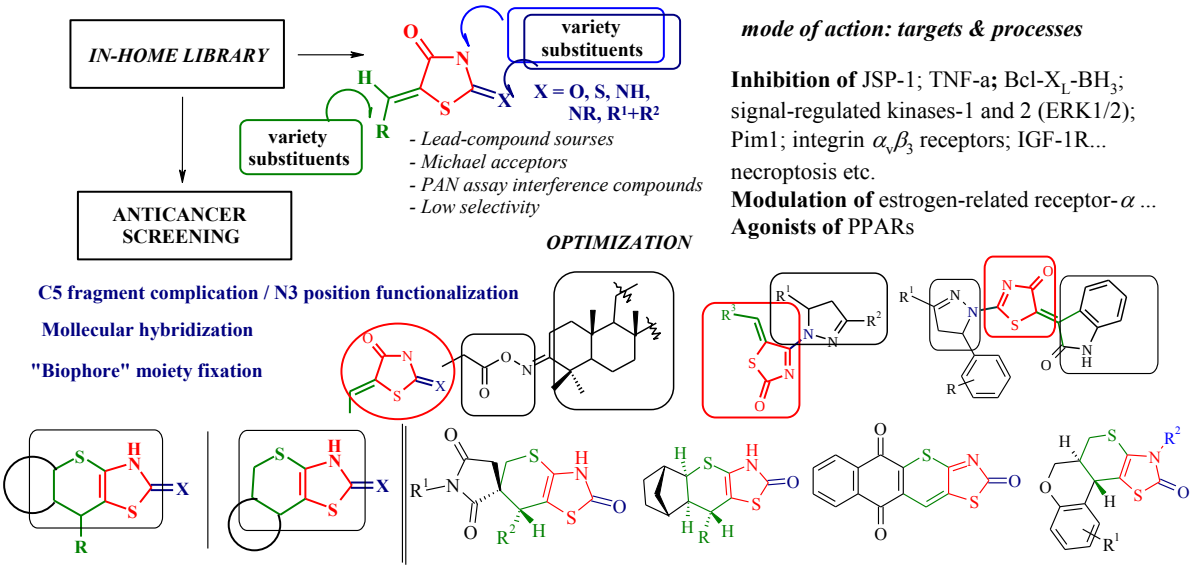
5-Ene-4-thiazolidinones: Promiscous or Polyfunctional Compounds in Drug Design

O-3

Lesyk R., Zimenkovsky B., Kaminskyy D., Kryshchyshyn A., Havrylyuk D., Zelisko N., Devinyak O., Khyluk D., Roman O., Lozynskyi A., Lelukh M., Wojtyra M.

Danylo Halytsky Lviv National Medical University, Pekarska 69, Lviv-10, Ukraine, dr_r_lesyk@org.lviv.net

5-Ene-4-thiazolidinone-based compounds are of special interest as powerful tool in the design of new drug-like molecules. It's reflected in the thesis about crucial role of the C5 substituent in the biological activity. Ene fragment conjugation to the C4 carbonyl makes compounds to be Michael acceptors. This characterizes them as frequent hitters or PAINs that may be useless in drug discovery because of insufficient selectivity. While, such Michael acceptors are among the most effective activators of Nrf2, which opens perspectives in the treatment of inflammation, cancer, etc. The project is aimed to explore 5-ene-4-thiazolidinones for anticancer agents design: pro & contra.



The in-house library of new 4-thiazolidinones have been designed and synthesized. Anticancer screening within NCI DTP protocol led to SAR database formation; lead-compounds identification; design of focused sub-libraries; formation and validation of hypotheses for structure optimization: *i*) complications of C5 fragment and/or functionalization of N3; *ii*) creation of the hybrid molecules; *iii*) annulation of 5-ene-4-thiazolidinones in fused heterocycles (thiopyrano[2,3-*d*]thiazoles were found as a cyclic isosteric mimetics); *iv*) the leukemia panel was detected to be the most sensitive cancer sub-type. Based on *in silico* and pharmacological data the arguments in favor of the apoptotic related and mild prooxidant actions of 4-thiazolidinones have been found.

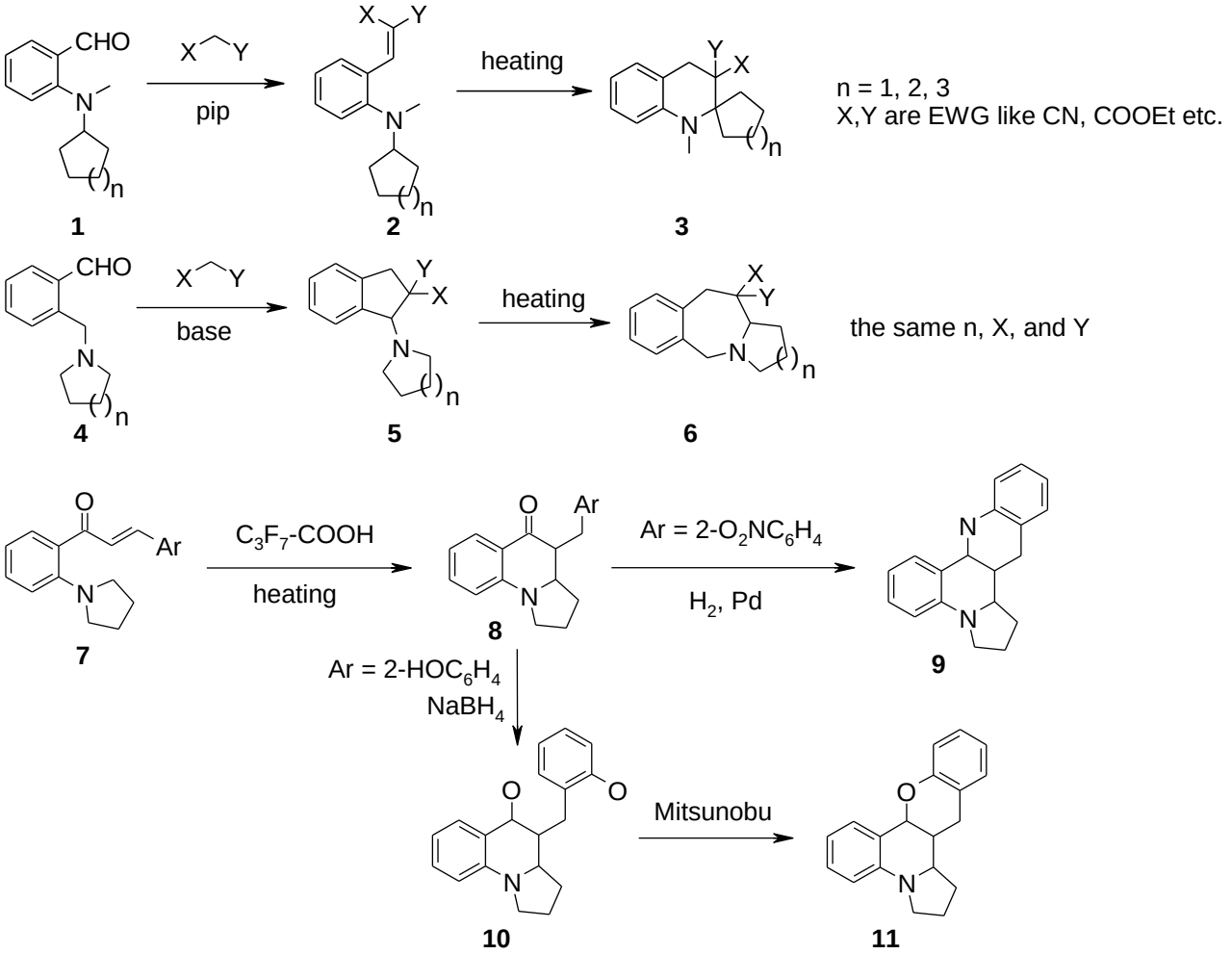
References:

O-4

Some Novel Types of tert-Amino Effect Reactions

A V. Tverdokhlebov, A. P. Gorulya, A. A. Tolmachev

Enamine Ltd., Chervonotkatska str. 78, 02094, Kiev, Ukraine; e-mail: a.tverdohlebov@mail.enamine.net



After the series of fundamental works of Verboom and Reinhoudt on discovery and investigation of the *tert*-amino effect was published in eighties, a lot of efforts of different research groups were applied to development of new applications of the reaction. The recent contribution in the field from our laboratory is present herein. First, the method was found to enable preparation of spiro derivatives **3** starting from the aldehydes **1**. Second, the so-called homologous *t*-amino effect has been discovered. Namely, heating of the aldehydes **4** with active methylenes afforded compounds **6**, the formal *t*-reaction products. Thorough investigation of the process revealed it to be a sequence of sigmatropic reactions occurred through indane intermediates **5**. And third, another new type of the *tert*-amino effect was observed upon heating of chalcones **7**. In the presence of acid catalyst pyrroloquinolines **8** were obtained. Noteworthy, application of the properly *ortho* substituted Ar residues allowed further preparation of more complex heterocycles **9** and **11**.

O-5

Synthesis of Heteroaromatic Carbenes and Applied Aspects of their Chemistry

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G.F.Rayenko[b], O.P.Shvaika[b]

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This review gives a brief analysis of fundamental research in chemistry of stable carbenes and applications in the field of "green" chemistry on their basis that were carried out at the L.M. Litvinenko Institute of Physical Organic & Coal Chemistry of UNAS over the last decade. The synthesis of new types of carbenes was carried out for the first time: benzimidazolylidenes, hyperstable conjugated biscarbenes, 1-alkyl-3,4-diaryl substituted 1,2,4-triazol-5-ylidenes, new types of carbenoids. A new method for the preparation of 1,3,4-triaryl substituted 1,2,4-triazol-5-ylidene, their sterically shielded and biscarbene analogues, synthesis of sterically shielded imidazol-2-ylidene were performed. The existence of hyperbasic and hypernucleophilic carbenes was theoretically predicted and experimentally evidenced.

Four areas of application of the carbene systems have been developed: 1) catalysis of organic reactions by nucleophilic carbenes; 2) catalysis of organic reactions by carbene complexes of transition metals; 3) search for biologically active carbene complexes of transition metals; 4) synthesis of new heterocyclic compounds.

It was found: 1) carbenes as highly effective catalysts for transesterification and benzoin condensation; 2) highly effective carbene complex catalysts for reduction reactions of haloarene and multiple bonds by alcohols, oxidation reactions of alcohols, cycloaddition of azides to acetylenes; 3) new antibacterial and antifungal agents of the carbenoid series. 4) Methods of organic synthesis with the help of stable carbenes were enriched by the following reactions: insertion reactions into C-H bonds, a carbene version of ester Claisen condensation (to form zwitterionic compounds), the Leuckart-Wallach autoreduction of carbenoid azolium salts (to afford azolines), Hofmann cleavage of aminocarbene insertion products, an induced tandem autotransformation of 1,2,4-triazol-5-ylidenes into 5-amidino-1,2,4-triazoles. New carbene additions, which lead to zwitterionic compounds, the deesterification and complexation reactions were also revealed.

New approaches have been developed and proposed to use in green chemistry technologies for neutralization of “persistent organic pollutants” and ecologically pure reduction processes in chemical and pharmaceutical industries.

O-6

Rearrangement of Heminal Azines and Oxazines under Vilsmeier-Haack Reaction Condition

Markov V.I.[a], Farat O.K.[b], Varenichenko S.A.[a], Nesterenko S.A.[a]

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[b]Department of Chemistry, M.V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation
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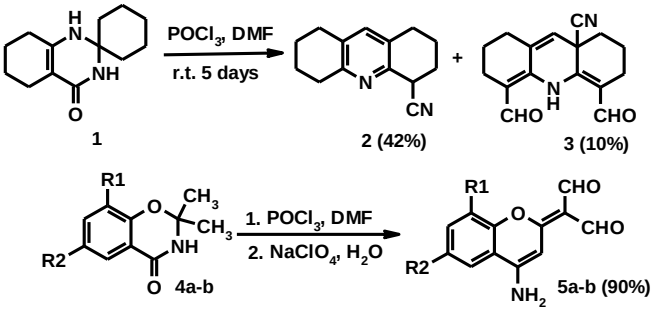
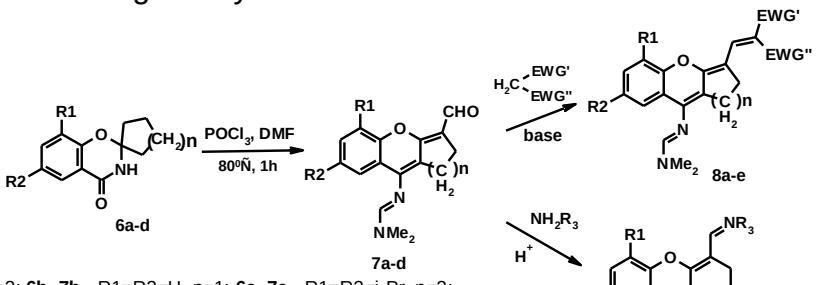
The development of a facile, efficient protocol for the domino reactions are very attractive as they allow synthesizing a wide range of heterocyclic compounds, and some of them have found practical application. In the report investigation a new multistage domino reaction is discussed. This reaction is a result of the deep-seated rearrangement of carbon skeleton of heminal azine (**1**) and oxazines (**4a-b)** and **(6a-d)** under Vilsmeier-Haack reaction conditions [1, 2].



The highly functionalized compounds **(5a-b)** and **(7a-d)** could serve as low-molecular-weight building blocks for organic synthesis.



6a, 7a - R1=R2=H, n=2; **6b, 7b -** R1=R2=H, n=1; **6c, 7c -** R1=R2=i-Pr, n=2;
6d, 7d- R1=R2=i-Pr, n-1; **8a** R1=R2=H, EWG'=EWG''=CN; **8b** R1=R2=i-Pr, EWG'=EWG''=CN;
8c R1=R2=H, EWG'=CN, EWG''=CO_2Et;
8d R1=R2=H, EWG'=CN,EWG''=  **8e** R1=R2=H, EWG'=EWG''= 
9a R1=R2=H, R3=Ph; **9b** R1=R2=H, R3=4-HO_2C-C_6H_4; **9c** R1=R2=H, R3=2-MeC_6H_4;
9d R1=R2=H, R3=3-HOC_6H_4; **9e** R1=R2=H, R3=4-BrC_6H_4

New chromene derivatives **(5a-b)** and **(7a-d)** showed fluorescent properties. For example, chromenes **(5a-b)** were strongly fluorescent in solid state and the compounds showed strong orange emission at a maximum 609-624 nm (Stoke shift ~200 nm) in solid state. The compounds **(7a-d)** were fluorescent in solution and showed green emission at a maximum 518-524 nm. The functionalized derivatives **(8a-e)** and **(9a-e)** characterized of highest molar extinction coefficient and showed absorption with maximum wavelength ranging from 290 to 360 nm.

[1] Markov V.I., Farat O.K., Varenichenko S.A., Velikaya E.V. // Mendeleev Commun. – 2012. – № 22. – P.101-102.

[2] Farat O.K., Markov V.I., Varenichenko S.A., Dotsenko V.V., Mazepa A.V. // Tetrahedron – 2015. – № 71. – P.5554-5561.

O-7

The Electrophilic Intramolecular Cyclization as the Strategy of Synthesis of New Fused Pyrimidine Systems

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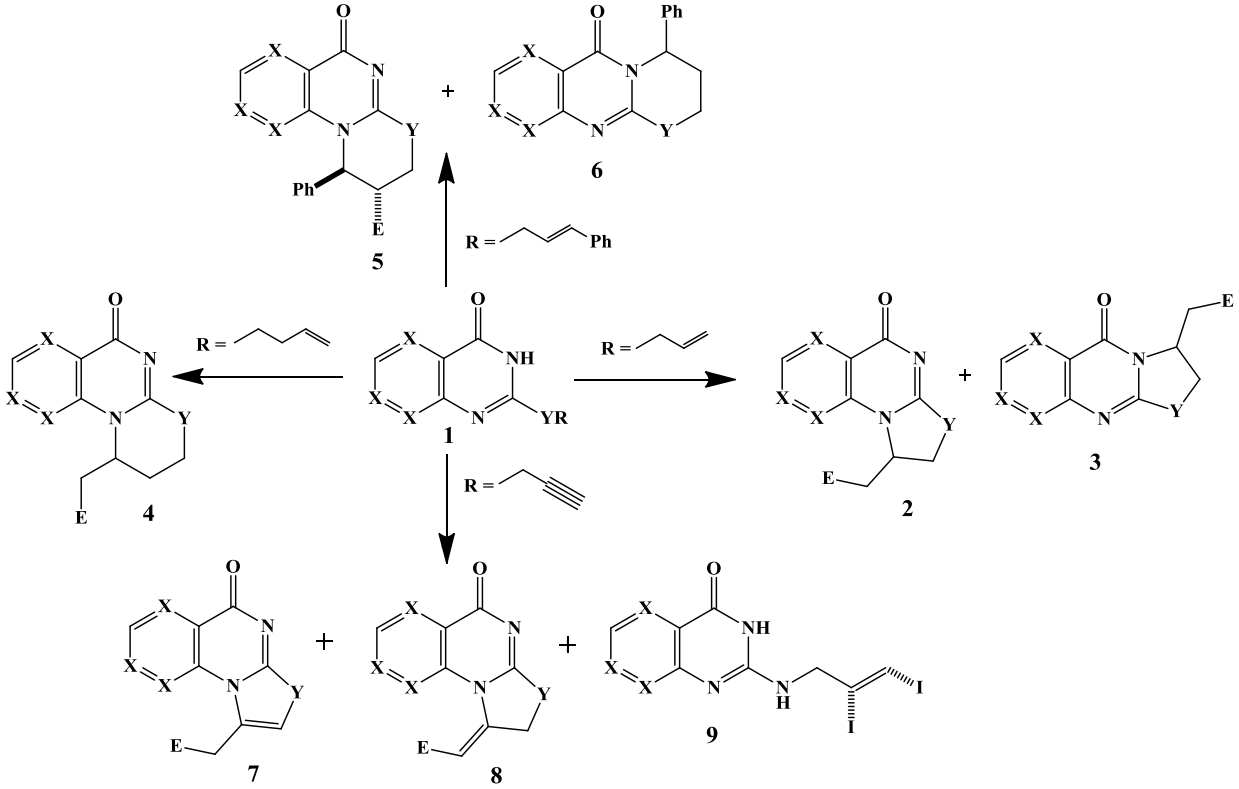
[b]*National Technical University of Ukraine "KPI", Pobedy av., 37, Kiyv*

The synthesis of hetero annelated fused pyrimidine systems, by means of broad spectrum of their biological activity, is the actual problem of modern heterocyclic chemistry. To receive new condensed pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones, pyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones and pteridin-4(3*H*)-ones we used the synthetic potential of the reaction of the electrophilic intramolecular cyclization with iodine, aryl sulphenylchlorides and polyphosphoric acid (PPA).

It was established that the action of these reagents on alkenyl(alkynyl)functionalized substrates formed products mainly of angular structure **2**, **4**, **5**, **7**, **8**. At the same time when using of PPA realized compounds of angular **2** and linear **6** structures.

For compounds 2 is developed version of functionalization of azido group, which has been used in «click-reaction» with monosubstituted acetylenes to produce bioperspective hybrids heterocycles.



O-8

Interaction of Benzo[*c,d*]indole-2(1H)-one with Alkylating Agents

Kartsev V.G., Isak A.D., Rozhinski Yu.I., Prunchak N.I.

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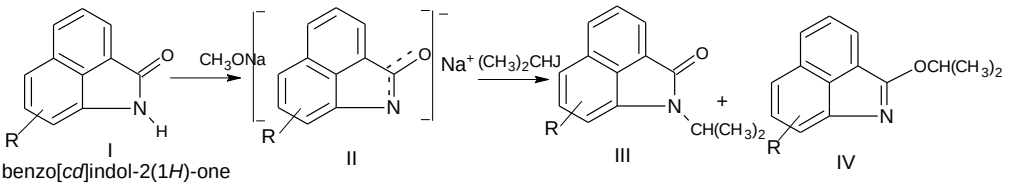
isak_ad@ukr.net

There is no information on the interaction of naphtostyryl with alkylating agents in the absence of alkaline agents in the literature. We have studied possibilities of N-alkylnaphostyryle manufacture by this method. It has been found out, that under the comparatively mild conditions by heating (100-120^{0}C, during 10 hours) naphtostyryl with iodide methyl, methyl benzolsulfonate, benzylchloride in benzenchloride or in the excess of an alkylating agent, even no traces of N-alkylnaphostyryle are formed. Ethers of aromatic sulfoacids and dialkylsulfates can react in two ways: to breaking O-C-bonds or S-O-bonds and to show alkylating or acidulating effects respectively.

It has been found out that at the transition from the primary haloid ethers to the secondary ones, naphtostyryl (II) salt shows bilateral (double) reactivity: its interaction with the secondary iodide propyls in the medium of N-methylpyrrolidone (50^{0}C, 1 hour) results in forming the mixture of N-alkyl- and O-alkyl derivatives of naphtostyryl (III, IV) with the output of 83% and 5% respectively.



I
benzo[*cd*]indol-2(1*H*)-one
Нафтостирил

II III IV

Lately the principle of hard and soft «*m i l d*» acids and bases proposed by Pirson has been widely used for explaining bilateral «*d o u b l e*» reactivity of different *ambident* ions. In the ambident anion of naphtostyryl (II) salt oxygen atom is a «*hard*» (has maximum charge) centre , with nitrogen atom being a «*soft*» (the most polarized) centre.

It has been Showed that on benzelation salt (II) under standard conditions (90^{0}C, 1 hour) the nature of solvent substantially effects the output of N-benzylnaphtostyryl. This, dipole aproton solvents are the most farouable medium for alkylation of sodium salts of naphtostyryl and substituted ones.

Isak A.D., Kartsev V.G., Chemistry of Naphtostyryls. Moscow, ICSPF, 2005, 752 pp.

Functionalized 3,4-Dihydropyrimidin-2(1H)-ones and 4,7-Dihydroazolo[1,5-*A*]pyrimidines

O-9

Maksim A. Kolosov, Muataz J.K.Al-Ogaili, Olesia G. Kulyk, Dmitriy A. Manuyenkov, Elena H. Shvets, Valeriy D. Orlov

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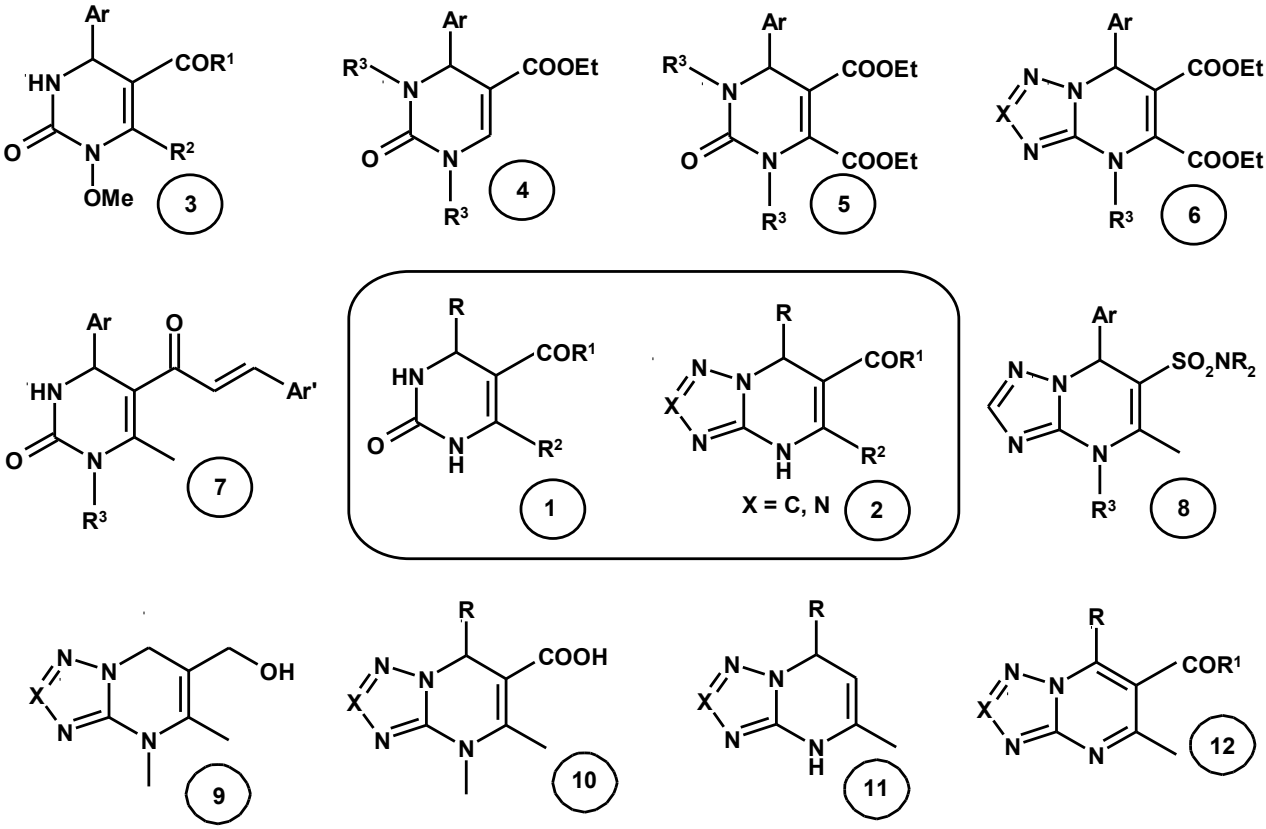
The synthesis and different properties of 5-COR-3,4-dihydropyrimidin-2(1H)-ones (Biginelli compounds, **1**) and relative 6-COR-4,7-dihydroazolo[1,5-*a*]pyrimidines **2** are under intensive investigation. At the same, the derivatives of the latter compounds with low molecular weight, as well as possessing SO_2NR_2, OMe and more than one EWG-substituent etc. are still poorly known, despite of their evident usability in biological activity evaluation and use as building blocks. Here we present our modest advance in the research of the synthesis of the mentioned compounds and their properties.



X = CH, N; R = H, Alkyl, Aryl; R^1 = Me, OAlkyl, NR_2; R^2 = H, Me, COOEt; R^3 = H, Alkyl

The stereochemical aspects of compounds' **3** structure are discussed, as well as details in compounds' **8** synthesis are given. The regioselectivity of compounds' **1** and **2** alkylation, the common methods of compounds' type **7** synthesis, and the synthetic pathways to building blocks **9**–**12** are considered.

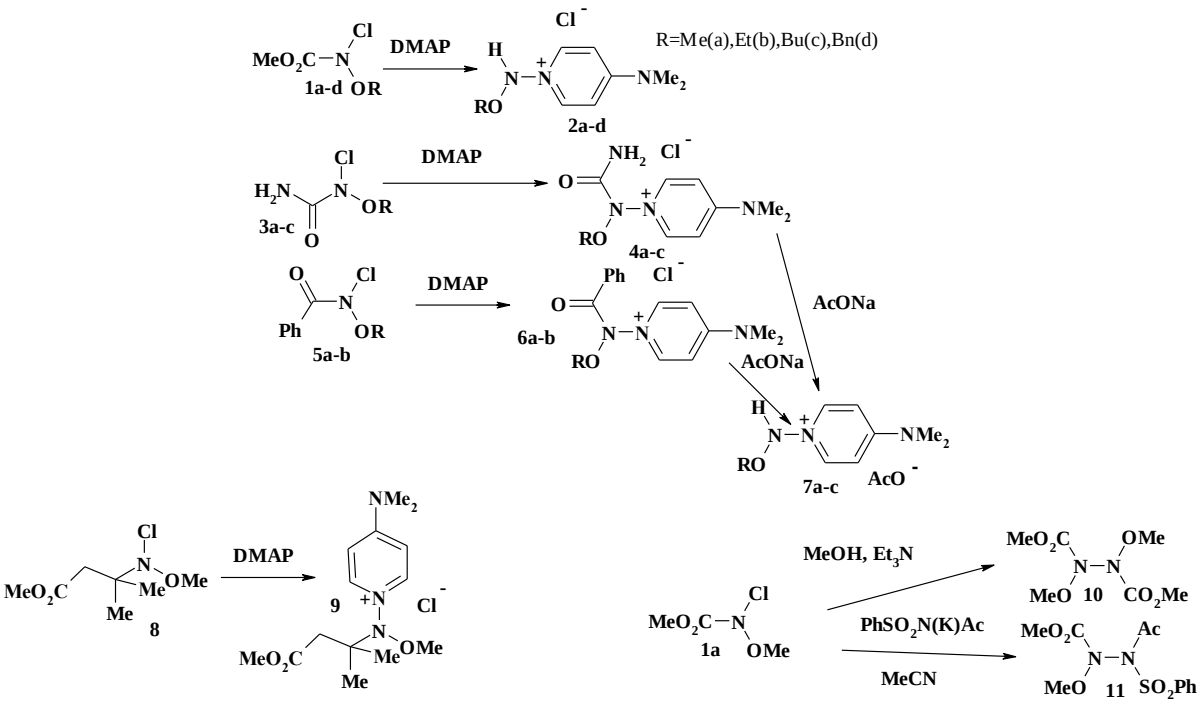
O-10

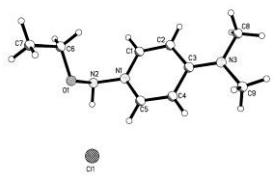
1-(N-Alkoxyamino)pyridine Derivatives and others N-Alkoxyhydrazines

Shtamburg V.G.[a], Tsyhankov A.V[b]., Shtamburg V.V.[a], Klotz E.A.[c], Shishkina S.V.[d], Zubatyuk R.I.[d], Mazepa A.V.[e]

[a]Ukrainian State University of Chemical Technology, e-mail: stamburg@gmail.com, [b]Kirovograd Flight Academy of National Aviation University, [c]Kirovograd State Pedagogycal University; [d]SSI "Institute for Single Crystals" of NAS of Ukraine; [e]A.V. Bogatsky Physiko-Chemical Institute of NAS of Ukraine

N-Chloro-N-alkoxycarbamates **1a-d** react with 4-dimethylaminopyridine (DMAP) yielding unknown chlorides of 1-(N-alkoxyamino)-4-dimethylaminopyridines **2a-d**. N-Chloro-N-alkoxyureas **1a-c** with DMAP form N-1-(4-dimethylamino)pyridinium-N-alkoxyureas chlorides **4a-c**. N-Chloro-N-alkoxy derivatives of benzamide **5a,b** and N-*tert*-alkylamine **8** converted in N-pyridinium-N-alkoxycompound **6**,**9**, respectively, by the action of DMAP. N-Chloro-N-alkoxycarbamates **1a** has been transformed in N-alkoxyhydrazines **10**, **11**.





The structures of compounds **2a,b,** and **4a**, **9-11** had been discussed.

3-Alkoxy(hydroxy)-5-aryl(heteryl)hydantoins, Synthesis and Structure

O-11

Shtamburg V.G.[a], Anishchenko A.A[b]., Shtamburg V.V.[a], Kravchenko S.V.[c], Zubatyuk R.I.[d], Mazepa A.V.[e]

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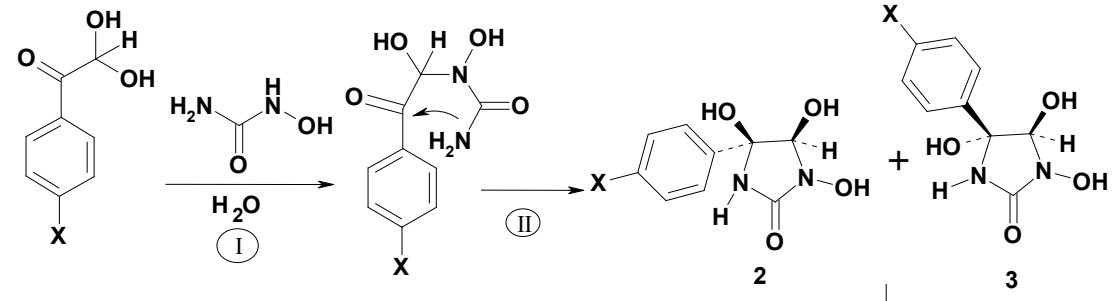
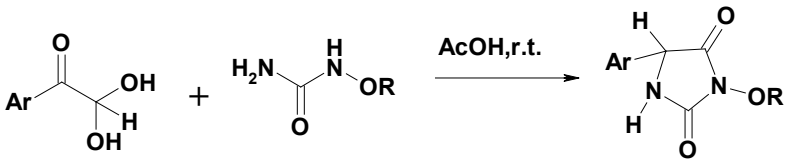
Arylglyoxals react with N-hydroxyurea in water solution yielding the mixture of the substituted N-hydroxyurea **1**, diastereomers of 3,4,5-tri(hydroxy)-5-arylimidazolidine-2-ones **2** and **3**, and 3-hydroxy-5-arylhydantoins **4**. The individual products separation has some difficulties. But the reaction of aryl(heteryl)glyoxals with N-hydroxyurea or some N-alkoxyureas in acetic acid solution at room temperature selectively yields 3-hydroxy-5-aryl(heteryl)hydantoins **4** and 3-alkoxy-5-aryl(heteryl)hydantoins **5**, respectively.



X = H, Cl, Br, F, Me, OMe, Ph

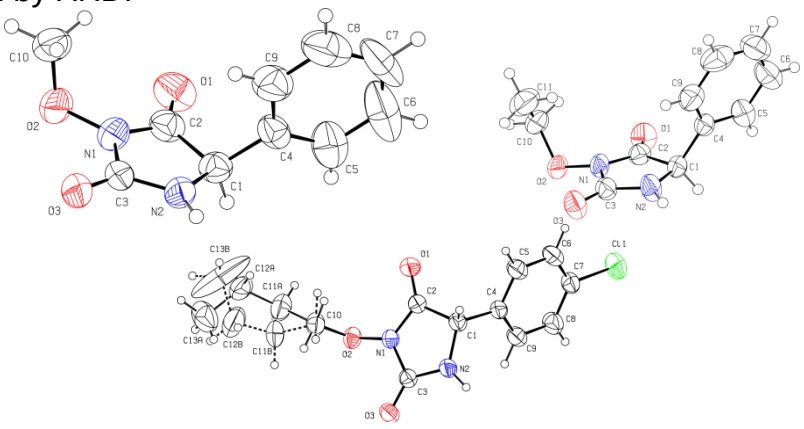


Ar = C_6H_4X, C_4H_3S, C_4H_3O

R = H, Me, Et, Bu

4, 5

The structures of 3-hydroxy-5-phenylhydantoin and some 3-alkoxy-5-arylhydantoins had been studied by XRD.



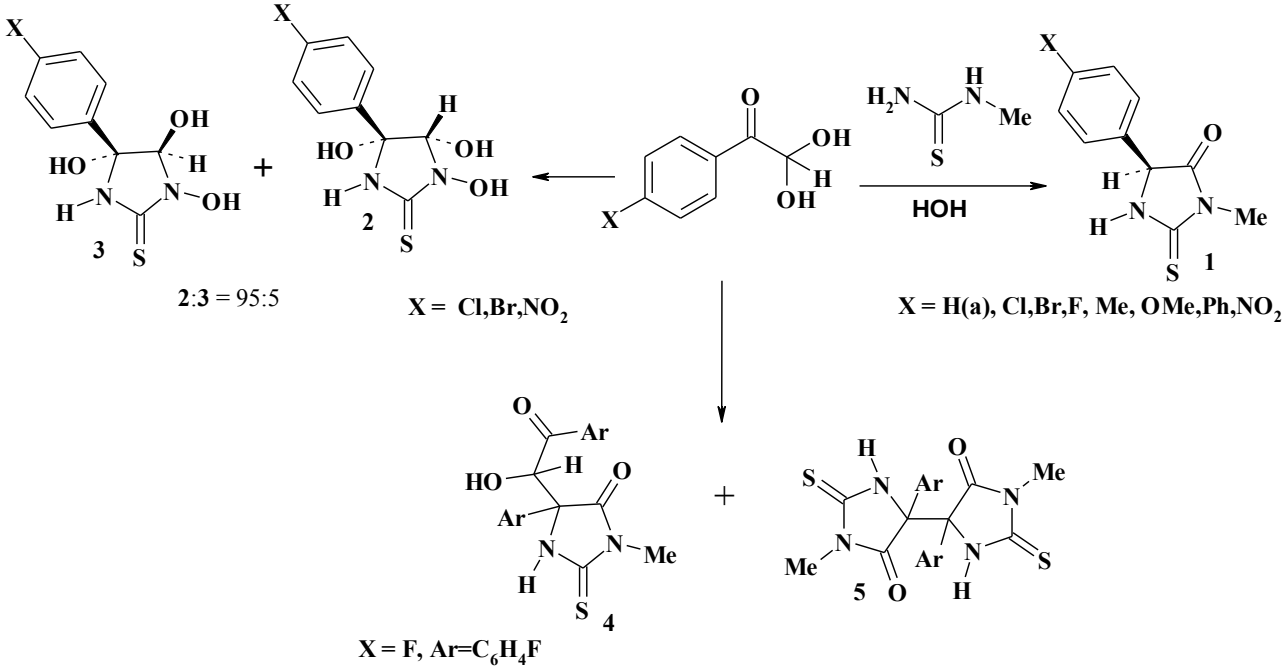
O-12

Arylglyoxals in Thiohydantoins and N-hydroxyhydantoins Syntheses

Anishchenko A.A[a]., Shtamburg V.V.[b], Zubatyuk R.I.[c]

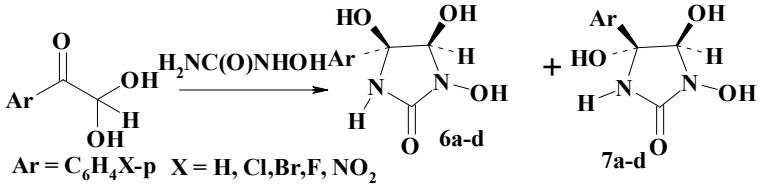
[a]O. Gonchar Dnipropetrovsk National University,49050, Dnipropetrpvsk, Nauchnaya str., 25, Ukraine, e-mail: koloxai@gmail.com, [b]Dnepropetrovsk National University, Ukraine State University of Chemical Technology, 49005, Dnepropetrovsk, Gagarina str.8,Ukraine , [c]SSI "Institute for Single Crystals" of NAS of Ukraine, 61001, Kharkiv, Lenina str., 60, Ukraine

Arylglyoxals react with *N*-methylthiourea in boiling water solution yielding 3-methyl-5-arylimidazolidine-2-one-3-thiones **1**. The 3-methyl-5-phenylthiohydantoin **1a** structure was established with the XRD help. *p*-Chloro-, *p*-bromo- and *p*-nitrophenylglyoxals react with *N*-methylthiourea at the cold (5°C, water) with the formation of diastereomeric 3,4,5-trihydroxy-3-methyl-5-arylimidazolidine-2-one-3-thiones **2**,**3** mixture. The diastereomer **2** is dominating.



p-Fluorophenylglyoxal forms with *N*-methylthiourea (5-10°C, MeOH – H_2O) the unexpected products **4** and **5**. Their structures were established by XRD-study.

p-X-Phenylglyoxals [X=H(a),Cl(b),Br(c),NO_2(d)] react with N-hydroxyurea in water solution (4-20°C) yielding the mixture diastereomers of 3,4,5-tri(hydroxy)-5-arylimidazolidine-2-ones **6a-d** and **7a-d**. The diastereomers **6a-d** are main components of this reaction mixtures.



O-13

A Peculiarity of Multicomponent Reaction of 1*H*-2,1-Benzothiazin-4(3*H*)-one 2,2-dioxide with Ethyl Cyanoacetate and Benzaldehydes

Lega D.A.[a], Chernykh V.P.[a], Starchikova I.L.[a], Gorobets N.Yu.[b], Shemchuk L.A.[a]

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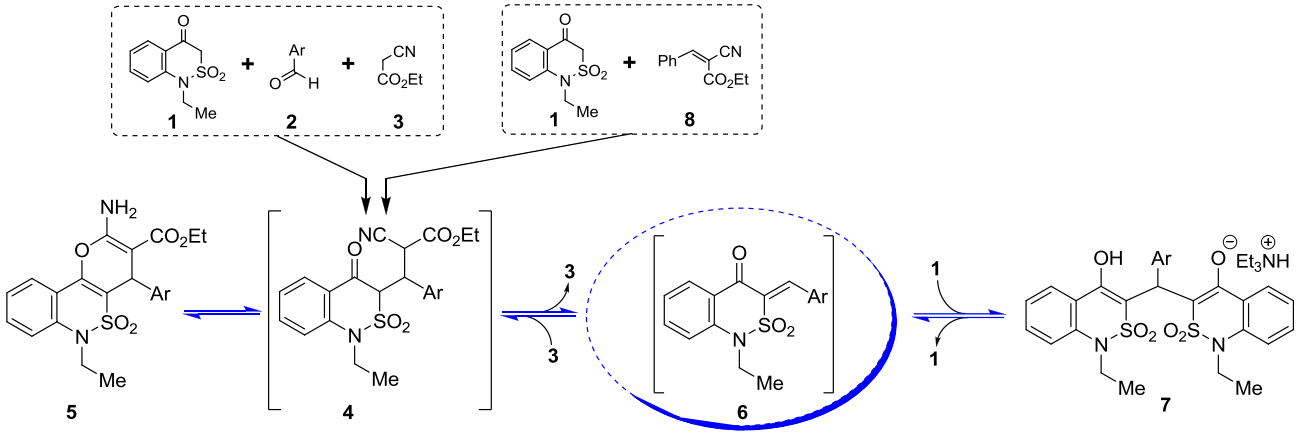
Multicomponent reactions (MCR) of enol-nucleophilic compounds with carbonyl compounds and active methylene nitriles are long time known for a variety of different substrates. In the most cases, this MCR is a direct route to facile formation of 2-amino-4*H*-pyran core [1]. In our recent work we have described an MCR of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**1**) with active methylene nitriles and isatines, which led to the fused 2-amino-4*H*-pyrans spirocondensed with 2-oxindol ring [2].

Application of building block **1** in this reaction with benzaldehydes (**2**) and malononitrile also provided high yields of corresponding condensed 2-amino-3-cyano-4*H*-pyrans. However, the use of ethyl cyanoacetate (**3**) in this MCR with **1** and **2** resulted in formation of two product types: the expected 4*H*-pyran derivatives (**5**) and/or bis-adducts (**7**). Model experiments were performed to establish the reaction mechanism showing, in particular, that arylidenes **6** are the key intermediates in the route to both **5** and **7**. The reaction conditions were further modified based on the suggested mechanism this allowed us to improve selectivity of the MCR and direct the process to the side of the target products formation (**5**).



[1] Y.M. Litvinov, A.M. Shestopalov. Synthesis, structure, chemical reactivity, and practical significance of 2-amino-4*H*-pyrans // in *Adv. Heterocycl. Chem.*, Academic Press – 2011. Vol.103. – P. 175-260.

[2] L.A. Shemchuk, D.A. Lega, R.G. Redkin, V.P. Chernykh, O.V. Shishkin, S.V. Shishkina. An efficient, three-component synthesis and molecular structure of derivatives of 2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-5,5-dioxide spirocombined with a 2-oxindole nucleus // *Tetrahedron* – 2014. Vol. 70. – P. 8348-8353.

O-14

The Use of Synthetic Potential of Alkyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates in Searching New Biologically Active Substances

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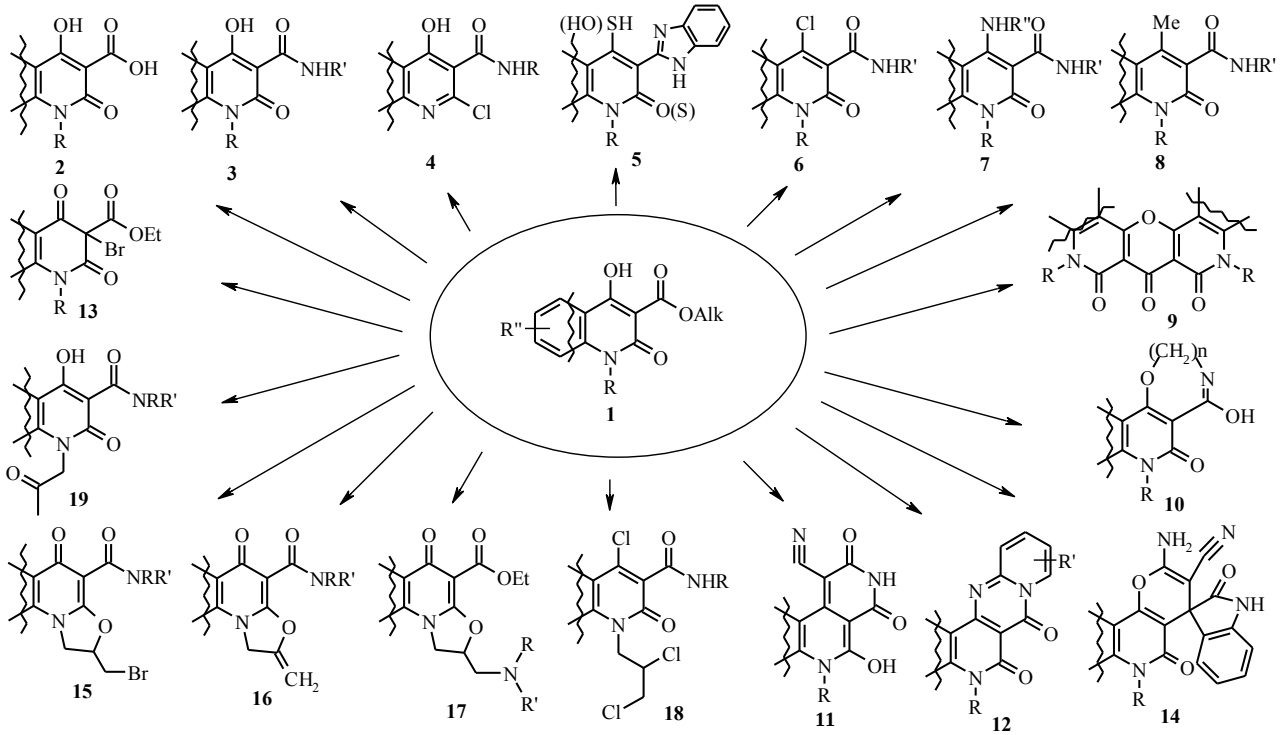
Having practically unlimited possibilities for chemical modifications alkyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates (**1**) are of particular interest as the base for the synthesis of a wide variety of biologically active products. A comprehensive study on the reactivity, structure and pharmacological properties of these compounds and their derivatives has been conducted.



Moreover, the possibility of modifying the ester fragment (acids **2** and amides **3**), 2-carbonyl (compounds **4** and **5**), 4-OH-group (chlorine, merkapto-, amino- and methyl derivatives **5-8**), simultaneously 4-OH- and ester groups (heterocycles **9-12**), as well as position 3 (quinolones **13-14**) has been shown. The effective halocyclization of 1-N-allyl derivatives into oxazolo[3,2-*a*]-quinolines **15-17**, which can be transformed in both dichloropropyl or acetonyl substituted quinolines **18-19**, is of particular interest.

The substances obtained exhibit the high analgesic, anticoagulant, anti-inflammatory, antimicrobial, diuretic, antituberculous antithyroid, antioxidant, antihypoxic and local anesthetic activities, as well as the ability to block opioid receptors.

Substituted Tetrazolo[1,5-*c*]quinazoline(6*H*)-5-ones(thiones): Synthesis, Modification and Biological activities

O-15

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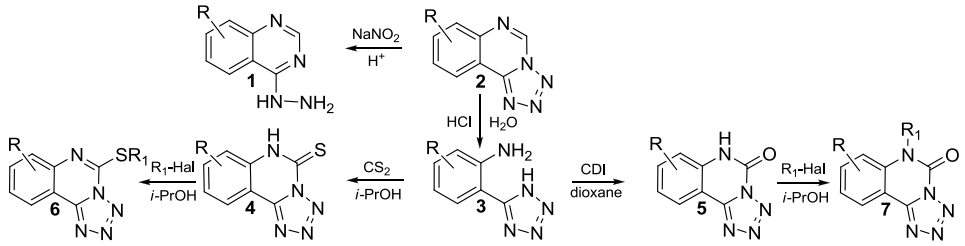
[a]*Zaporizhzhya State Medical University, Mayakovsky ave., 26, Zaporizhzhya, 69035, Ukraine, e-mail: antypenkoan@gmail.com*

Tetrazoloquinazolines is a quite interesting heterocyclic system, especially from the pharmacological aspect, due to the presence of fungicide, pesticide, anti-allergic, bactericide, bronchodilator, antiulcer, anti-inflammatory, analgesic, and antihypertensive properties [1]. Besides tetrazolo[1,5-*c*]quinazolines (**2**) are not so wide explored.

7-R_1-8-R_2-9-R_3-10-R_4-tetrazolo[1,5-*c*]quinazolines (**2**) were prepared by [4+1]-cyclocondensation process using substituted 4-hydrazonoquinazolines (**1**) as starting compounds (Scheme).



Further, pyrimidine ring of 7-R_1-8-R_2-9-R_3-10-R_4-tetrazolo[1,5-*c*]quinazolines (**2**) underwent nucleophilic cleavage by hydrochloric acid with formation of 3-R_1-4-R_2-5-R_3-6-R_4-2-(1*H*-tetrazol-5-yl)anilines (**3**). The last ones were a very promising binucleophiles, which could serve as a initial compounds for introducing substituents at the 5 position of tetrazolo[1,5-*c*]quinazolines. In our research, 3-R_1-4-R_2-5-R_3-6-R_4-2-(1*H*-tetrazol-5-yl)anilines (**3**) were [5+1]-cyclocondensated, namely with potassium ethyl xanthate or carbon bisulfide; and with *N*,*N*'-carbonyldiimidazole or isocyanates 7-R_1-8-R_2-9-R_3-10-R_4-tetrazolo[1,5-*c*]quinazoline-5(6*H*)-thiones (**4**) and 7-R_1-8-R_2-9-R_3-10-R_4-tetrazolo[1,5-*c*]quinazolin-5(6*H*)-ones (**5**) were obtained correspondingly. The last ones (**4**,**5**) were treated with halogen derivatives with formation of compounds **6**,**7**. Compounds were tested for anticancer, inhibition of bioluminescence, antimicrobial, antifungal, actoprotective and hypoglycemic activities. Namely *N*-aryl(benzyl,heteryl)-2-(tetrazolo[1,5-*c*]quinazolin-5-ylthio)acetamides were tested in US National Cancer Institute, some of them highly inhibited growth of leukemia, SR cell line. Based on that data QSAR-models of anticancer activity were calculated.

[1] M.A.E. Shaban, M.A.M. Taha, E.M. Sharshira Synthesis and biological activities of condensed heterocyclo [*n*,*m*-*a*,*b*, or *c*]quinazolines // Adv Heterocycl Chem. – 1991. №52. – P. 1-153.

O-16

In Silico Studies in Directed Synthesis of Potential Anticonvulsants

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National University of Pharmacy, Kharkov, Ukraine, e-mail: medchem@ukrfa.kharkov.ua

Work is devoted to targeted search for potential anticonvulsants, taking into account the specificity of different methods of computer prediction and relationship between them. We have carried out the construction of 50 groups substances derivatives 1,2,3(1,2,4) triazoles, 1,3,4-oxa(thia)diazoles. Molecular design of new compounds was performed according to the algorithm, which included successive stages. Based on research *in silico* (virtual pharmacological screening, PASS-computer program, testing for compliance with the concept of "drug-likeness", molecular docking to biotargets) eleven groups of compounds derivatives of five-membered di(three)azaheterocycle was selected for further screening as perspective anticonvulsants. We have identified possible mechanisms of anticonvulsant action and proposed experimental models for pharmacological studies of anticonvulsant activity. In order to determine the potential anticonvulsant activity of 1,2,3(1,2,4)triazole, 1,3,4-oxa(thia)diazole we investigated the mechanisms of action that involve the interaction of the ligand NMDA-, $GAMK_a$- or glutamate receptors and GABA-AT ligand-enzyme. GABA-ergic mode of action for 8 groups of derivatives and glutamatergic mode of action for 3 groups of derivatives five-membered di(three)azaheterocycle was predicted.

The correctness of the algorithm propoused have been proved experimentally by purposeful synthesis of predefined groups of new derivatives of five-membered di(three) aza-heterocycles and pharmacological research in comparison with known anticonvulsant drugs. Pharmacological studies of new derivatives on manifestation of their anticonvulsant activity have been conducted on different animal convulsive models according to the predicted mechanism of action. It should be noted that result of docking research coincided with the results of PASS prediction for eight groups of compounds. Proof of effectiveness of the proposed methodological approach to targeted synthesis of potential anticonvulsants agents was the discovery of new anticonvulsants derivatives 5-methyl(amino)-1,2,3-triazoles(1*H*), [1,2,4]-triazolo[1,5-a]pyrimidine, 1,3,4-oxadiazoles and 1,3,4-thiadiazole with a significant level anticonvulsive action exceeding the activity of referens drug [1]. We have determined the dependence anticonvulsive activity in these groups of compounds from modifying the structure (SAR analysis).

[1] Perekhoda L.O. The progress of recent years in a search of potential anticonvulsants among the derivatives of aza-heterocycles // Annals of Mechnikov Institute– 2015, № 3, – P. 37-45

O-17

Synthesis and Molecular Diversity of Spirooxindoles in a Search for Potential Inhibitors of Protein Kinases: Convergence of Ligand-based and Structure-based Approaches

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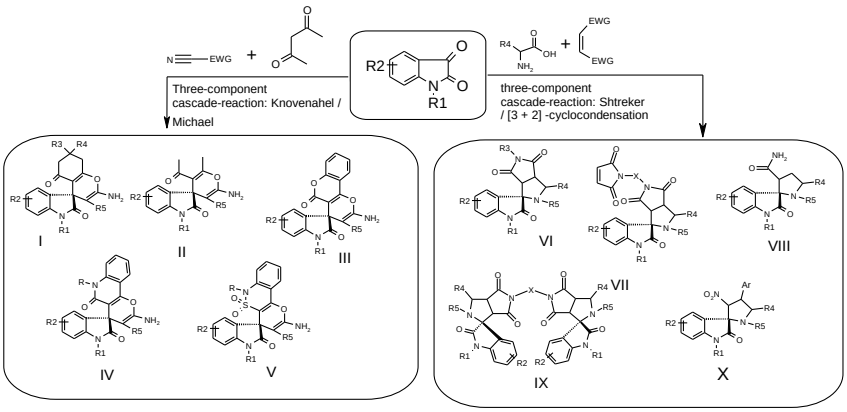
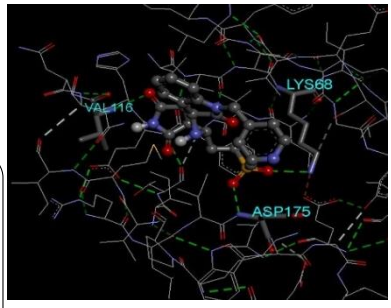
Identification of protein kinase inhibitors is an urgent task in the field of present-day medicinal chemistry, pharmacology and experimental medicine in general. The overwhelming majority kinase inhibitors known by now are flat or flattened structure, resulting in the presence of specific cavities either above or below the plane of the inhibitor can not be used to create selective molecules. There was a target-oriented search (*in silico* and *in vitro*) for drug-like molecules and potential anticancer agents being CK2 and FGFR1 kinase inhibitors among 1000 structures I-X of spiro-2-oxindoles focus-library (Fig.), which was synthesized by diversity-oriented synthesis MCRs way [1,2].





The complex of a ligand to the ATP-binding site of the protein kinase CK2

The study algorithm comprises three stages: 1) calculation and analysis of structure molecular descriptors using the *Molinspiration* software complex (chemoinformatics method); 2) molecular modeling of binding a collection of compounds with CK2 and FGFR1 protein kinases *in silico* and selection candidates for biochemical tests based on the binding energy (bioinformatics method); docking was carried out in ATP binding sites of CK2 protein kinases (RCSB code: 3NSZ – 1.30 Å) and FGFR1 (RCSB code: 3GQI – 2.50 Å) using the Autodock4 software; 3) *in vitro* screening the selected compounds relative to CK2 and FGFR1. Accordingly, to the *in silico/in vitro* screening results CK2 inhibitors is {VIII, 1 active compound with rest of kinase activity, 49% (33μM)} and FGFR1 compound inhibits only {VII, 1 active compound with rest of kinase activity, 53% (33μM)}.

[1] *Tetrahedron. – 2014. – Vol. 70. – P. 8348-8353.*
[2] *Mol. Divers. – September 2015. – P. 1-46.*

O-18

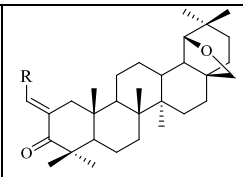
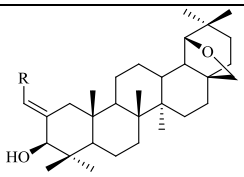
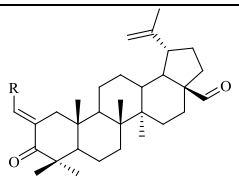
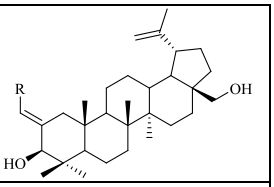
Pyrrol-2-yl- and Pyrazol-4-ylmethylidene Derivatives of Lupane Series as a New Chiral Dopants for Cholesteric Liquid-Crystal Compositions

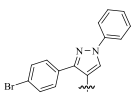
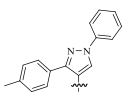
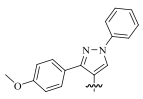
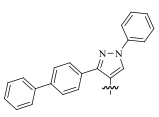
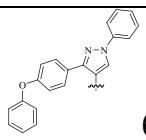
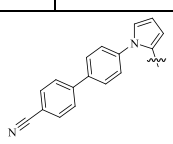
Babak N.L.[a], Shishkina S.V.[a,c], Semenenko A.N.[a], Morina D.A.[c], Gella I.M.[a,c], Lipson V.V.[a-c]

[a]*State Scientific Institution "Institute for Single Crystals", Kharkov, Ukraine, e-mail: lipson@ukr.net*
[b]*Medicinal Chemistry Department, State Institution "V.Ya. Danilevsky Institute for Endocrine Pathology Problems", Kharkov, Ukraine*
[c]*V.N. Karazin Kharkov National University, Chemistry Department, Kharkov, Ukraine*

Aldol-crotonic condensation of allobetulone and betulonic aldehyde with N-substituted pyrrole-2- and pyrazole-4-carbaldehydes afforded a new α,β-unsaturated ketones of lupane series. Reduction of these compounds provided 2-ylidene derivatives of allobetulin and betulin. Cyclopropanation of α,β-unsaturated ketones by trimethylsulfoxonium iodide of allobetulin or betulin led to potential chiral components of liquid crystal materials. Structures of synthesized compounds were established by X-ray diffraction study. The relationship between spatial structure of these compounds and their ability to induce cholesteric helix in 4-pentyl-4'-cyanobiphehyl nematic solvent were examined. The values of the helical twisting power |β| of some synthesized compounds 1-7 are shown in the table.

Table. Twisting power |β|, $\mu m^{-1} \cdot mol.\ f^{-1}$/$\mu m^{-1} \cdot mass.\ f^{-1}$, of compounds **1**-**7** in solvent 5CB

Scaffold / R				
1	108.86 ±4.31/ 36.40 ±1.44	51,87±1.64/ 17,17±0.64	80.32 ±1.40/ 26.93 ±0.44	84.32 ± 3.40/ 28,06 ± 1,0
2	129.94 ±2.81/ 47.53 ±8.34	52.74±2.11/ 19,35±1.28	70.51 ±1.67/ 25.83 ±0.61	83.14±2.49/ 30,39±0.41
3	145.02 ±1.28/ 51.97 ±0.27	63.83 ± 0.30/ 22,72 ± 0,11	58.34 ±1.32/ 20.91 ±0.47	62,96±1.51/ 22,42±0.54
4	158.61 ±8.70/ 53.28 ±2.92	61,67±1.33/ 20,66±0.72	77.43 ±3.1/ 26.08 ±1.4	77.77 ±0.11/ 26.12 ±0.04
5	106.41 ±2.42/ 34.61 ±1.59	49,19±2.02/ 16,40±0.82	58.87 ±1.65/ 19.41 ±0.51	70,24±0.81/ 22,99±0.04
6	89.67; 79.58/ 32.4; 28.71			
7	6,75/ 2,71			

R 1  2  3  4  5  6  7 

One-pot Synthesis of Polysubstituted Tetrahydroindoles

O-19

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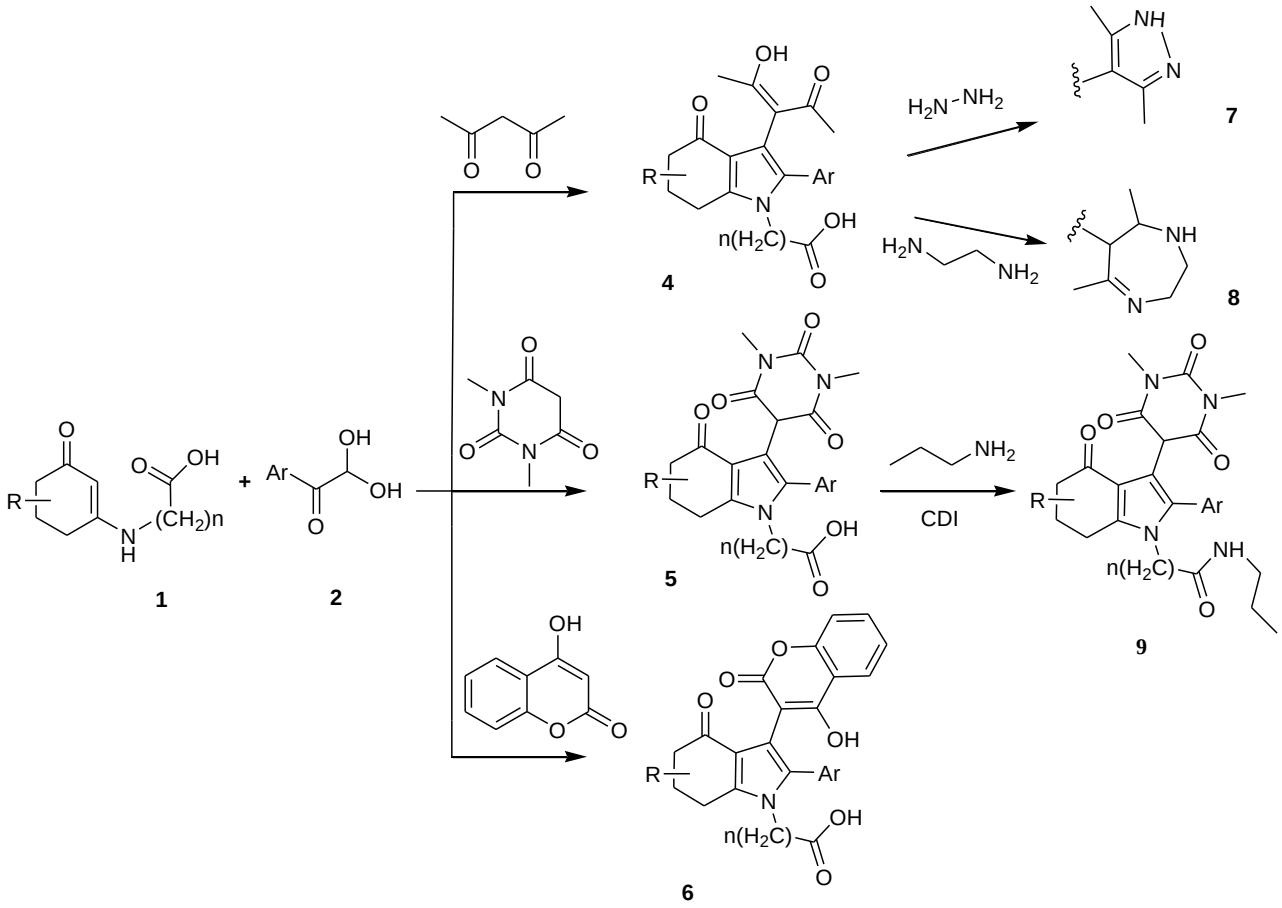
The development of new convenient and economical approaches to the synthesis of polysubstituted indoles is presence considerable interest and has huge value for modern organic and medicinal chemistry in terms of synthesis of effective drugs. One of such methods for the synthesis of these compounds can be domino reactions involving enaminoketones **1**, hydrates of arylglyoxals **2** and different nucleophilic reagents.



1 **2** **4** **5** **6** **7** **8** **9**

The corresponding amides were obtained in the reactions of indoles **5** with propylamine, and prolonged reflux of products **4** with hydrazine or ethylenediamine synthesized pyrazoles **7** and diazepines **8**, respectively.

The structures of the synthesized compounds were proved by modern physico-chemical methods of analysis (1H-NMR, 13C-NMR spectroscopy, mass spectrometry and X-ray analysis).

O-20

Mechanism of the Reaction of 4-(2-Benzylidenehydrazinylidene)cyclohexa-2,5-dienones with Primary Aliphatic Amines

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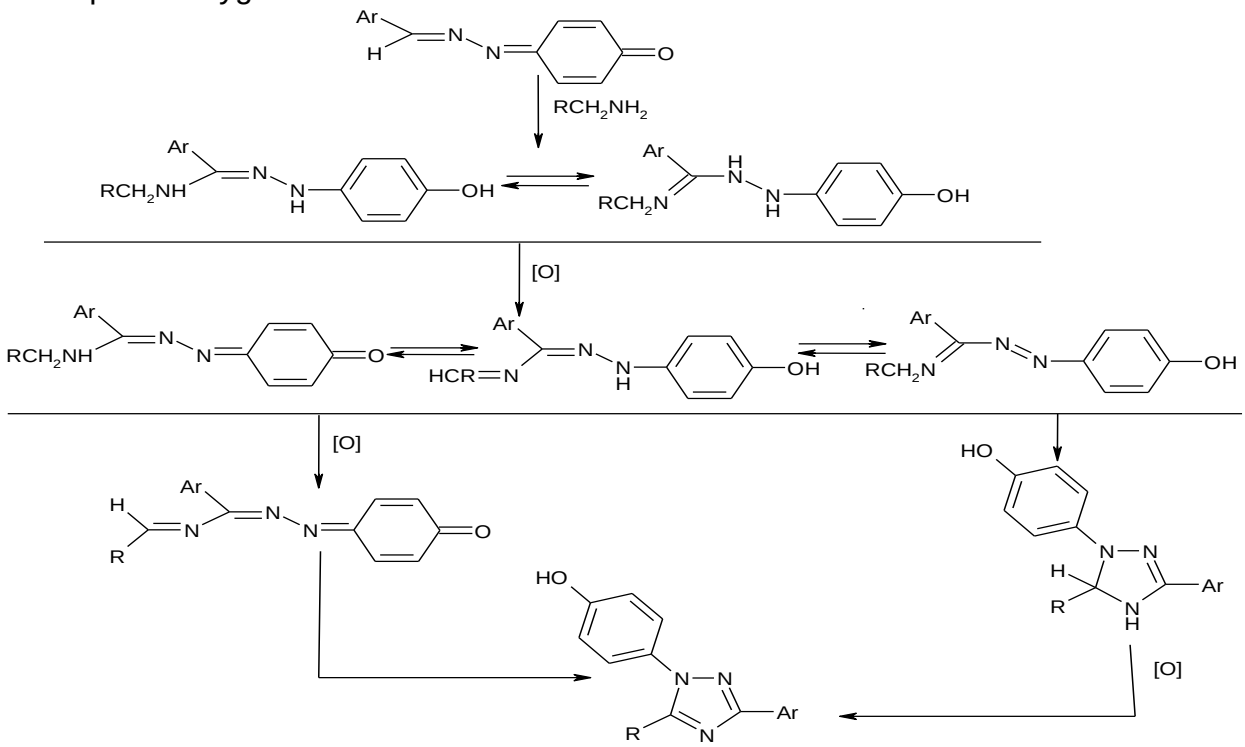
The reaction path of 4-(2-benzylidenehydrazinylidene)cyclohexa-2,5-dienones with primary aliphatic amines which led to formation of the 1,3,5- substitute 1,2,4-triazoles has been offered. In accordance with the proposed reaction path the first stage of the process is the reaction of 1,8-addition of an amine to azine with the formation of triazene, existing as two tautomeric forms. The oxidation of triazene occurred under the influence of atmospheric oxygen.



The scheme was confirmed by the data of spectrophotometric studies, quantum chemical calculations and the results of the independent synthesis. The structure of a number of intermediate compounds has been established. The reaction speed constant has been calculated. The rate-limiting step has been defined.

O-21

Enamines in Reactions with Unsaturated Ketones as Method for the Carbocycle Synthesis

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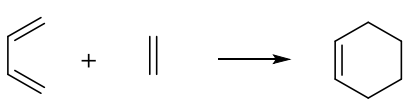
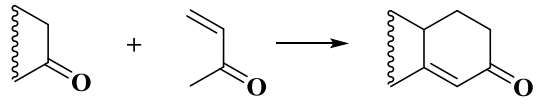
dsidorenko@mail.ru

A lot of carbocyclization reactions is known. But most part of this reaction can be summarized in several groups. There are Diels-Alder and Robinson type reaction by scheme [2+4], and multicomponent reactions.

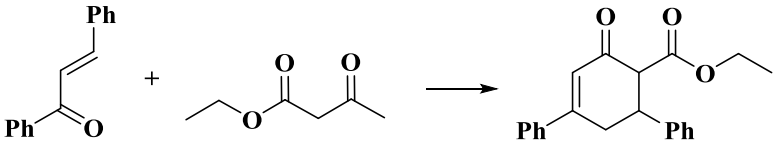


Diels-Alder reaction



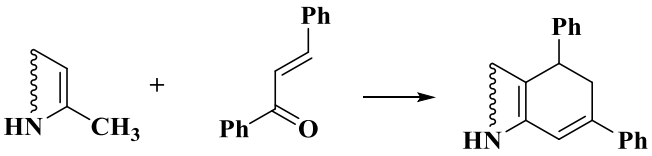
Robinson reaction

Also known reactions which going by scheme [3+3], but they do not known so much. One of the first in this series was opened a Knoevenagel reaction - interaction of chalcone with acetoacetic ester lead to formation of cyclohexenonic fragment. The key stages of this reaction is Michael addition and condensation of activated methyl group and ketone fragment.



Knoevenagel reaction

We investigate a similar reaction with using cyclic enamines (a number of azolopyrimidines, indole derivatives, -pyrimidinedione and pyrimidinone) and unsaturated ketones. The general character of this cyclocondensation reaction is set, but reaction conditions very different in some cases.



Furthermore, it was investigated the effect of ultrasound irradiation for the reaction activation. It was found that in most cases the use of ultrasound will significantly reduce the reaction time, increase product yield and purity.

O-22

Multicomponent Heterocyclizations of 5-Amino-3-methylisoxazole with Carbonyl Compounds

Tkachenko V.V.[a,b], Muravyova E.A.[a], Desenko S.M.[a], Shishkin O.V.[a,b], Shishkina S.V.[a,b], Müller Th.J.J.[c], Chebanov V.A.[a,b,c]

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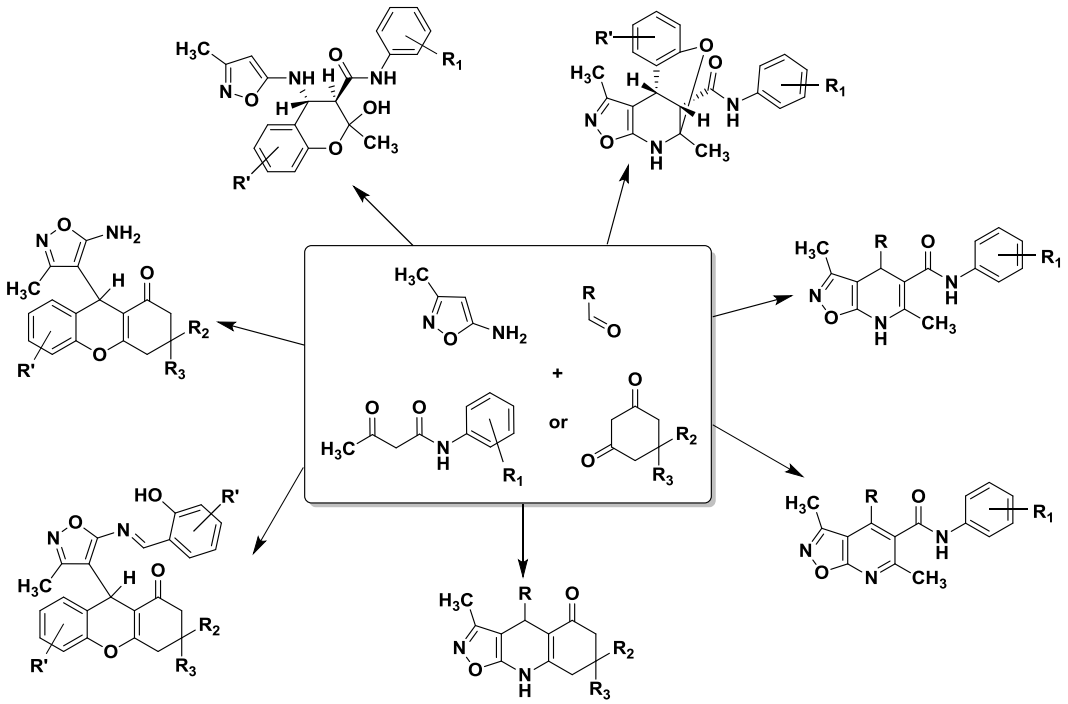
In case of multicomponent heterocyclizations the problem of selectivity becomes especially urgent that arises from the possibility of passing several parallel reactions leading to different final products. Control of these alternative reactions allows to selective obtaining several different types of heterocycles from the same starting materials, solving the problem of heterocyclic systems molecular diversity. This work is devoted to the finding the rules in the behavior of multicomponent reactions involving 5-amino-3-methylisoxazole, aldehydes and 1,3-dicarbonyl compounds, as well as to developing the methods for selective synthesis of fused heterocyclic systems containing isoxazole ring.

It was found that the three-component heterocyclizations of 5-amino-3-methylisoxazole, derivatives of cyclohexanedione and aldehydes selectively lead to isoxazolo[5,4-*b*]quinolinones. Salicylic aldehydes as a substrates gave isoxazolo[5,4-*b*]-quinolinones or 2,3,4,9-tetrahydro-1H-xanthen-1-ones. Three-component reactions involving 5-amino-3-methylisoxazole, salicylic aldehydes and *N*-arylacetoacetamides may be switched between three pathways leading to the formation of 4-(isoxazol-5-ylamino)chroman-3-carboxamides, isoxazolo[5,4-*b*]pyridine-5-carboxamides, or benzo[*g*]-isoxazolo[5,4-*d*][1,3]oxazocine-12-carboxamides.



O-23

Synthesis and Biological Activity of the Novel Derivatives of 4-Hydrazino-5-methylthieno[2,3-*d*]Pyrimidine-6-carboxylic Acid and their 6-Hetaryl and 4-Thio Analogs

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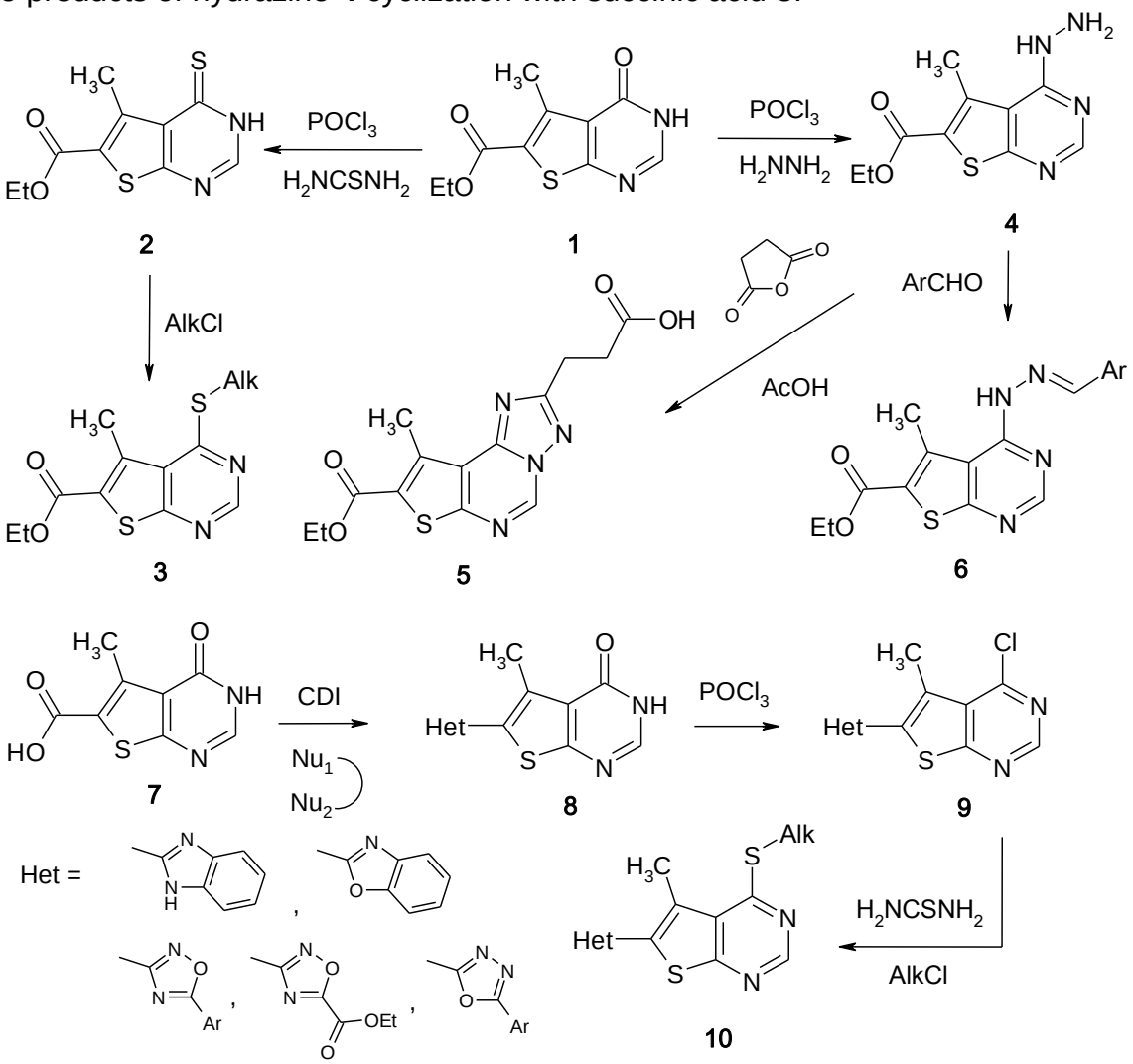
By the transformations of ethyl 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate **1** the series of 4-S-alkyl **3** and their 4-arylidenehydrazino analogs **6** together with the products of hydrazine **4** cyclization with succinic acid **5**.



The other part of our work was devoted to the synthesis of 5-methyl-6-hetaryl-4-(alkylthio)thieno[2,3-*d*]pyrimidines **10** starting from 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid **7**.

The structure of the compounds obtained was confirmed using NMR and chromato-mass spectral methods. For the compounds obtained their antimicrobial, anti-inflammatory and anticancer activity was studied.

O-24

[1,2,4]Triazino[2,3-*c*]quinazolines: Synthesis, Transformations and Biological Activity

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The history of investigations, focused on the search of the novel bioactive compounds among heterocyclic compounds lasts for more than a century. It reasoned the fact that, mentioned above class of the compounds is well studied and sufficient quantity of synthetically available heterocyclic systems were previously described at least by single examples. As usually it was enough for evaluation of their structural features and some chemical properties, but not for pharmacological potential. That's why systematic studies, aimed to the expanding the series of previously known heterocyclic compounds and studying of the synthesized compounds bioactivity, are of considerable interest. We are interested in [1,2,4]triazino[*c*]quinazolines, which were sporadically described, but were not systematically studied. During our investigation original approach for synthesis of [1,2,4]triazino[2,3-*c*]quinazoline system derivatives was elaborated. Mentioned methods are based on 3-(2-amino-3-R_2-4-R_3-5-R_4-6-R_5-phenyl)-6-R_1-1,2,4-triazine-5(2*H*)-ones modification, which are the products of 3-R_1-8-R_2-9-R_3-10-R_4-11-R_5-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones nucleophilic cleavage. The last ones, as we found may be prepared *via* [4+2]-cyclocondensation processes using substituted 4-hydrazono-3,4-dihydroquinazolines as initial compounds. Carbonyl-containing compounds (aldehydes, ketones, aldehydocarboxilic acids, ketocarboxilic acids), anhydrides of carboxylic acids, acylhalides, carbon disulphide, carbonyldiimidazole, esters of propiolic and but-2-ynedioic acids, nitrous acid, organic isocyanates and isothiocyanates were used in reactions with 3-(2-amino-3-R_2-4-R_3-5-R_4-6-R_5-phenyl)-6-R_1-1,2,4-triazine-5(2*H*)-ones. Using mentioned transformations substituted 6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-2-ones, [1,2,4]triazino[2,3-*c*]quinazoline-2-ones, benzo[*e*][1,2,4]triazino[2,3-*c*][1,2,3]triazin-2-ones, 3-R_1-5*a*-R_2-6,7-dihydro-2*H*-pyrrolo[1,2-*a*][1,2,4]triazino[2,3-*c*]quinazoline-2,8(5*aH*)-diones and 2-R-3*H*-isoindolo[2,1-*a*][1,2,4]triazino[2,3-*c*]quinazoline-3,10(14*bH*)-diones, as well as products of their further modification were obtained.

Conducted assay for synthesized compounds biological activity allowed to found agents with anticancer, analgetic, cerebroprotective, hypoglycemic and hypolipidemic properties.

O-25

Influence of Amide and Thioamide Groups on the Electronic Structure and Diene System Activity of Tetrazolo[5,1-*a*]isoindole

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Until recently, all the chemistry of isoindoles can be divided into two almost independent parts: 1) isoindoles, that exist in isoindole tautomeric form. The most characteristic reaction is the [4+2] cycloaddition reaction; 2) isoindoles, that exist in isoindoline tautomeric form, which does not contain *o*-quinoid structure and don't exhibit diene activity [1]. In some of our studies we have shown that substituents can influence the diene activity of isoindole system: for example, 1-aminoisoindole, which exists chiefly in isoindoline tautomeric form, can react with maleimides with the formation of Diels-Alder adducts according to the Curtin-Hammet principle [2]. Conversely, acylated tetrazoloisoindole, which has *o*-quinoid structure, don't exhibit diene activity [3, 4]. Therefore, actual problem is a deeper analysis of the factors influencing the electronic structure of isoindole systems.

We have synthesized a series of amides and thioamides derivatives of tetrazoloisoindole. In the case of amides the isoindole structure remains.Thioamides exist as structures with separate charges that don't have diene activity. For molecular structures of amides and thioamides, obtained by X-ray studies, natural bond orbital analysis were conducted and Fukui indices were calculated. Obtained data provide information on centers of nucleophilic, electrophilic or radical attacks. Intramolecular interactions were studied for molecules in a vacuum and taking into account the influence of the environment.

[1] V.A. Kovtuneko, Z.V. Voitenko. The chemistry of isoindoles // Rus. Chem. Rev. – 1994. – №63. – P. 997 -1018.

[2] I.V. Levkov, O.V. Turov, O.V. Shishkin, S.V. Shishkina, Z.V. Voitenko. The Curtin-Hammett principle in action: 1-amino-3H-isoindole in cycloaddition reactions // Tetrahedron. – 2010. – №2. – P. 508-512.

[3] Z.V. Voitenko, T.V. Yegorova, A.I. Kysil', C. André, J.G. Wolf. New cyanine dyes derived from tetrazolo[5,1-a]isoindoles // Tetrahedron. – 2004. – №1. – P. 195-201.

[4] Z.V. Voitenko, M. T. Boisdon, T.V. Yegorova, A.I. Kysil, J. Favrot, J.G. Wolf. IR spectroscopic study of the reactivity of aromatic 5-acyltetrazoloisoindoles // J. Mol. Structure. – 2003. – №3. – P. 171-177.

O-26

QuS: A Software for Automated QSAR Analysis of Biologically Active Compounds

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A new software tool for automated QSAR analysis of organic bioactive compounds called QuS (read as 'Kues' short QSARServer) were created. One of its tasks is to integrate and coordinate the work of other software tools that perform individual stages of analysis. This development consists of two parts: the user interface in a Web page and Web server. Program Management (web server) is held through a web page that contains the necessary tools and analysis of results are displayed.

This software development was made in ObjectPascal (web server) and JavaScript (UI) with using of classes and libraries (AraratSynapse, LCLBase, SynEdit) with open source.

Detailed methodologies for QSAR analysis to build a mathematical model of «structure-toxicity» were developed. Factors molecular structure of 4-thioquinoline that affect the value of their semi lethal doses built some appropriate QSAR model "structure-toxicity." There were made a number of tests for correlation models built using from 1 to 5 molecular descriptors and usable genetic algorithm for finding the mathematical models was used. Mathematical models associated features of the structure of 2-methylquinolin-4-thiol with their size semi lethal dose and the most influential factors determining molecular structure that influence on toxicity. Statistical characteristics of the results were compared with the equations in the relevant publications and experimental data. Built models were tested. A sufficient level of predictive power of the experimental determination of the average of the lethal dose LD_{50} of 2-methylquinolin-4-thiol derivatives was found.

Result demonstrates the sufficient reliability of the program and also shows that the optimal set of software tools and general methods of analysis program QuS were selected.

POSTERS

One-Pot Synthesis of 5-aryl/heterylidene-2-(2-hydroxyethylamino)- and 2-(3-hydroxypropylamino)-4-thiazolidinones as Potential Bioactive Molecules

P-1

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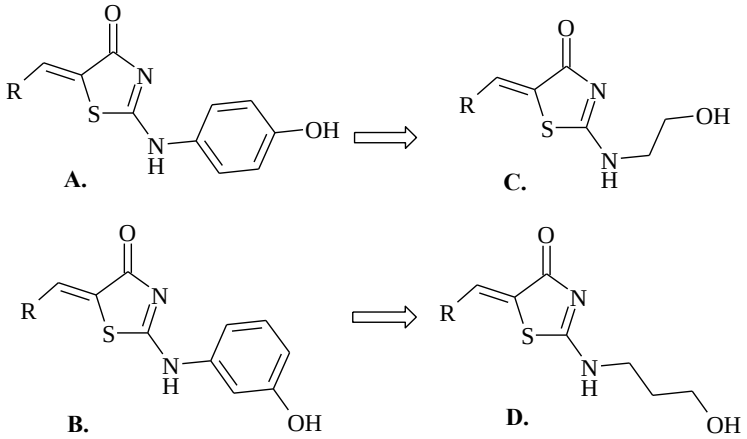
4-Thiazolidinones are well-known heterocycles with a wide spectrum of pharmacological activity [1]. Some leads with high level of antitumor activity were identified among 5-ilidene-2-(3(4)-hydroxypenylamino)-4-thiazolidinones (**A**, **B**) [2]. As a possible pathway for leads structure and properties optimization a one-pot synthetic methods for synthesis of early undescribed 5-aryl/heterylidene-2-(2-hydroxyethylamino)- and 2-(3-hydroxypropylamino)-4-thiazolidinones (**C**, **D**) were proposed. As general conception of methods involves simultaneous aminolysis of activated thioxo group and catalysis of Knoevenagel condensation by aminoalcohols.



^{1}H NMR and LC-MS spectra were used for structure determination. The amine-imine prototropic tautomerism was observed for synthesized compounds according to the spectral dates. Pharmacological screening of obtained compounds is in progress.

[1] R.B. Lesyk, B.S. Zimenkovsky. 4-Thiazolidones: centenarian history, current status and perspectives for modern organic and medicinal chemistry// Curr. Org. Chem.- 2004. - 8 (16). P. 1547-1577
[2] I. Subtel'na et al. Synthesis of 5-arylidene-2-amino-4-azolones and evaluation of their anticancer activity// Bioorg. Med. Chem. –2008.– 18.– 2010.P. 5090–5102.

P-2

CH...N Intramolecular Hydrogen Bonding in Some Pyridine and Indolizine-Based Heterocyclic Systems

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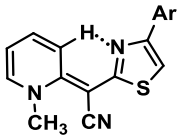
Quantum chemical calculations of compounds **1, 2** were carried out to confirm the presence of intramolecular hydrogen CH...N bonding in compounds **3-11**. Manifestations of such interactions in ^{1}H NMR spectra are demonstrated. The possible *π*-stereoselectivity in preparation of compounds **3-6** (Ad_NE) and their subsequent cyclization to indolizine systems **7-11** are discussed.

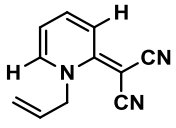


1

2

Ar = C_6H_5 (a), 4-ClC_6H_4 (b), 2-$CH_3OC_6H_4$ (c), 3-$NO_2C_6H_4$ (d)

Com-pound	**1a**	**1b**	**1c**	**1d**	**2**
C^3H	8.57	8.57	8.56	8.57	7.16



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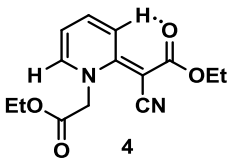

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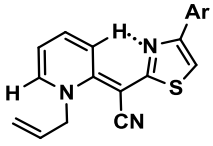

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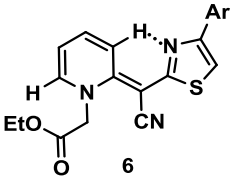
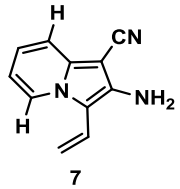


6

Ar = C_6H_5 (a), 4-ClC_6H_4 (b), 4-$CH_3OC_6H_4$ (c), 4-$NO_2C_6H_4$ (d)

Com-pound	**3**	**4**	**5a**	**5b**	**5c**	**5d**	**6a**	**6b**	**6c**	**6d**
C^3H	7.27	8.10	8.73	8.70	8.71	8.74	8.67	8.65	8.65	8.70
C^6H	7.90	8.10	7.81	7.83	7.79	7.88	7.87-7.95	7.87-7.95	7.82-7.88	7.95



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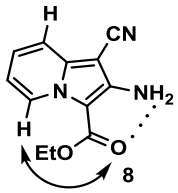

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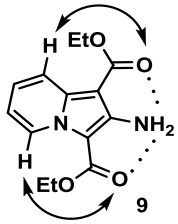

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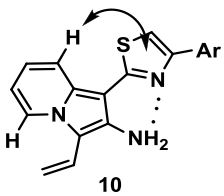

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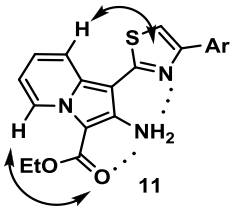

11

Ar = C_6H_5 (a), 4-ClC_6H_4 (b), 4-$CH_3OC_6H_4$ (c), 4-$NO_2C_6H_4$ (d)

Com-pound	**7**	**8**	**9**	**10a**	**10b**	**10c**	**10d**	**11a**	**11b**	**11c**	**11d**
C^8H	7.34	7.41	7.94	7.74	7.73	7.73	7.77	7.81	7.83	7.79-7.83	7.85
C^5H	8.32	9.24	9.32	8.35	8.35	8.35	8.48	9.37	9.39	9.36	9.38
NH_2	5.31	6.32	6.48	6.18	6.14	6.19	6.26	7.07	7.05	7.05	7.10

1,8-Bis(9'-carbazolyl)-3,6-dioxaoctane: Synthesis and Structure

P-3

Shtamburg V.G.[a], Shtamburg V.V.[a], Zubatyuk R.I.[b], Kravchenko S.V.[c], Klotz E.A.[d], Distanov V.B.[e], Uspensky B.V.[e]

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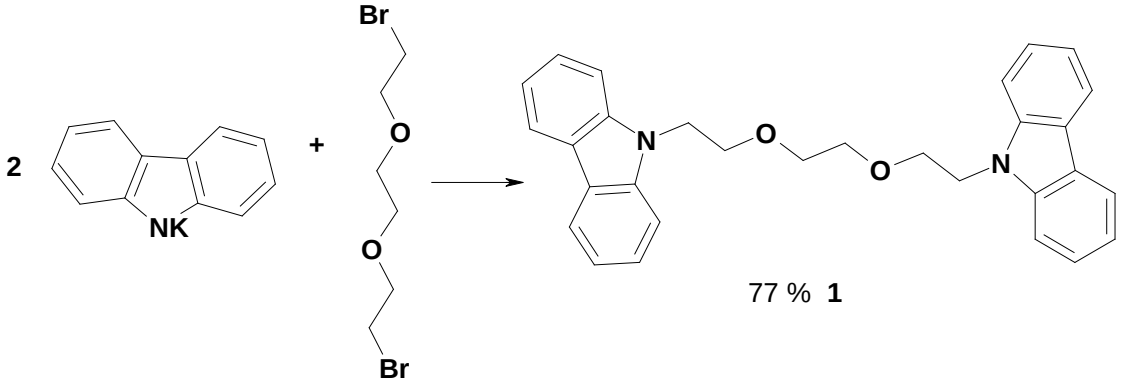
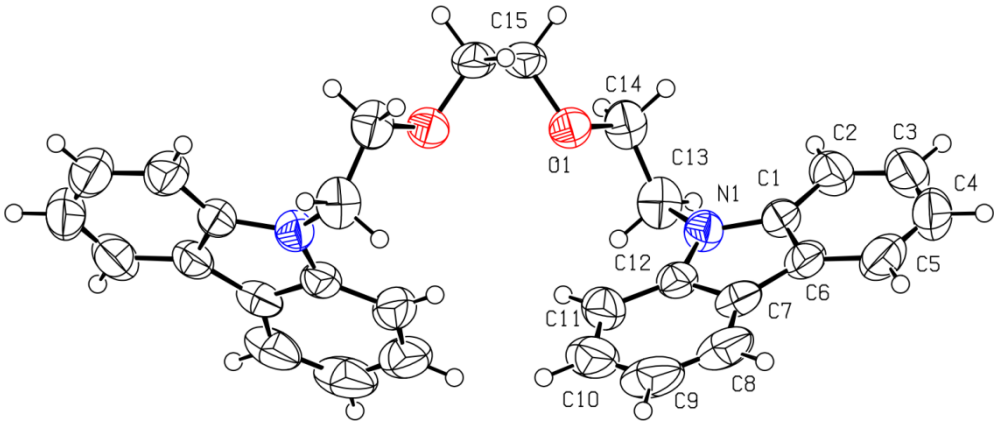
[b]*SSI "Institute for Single Crystals" of NAS of Ukraine*
[c]*Dnipropetrovsk State Agricultural-Economical University;*
[d]*Kirovograd State Pedagogical University;*
[e]*National Technical University "Kharkov Polytechnic Institute"*

1,8-Dibromo-3,6-dioxaoctane easy reacts with the potassium salt of carbazole in the boiling 1,4-dioxane solution yielding 1,8-bis(9'-carbazolyl)-3,6-dioxoctane **1**.



77 % **1**

The structure of 1,8-bis(9'-carbazolyl)-3,6-dioxoctane **1** has been studied by XRD



In the crystal the molecule **1** is located in a special position an 2_1 screw axis, which passes through the central C-C bond of polyester chain. The angle between the carbazolyl moieties plains is 76.8°. These carbazolyl groups are oriented towards each other with H11 hydrogen atoms. This orientation results in the formation of the short intra molecular contact H11…H11 2.24 Å (van der Waals radii sum is 2.32 Å). In the crystal molecules **1** are linked into infinite along *c* axis due to formation of weak C14-H14…O1^{i} [i: x,2-y,-1/2+z] hydrogen bonds between the polyester chains.

P-4

Geminal System O-N-O: XRD Studies of Structure of Cyclic *N,N*-dialkoxyderivatives of Amines and Ureas

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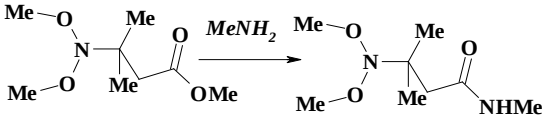
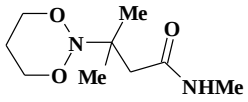
[b]*Kirovograd Flight Academy of National Aviation University, 25005 Kirovograd, Ukraine, e-mail geminalsystemsn@gmail.com*
[c]*Kirovograd State Pedagogycal University*
[d]*N.N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

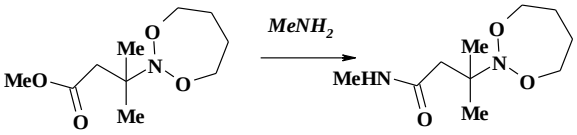
Acyclic *N,N*-dimethoxyamine **2**, perhydro-1,3,2-dioxazine **3** and perhydro-1,3,2-dioxazepine **5** had been synthesized. Their structure has been studied by XRD.



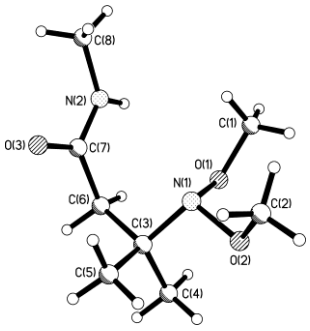
1 81% **2**



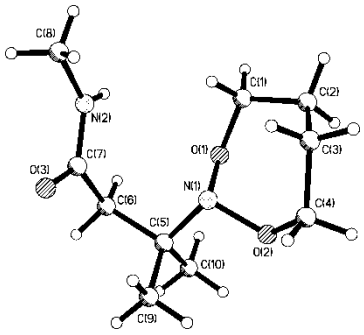
3



4 **5** *88%*

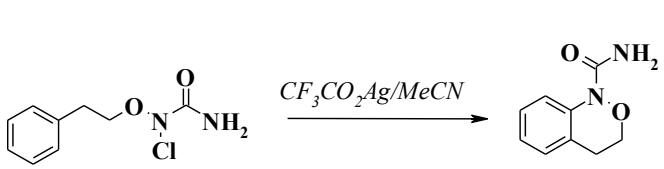


2

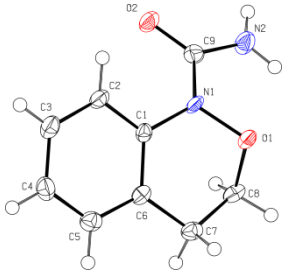


5

The formation of 1-carbamoyl-3,4-dihydro-1H-2,1-benzoxazine **7** is the first example of intramolecular nucleophilic substitution in the N-chloro-N-alkoxyureas. The structure of benzoxazine **7** has been studied by XRD.



6 **7** *71%*



1-carbamoyl-3,4-dihydro-1H-2,1-benzoxazine **7**

Synthesis of New Thiazolo[4,5-*b*]pyridines Based on Arylidene Pyruvic Acids and Chalcones via Reaction of [3+3]-Cyclocondensation

P-5

Lozynskyi A., Zimenkovsky B., Lesyk R.

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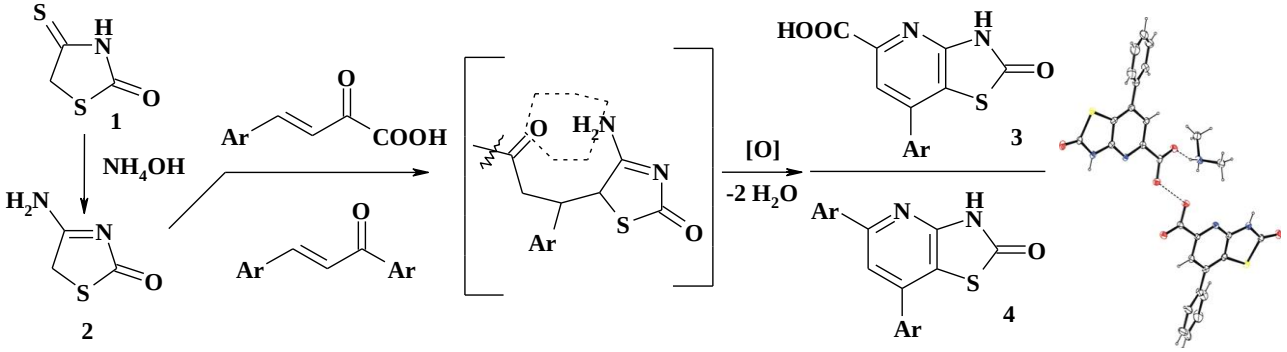
The construction of multiple carbon-carbon bonds in a single chemical step represents a particularly efficient approach to the synthesis of complex molecular structures. In support of this view, the reaction of [3+3]-cyclocondensation has particularly evolved as an efficient route to wide range of condensed compounds.The thiazolo[4,5-*b*]pyridines constructed on this principle formed a central skeleton of compounds which are known for their anti-inflammatory, antimicrobial and antioxidant activity [1].

All the new 2-oxo-7-phenyl-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acid and 5,7-diphenyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives were synthesized from 4-amino-5*H*-thiazol-2-one and various arylidene pyruvic acids and chalcones in the reaction [3+3]-cyclocondensation. The synthesis procedure included at first the reaction of 4-thioxo-2-thiazolidinones **1** with aqueous ammonia solution [2,3]. The obtained 4-amino-5*H*-thiazol-2-one **2** was utilized in the reaction [3+3]-cyclocondensation with a series arylidene pyruvic acids and chalcones. The structures of all new synthesized compounds **3,4** have been confirmed by ^{1}H NMR spectroscopy and X-ray analysys.



References

1. Synthesis and antioxidant activity evaluation of novel 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridines / T. I. Chaban et al. // Phosphorus, Sulfur, and Silicon and the Related Elements. – 2013. – Т. 188. – №. 11. – С. 1611-1620.
2. Komaritsa I. D. Studies on azolidones and their derivatives / I. D. Komaritsa // Chemistry of Heterocyclic Compounds. – 1968. – Т. 4. – №. 3. – С. 324-325.
3. Synthesis and evaluation of anticancer activity of 5-Ylidene-4-Aminothiazol-2(5*H*)-one derivatives / D. Kaminskyy et al // Medicinal chemistry. – 2015. – Т. 11. – №. 6. – С. 517-530.

P-6

Synthesis of N-Carboxyalkyl-1,8-Naphthalimides Containing Fragments of Primary and Secondary Amines in Positions 4 And 5

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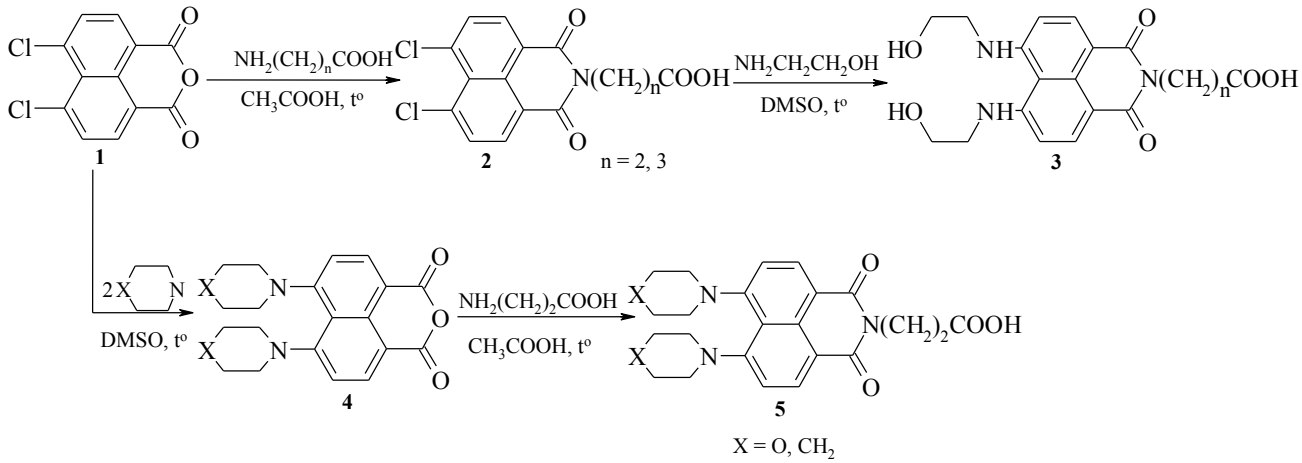
1,8-Naphthalimide derivatives containing electron donating substituent in position 4 of naphthalene ring are useful as fluorophores. Introduction of the second electron donating substituent in position 5 can improve the effective fluorescence properties.

N-2-Carboxyethyl- and N-3-carboxypropyl-1,8-naphthalimides with residues of ethanolamine in position 4 and 5 (**3**) were synthesized by aminolysis of 4,5-dichloro-1,8-naphthalic anhydride (**1**) with β-alanine or γ-aminobutyric acid in acetic acid and by further interaction of imides (**2**) with ethanolamine in DMSO.

N-2-Carboxyethyl-1,8-naphthalimides with residues of piperidine and morpholine in positions 4 and 5 (**5**) were obtained by interaction of 4,5-dichloro-1,8-naphthalic anhydride (**1**) with corresponding secondary amines in DMSO followed by aminolysis of anhydrides (**4**) with β-alanine.



The target products (**3**, **5**) are crystalline substances with luminescence in yellow-green region of the spectrum.

4,5-Dipiperidino-, 4,5-dimorpholino- and 4,5-di(2-hydroxyethylamino)-N-carboxyalkylnaphthalimides are potential fluorescent probes for various biological objects capable of covalent binding to amino groups due to the presence of carboxyl group in their structure.

The Reaction of Alloxane and Arylglyoxals with Furanes and Indole

P-7

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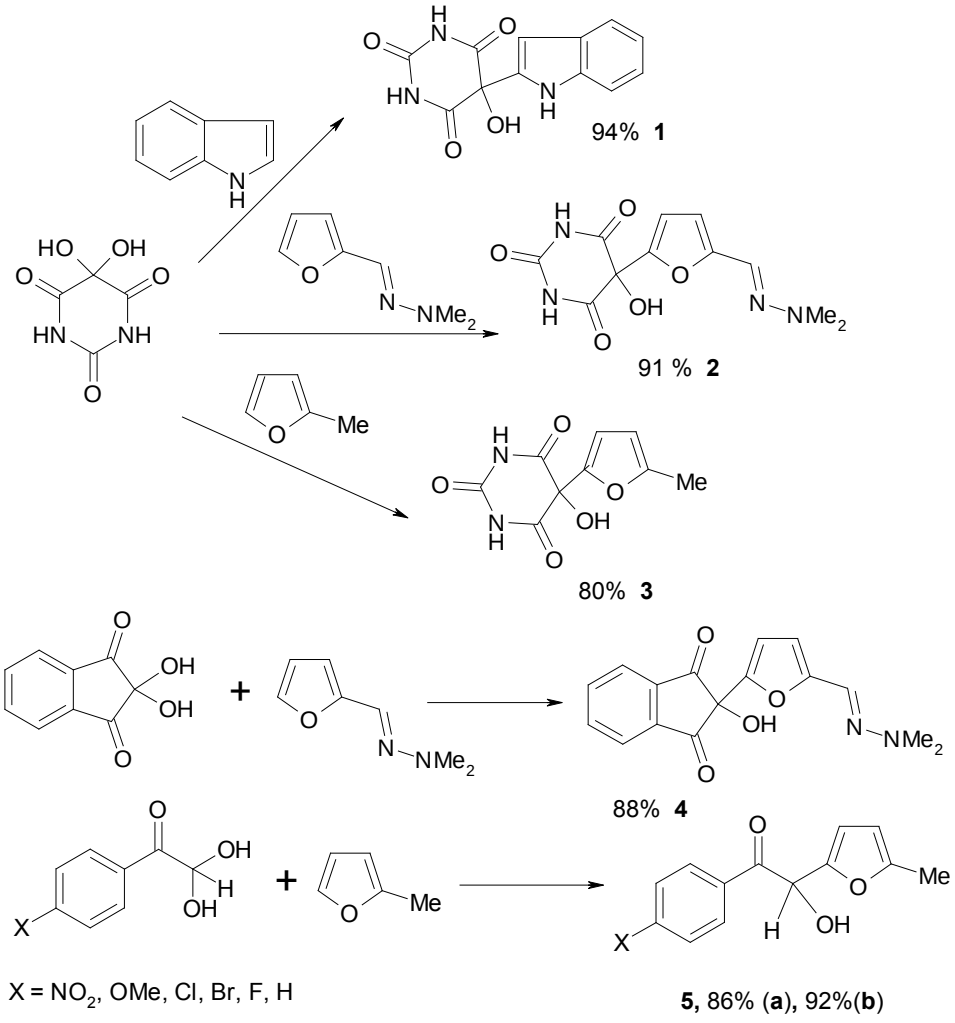
[a]Ukraine State University of Chemical Technology, 49005, Dnepropetrovsk, Gagarina str.8, e-mail: polytehnik@gmail.com, [b]Dnepropetrovsk National University

Alloxane hydrate reacts with indole (in MeOH solution), with N,N-dimethylhydrazone of 2-furanecarbaldegyde (in EtOH solution, r.t.) and with 2-methylfurane (in AcOH solution, r.t.) yielding the proper derivatives **1-3**. Indantrione reacts with N,N-dimethylhydrazone of 2-furanecarbaldegyde (in MeCN – PhH solution, r.t.) yielding the derivative **4.** The reaction of arylglyoxals with 2-methylfurane (AcOH solution, r.t.) selectively yields the proper aryl(furyl)benzoins **5a-f**.



P-8

Reactions of Thioacetamide Derivatives with Sulfonyl Azides. A novel Approach to Active Methylene N-Sulfonyl Acetamidines and Thiadiazoles

Beryozkina T.V., Dianova L.N., Efimov I.V., Berseneva V.S., Galata K.A., Filimonov V.O., Bakulev V.A.

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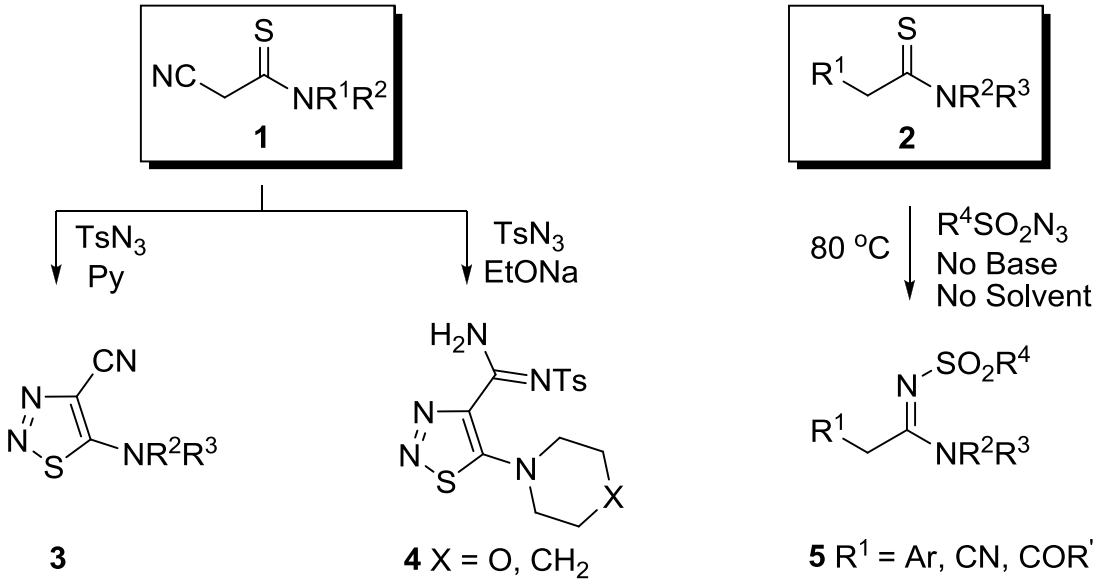
tetber@mail.ru

We have studied reactions of sulfonyl azides with thioacetamide and thiomalonamide derivatives **1**, **2**. It has been found that in the absence of a base the transformation of thioamide group to amidine group takes place to afford methylene active *N*-sulfonylamidines **5** in 62−98% yields. Various procedures for the reactions with the use of pyridine, boiling ethanol and water and in the absence of a base and solvent were carried out and compared. The solventless variant is the best in respect of the yields, and because it does not require the use of an excess of toxic and hazardous azides.

Conversely, reactions of sulfonyl azides with cyanothioacetamides **1** in pyridine lead to 5-amino-1,2,3-thiadiazoles **3** and to 4-tosylamidino-1,2,3-thiadiazoles **4** in the presence of EtONa.



3

4 X = O, CH_2

5 R^1 = Ar, CN, COR'

NR^2R^3 = NH_2, N⟨⟩O, N⟨⟩, N⟨⟩, N⟨⟩NMe ;

Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$;

R^4 = Me, 4-MeC_6H_4, 2,4-$Me_2C_6H_3$, 4-FC_6H_4, benzo[1,2,5]thiadiazole-4-yl

This project was supported by the Russian Scientific Foundation (15-13-10031).

Synthesis of New Pyridine-Thiazoles/Thiazolidinones and their Biological Activity

P-9

M.N. Wojtyra, R.B. Lesyk

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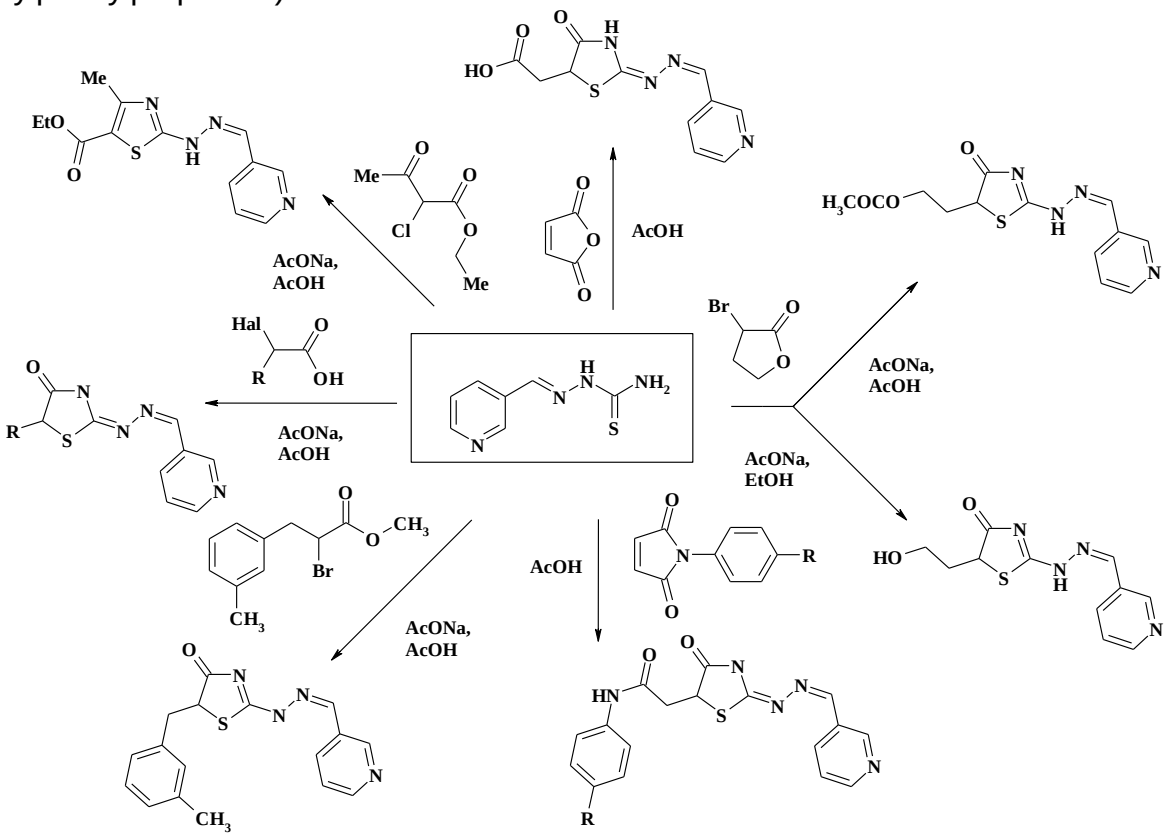
Thiazoline, thiazolidinone and pyridine derivatives posses a broad spectrum of biological activity. Therefore, it seemed of interest to design new pyridines bearig thiazoline and thiazolidinone moieties. The application of the [2+3]-cyclondensation reaction for the synthesis of 3-pyridine substituted thiazole-based compounds using different reagents (α-halogenocarboxylic acids, ethyl-2-chloroacetoacetate, maleic andydride, α-bromo-γ-butyrolactone, derivatives of maleic acids, methyl-2-bromo-3-methylphenylproponate) has been studied.



The structure of compounds synthesized has been confirmed by ^{1}H NMR and LCMS spectra. Pharmacological screening of anticancer, antimicrobial, antifungal and antitrypanosomal activities for synthesized compounds is in progress.

P-10

Structure of Sodium 3-Benzylcarbamoyl-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-4-olate

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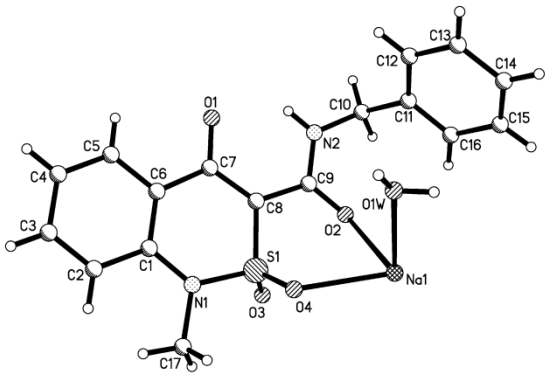
Numerous studies of the spatial structure of derivatives of 1-R-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acids – esters, hetaryl-, alkylamides and anilides carried out with the help of X-ray crystallographic analysis have shown that, as a rule, the thiazine nucleus that forms their base is in a *"half-chair"* conformation or in an intermediate conformation between a *"twist-bath"* and a *"sofa"* [1-3].

However, in the case of sodium 3-benzylcarbamoyl-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-4-olate obtained by crystallization from water a completely different result is observed. The dihydrothiazine ring of this compound unexpectedly appeared to be flat with the accuracy of 0.02 Å. The cyclic nitrogen atom has a planar configuration, the sum of bond angles centralized on it is 360°. The carbamide group of the substituent at C(8) atom is coplanar with the endocyclic C(7)-C(8) double bond (the torsion angle is C(7)-C(8)-C(9)-N(2) 5.5(6)°). Apparently, it is stabilized by formation of the intramolecular hydrogen bond N(2)-H…O(1) (H…O 1.95 Å N-H…O 136°) and leads to lengthening the C(7)-C(8) 1.405(6) Å bond. The benzyl fragment is in *ap*-conformation in relation to the C(8)-C(9) bond (the torsion angle is C(8)-C(9)-N(2)-C(10) -177.9(3)°), and the aromatic cycle is orthogonal to the plane of the carbamide fragment and turned towards the N(2)-C(10) bond (the torsion angles are C(9)-N(2)-C(10)-C(11) -80.2(6)°; N(2)-C(10)-C(11)-C(16) 104.4(5)°). The steric repulsion between atoms of the methyl substituent and the bicyclic fragment causes lengthening the C(17)-N(1) bond up to 1.502(9) Å compared to its mean value 1.469 Å.

The coordination polyhedron of a sodium cation is a distorted octahedron. A pair of sodium cations is linked with two bridging anions by the chelated type coordinating by atoms O(2), O(3) and O(4). In the terminal each sodium atom is coordinated by O(1) atom of the third anion binding pairs of atoms of sodium and by a water molecule. As a result, the infinite polymer chain is formed in the crystal.



[1] Ukrainets, I.V.; Petrusova, L.A.; Dzyubenko, S.P. // Chem. Heterocycl. Comp. – 2013. – Vol. 49, No. 9. – P. 1378.

[2] Ukrainets, I.V.; Petrusova, L.A.; Dzyubenko, S.P.; Liu, Y. // Chem. Heterocycl. Comp. – 2014. – Vol. 50, No. 4. – P. 564.

[3] Ukrainets, I.V.; Petrusova, L.A.; Sim, G.; Bereznyakova, N.L. // Chem. Heterocycl. Comp. – 2015. – Vol. 51, No. 1. – P. 97.

A Study of Heterocyclization Reactions of Pyruvic Acid Esters with 4-Substituted 5-Aminopyrazoles

P-11

Sakhno Ya. I.[a], Kozyryev A. V.[b], Sen`ko Y. V.[a], Chebanov V. A.[a,b]

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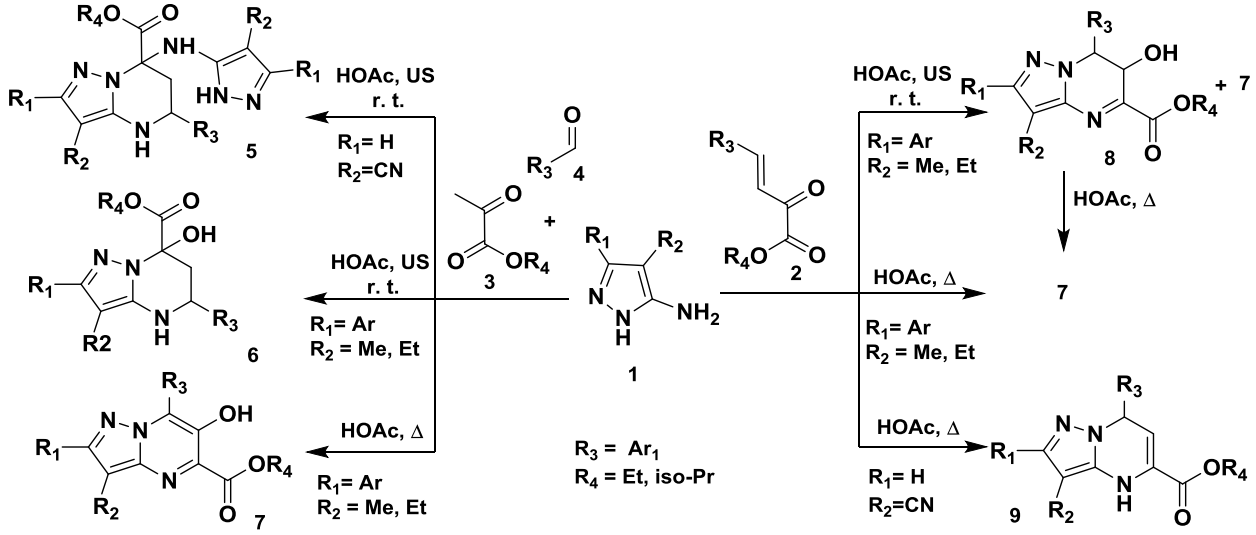
[b]*V. N. Karazin Kharkiv National University, e-mail: chebanov@isc.kharkov.com*

The present work is dedicated to the study of linear and multicomponent heterocyclizations of 4-substituted 5-aminopyrazoles (**1)** with pyruvic acids esters (**3)**. An interest to these reactions is caused by ambiguity of their direction, which was observed earlier in the treatments involving 5-aminopyrazoles and pyruvic acids [1,2].

It was found that refluxing pyruvic acid esters (**3)** with aromatic aldehydes (**4)** and 4-alkyl-5-aminopyrazoles (**1)** in acetic acid led to the formation of pyrimidine-5-carboxylates (**7)**. The same heterocycles were isolated in case of reaction of arylidenpyruvic acid esters (**2)** and their treatment with aminopyrazole (**1)** in boiling acetic acid. On the other hand, the same reaction carried out under ultrasonication was nonselective and yielded pyrazolopyrimidines (**7)** and (**8)**. Refluxing compounds (**8)** in acetic acid allowed to obtain heterocycles (**7)**. The interaction of pyrazoles (**1)** and aldehyde (**4)** with esters (**3)** under ultrasonication resulted in formation of 7-hydroxytetrahydropyrimidines (**6)**.



Introduction of a carbonitrile substituent in the fourth position of pyrazole (**1)** in case of multicomponent reaction with aldehydes (**4)** and esters (**3)** under ultrasonication led to heterocycles (**5)**. The treatment of the same pyrazole (**1)** with compounds (**2)** under conventional refluxing resulted in formation of dihydropyrazolopyrimidines (**9)**.

[1] V. A. Chebanov, Ya. I. Sakhno, S. M. Desenko [et al.], *Tetrahedron* **2007**. Vol. 63, P. 1229−1242.
[2] Ya. I. Sakhno, S. V. Shishkina, O. V. Shishkin [et al.], *Mol. Divers* **2010**. Vol. 14, P. 523−531.

P-12

3(5)-Aminoisoxazoles in Multicomponent Reactions with Aromatic Aldehydes and Cyclic Active Methylene Compounds

Morozova A.D.[a], Muravyova E.A.[a], Shishkina S.V.[a], Desenko S.M.[a], Chebanov V.A.[a,b]

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Isoxazole derivatives with various types of bioactivity are widely used in medicine. The diversity of molecular drug targets for isoxazole-containing compounds, as well as numerous matters solved with their help, determines the high interest to them.

However, multicomponent reactions of 5(3)-aminoisoxazole involving carbonyl compounds have been represented in very limited number of publications.

In our study it was shown that multicomponent reaction of the selected aminoazoles, aromatic aldehydes and cyclic active methylene compounds resulted in products of heterocyclization reaction only in the case of 5-amino-3-methylisoxazole **1**. Ultrasonication of the initial compounds in EtOH gave spiro-fused heterocycles **6**, **7**. On the other hand, refluxing aminoisoxazole **1**, aldehyde **3** and Meldrum's acid **4** led to pyridones **8**. It was also shown that heating under MW-irradiation of compound **6** resulted in the formation of **8** in low yields. The formation of compound **9** during three component treatment with N,N'-dimethylbarbituric acid **5** wasn't observed in despite of the diversity methods used.

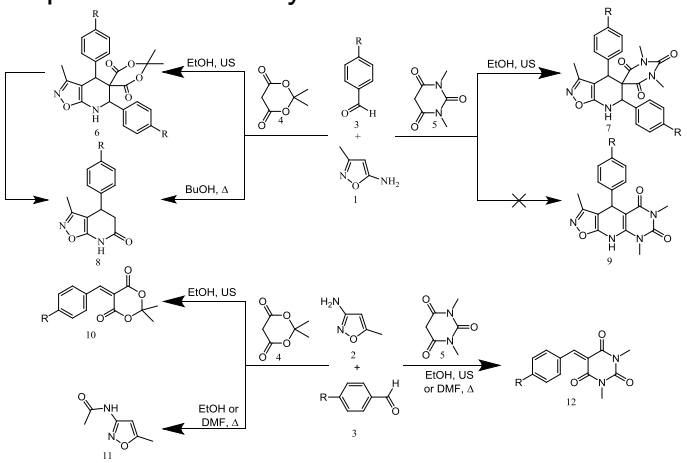

Figure 1

In contrast, in the case of isomeric 3-amino-5-methylisoxazole **2**, its multicomponent reaction with aldehyde **3** and active methylene compounds **4** or **5** under ultrasonication resulted in the formation of the arylidene derivatives **10** and **12**. Refluxing of the starting materials gave compound **12** and acylation reaction of 3-amino-5-methylisoxazole with Meldrum's acid. No product of heterocyclization was observed.

Unexpected One-Pot Synthesis of Pyrazolone Derivatives

P-13

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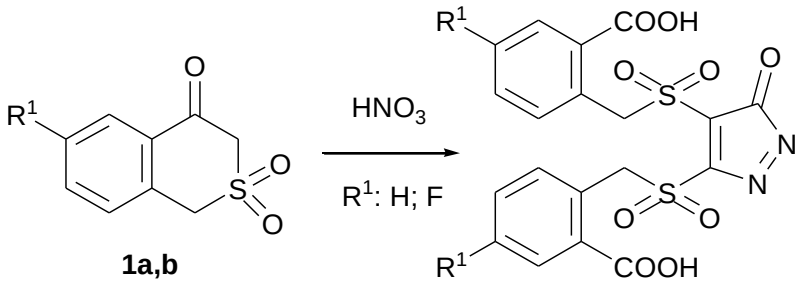
[b]Division of Functional Materials Chemistry, SSI "Institute for Single Crystals" of National Academy of Science of Ukraine, 60 Lenina ave., Kharkiv, 61001, Ukraine
[c]Department of Chemistry, V. N. Karazin Kharkiv National University, 4 Svobody sq, Kharkiv, 61122, Ukraine

In many families from different countries, the pyrazolone derivatives, which include dipyrone, antipyrine, aminopyrine and propyphenazone, are widely used analgesics. However, the synthesis of pyrazolone ring always requires the participation of the N-N fragment (hydrazine, hydrazide, etc). At the same time, sulfones are an important class of compounds that have attracted considerable attention. Recognizing the value of this heterocyclic system, chemists continue to develop novel routes for their synthesis.

We introduce the interesting behavior of isothiochromanones in the environment of nitric acid [1].

The structure of 2,2'-[(3-oxo-3*H*-pyrazole-4,5-diyl)bis(sulfonylmethylene)]dibenzoic acid (**2a**) was proved by X-ray diffraction, because NMR and IR spectroscopy proved uninformative for interpretation of the structure of this compounds.



1a,b **2a,b**

[1] Shyshkina O.O., Medvediev V.V., Shishkin O.V., Kysil A.I. and Volovenko Yu.M. Unexpected synthesis of pyrazolone derivatives, Tetrahedron. – 2015. – Vol. 71. – P. 1283 – 1286.

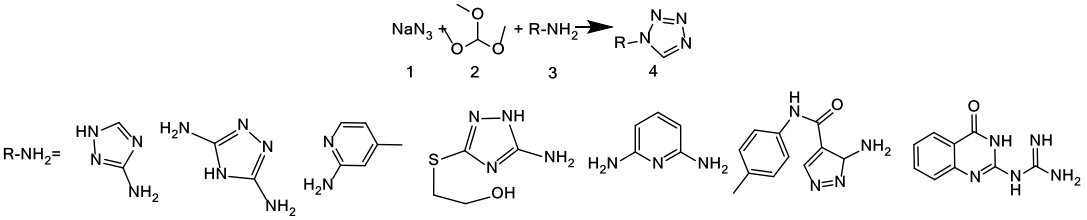
P-14

Synthesis and Complexation Properties of Some Polyazoles and Salicylic Aldehyde Derivatives

Zviagin I. M.[a], Saraev V. E.[a], Bryleva E. Yu.[a], Blank T. A.[a], Khimchenko S. V.[a], Morozova A. D.[a], Muravyova E. A.[a], Chebanov V. A.[a,b]

[a] *SSI "Institute for Single Crystals" of NAS of Ukraine, Lenina ave., 60, Kharkiv, Ukraine 61001, chebanov@isc.kharkov.com;*
[b] *V.N. Karazin Kharkiv National University, Svobody sq., 4, Kharkiv, Ukraine 61022*
izviagin@gmail.com

The one-pot reaction of sodium azide **1**, orthomethylformiate **2** and amines **3** in acetic acid resulted in the synthesis of diverse substituted tetrazoles **4**, which can behave as complexones (Scheme 1).



The derivatives of salicylic aldehyde **5-8** were obtained as well and their complexation properties were analyzed. The results are shown in Table 1.

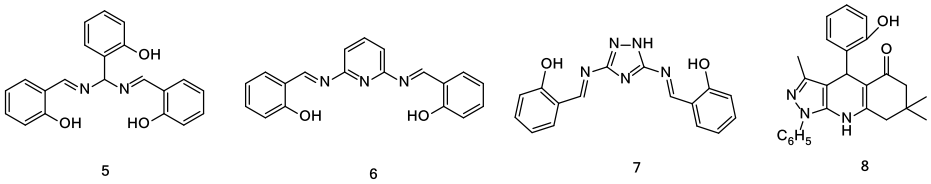


Table 1. Complexation results for compounds **5-8**

Compound	lg β							
	Water					CH_3CN:EtOH (1:1)		
	Cu^{2+}	Pb^{2+}	Cd^{2+}	Eu^{3+}	Sr^{2+}	Cu^{2+}	Pb^{2+}	Cd^{2+}
5	4.11	5.64	4.15	-	-	6.16	4.95	4.12
6	poor	poor	poor	-	-	2.05	poor	1.06
7	poor	poor	poor	-	-	6.11	4.11	poor
8	2.45	-	-	7.33	0.14	-	-	-

The modified analogues of compound 5, linked to the surface of silica gel and Merrifield resin, are currently analyzed for their complexation properties with metal ions shown in table 1.

Synthesis of 1-Methyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones Library via Reaction of 2-Hydrazinoquinazolin-4(3*H*)-ones with Acetylacetone

P-15

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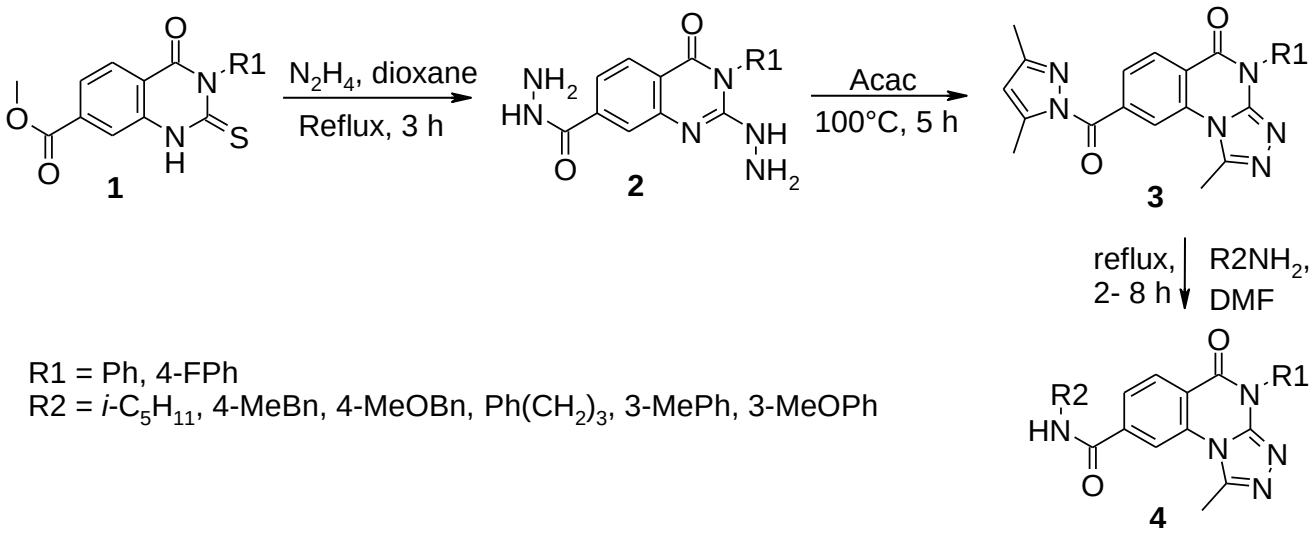
Formerly we have observed the formation of 1-methyl[1,2,4]triazolo[4,3-*a*]-quinazolin-5(4*H*)-ones **3** instead of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)quinazolin-4(3*H*)-ones by reaction of2-hydrazinoquinazolin-4(3H)-ones **2** with acetylacetone. Under similar conditions, the7-carbohydrazide group in quinazolin-4(3*H*)-one moiety is transformed into a pyrazole derivative **3**, which can be replaced by amine with amide **4** formation.

We utilized these reactions for synthesis of the library of amide derivatives of 1-methyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one **4** according the scheme.



R1 = Ph, 4-FPh
R2 = *i*-C_5H_{11}, 4-MeBn, 4-MeOBn, $Ph(CH_2)_3$, 3-MePh, 3-MeOPh

The purity and structures of synthesized compounds have been proven by elemental analysis and ^{1}H NMR spectroscopy data. The structure of 1-methyl-*N*-(3-methylbutyl)-5-oxo-4-phenyl-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide **4** (R1 = Ph, R2 = *i*-C_5H_{11}) was confirmed by LCMS data in addition.

P-16

Spiro Derivative of Dihydro-1.2.3-triazolo[1,5-a]pyrimidine as a Product of Multicomponent Condensation

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Bila I.G.[a], Komykhov S.A.[a,b], Desenko S.M.[a]

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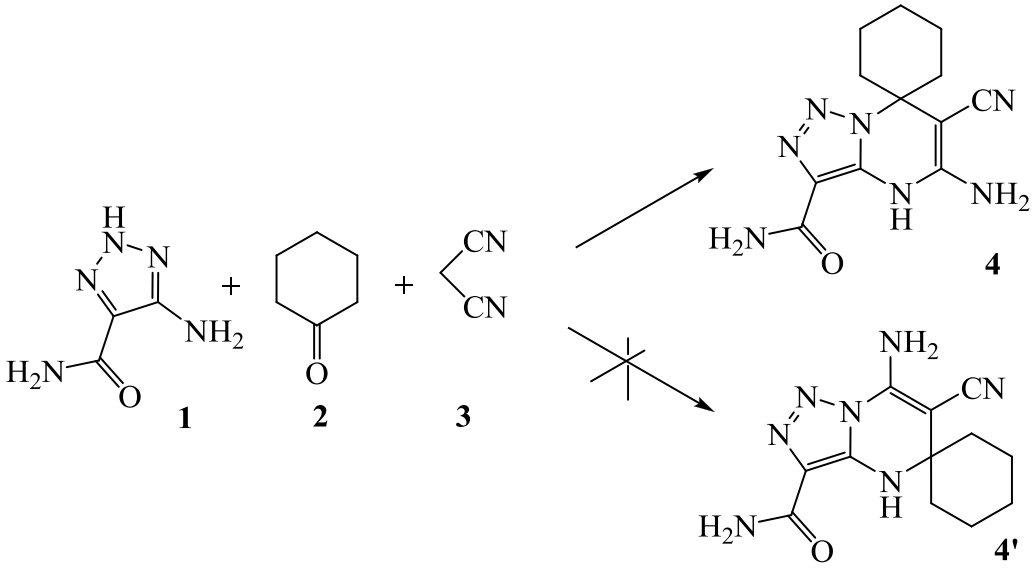
New spiro derivative of 4,4-dihydro-1,2,3-triazolo[1,5-a]pyrimidine (**4**) was prepared by Biginelly-like three-component condensation of 5-amino-2H-1,2,3-triazole-4-carboxamide (**1**) with malondinitrile (**3**) and cyclohexanone (**2**) in ethanol either by microwave irradiation or by conventional heating.



The structure of **4** was established by NMR ^{1}H and ^{13}C method and XRay analysis. It was shown that cyclocondensation undergoes regioselectively leading to single product, the structure of which corresponds to 4,7-dihydro derivative, in contrast to the results obtained in similar way from 3-amino-1,2,4-triazole [1].

The reaction conditions (temperature, solvent), for optimized product yield were proposed.

[1] A. Dandia, P. Sarawgi, K. Arya, S. Khaturia // Arkivoc. – 2006. – Vol. XVI. P. 83-92.

7-Unsubstituted 4,7-Dihydro-1,2,4-triazolo[1.5-a]pyrimidines as Products of Multicomponent Condensations in Water Medium

P-17

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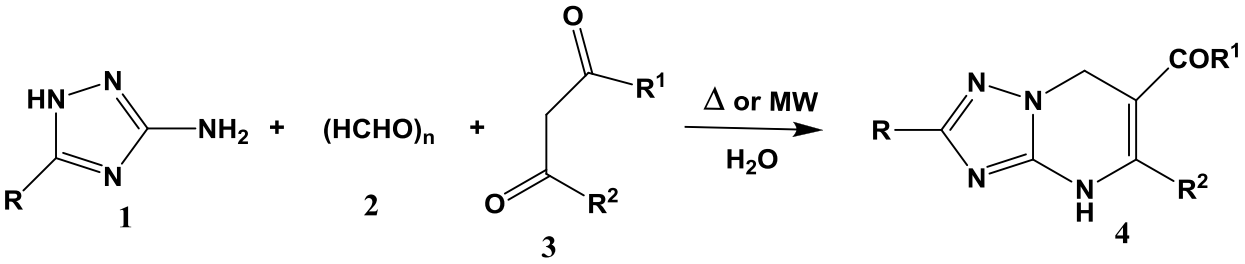
[b]*V.N. Karazin Kharkiv National University, Kharkiv, Ukraine.*
[c]*Zaporozhye State Medical University, Zaporozhye, Ukraine.*

New low molecular mass 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines **4** were obtained by Biginelli-like three-component condensation using 3-amino-1,2,4-triazole (**1**), paraformaldehyde (**2**) and 1,3-dicarbonyl compound **3**. As a "green solvent", water proved to be an excellent reaction medium.

.



R = H, COOMe; R^1 = Me, OMe, OEt, $O(CH_2)_2OMe$; R^2 = Me, n-Pr.

The structures of compounds **4** were confirmed by their spectral data (NMR ^1H and ^{13}C, IR and EI mass spectra).

It was shown, that the direction of the cyclocondensation corresponds to those which are traditional for reaction of aminoazoles with □□□-unsaturated compounds [1], leading to 4,7-dihydro derivatives; the reaction mechanism was discussed.

Compounds **4** showed *in vitro* antimicrobial and fungicidal activity comparable with standard drugs.

[1] S. M. Desenko S. M. // Khim. Geterotsikl. Soedin. -1995. –P. 147; Chem. of Heterocycl. Compd. (Engl. Transl.). -1995. –V. 31. –P. 125.

P-18

A Study of Reaction of Pyridine-4-ylmethylene Hydrazide 1-Hexyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid and Molecular Bromine

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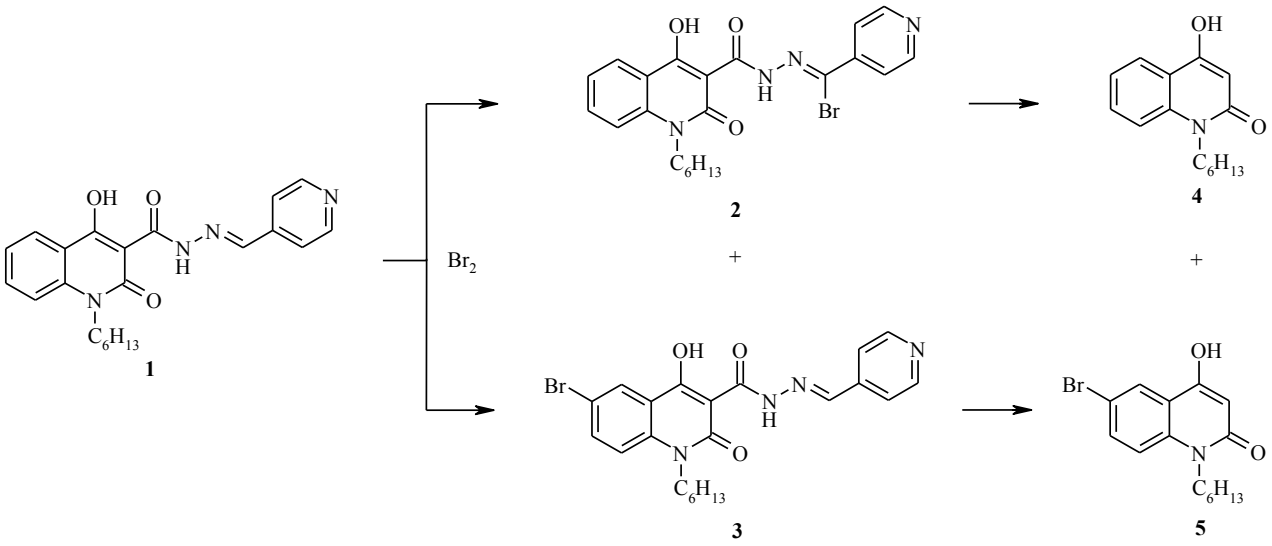
Chemical reactions of various amide derivatives of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids with molecular bromine do not always proceed in an unambiguous manner, often leading to the formation of quite unexpected final products and therefore attracting special attention from organic chemists. Thus, using pyridine-4-ylmethylene hydrazide 1-hexyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) as an example, we have shown that, regardless of external conditions, its bromination in glacial acetic acid leads to the formation of two different types of products. Under ordinary conditions, it is the less reactive center - the azomethine carbon atom that mostly undergoes bromination to yield (bromopyridine-4-ylmethylene) –hydrazide (**2**).



As it turned out, in the hydrazone molecule (**1**), another real target for an electrophilic attack is the 6 position of the quinolone nucleus, and the result of its involvement in the reaction under study is a minor 6-bromo hydrazone (**3**). If the reaction is carried out in a sealed tube, more profound chemical transformations occur leading to the destruction of both hydrazones and the formation of 1-hexyl-4-hydroxy-1H-quinolin-2-one (**4**) and of its 6-bromo analogue (**5**).

Isocyanide-based Multicomponent Reactions Involving Aminoazoles and Azoloazines

P-19

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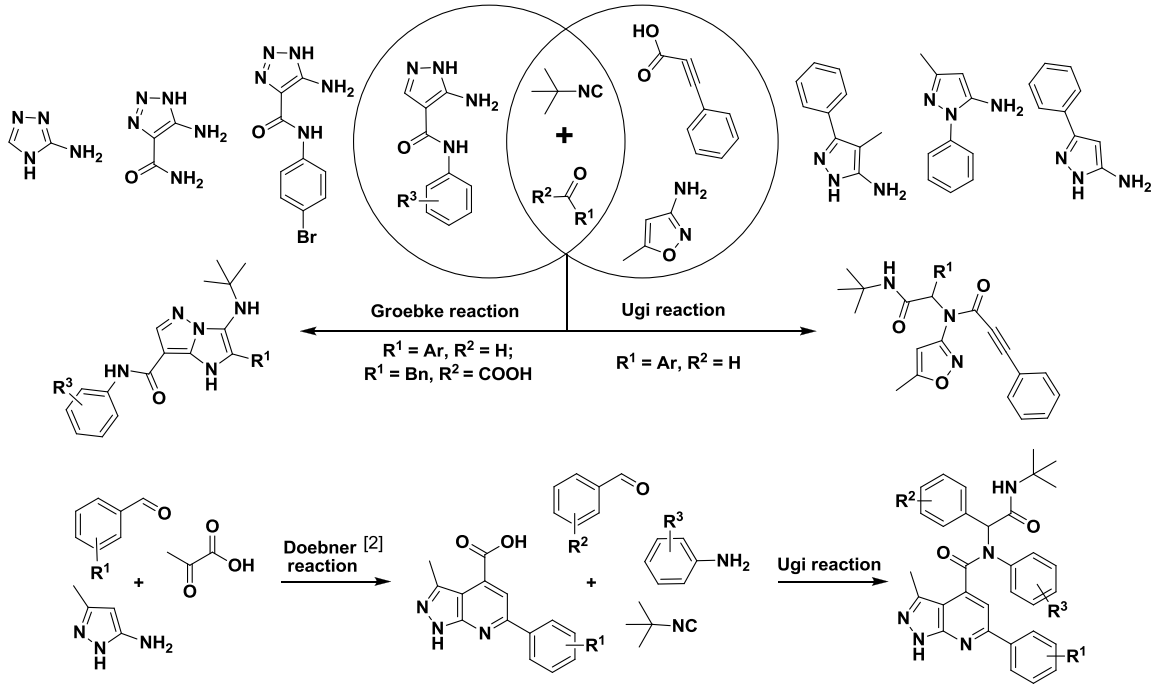
The rapid development of combinatorial and medicinal chemistry dealing primarily with drug discovery has led to the exigency of applying Diversity Oriented Synthesis[1,2]. From this point of view, isocyanide-based MCR*s* especially in combination with Doebner-type reaction are the powerful tool to access the diversity as well as the complexity of final compounds in one-pot procedure[3].

In the present study among the big series of aminoazoles applied 5-amino-*N*-phenylpyrazole-4-carboxamides and 3-amino-5-methylisoxazole showed good reactivity in Groebke and Ugi reactions, correspondingly. Moreover, the modification of classical Ugi reaction by introducing heteroaromatic carboxylic acids [2] previously synthesized in Doebner reaction was carried out.



[1] V. Chebanov, K. Gura, S. Desenko, Top. Heterocycl. Chem., 23, 2010, 41–84.
[2] V. A. Chebanov, Y. I. Sakhno, S. M. Desenko, V. N. Chernenko, V. I. Musatov, S. V. Shishkina, O. V. Shishkin, C. O. Kappe, Tetrahedron, 63, 2007, 1229-1242.
[3] Dömling A., Ugi I., Angew. Chem. Int. Ed. 39, 2000, 3168-3210.

P-20

Preparation of Protected Hydrazinoalkylindoles via Hydrazine Alkylation

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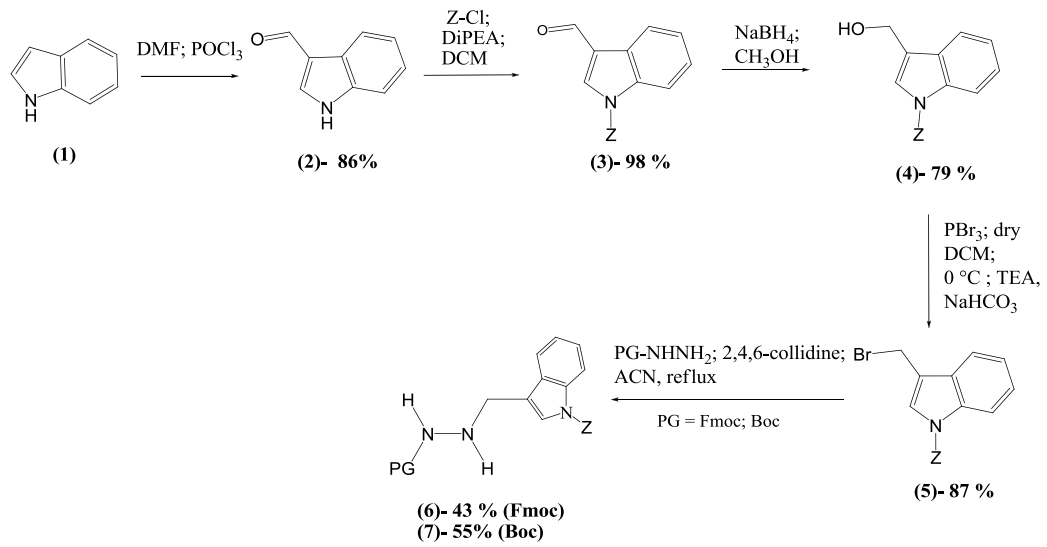
Protected hydrazinoalkylindoles, which are used as a stable precursors for aza-tryptophane introduction into peptidomimetics, have been prepared by using $Pd(OH)_2/H_2$ reduction of Fmoc-protected hydazones of N-(Boc)-indole-3-aldehyde [1], or by reduction of Ddz-protected hydrazones of N-(Boc)-indole-3-aldehyde in the presence of large excess of $NaBH_3CN$/AcOH [2]. If the former method requires expensive catalyst and specific apparatus for hydrogenation at elevated pressure, the latter method was found to be inefficient in the case Fmoc-protected hydrazones. Therefore we have worked out an alternative synthetic route for preparation of hydrazinoalkylindoles. This process is based on direct alkylation of protected hydrazines by N-Z-3-(bromomethyl)indole [3], as described below.



In this synthesis indole (**1**) was converted into N-(Z)-3-(bromomethyl)indole (**5**), and further used for alkylation of Fmoc-, and Boc-protected hydrazines in refluxing acetonitrile in the presence of 2,4,6-collidine as a base. The required Fmoc and Boc hydrazinoalkylindoles (**6** and **7**) were obtained in moderate yields.

[1] Boeglin, D., Lubell, W. D., *J. Comb. Chem.*, 2005, 7, 864-878.
[2] Freeman, N. S., Hurevich, M., Gilon, C., *Tetrahedron*, 2009, 65, 1737-1745.
[3] Mastitski, A., Haljasorg, T., Kipper, K., and Järv, J., *Proceedings of the Estonian Academy of Sciences*, 2015, 64, 2, 168–178.

Synthesis and Reactions Of ω-Aminoalkylthiophene Derivatives

P-21

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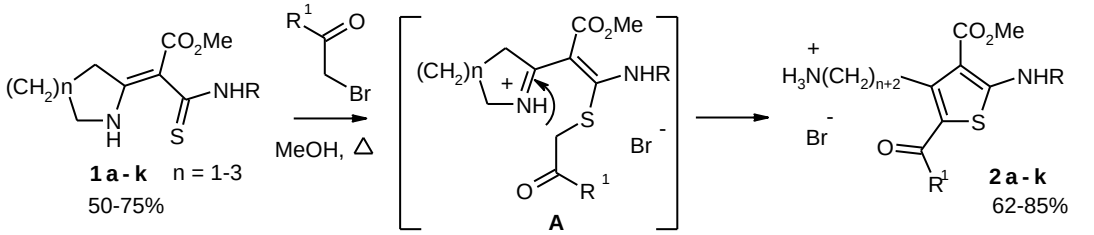
One of the common synthetic approaches to substituted thiophenes is an interaction of α-functionalized thiocarbonyl compounds with alkyl halides bearing electron withdrawing groups. In the present work in the synthesis of ω-aminoalkylthiophenes we have used carbamoyl derivatives **1**, which were obtained utilizing the reaction of enaminoesters with isothiocyanates [1]. The reaction of thioimidates **1** with aromatic α-haloketones in refluxing methanol in the absence of a base resulted in formation of ω-aminoalkyl derivatives of thiophene-3-carboxylic acids **2**. These compounds are formed as a result of the recyclization reaction of the intermediate A, which was in turn obtained by means of sulfur alkylating process. On treatment of hydrobromides **2** with triethylamine or sodium alkoxide, one can obtain free bases **3** featuring a 5-aminopentyl moiety. Under these reaction conditions 3- and 4-aminoalkylderivatives are cyclized into thieno[2,3-c]azepines and thieno[2,3-c]azocines **4,** respectively whose structures were studied by X-ray analysis. While treatment of salt **2** with $NaBH_4$ in methanol resulted in formation of secondary alcohols **5,** bicyclic compounds **4** gave 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine derivatives **6**.

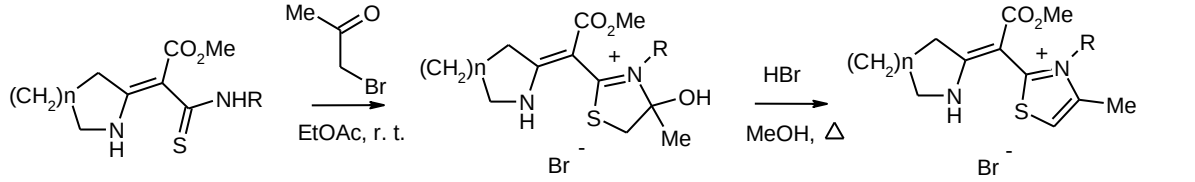


1 a - k n = 1-3 50-75% — **2 a - k** 62-85%

3 a - d 85-98% — **4 a - g** n = 1,2 70-93% — **5 a - h** n = 1-3 65-94% — **6 a - c** 68-86%

R = Me, Et, Ph, *m*-MeC_6H_4, *m*-ClC_6H_4; R^1 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-MeC_6H_4

It's worth mentioning that bromoacetone reacts in Hantzsch-type mode affording 4-hydroxythiazoline salts **7**. Heating the latter in methanol in the presence of catalytic amount of HBr resulted in thiazole salts **8**.



1 a-d n = 1, 3 R = Ph, *m*-MeC_6H_4 — **7 a, b** 60-93% — **8 a-d** 69-83%

[1] Davies C.D., Elliott M.C., Wood J.L. Tetrahedron 62 (2006), 11158-11164.

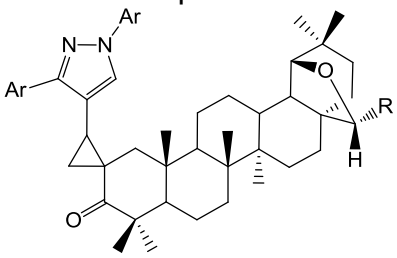
P-22

New Chiral Dopants for Cholesteric Liquid-Crystal Compositions Based on Lupane and Steroid Cores with Pyrazol Substituents

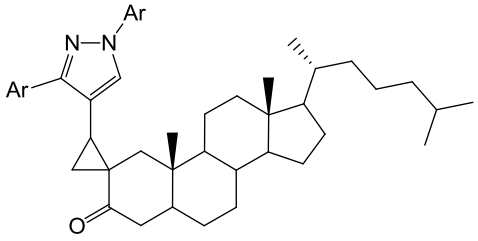
Semenenko A.N.[a], Babak N.L.[a], Shishkina S.V.[a,c], Gella I.M.[a,c], Yaremenko F.G.[b], Vakula V.N.[b], Novikova N.B.[a], Lipson V.V.[a-c]

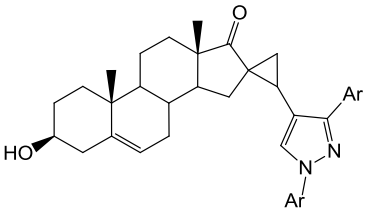
[a]*State Scientific Institution "Institute for Single Crystals", Kharkov, Ukraine, e-mail: lipson@ukr.net*
[b]*Medicinal Chemistry Department, State Institution "V.Ya. Danilevsky Institute for Endocrine Pathology Problems", Kharkov, Ukraine*
[c]*V.N. Karazin Kharkov National University, Chemistry Department, Kharkov, Ukraine*

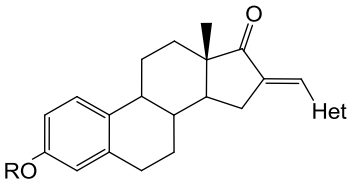
New series of chiral dopants for cholesteric liquid-crystal compositions were synthesised on the base of 2-substituted allobetuline, cholestanone, 16-substituted epiandrosterone and estrone cores [1-3]. The synthetic routes for these compounds are discussed. Their steric structure was determined by X-ray analysis. The relationship between spatial structure of the target dopants and their ability to induce cholesteric helix in the series of nematic solvents were examined. The highest values of the helical twisting power |***β***| (210.23 ± 3,4) and (158.61 ± 8,7) $mkm^{-1}mol{\cdot}pats^{-1}$ showed (2*R*,3*R*)-[3-(4′-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,2′-spiro-cyclopropanoallobetulon and (*E*)-2-{[3-(1,1'-biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylidene}allobetulone correspondingly. It is shown how the value of |***β***| in this series of chiral dopants varies depending on the spatial arrangement relative to the substituent in the position 2 of the chiral core.



R=H, Ph







[1] N.I. Shkol'nikova, Zh.O. Sheshenko, V.M. Vakula, O.V. Vashchenko, N.B. Novikova, F.G. Yaremenko, V.V. Lipson, O.D. Rosahl', I.V. Taidakov, Ukrainian Patent № 106657, 2012; Bull. Prom. Sobstv., 2014, № 18.
[2] I.M. Gella, M.L. Babak, N.I. Shkol'nikova, N.B. Novikova, V.V. Lipson, Ukrainian Patent № 106706, 2013; Bull. Prom. Sobstv., 2014, № 18.
[3] N.L. Babak, A.N. Semenenko, I.M. Gella, V.I. Musatov, S.V. Shishkina, N.B. Novikova, D.S. Sofronov, D.A. Morina, V.V. Lipson. Synthesis of pyrrol-2-yl- and pyrazol-4-ylmethylidene derivatives of betulin and allobetulin // Russ. J. Org. Chem. – 2015. – vol. 51. – P. 731-742.

P-23

Three Component Reactions of 3-Methyl-5-aminopyrazole with Aryl(hetaryl)aldehydes and Cyclic CH-acids

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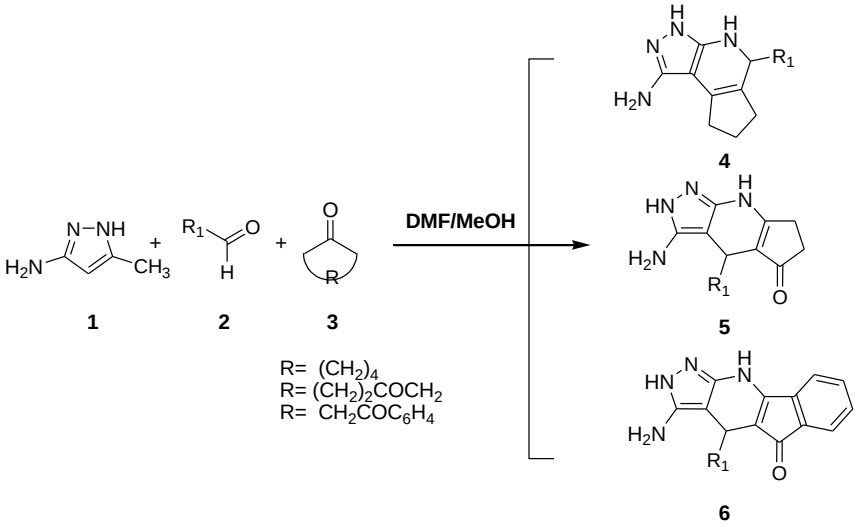
*[b] Medicinal Chemistry Department, State Institution "V.Ya. Danilevsky Institute for Endocrine Pathology Problems" of the National Academy of Medical Sciences of Ukraine, Kharkov, Ukraine, *E-mail: lipson@ukr.net*
[c] V.N. Karazin Kharkov National University, Chemistry Department, Kharkov, Ukraine

Pyrazolopyridine systems among different azoloazines have received more attention as one of the "privileged medicinal scaffolds" which are used for the development of new drug candidates of various applications. In the past several years, we and others have developed various domino-reactions based on interaction of dimedone and 1,3-cyclohexanedione or its derivatives with carbonyl compounds and different nitrogen-containing 1,3-binucleophiles that can provide facile route to partially hydrogenated pyrazolopyridines. In this investigation we have established that three component reactions of 3-methylpyrazol-5-amine with aromatic or heterocyclic aldehydes, cyclopentanone, cyclopentane-1,3-dione or indane-1,3-dione in DMF or in alcoholic environment proceed regioselectively and lead to the formation of partially hydrogenated 4-aryl(hetaryl)-substituted cyclopenta[*d*]-pyrazolo[3,4-*b*]pyridine (**4**), cyclopenta[*b*]pyrazolo[4,3-*e*]pyridin-5(2*H*)-one (**5**) or indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(2*H*)-one (**6**) systems respectively. The structures of obtained compounds were confirmed by X-ray diffraction.



1 **2** **3** **4** **5** **6**

P-24

The Reduction of N-Substituted 5-Salicylidene Rhodanines: an Unexpected Route to the Novel Thiazole-2-thione Derivatives

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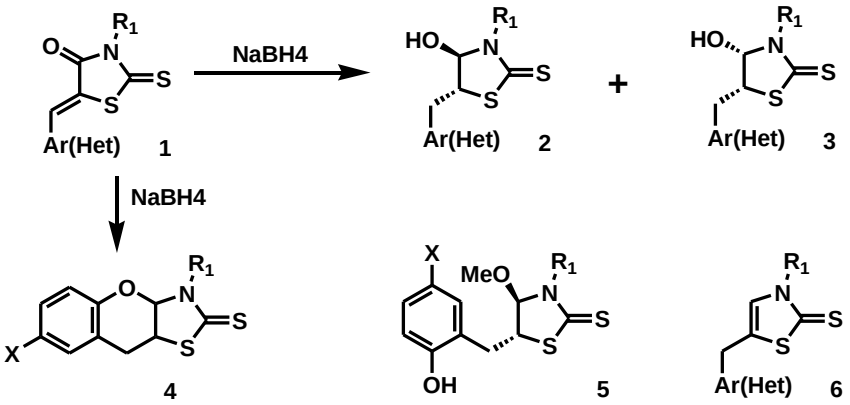
Among the five-membered heterocycle rings, the partially reduced 5-arylidene rhodanine derivatives possess highly antidiabetic and anti-inflammatory activities. The methods for the reduction of 5-arylidene-1,3-thiazolidinones(thiones) include the hydrogenation of the exocyclic double bond by using sodium amalgam, $NaBH_4$ in DMF media, $LiBH_4$/pyridine in THF media. We have established [1] that the utilizing of the excess of $NaBH_4$ in alcoholic media on the N-substituted arylidene rhodanines **1** leads to the 4-hydroxythiazolinethiones with a predominance of the *trans*-izomer **2** (as it was proven by X-ray studies for the isomer **2** when R_1 = Me; Ar =4-MeO-C_6H_4) with 70-90 % of total yield. The acid catalyzed dehydration of compounds **2, 3** gives thiazolinethiones **6** [2]. At the same time, these compounds can be obtained directly from **1** when Ar = C_6H_4COOH .



The reduction of N-substituted salicylidene rhodanines **1** (Ar = 2-C_6H_3OH(X)) leads to the mixture of compounds **4-6** with the predominance of the novel heterocycles 7-X-3-R_1-3,3a,9,9a-tetrahydro-2H-chromeno[2,3-d][1,3]thiazole-2-thiones **4**. The last ones can have *cys*-izomers **3** as precursors**.** The *trans*-izomers **2** convert to the 4-methoxy derivatives **5** in MeOH media. Utilizing of high boiling alcohols leads to the dehydration of *trans*-izomers **2** to compounds **6**.

All represented compounds (except of some from series **1**) weren't earlier described and their structures were proved by spectral methods .

1. Pat. 68369 UA
2. Pat. 82988 UA

P-25

Synthesis of Novel Spirooxindoles through the Three-Component Condensation of Isatins, Aminoazoles and CH-Acids

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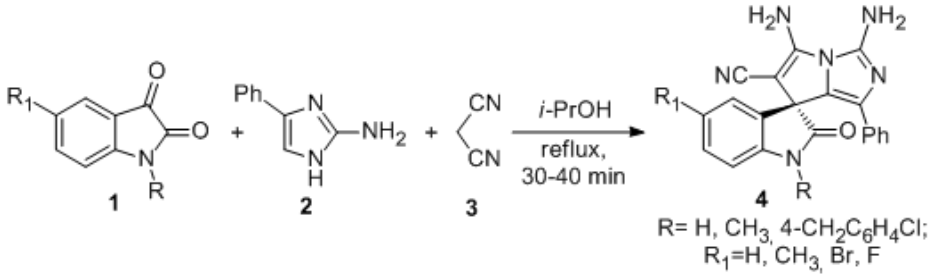
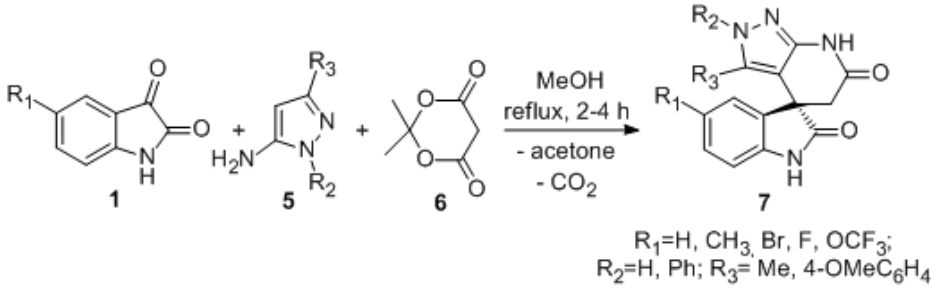
The spirooxindoles, especially those spiro-annulated with aminoazoles at the 3-position, have been found as core structure of numerous natural alkaloids and pharmacological agents [1]. The presence of four nonequivalent nucleophilic centres in 2-amino-4-phenylimidazole creates ambiguity in the direction of their interaction with bielectrophiles. We have found that the three-component condensation of equimolar amounts of isatins **1**, 2-amino-4-phenylimidazole **2** and malononitrile **3** give spirooxindole fused pyrrolo[1,2-*c*]imidazoles **4** in good to moderate yields.



The spiro[indoline-3,4'-piperidine] scaffold has been considered as a ''privileged structure'' for drug research [2]. We have established the interaction between 5-amino-3-alkyl(aryl)pyrazoles **5**, Meldrum's acid **6** and isatin **1** in alcoholic media, leading to the formation of several spiro-pyrazolo[3,4-b]pyridine derivatives **7** followed by release of acetone and carbon dioxide.



The structure of all novel compounds was confirmed by means of spectral and X-ray diffraction methods.

[1] Kang T.H. Eur. J. Pharmacol. – 2002, V. 444 – P. 39–45. [2] Bondensgaard K. J. Med. Chem. – 2004, V. 47 – P. 888–899.

P-26

Synthesis and some Synthetic Properties of 2-Halogenpyridinium Salts

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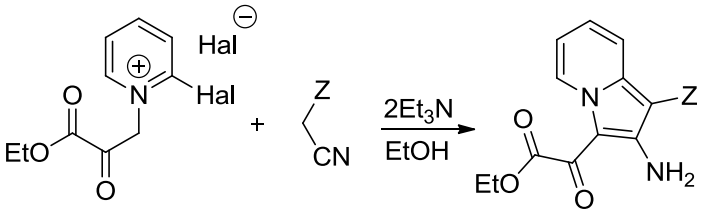
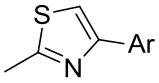
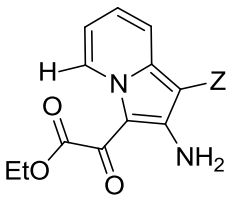
Salt **1**, obtained by heating 2-chloropyridine and ethyl 3-bromo-2-oxopropanoate, reacts with derivatives of acetonitrile **2** to form indolizines **3**. The lattest one is are the convenient building block of polynuclear heterocyclic systems.



1 **2** **3**

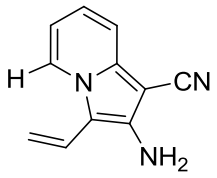
Hal = Cl, Br; Z = CN **(a)**,  **(b)**

The ^{1}H NMR spectra of compounds **3** signal C^{5}H of pyridine cycle is strongly shifted downfield is manifested in the the form of a widened singlet. Probably spectral effect due to the presence of the intramolecular hydrogen bond between C^{5}H and the oxygen atom of the carbonyl group in the third position of indolizine system. A similar signal in the compound **4** prepared early is shown in a stronger field.



3

δ 9,63 (C^{5}H)



4

δ 8,32 (C^{5}H)

Regioselective Electrophilic Heterocyclization of 3-Alkenylthio-1,2,4-triazole

P-27

Mikhailo V. Slivka, Natalia I. Korol, Ivan F. Rusin, Natalia P. Khripak, Vasil' G. Lendel*

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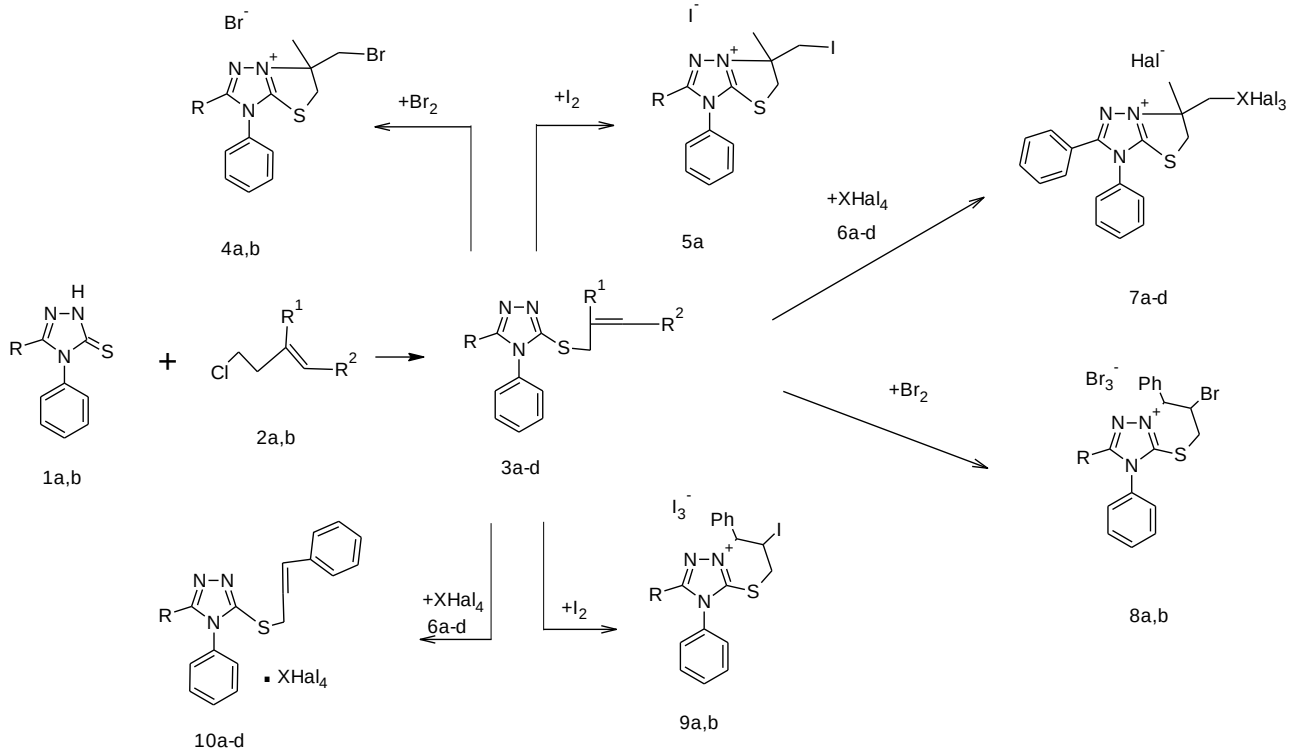
In our previous work we showed possibility of receiving of [1,3]thiazolo[2,3-c][1,2,4]triazoles due to halogenation of 3-allylthio-4,5-diphenyl-3*H*-1,2,4-triazole. In order to research of regioselectivity of electrophilic cyclization process as starting materials we used the alkenyl derivatives of 3-mercapto-1,2,4-triazole **3.**



Thus, it is shown that in case of bromination, iodination, selenium and tellurium tetrahalogalogenation of methallyl thioethers **3a** – the target condensed monohalogenides **4,5,7** were occurred with annelation of fife-membered thiazoline cycle. In the study of halocyclization of the cinnamyl thioethers **3** we have established that the regioselectivity of process is different (in comparison with methallyl derivatives) and cyclization is accompanied by an annelation of six-membered thiazine cycle to form bromides **8** and iodides **9**. The difference in halocyclization selectivity we explain by the powerful steric action of aromatic substitutient in cinnamyl fragment.

The compounds **4-10** were characterized by means of NMR spectroscopy (^{1}H, ^{13}C, 79Se, NOE, COSY experiment), elemental analysis and MS analyses.

P-28

Specificity of Alkylation of 5-R-Amino-4-aroyl-1,2,4-triazole-3-thione

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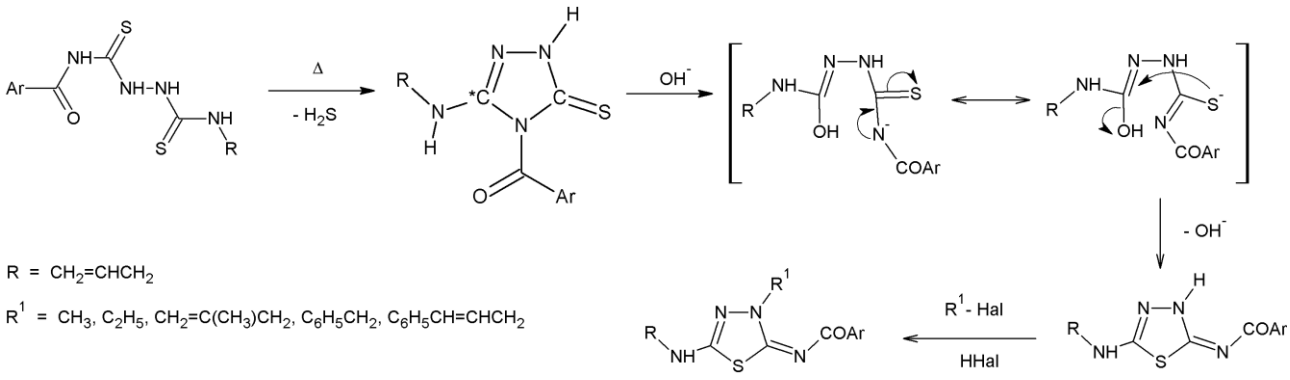
It was investigated the alkylation reaction of 5-R-amino-4-aroyl-1,2,4-triazole-3-thiones. Initial triazoles had been received after heating of aroyl-*bis*-thoureas in n-butanol or acetonitrile medium up to full releasing of hydrogen sulfide.



Alkylation was carried out in alcoholic medium at base presence. It was shown, that Dymrot rearrangement with 1,3,4-thiadiazole ring formation is realized under above mentioned conditions.

At the first stage the nucleophilic attack (formal by **OH^-**) of nodal carbon (**C***) in triazole cycle with following ring disclosure and anion formation is took place. Further, the formation of thiadiazole cycle is down as consequence of coupling redistribution of electron density and high nucleophilic ability of Sulfur. Next, the alkylation of 1,3,4-thiadiazole is carried out with selective formation of 3*N*-substituted 1,3,4-thiadiazoles. Target alkylated 1,3,4-thiadiazoles were precipitated from reaction mixture and recrystallized from diethyl ether.

The composition and structure of the target products were carefully investigated by elemental analysis and complex spectral research (IR, ^{1}H NMR, ^{13}C NMR, chromato-mass spectrometry). The structure of rearrangement-product was unambiguously confirmed by single-crystal X-ray crystallography.

Heterocyclization of 2-(3-Methylbut-2-en-1-ylthio(seleno))quinoline Carbaldehyde

P-29

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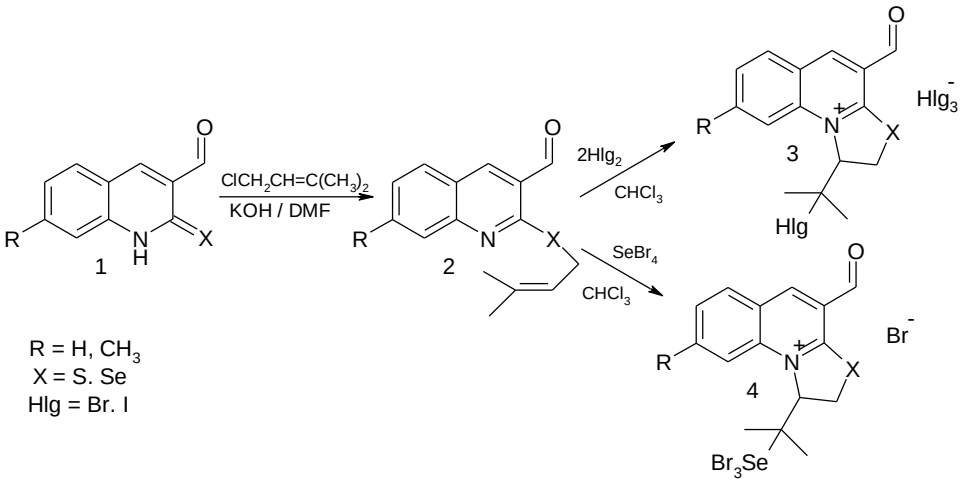
Among the large number of Nitrogen-containing heterocyclic compounds one of the most important in biological terms there is a system of quinoline; its derivatives are common in nature and involved in many biological processes. Annelation of additional cycle to quinoline with introducing of new functional groups enhance practical use of last. Therefore, the use of electrophilic heterocyclization as simple and efficient approach to the synthesis of polycyclic systems based on quinoline is scientifically justified and urgent problem.

Electrophilic heterocyclization of model compound 2-(3-methylbut-2-en-1-ylthio(seleno)) quinoline-3-carbaldehyde (**2**) (obtained by alkylation of formil- quinoline-2-thione(selenone) (**1**)) was carried out under action of halogens and selenium tetrabromide in the chloroform medium. In results, it was obtained thiazolo(selenazolo)[3,2-a]quinoline halides (**3, 4**), whose structure was proved by ^{1}H NMR spectra and ^{13}C NMR. Trihalogenide (**3**) was dehalogenated to monohalide by acetone and sodium iodide in acetone.



The signal of endocyclic Carbon of N^{+}-CH-group in ^{13}C NMR spectrum indicates about annelation of thia(selena)zoline moiety. Formation of thiazoline cycle successfully correlates with previous studies about heterocyclization of allyl, methallyl thio(seleno) ethers of quinoline-3-carbaldehyde. Primary screening indicated that the bromide (**4**) shows high antibacterial and antifungal activity against reference strains of gram-positive and gram-negative bacteria.

P-30

Heterocyclization of N-Alkenyl Derivatives of Thiothieno(pyrazolo)pyrimidinone by Aryltellurium Trichloride

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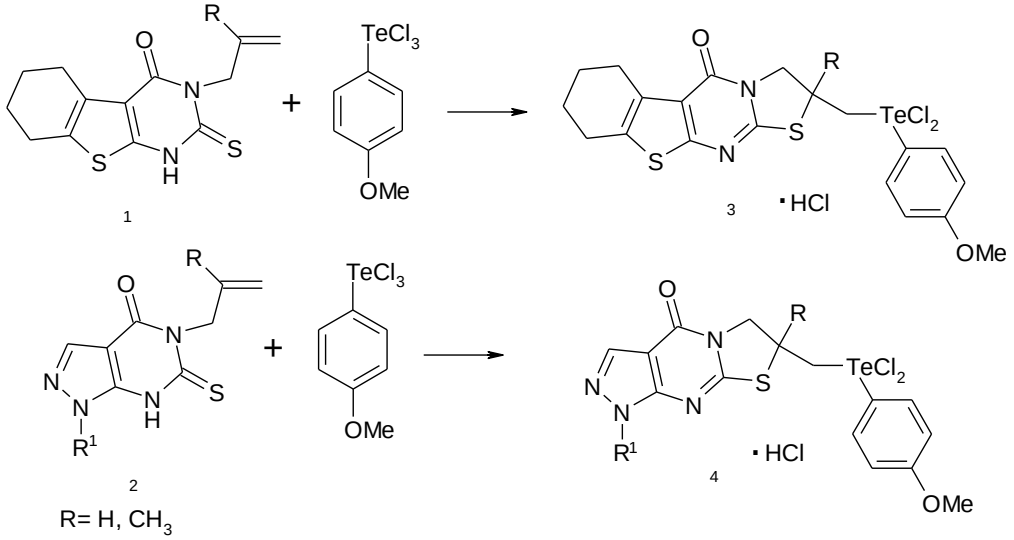
Tellurium-containing organic compounds are an important object of study because of their unique physical, chemical and biological properties.

The electrophilic heterocyclization of unsaturated substrates under tellurium tetrahalides is widely used to obtain tellurium-containing poli-condensed heterocyclic systems, while application for these purposes of aryltellurium trihalogenides practically is not described in literature.

The N-allyl and N-methallyl derivatives of thiothieno(pyrazolo)pyrimidinone **1, 2** was selected as the objects for research of halkogenheterocyclization. The heterocyclization of **1, 2** was carried out under action of *p*-methoxypheniltellurium trichloride in glacial acetic acid medium, chloroform or acetonitrile at different temperatures. The optimum conditions were turned using acetic acid at room temperatures. As the results, the linear cyclic structure salt-like systems **3.4** with exocyclic tellurium moiety had been obtained, that is confirmed by mass spectrometry.



The composition and structure of the target products were studied due to elemental analysis and complex spectral research (IR, 1H NMR, 13C NMR, chromatography-mass spectrometry).

P-31

Highly Efficient Catalysts for the Reduction of Ketones With Alcohols in Alkali Medium

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[b]*The L.M.Litvinenko Institute of Physical Organic and Coal Chemistry of UNAS*
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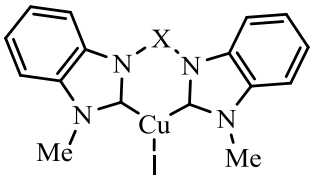
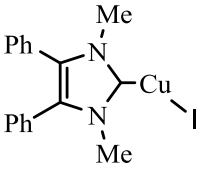
In order to find new effective catalysts for multiple bonds reduction with alcohols in alkaline medium (hydrogen transfer) new chelate and linear complexes of carbenes and copper(I) iodide were synthesized, **1a,b**, **2-4** by the interaction of copper iodide (I) with heteroaromatic carbenes generated *in situ* from the respective azolium and bisazolium salts in tetrahydrofuran.



1a,b

1a X = CH_2;
1b X = $(CH_2)_3$



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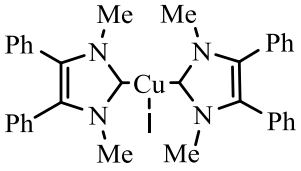

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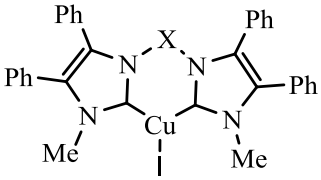
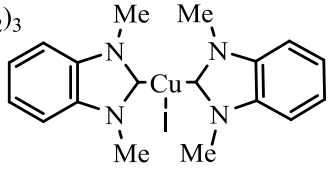
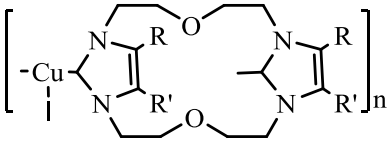


4

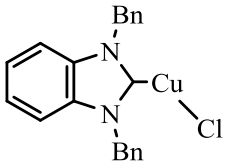
X = CH_2



5



6 R, R' = $(CH)_4$



7

The catalytic properties were studied for the synthesized carbene complexes in the reduction reaction of phenyl-4-diphenylylketone with isopropanol in the presence of KOH. It was established that the effectiveness of catalytic compounds **1a,b** in this reaction (TON 45000-47000, TOF 15000- 15667 h^{-1}) almost reaches the level of biscarbene complex **5** (TON 50000, TOF 20000 h^{-1}). But the indices of TON and TOF for 4,5-diphenylimidazol-2-ylidene complexes **2-4** are much lower (3500-4200, 583-700 h^{-1}). Even the efficiency of monocarbene benzimidazol-2-ylidene complex **7** appeared to be higher (TON 5300, TOF 883 h-**1**) than that for complexes **2-4**. The highest efficiency is inherent to benzimidazole-2-ylidene polymer complex **6** (TON 85000, TOF 28330 h^{-1}).

From these data can be concluded about much stronger influence of the fused benzimidazole-2-ylidene nuclei on the catalytic efficiency of complexes **1a,b,5** than that for 4,5-diphenylimidazol-2-ylidenes ligands in compounds **2-4**.

P-32

Synthesis of Triaryl Substituted 1,2,4-Triazol-5-ylidenes

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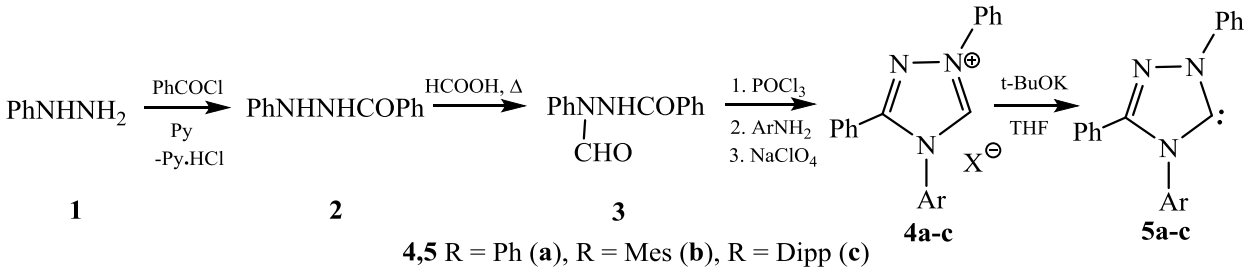
A new method for the synthesis of 1,3,4-tryaryl substituted 1,2,4-triazol-5-ylidenes, including sterically shielded ones was developed, which can be used as ligands for obtaining metal carbene complexes efficient catalysts of organic reactions. A four step process comprises acylation of phenylhydrazine **1** with benzoyl chloride or benzoic esters, formylation of the obtained 2-benzoylphenylhydrazine **2** with formate acid and cyclization of the intermediate 2-benzoyl-1-formylphenylhydrazine **3** according to Vielsmeier-Bredereck method under the action of phosphorus chloroxide and anilines. The deprotonation of the synthesized 1,3,4-tryaryl-1,2,4-tryazolium salts **4a-c** was carried out by potassium *tert*-butoxide in tetrahydrofuran or in a mixture of toluene and isopropanol to form carbenes **5a-c** in one stage.

Compared to the synthesis of 1,3,4-triphenyl-1,2,4-triazol-5-ylidene **5a** according to Enders that was performed in 6 steps from aniline, the new method allows to increase the yields for the intermediate salts **4a-c** (to 62-70%), as well as for final carbenes (to 50-56%) from phenylhydrazine, introduce sterically shielding groups at 4 position of the triazolylidene ring (the Enders yield of 1,3,4-triphenyl-1,2,4-triazolium salt **4a** is 45% and 1,3,4-triphenyl-1,2,4-triazole-5-ylidene **5a** is 28% from aniline).



4,5 R = Ph (**a**), R = Mes (**b**), R = Dipp (**c**)

The composition and structure of the obtained compounds **4a-c** and **5a-c** were evidenced by the methods of elemental analysis, ^{1}H and ^{13}C- NMR spectroscopy.

Synthesis and Enzymatic Activity (2-Methyl(phenyl)-*6-R*-quinolin-4-ylthio)carboxylic Acids and their Derivatives

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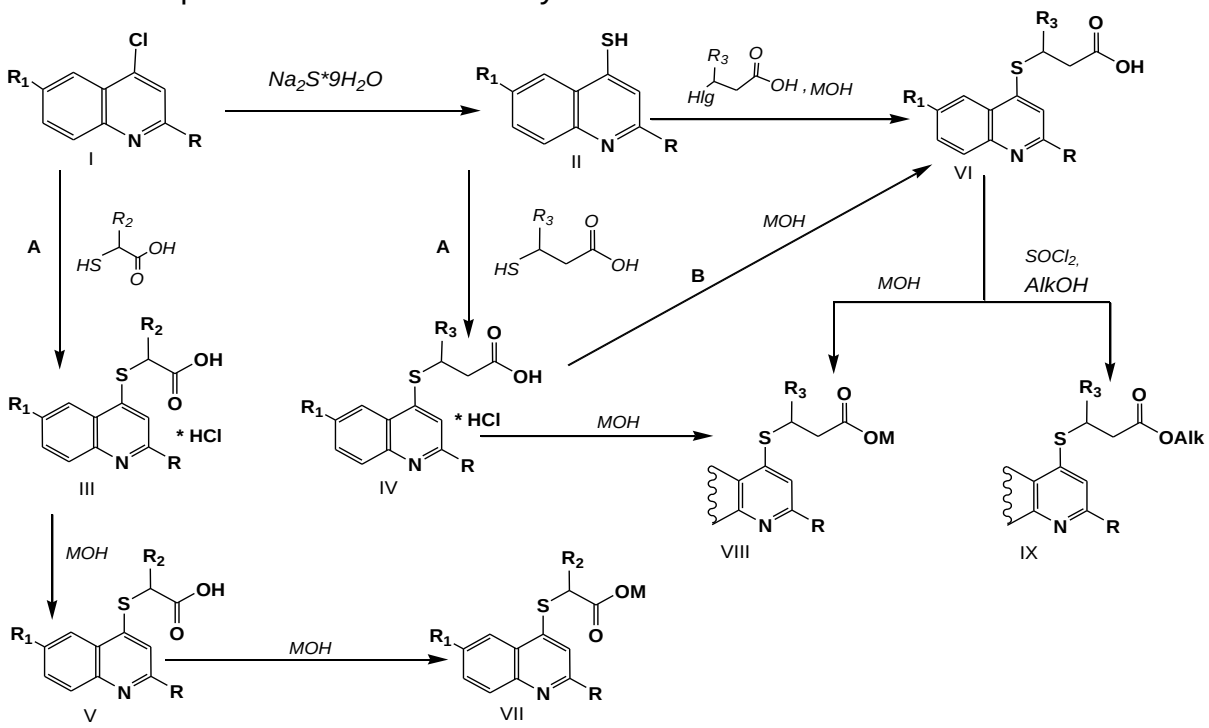
(2-Methyl(phenyl)-*6*-*R*-quinolin-4-ylthio)carboxylic acids (**V, VI**) were synthesized by methods **A** and **B**. Reaction (**A**) results in the formation of sediment acid hydrochloride (**III, IV**), which is neutralized with alkali. Among other S-substituted 4-mercaptoquinoline attention attracted the salt (**VII, VIII**) and esters (**IX**) (2-methyl(phenyl)-*6*-*R*-quinolin-4-ylthio)carboxylic acids as potential biologically active molecules. Structure and purity of synthesized compounds were confirmed by ^{1}H-NMR and MS.



R=CH_3, C_6H_5; R^1=H, F, OCH_3, OC_2H_5; R^2=H, CH_3; R^3=H, COOH; M=Na, K; Alk=CH_3

The influence of chemical structure and spatial structure of the synthesized compounds on enzymatic activity was studied in eight enzyme blood: alanine aminotransferase, aspartate aminotransferase, total creatine kinase, creatine kinase MB, lipase, lactate dehydrogenase, alkaline phosphatase, a-amylase. These enzymes are differ in a structural organization and functional purpose. The majority of the investigated compounds affect the activity of enzymes, activating or inactivating them. The more detailed analysis of the results can be the key to understanding the mechanism of biological effects and toxicity of compounds.

P-34

Winreb Amides – Perspective Building-Blocks for Synthesis of Nornicotine and Anabasine Analogues

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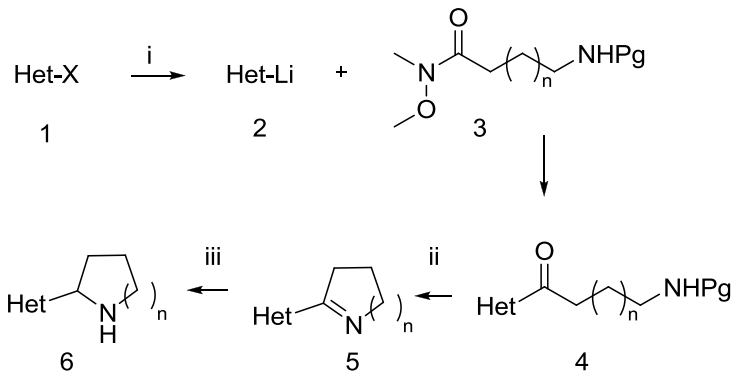
State Institution "Institute of pharmacology and toxicology National academy of medicinal science of Ukraine", Ukraine, 03057, Kiev, Eugene Potie str., 14
E-mail: khairulin.chem@gmail.com

The nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels belonging to the Cys-loop receptor family. The involvement of nAChRs in a wide range of diseases as well as neurodegenerative and psychiatric disorders has made this class of receptors a popular target for drug discovery. During the last time, structural modifications of nicotine have been the starting point for many drug discovery programs.



Reagents and conditions : (i) BuLi, (ii) deprotection, (iii) Pd/C

X=Br,H; Pg=Cbz, Boc; n=1,2.

The first synthetic strategy towards **6** from the commercially available heterocycles, such as 3-bromopyridine, 1-methylimidazole, 2-bromothiophene, benzothiophene. Lithiation of this heterocycles and subsequent trapping with N-protected Winreb amide **3** followed by formation of the pyrrolidine or piperidine moiety via intramolecular reductive amination.

Starting heterocycle **1** was selectively lithiated in dry THF with buthyllithium and subsequently quenched with Winreb amide **3** to give N-protected aminoketones **4** in good yields. After deprotection of the amino group by different methods, the amine underwent an in situ cyclization resulting in the formation of an imine **5**, which was reduced to the corresponding pyrrolidine or piperidine **6** using H_2 /Pd/C system in methanol. Structures of all compounds are determinated by NMR, GS/MS and LC/MS analysis.

P-35

Synthesis of Pyrrolo-[3,4-d]triazolyl-4,6-dions of Dianhydrohexitols Starting from Isosorbide

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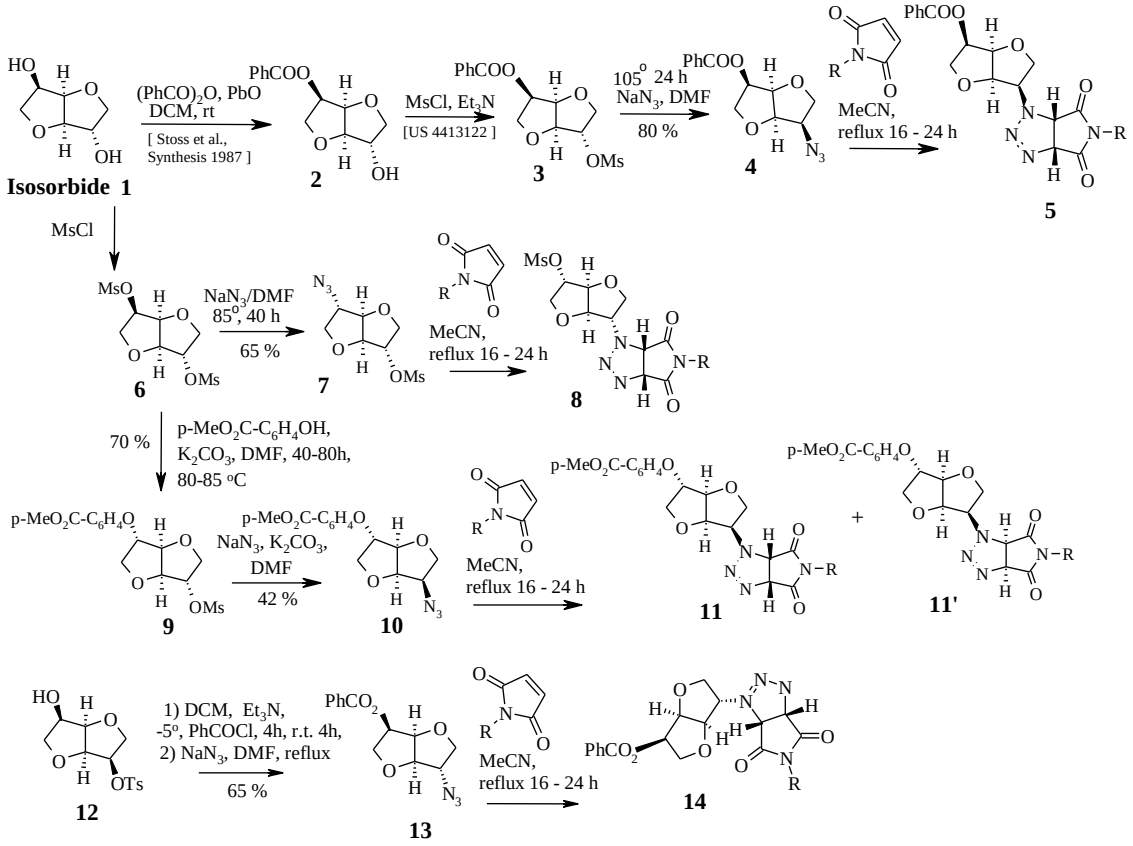
[b] *V.N.Karazin Kharkiv National University, Svobody sq., 4, Kharkiv, Ukraine*
[c] *State Institution "V.Ya.Danilevsky Institute for Endocrine Pathology Problems" of National Academy of Medical Sciences of Ukraine, Kharkiv, 61002, Ukraine*

In the reaction of dianhydrohexitols derivatives obtained from isosorbide with N-arylmaleimides, practically absence of asymmetrical induction in dipolar 3+2 cycloadditions was observed. However diastereomerically pure products have been obtained by chromatographic separation with following crystallization. These products are interesting because of their structural likeness to substances, significant for pharmaceutics, first of all to griseolic acid derivatives and dihydropyrrolotriazoles.



R = 4-MeC$_6$H$_4$ (**a**), 3-F-C$_6$H$_4$ (**b**), 3-Br-C$_6$H$_4$ (**c**), 3-Cl-MeC$_6$H$_4$ (**d**), 3,4-(CH$_2$)$_3$C$_6$H$_4$ (**e**), 4-EtC$_6$H$_4$ (**f**)

^{1}H and ^{13}C NMR 1D and 2D and X-ray analyses were used for the proof of the structure.

P-36

Vicinal Pyrrolylphosphane Aldehydes

Aleksandr S. Savateev[a], Vitalii N. Smal[a], Nataliya A. Shtil[a], Radomyr V. Smaliy[a], Aleksandra A. Chaikovskaya[a], Aleksandr N. Kostyuk[a]

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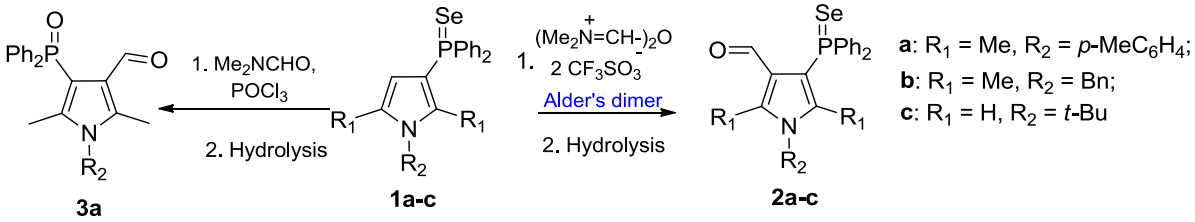
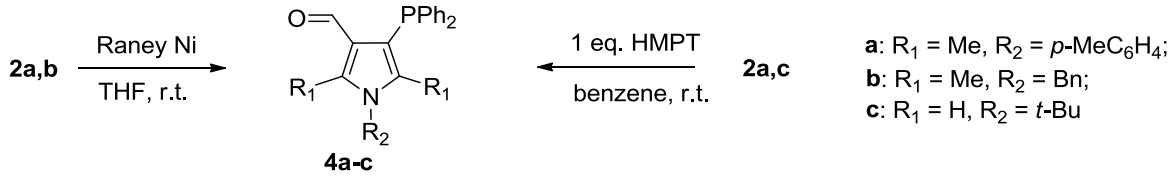
Derivatives of 2-diphenylphosphanyl-benzaldehyde are widely used as ligands for organometallic catalysts. [1] While pyrrole is an attractive scaffold for construction of such ligands because fine tuning of its core can be accomplished easily, pyrrole-based phosphane aldehydes are represented poorly. In our recent work we showed that formylation of $P(Se)Ph_2$-phosphorylated (pyrroles **1** under Vilsmeier-Haack reaction conditions proceeded at the pyrrole ring along with electrophilic attack at the phosphorus atom affording (upon alkaline hydrolysis) exclusively $P(O)Ph_2$-phosphorylated pyrrolylcarbaldehyde **3a**. [2]



At the same time an electrophilic reagent - Alder's dimer reacted with phosphorylated pyrroles **1a-c** predominantly at the pyrrole ring affording after hydrolysis the corresponding phosphoroselenoyl carbaldehydes **2a-c**.



Reduction of selenides **4a-c** in the presence of aldehyde group was accomplished either with Raney Ni or HMPT giving the corresponding vicinal phosphane aldehydes.

References:

[1] (a) A. Bacchi, M. Balordi, P. Pelagatti, C. J. Pelizzi, *Organomet. Chem*. **2009**, *694*, 3281; (b) A. Franzke, A. Pfaltz, *Chem. Eur. J.* **2011**, *17*, 4131; (c) A. Franzke, F. Voss, A. Pfaltz, *Tetrahedron* **2011**, *67*, 4358.

[2] R. V. Smaliy, A. A. Chaykovskaya, N. A. Shtil, A. S. Savateev, A. N. Kostyuk, *Heteroatom Chemistry* **2013**, *24*, 146.

P-37

Aggregation Behavior And Nucleophilic Reactivity Of Comicellar System 1-Hexadecyl-3-Methyl-2-(hydroximinomethyl)imidazolium Bromide / Tween 80

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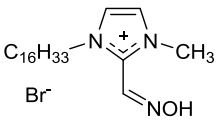
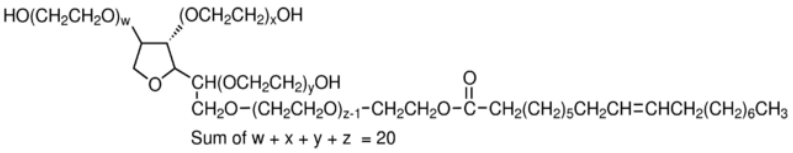
Micelles and comicelles of surfactants are very attractive systems for industry and biomedical application. Over the last years a variety of surfactant-based compositions has been elaborated and successfully used for drug delivery. 1-Hexadecyl-3-methyl-2-(hydroximinomethyl)imidazolium bromide (HMHImBr) is one of the highly efficient reagents for decomposition of acetylcholinesterase (AChE) organophosphorous inhibitors and potential AChE reactivator. For using in biological systems, biocompatibility of HMHImBr can be enhances by creating comicellar systems with a nonionic surfactant Tween 80.



HMHImBr



Tween-80

We investigated aggregation behavior (namely, critical micelle concentration, CMC) of comicellar system HMHImBr / Tween 80 and individual surfactants by means of comprehensive instrumental methods. Analysis of the obtained data using Clint equation revealed the presence of antagonism in micelle formation for system HMHImBr (cationic) / Tween 80 and full compliance with ideal mixing for system HMHImBr (zwitter-ionic) / Tween 80.

Nucleophilic reactivity of HMHImBr in comicelles with Tween 80 ($\alpha_{HMHImBr}$ = 0.3 and 0.5) toward the decomposition of pesticide paraoxon (4-nitrophenyl diethylphosphate) is comparable with that obtained previously for HMHImBr in comicelles with CTABr. Second-order rate constant for HMHImBr in this processes is ~ 0.01 $M^{-1}\cdot s^{-1}$ which in view of its relatively low basicity (pK_a ~ 8.4 – 8.6) places it among the most efficient reagents for the destruction of toxic organophosphates. The half-lives of paraoxon in the presence of comicelles HMHImBr / Tween 80 are determined to be 5 min and 2 min for $\alpha_{HMHImBr}$ = 0.3 and 0.5, correspondingly.

This work was supported by Russian Scientific Foundation (grant № 14-50-00014).

P-38

Nucleophilicity of Monomeric and Dimeric Oximate-Functionalized Imidazolium Surfactant in Acyl Group Transfer

Kapitanov I.V.[a,b], Belousova I.A.[b], Shumeiko A.E.[a,b], Kostrikin M.L.[b], Prokop'eva T.M.[b], Razumova N.G.[b], Serdyuk A.A.[a,b], Karpichev Ye.A.[a,b], Popov A.F.[b]

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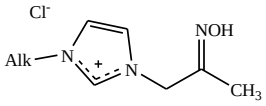
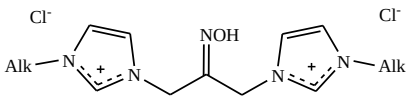
Nucleophilic reactivity of micelles of monomeric (I) and dimeric (II) oximate-functionalized imidazolium surfactants in processes of acyl group transfer were studied.



I



II

Alk = $C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$

Nucleophilicities of the oximate ions I and II in the reaction towards 4-nitrophenyl esters of phosphorus and sulfur acids follow Brønsted relationship for monomeric functionalized surfactants and non-micelle forming oximes. As compared to the single-chain analog (I), the dimeric surfactants (II) ensured the same observed rate of substrate decomposition being taken at lower concentration and lower pH and therefore provide more significant micellar effects under optimal condition. Micellar effects of the dimeric surfactants in these reactions reach a value of $\sim 10^3$ and are determined mainly by concentration of substrate in the micellar pseudophase.

Alkyl chain length variation causes the similar rate effect for the two surfactant series, monomeric (I) and dimeric (II) surfactants. Increasing the chain length leads to increase in micellar effects which demonstrates that the observed micellar effects in the studied systems are primarily controlled by hydrophobic interactions.

High observed rates of acyl transfer reactions in micellar system based on dimeric oximate-functionalized imidazolium surfactants (II) make it very attractive for practical use in formulations for decomposition of acyl-containing ecotoxicants.

This work was supported by French-Ukrainian International Network on Molecular Chemistry (GDRI) and NASU-RFBR joint research project.

Regularities in Changes of Acid-Base Properties in the Series of Pyridine and Pyridinum Oximes

P-39

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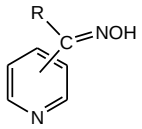
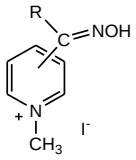
[b] *L.M.Litvinenko Institute of Physical Organic Chemistry & Coal Chemistry, NAS of Ukraine*

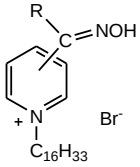
Regularities in changes of acid-base properties in the series of oximes (I–III) among derivatives of pyridine have been determined (see Table).



I



II



III

Table. Values of the acid ionization constant (pK_a) of the compounds (I–III) and their tendency to change in series I > II > III

Substituent	Position of substitution	pK_a (I)	pK_a (II)	pK_a (III)	Δ (I–II)	Δ (II–III)	Δ (I–III)
-CH=NOH	2-	10.00	8.04	7.21	1.96	0.83	2.79
	3-	10.20	9.51	8.68	0.69	0.83	1.52
	4-	9.81	8.61	7.91	1.20	0.70	1.90
-C(CH_3)=NOH	2-	10.85	9.25	8.57	1.60	0.68	2.28
	3-	10.85	10.03	9.29	0.82	0.74	1.56
	4-	10.52	9.57	8.83	0.95	0.74	1.69

Notes. pK_a for compounds (III) have been as values for comicellar systems (III / CTABr) (mole fraction III in the comicelles ≤0.25).

The decreasing of acid ionization constant value of the functional oxime group has been shown to occur within the series: (pyridine oximes; I) > (N-methyl derivatives of pyridine oximes; II) > (N-hexadecyl derivatives pyridine oximes; III).

Values of Δ pK_a (I–II) decrease in the series 2- > 4- > 3-substituted compound with the transition from (I) to (II). This is entirely in agreement with the laws of change of the induction effect and conjugation for these compounds. Δ pK_a (II–III) values are only slightly dependent on the position of the substituent and are shown to be ~0.7–0.8 units in the case of transition from non-micelle forming systems (II) to the comicellar systems (III/CTABr). This observation suggests nonspecific effect of micellar media on the deprotonation of oxime group. In general, apparent acidity constant (pK_a) of the oxime group for comicellar systems (III/CTABr) by ~1.5–2.8 units lower than for the corresponding compounds (I).

This work was supported by French-Ukrainian International Network on Molecular Chemistry (GDRI) and NASU-RFBR joint research project.

P-40

NMR Study of 1-Alkyl-3-(2-hydroximinopropyl)imidazolium Salt in Water / D_2O Mixture: Stability and Isotope Exchange Processes

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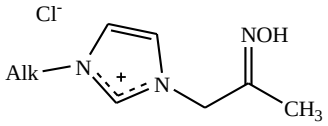
1-Alkyl-3-(2-hydroximinopropyl)imidazolium chlorides are very efficient reagents in the processes of acyl ecotoxicant decomposition. Stability of these compounds in water solution is a principal issue for their successful practical use in the decontamination system.



Alk = CH_3 (I)
Alk = $C_{16}H_{33}$ (II)

We have investigated a series of solutions of 1-alkyl-3-(2-hydroximinopropyl)-imidazolium chlorides (I) and (II) in H_2O / D_2O mixture at different pH by means of a series of NMR methods (^1H and ^{13}C 1D spectra, APT, ^1H-^{13}C COSY NMR). The studied compounds have been demonstrated to remain stable in wide range of the acidity of solution (pH 2.0 – 13.5).

At the pH beyond 9.5, hydrogen atom in C2 position of the imidazolium ring of (I) and (II) was found to be involved in the isotopic exchange, the rate of which increases regularly with increasing pH. This process does not affect the stability of molecules (I) and (II) in solution.

Similar isotopic exchange rates for non-micelle forming (I) and micelle forming (II) oximes demonstrates that the interface of the micelles of compound (II) (where imidazolium ring is supposed to be localized) is well saturated with water and its properties are close to those of water. This conclusion is confirmed by the analysis of reactivity of non-micelle forming (I) and micelle-forming (II) in the processes of acyl substrates decomposition: nucleophilicity of oxime group remains about unchanged when reaction is transferred from water to the surfactant micelles.

This work was supported by French-Ukrainian International Network on Molecular Chemistry (GDRI) and NASU-RFBR joint research project.

P-41

Synthesis of Quinolin-4-one Derivatives Containing an Azoles Nucleus as Potential Anti-Inflammatory Agents

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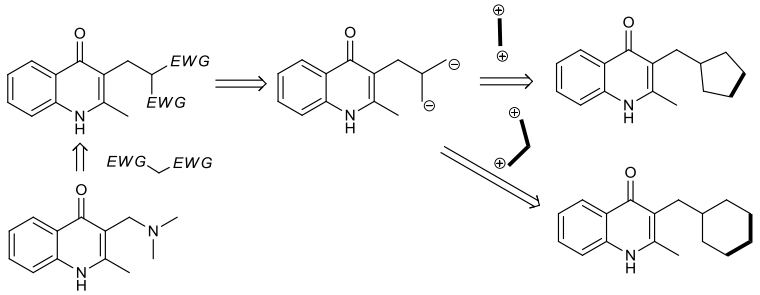
[b]*Ivano-Frankivsk National Medical University, str. Galitska 2, Ivano-Frankivsk 76000, Ukraine.*

Previously it has been shown that 3-dimethylaminomethyl-2-methyl-1,4-dihydroquinoline-4-ones can act as alkylating agents in the reaction with methylene active compounds [1,2]. This chemical reactivity opens more opportunities in using the "2 + 3" and "3 + 3" strategies in synthesis of new heterocycles - derivatives of quinolin-4-ones (Scheme 1).

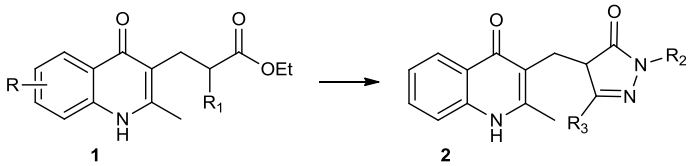
Scheme 1



To provide a preliminary assessment of the pharmacological potential of new quinolone scaffolds, determination of 2D molecular similarity of synthesized compounds with the biologically active structures in the ChemBl_20 database, using ChemAxon software was conducted. Virtual screening has shown that the quinolin-4-one derivatives containing an azoles nucleus would be potential leads in finding and developing of new NSAIDs.

Systematic libraries of new derivatives of 2-methyl-3-[(5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl]-1,4-dihydroquinolin-4-ones **2** have been obtained by condensation of alkylated active methylene compounds **1** with arylhydrazines and hydrazine hydrate under base catalysis with high yields (Scheme 2).

Scheme 2



1 **2**

R_1 = CN; $COCH_3$ R_2 = H; Ar R_3 = NH_2; CH_3

[1]. Zubkov V. O. et al. Journal of Organic and Pharmaceutical Chemistry, 2011, Vol. 9, No.4, pp.38-41.
[2]. V.O.Zubkov et al. Journal of Organic and Pharmaceutical Chemistry. 2015, Vol. 13, Iss. 1 (49), pp.32-36.p

P-42

Chlorosulfonation of Quinoline-2 and Quinoline-4-one by Chlorosulfonic Acid

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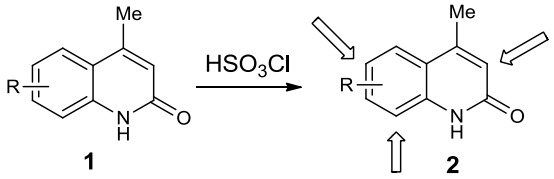
Quinolones are one of the most significant classes of nitrogen containing heterocycles in medicinal chemistry. At the moment, sulfonated derivatives of quinolones are not widely studied compounds as reagents and biologically active substances. It makes sulfoquinolones attractive objects for creation of new scaffolds and molecular diversity in chemical space.

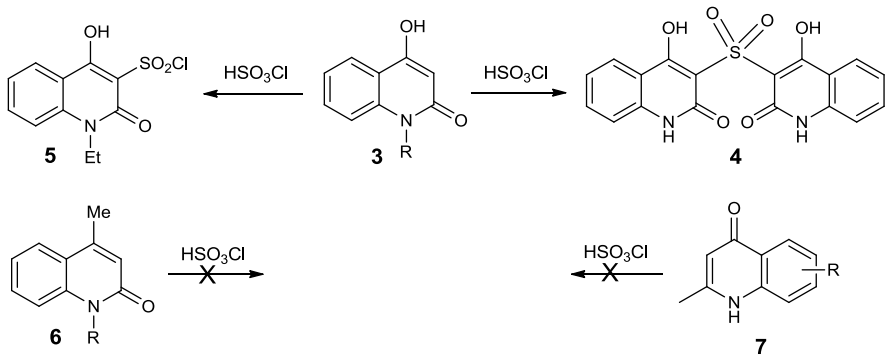
Previously we have investigated the reaction of 4-methyl-1,2-dihydroquinolin-2-ones **1** with chlorosulfonic acid [1,2]; and it was found that chlorosulfonation, depending on arrangement of substituents, can take place at the C-6, C-8, or C-3 position of the quinolone cycle (Scheme 1).

Scheme 1



To continue this research the chlorosulfonation reaction of 4-hydroxy-1,2-dihydroquinolin-2-ones **3**, N-substituted 4-methyl-1,2-dihydroquinolin-2-ones **6**, as well as 2-methyl-1,4-dihydroquinolin-4-ones **6** with chlorosulfonic acid was studied (Scheme 2).

Scheme 2



Successful results was obtained in case of 4-hydroxy-1,2-dihydroquinoline-2-ones **3**; the products of the chlorosulfonation (compounds **4** and **5**) crucially depended on the presence of a substituent on nitrogen of the quinolone cycle. When quinolones **6** and **7** were treated with chlorosulfonic acid under different conditions (such as molar ratio of reactants, time, temperature) only initial compounds were isolated.

[1] В.О. Зубков, І.С. Гриценко, Т.О. Цапко, О.Г. Гейдеріх. Синтез та антимікробна активність 4-метил-2-оксо-1,2-дигідрохінолін-6-арилсульфамідів // ЖОФХ. – 2008. – Т.6, вип. 3(23). – С. 39-43.
[2] В.О. Зубков, І.С. Гриценко, Т.О. Цапко. Синтез та вивчення антимікробних властивостей 6-алкілсульфамідів 4-метилхінолін-2-онів // Фарм. часопис. – 2009. – № 2. – С. 6-10.

Regioselective Alkylation of Quinolin-2-ones by Chloroacetic Acid Amides

P-43

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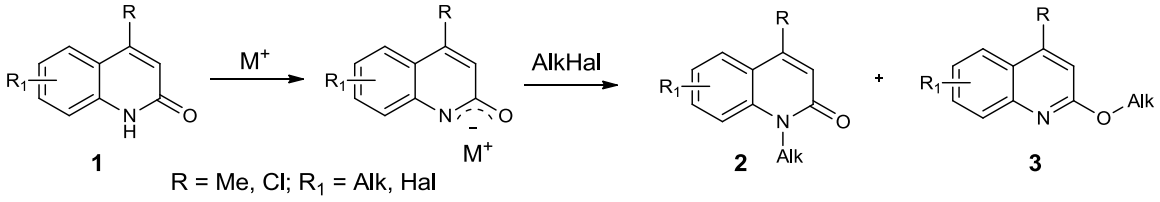
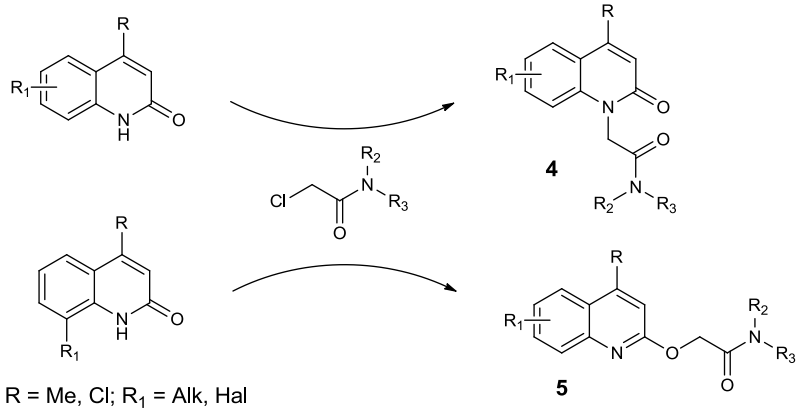
N-alkylated quinolin-2-ones are the prominent pharmacophores because of the N-alkyl quinoline-2-one skeleton that is present in large number of natural products, as well the synthetic alkyl derivatives of quinolone have a wide range of biological activity. However, the simplest synthesis of these compounds by direct alkylation of N-unsubstituted quinolin-2-ones using alkyl halides in presence of inorganic bases involves a competitive alkylation leading to the mixture of N- and O- alkylated products (Scheme 1). The ratio of N-alkylation *versus* O-alkylation is highly dependent on the nature of substituents and the nature of inorganic base.

Scheme 1



It was found, that in the case of using chloroacetic acid amides as alkylating agents in the presence of potassium carbonate the alkylation takes place regioselectively in N- (compounds **4**) or O- position (**5**) of quinolones (Scheme 2). This selectivity is connected with the presence or absence of substituents at the 8-position of quinolone cycle.

Scheme 2



A plausible mechanism of regioselective alkylation of quinoline-2-ones is proposed on the basis of the quantum chemical calculations and NMR spectroscopy data. The nature of metal in inorganic base and intermolecular hydrogen bonds formed between the reactants play the key roles in this possible mechanism.

P-44

Synthesis of N-Alkylnaphthalimides Derivatives in Interphase Conditions and their Research

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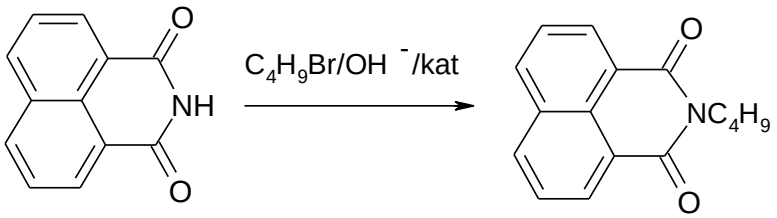
Phase-transfer catalysis are used in various fields of organic synthesis as a method for obtaining of many important substances. It is also often introduced in industry due to the simplicity of the process, undemanding characteristics with respect to solvents and reagents.

Substances, stated below, can be used as catalysts in phase-transfer catalysis: kraunether, quaternary ammonium salts and so on. Type of the solvent also influence on the behavior of reaction significantly. Benzene and toluene are used in many cases in the capacity of solvents.

Phase-transfer catalysis did not used for synthesis of naphthalimide derivatives before. These derivatives can be used for various purposes, namely as fluorescent components of daytime fluorescent pigments with different applications, as components of defectoscopic materials, analytical reagents for series of elements test, as fluorescent probes for medicobiological investigations etc.

Proposed method of obtaining naphthalic acid alkylderivatives can lead to the synthesis of essential products with given properties as follows:



On the assumption of use in scientific research such catalysts as PEG-9 and podandes, which based on quaternary salts, product yields in some degree higher than using kraunethers. Substitution of TEBAH to PEG-9 did not effect significantly on the yield of final product, last-named is more accepted in industry and thought the instrumentality of it we can substitute TEBAH in a romp.

This paper reports about substitution of classical solvents, most of which are classified as precursors, to more accepted solvents in terms of their ecological compatibility.

New Synthesis of Triazine Trisazo Compounds

P-45

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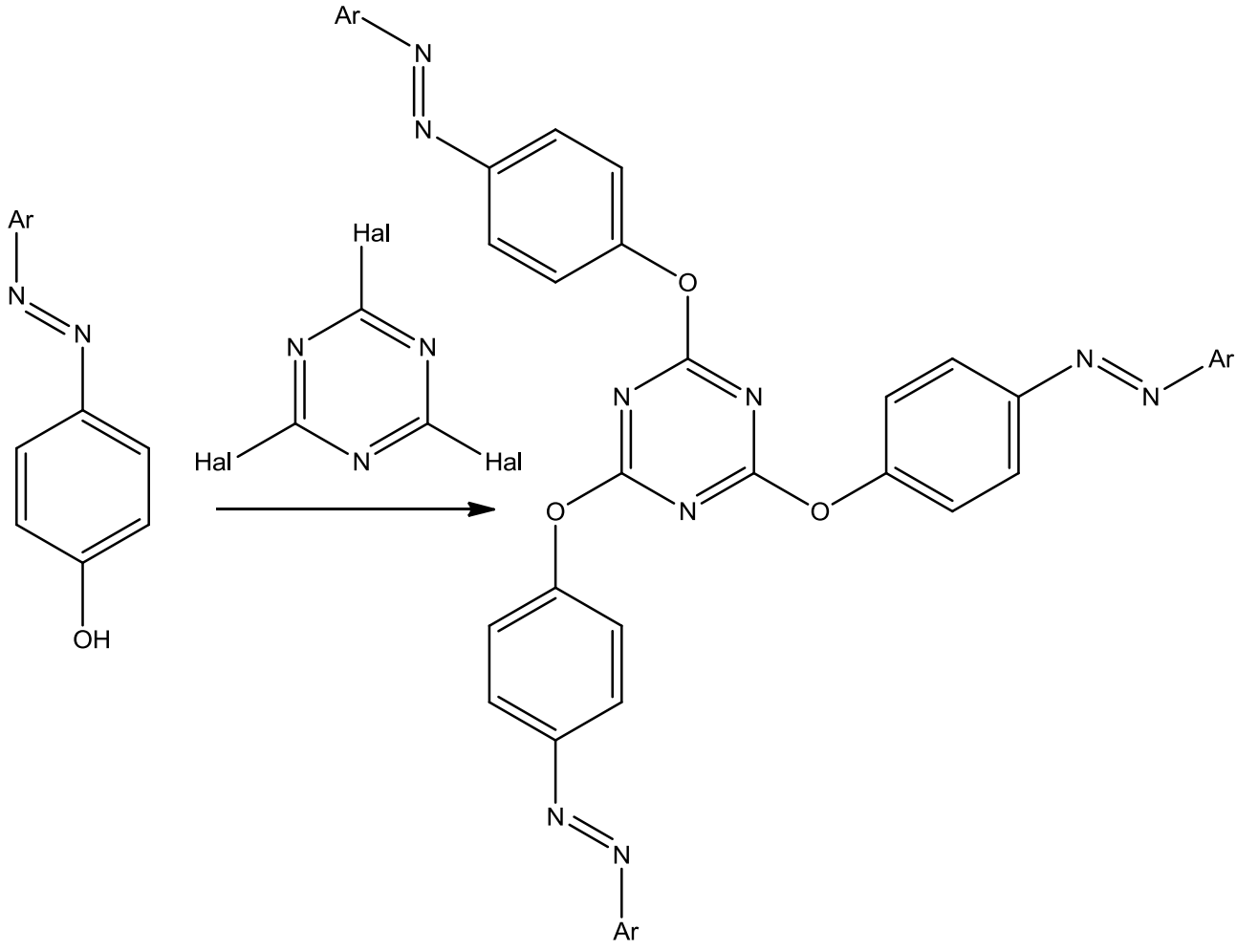
Triazine trisazo compounds (I, Ar = Ph, Ph-p-NO_2) earlier were obtained by trimerization of corresponding cyanate esters [1, 2].

In order to avoid synthesis using poisonous halogenocyanes we have elaborated the new way to I synthesis using trihalotriazine reagent (Hal = Cl, Br).



I

Ar = Ph, PhMe, PhOAlk, PhHal, $PhNO_2$, 1-naphthyl.

References

1. M. Hedayatullah, A. Nunes. C. R. Acad. Sci., Paris, Ser. C. 1967, 265(20), 1124-1126.
2. M. Hedayatullah, A. Nunes, A. Binick, L. Denivelle. Bull. Soc. Chim. Franc. 1969, (8), 2729-2734.

P-46

Biological Activity of S-Heterilsubstitutes Carboxylic Acid

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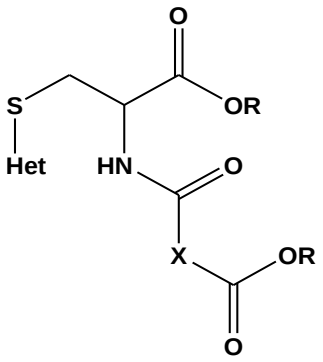
Pyridine, quinoline and acridine chemistry for the last decades grew into one of the widest division of chemistry of heterocyclic substances. Substances, that show an antioxidant, antimicrobial, fungicide, cardioactive, analgetic, neurotropic and other types of activity, were found among them. Most of biological active organic acids that is an universal energy source in an organism causes an interest the last time. Combination of nitrogen-containing heterocycle and mercaptocarboxylic acids influence on strengthening of biological action or appearance of new effects. Therefore a search of new bioactive substances containing in the molecule a heterocycle and a deputy with high antioxidant properties such as carboxylic acid is perspective. That's why S-heterilsubstitutes of carboxylic acids were selected for the research.



Het – pyridine, quinoline, acridine

Computer analysis of the results of screening using PASS revealed the likely impact on the structural parameters of biological activity. The level of activity and mechanism of action of the investigated substances depended from the nature of the carboxylic acids.

The virtual library of bioregulators was created. It demonstrates considerable potential of cytoprotectors, hepatic protectors, membrane protectors, and substances with fungistatic activity.

The studies of sharp toxicity proved that S-heterilsubstitutes carboxylic acid is more or less safe according to the classification of Sidorov at intra-abdominal introduction. LD_{50} of substance presents 1000-2000 mg/kg.

P-47

Synthesis and *in silico prediction* of the physiological activity of 3-[4-(3-ethyl-[1,2,4]oxadiazol-5-yl)-[1,2,3]triazol-1-yl]-piperidine

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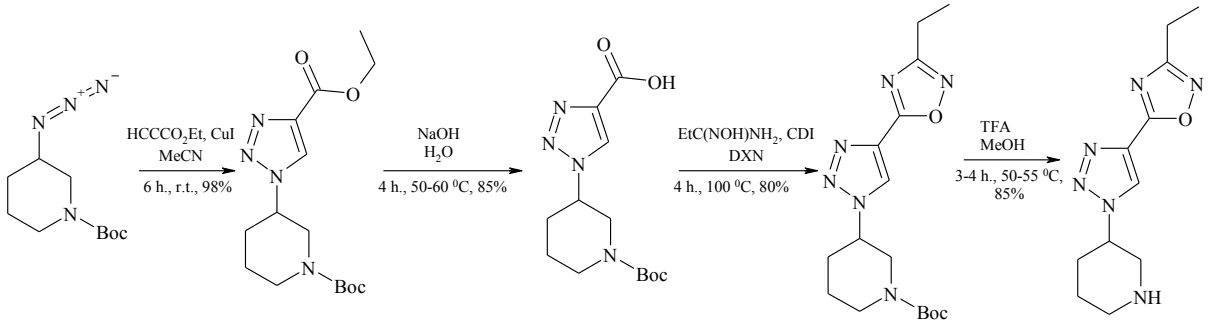
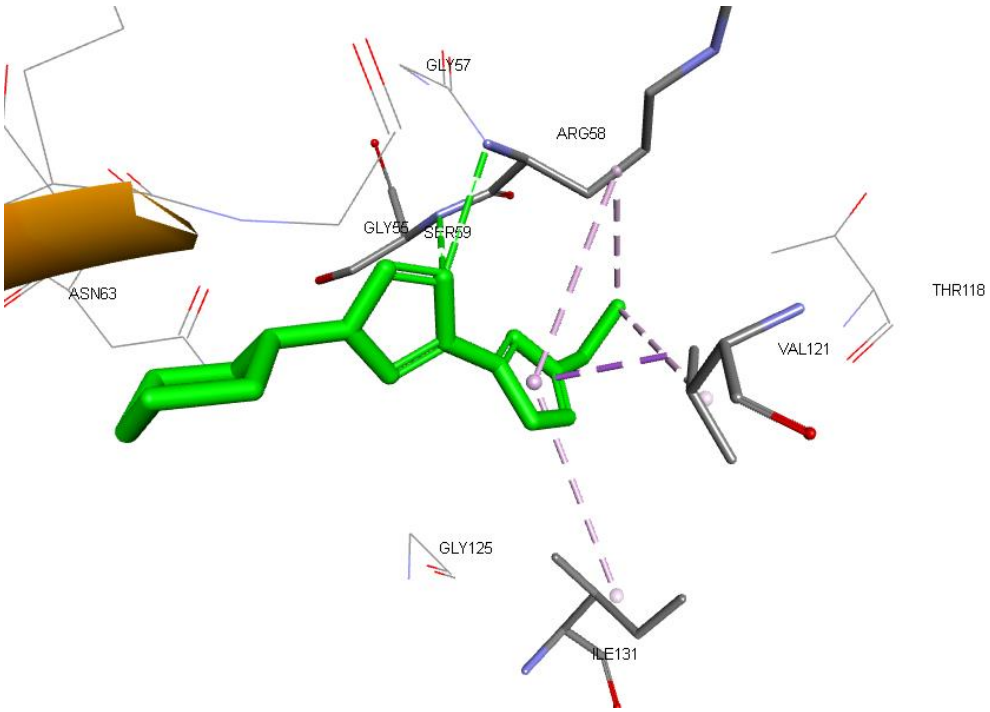
The data of recent years' experiments prove efficiency of using compounds which contain a fragment of 1,2,3-triazole as antimicrobial, in particular antituberculous agents. The action of majority of these drugs is mediated by an effect on the DprE1 protein of *Mycobactérium tuberculósis* strain. The goal of our work is the synthesis and *in silico* research of new, before unreported, compounds and their affinity to the protein mentioned above. Synthetic pathway of the investigated molecule is depicted on the scheme below.





A computer simulation of the obtained compound interaction with DprE1 protein's active site was carried out. The result is that examined molecule binds the same amino acid residues ARG58, ILE131, VAL121 as well as its structural analog [*Med. Chem. Commun*., **2015**, *6*, 1104-1116]. Thus, we can conclude that studied compound can show antituberculous activity in biological experiment.

P-48

Synthesis of Novel Pyrimido[6,1-c][1,2,4]triazinones

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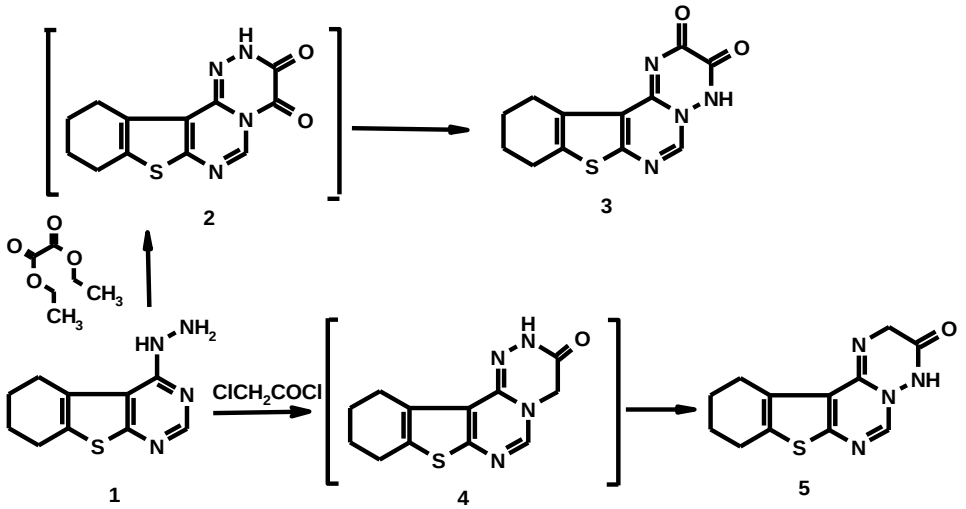
Pyrimidines and fused pyrimidines are the integral parts of DNA and RNA. They play an essential role in many biological processes and also have considerable chemical and pharmacological importance [1-2].

In our previous works we have reported the synthesis of pyrimido[6,1-c][1,2,4]triazin-4-ones system [3-4]. It was discovered that this reaction occurs via Dimroth-like rearrangement. In this research we continued to investigate the reactivity of 4-hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine **(1)** with other cyclization agents (diethyloxalate and chloroacetyl chloride). The reaction with diethyloxalate was carried out in ethanol. The interaction of hydrazine **(1)** with chloroacetyl chloride was carried out in pyridine.

Both reactions occur via initial cyclocondensation with formation of intermediates **(2)** and **(4)** followed by their quick Dimroth-like rearrangement yielding compounds **(3)** and **(5)** correspondingly.



Thus, this convenient synthetic paths helped us to enlarge the number of novel benzothieno[2,3-d]pyrimidines derivatives with annelated triazinone cycle.

[1] Arya P., Chou D.T.H., Becek M.G. // Angew. Chem., Int. Ed. − 2001. − № 40. − P.339.
[2] Shaban M.A.E., Morgaan A.E.A. // Adv. Heterocycl. Chem. − 2000. − № 77. − P.345.
[3] Gajda K., Astakhina V., Ejsmonta K., Kolomeitsev D., Kovalenko S., Zarychta B. // J. Molecular Structure. − 2015. − 1083. − P.137.
[4] Dimroth-like rearrangements in new pyrimido[6,1-c][1,2,4]triazin-4-ones derivatives / D. Kolomieitsev, V. Astakhina, V. Markov, S. Kovalenko // Chemistry and biology: poster prez. 22nd Young research fellows meeting, 4-6 February 2015. – Paris, 2015. – PO-070.

New Method of Synthesis of 4*H*-1,3,5-Oxadiazine Derivatives

P-49

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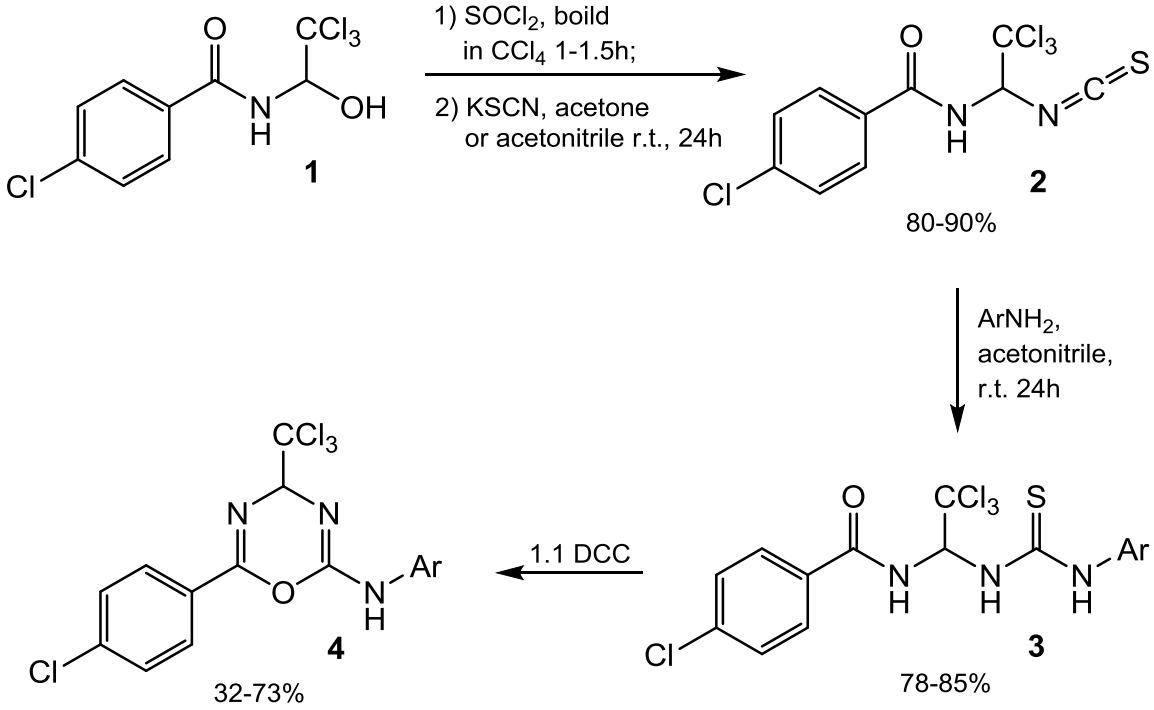
A series of *N*-amidoalkilated thioureas **3** have been obtained on the base of 4-chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)benzamide **1** via the intermediate stage of the isothiocyanate **2** formation. The compounds **3** are perspective and polyfunctional reagents. They have been used successfully by us as synthons in the new 4*H*-1,3,5-oxadiazine derivatives synthesis. Degidrosulfurization of thioureas **3** have been conducted at reflux in anhydrous acetonitrile with 10%-excess of dicyclohexylcarbodiimide (DCC) for 50-60 min.



Compound **4** has been prepared in acceptable yields and without special difficulties isolated from the reaction mixture.

The synthesized structures of the compounds have been fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallographic analysis.

P-50

Synthesis and Peculiarities of 6-Methyl-2-(2-phenyl-2-arylhydrozonoethyl)-3H-pyrimidine-4-ones Oxidation by Hydrogen Peroxide and Selenium Dioxide

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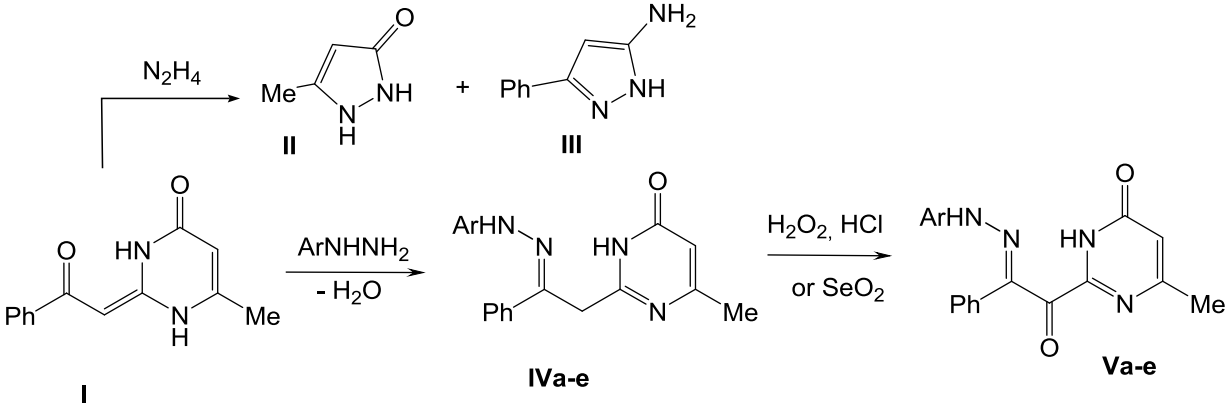
In continuation of our researches devoted to pyrimidines reactions with nitrogen containing nucleophiles, it was found that in contrast to the interaction of 6-methyl-2-(2-oxo-2-phenylethylliden)-2,3-dihydropyrimidine-4(1H)-one (I) with hydrazine hydrate resulting in the conversion of I to pyrazoles II and III [1], the reaction of I with arylhydrazines completed at the formation of hydrazones IVa-e and, in addition to that, ethylidene substituent in the starting enamine I is transformed into ethyl.



Ar = Ph (**a**), *o*-ClC_6H_4 (**b**), *o*-BrC_6H_4 (**c**), *p*-ClC_6H_4(**d**), *p*-BrC_6H_4(**e**)

Hydrazones IVa-e, stable in the crystalline state, are easily oxidized in organic solvents by atmospheric oxygen to form unstable hydroperoxides. At the same time, under the action of hydrazones IVa-e by hydrogen peroxide in ethanol, in the presence of hydrochloric acid, the main products are 6-methyl-2-[2-phenyl-2-(R-phenylhydrazono) ethyl]-3H-pyrimidin-4-ones Va-e, which are separated with the yields not less than 40-60%. The same result was obtained in the oxidation of compounds IVa-e by selenium dioxide in the solid phase at the mechanical activation of reagents.

1. A.A. Yavolovskii, L.V. Grishchuk, I.M. Rakipov, et al. Reaction of 6-methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1*H*)-one with hydrazine and hydroxylamine. *Chemistry of Heterocyclic Compounds,* 2013, 48 (10), pp 1487-1491.

This work was carried out in the frame of Comprehensive program of basic research of the NAS of Ukraine "Fundamental problems of the creation of new substances and materials of chemical production" (Project № 34-15).

P-51

Complexation Ability of Pyrimidine Derivatives as Polyfunctional Ligands in Reactions with Cu(I) And Pd(II) Ions

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[b] V.I. Vernadskiy Institute of General and Inorganic Chemistry NAS of Ukraine; Kyiv
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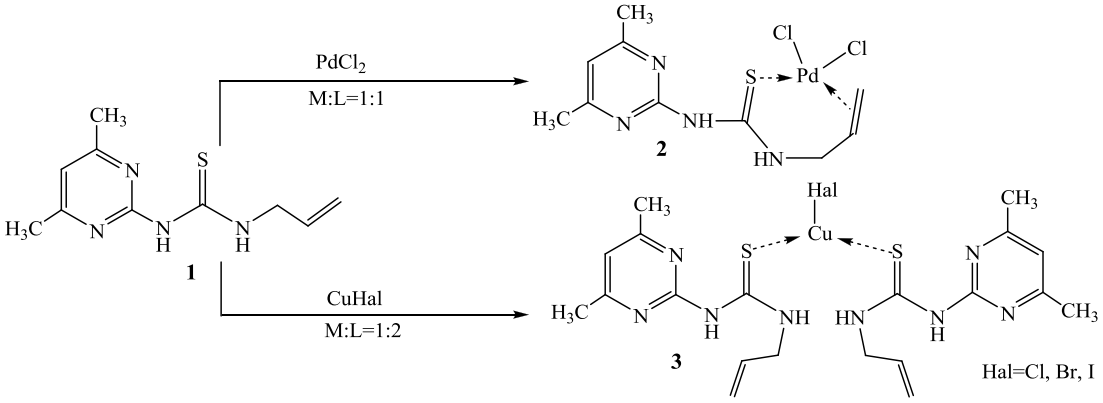
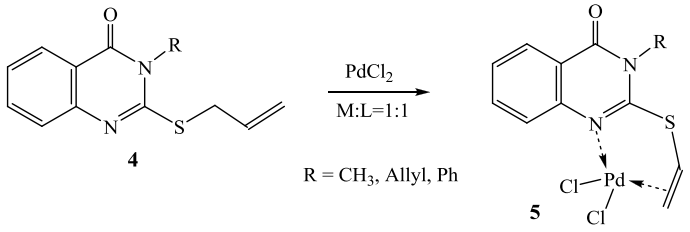
Metal complexes of pyrimidine derivatives have been extensively studied in recent years related to their great variety of biological activity. The introduction of additional functional groups into the structure of pyrimidine allows to expand the range of their biological activity and to increase the denticity of these ligand systems. As a reagent to produce complex compounds of transition metal ions we synthesized N-(4,6-dimethylpyrimidin-2-yl)-N'-(prop-2-en-1-yl)thiourea **1** containing a number of nucleophilic reactive centers as well as biologically active fragments: pyrimidine nucleus and thiourea functional group. By reacting compound **1** with $PdCl_2$ was prepared π-complex **2** wherein the ligand is coordinated to the central ion by a sulfur atom and a double bond of the allyl group. However, in the reaction with Cu(I), there was prepared complex **3**, in which potentially polydentate ligand **1** is coordinated only by sulfur atom depending on different electron affinity of central metal ions and reaction conditions.



3-R-2-Prop-2-enylthio-3-hydroquinazolin-4-ones **4** react with $PdCl_2$ to afford π-complex **5** with the coordination of allyl double bond to Pd(II) ion as in the product **2**.



Since the palladium and copper coordination compounds have antiproliferative activity against the tumor cells, the obtained products **2**, **3**, **5** are of interest as potential anticancer agents.

P-52

Investigation of Alkylation Reaction of 2-Arylsubstituted Pyrimidine-4(*3H*)-ones and Screening of Anticonvulsant Activity of Alkylated Products

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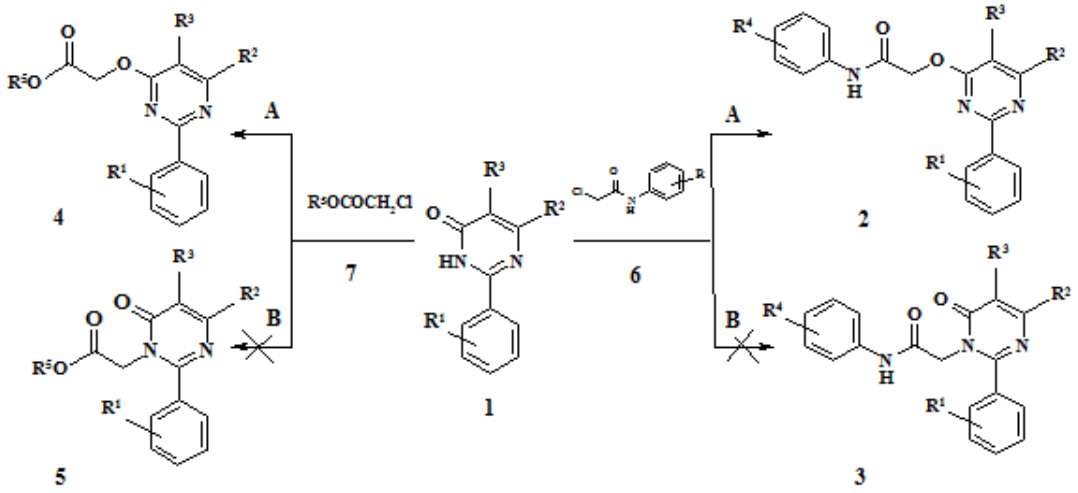
Currently pyrimidine derivatives are known by their broad spectrum of biological activity including a significant effect on the CNS. Thus, among pyrimidines there were found the compounds with sedative, anxiolytic [1], antipsychotic [2] and anticonvulsant effects [3].

Consequently, our study aimed to synthesize a series of O-alkylated pyrimidine-4(*3H*)-one derivatives and investigate their anticonvulsant activity. Based on the PASS-prediction data which showed a high possibility of antiepileptic and neuroprotecive activity of the planned compounds we performed an alkylation of 2-aryl-6-methylpyrimidine-4(*3H*)-ones by N-arylsubstituted α-chloroacetamides **(6)**, chloroacetic acid and its ester **(7)**. The reaction was carried out while heating in dioxane medium in the presence of sodium bicarbonate. Planning the synthesis we divined the possibility of two directions of the reaction due to the presence of a few reactive centers in molecules of initial pyrimidine-4(*3H*)-ones. This reaction could result into the formation of N- and O-alkylation products or their mixture (Scheme).



The data of NMR ^{1}H and ^{13}C-spectroscopy confirmed the formation of O-alkylated products **(2, 4).**

For screening the anticonvulsant activity of synthesized compounds the pentylenetetrazole-induced seizure model was used. The results of the study revealed a pronounced antiepileptic activity among compounds of this series.

[1] S. Selleri, F. Bruni, C. Costagli [et al.] J. Med. Chem., 2005, Vol. 48, №21, pp. 6756-6760.
[2] H.B. Simpson, E.B. Foa, M.R. Liebowitz [et al.] JAMA Psychiatry, 2013, Vol. 70, №11, pp.1190-1198.
[3] S.B. Wang, X.Q. Deng, Y.P. Yuan [et al.] Eur. J. Med. Chem., 2012, Vol.56, pp. 139-144.

Nucleophilic Ring Opening of Epoxy-2-methylenecyclohyxanecetate

P-53

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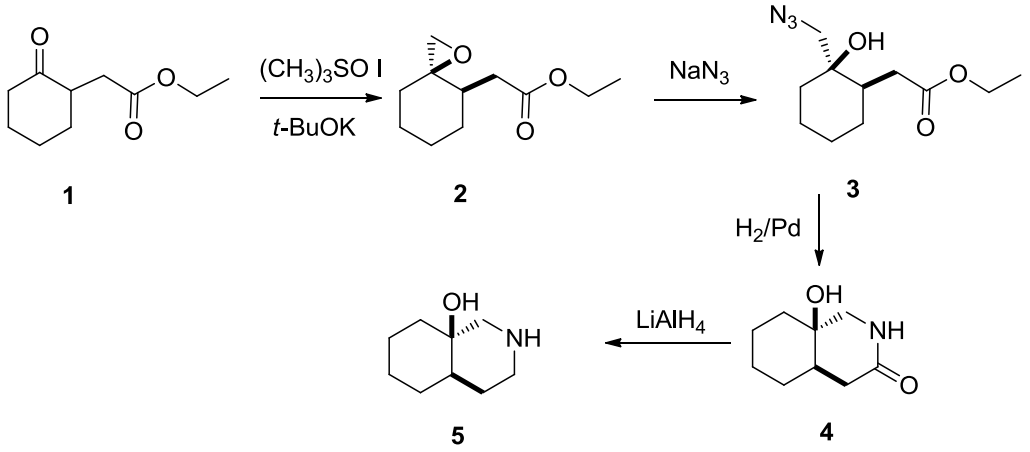
δ-Lactams are crucial intermediates in synthethis of various biologically active compounds and natural products analogues. With the aim of synthesis of cyclohexane fused δ-lactam **4** we have decided to examine an epoxide ring-opening reaction by different nucleophilic reagent for oxirane **2** derived from cyclohexanone acetic acid **1**.

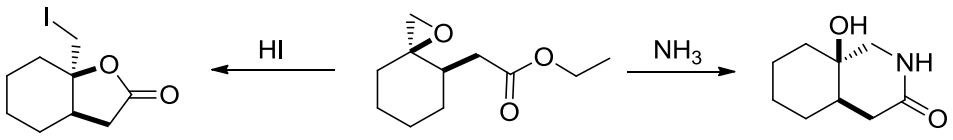
According to Tsuda [1] the *syn* epoxide **2** was formed diastereoselectively in Corey-Chaykovsky methylenation of ketone **1**. It was reported that it is possible to get 5- or 6-membered ring using different nucleophilic reagents.

As result of ring-opening by sodium azide for **2** we have obtained corresponding azidoalcohol **3**, which was cyclized to δ-lactam **4** after the subsequent reduction. Stereochemistry of **4** was proposed in view of reaction mechanism. After the reduction with the lithium aluminum hydride we got synthetically valuable azadecalinol **5**.



1 **2** **3** **4** **5**

Using the ammonia as a nucleophile get a corresponding lactam **4** in one step. Oxirane opening by hydrogen iodide gives iodolactone **6**



6 **2** **4**

[1] Y. Tsuda, A. Ishiura, S. Takamura. *Chem. Pharm. Bull.* **1991**, *39(11),* 2797-2802.

P-54

Study of Reaction of Methyl Esters' Hydrozinolysis of 5-Bromine-3-Sulphamoil-2-chlorobenzoic Acids, and their Pharmacological Activity

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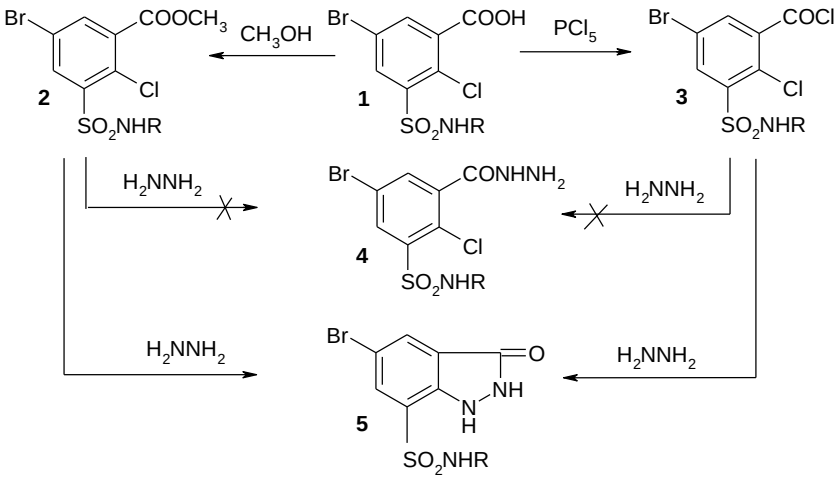
Derivatives of 5-bromine-3-sulphamoil-2-chlorobenzoic acid occupy focused attention of the NUPh scientists as potential compounds which reflect different pharmacological activity.

An object of our research was chosen to be methyl esters of 5-bromine-3-sulphamoil-2-chlorobenzoic acids (2), obtained by esterification of the mentioned above acids (1) by methanol in the presence of concentrated sulphate acid.

Scheme 1



Upon the reaction of methylic esters hydrazinolysis (scheme 1) of 5-bromine-3-sulphamoil-2-chlorobenzoic acids (2) at warming up for 30 minutes, particular substituted 5-bromine-3-oxo-1,2-dihydroindalize (5) have been obtained. Running the reaction of the esters' hydrozinolysis (2) in the cold also has not resulted in creation of hydrazides of 5-bromine-3-sulphamoil-2-chlorobenzoic acids (4). Probably, easiness of cyclization as a process can be explained by reactive capacity of chlor in the other position because of polarity rise of the connection C-Cl by means of ortho- influence of sulphamoil and carboxylic groups, that is approved by the research have conducted prior.

The products of cyclization (5) have also been synthesized by us through the direct effect of the phosphorus chloride (3) onto the 5-bromine-3-sulphamoil-2-chlorobenzoic acids (1) without disengagement of chloranhydrates and further addition of hydrate hydrazine. In support of creation of the products of cyclization (5) the negative reaction of "silver miracle" says.

The structure of obtained compounds (2-5) is proved by the modern methods of analysis.

The synthesized substances (2, 5) displayed medium antimicrobial and antifungal activity in the dose of 5-20 mg/ml.

P-55

Application of Acidochromal Condensation for 4,5-Dihydro-3*H*-thieno[2,3,4-*ij*]isoquinoline System Construction

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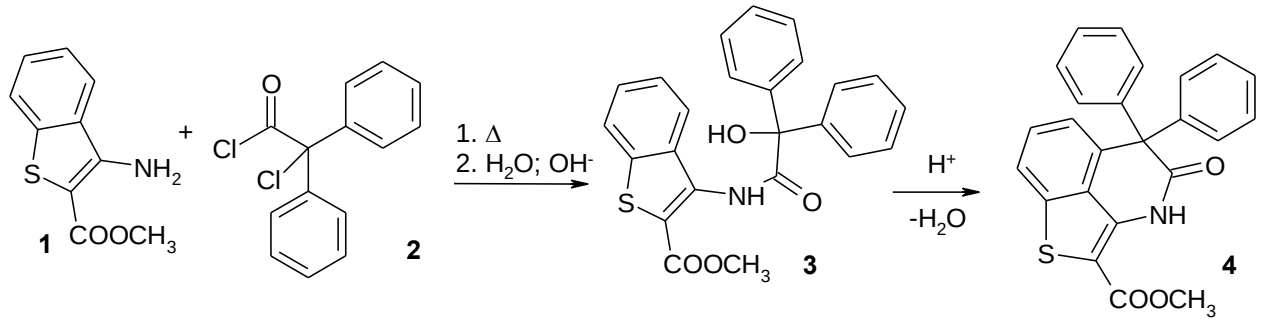
Design of new synthetic methods for polycondensed heterocycles construction is a promising route for creating of new drugs. Researches in this area have been attracting a considerable attention of synthetic community for a long time [1]. Despite, such systems are poorly studied. This was the reason for us to obtain a polyfused ring system using acidochromal condensation. It was shown that N-heterylamides of benzilic acid are the precursors for fused heterocycles, such as 1*H*,3*H*-thieno[3,4-*b*]pyrrol-2-one; 5-oxo-5,6-dihydro-4*H*-benzo[*d*]thieno[3,4-*b*]azepine; 5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-2,4,6-triones [2,3].

Here, we report the interaction of 3-aminobenzothiophene (**1**) with chloroanhydride of 2,2-diphenyl-2-chloroacetic acid (**2**) which led to the 4-oxo-5,5-diphenyl-4,5-dihydro-3*H*-thieno[2,3,4-*ij*]isoquinoline-2-carboxylate (**4**) through the formation of intermediate amide (**3**). To obtain the target polyfused derivative (**4**), amide (**3**) was heated in the presence of acid. An interesting feature of this interaction is the red coloration of reaction mixture. The disappearance of red color is the evidence that the transformation is complete. The structure of the synthesized compounds was proved by the ^{1}H NMR-, ^{13}C NMR-, IR-spectroscopy and mass-spectrometry.



[1] S.Tumkyavicius, R.Bernotaite. A new system 4-thia-1,3,7a,9-tetraazacyclopenta[def]phenantrene // Chemistry of heterocyclic Comounds, vol.34, №12, 1998, 1445-1446 P.

[2] Использование ацидохромной циклоконденсации в синтезе производных 2-оксо-3,3-дифенил-2,3-дигидро-1Н-тиено-[3,4-b]пиррол-6-карбоновой кислоты / К.М. Сытник, Л.А. Шемчук, М.Е. Кончаковская, В.П. Черных // Журнал орг. та фарм. хімії. – 2007. – Т. 5, вип. 1(17). – С. 21-26.

[3] Використання 1-R-6-аміноурацилів в одностадійному синтезі 1-R-5,5-дифеніл-5,7-дигідро-1Н-піроло[2,3-d]піримідин-2,4,6-тріонів / К.М. Ситнік, Г.В. Григорів, Л.А. Шемчук та ін. // Журнал орг. та фарм. хімії. – 2011. – Т. 9, вип. 2 (34). – С. 3–8.

P-56

Cyclization *N*-Thiophene Amides of Styrylacetic Acids under the Action of Electrophilic Reagents

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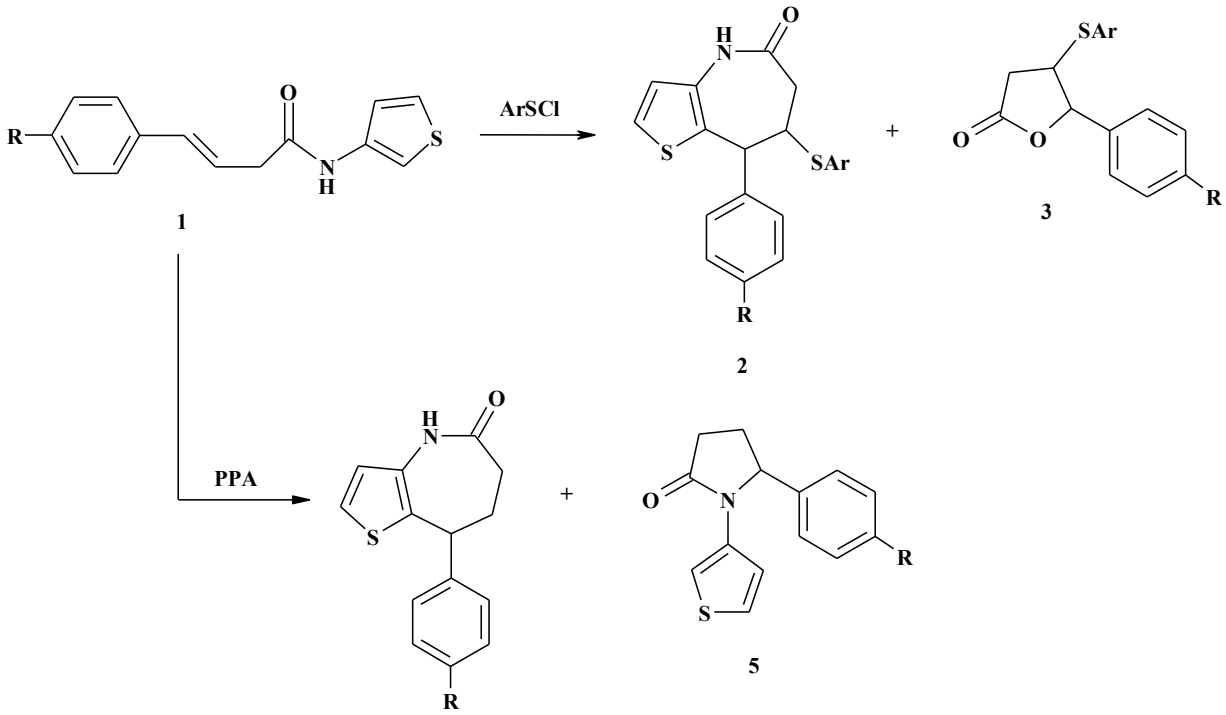
Amides of unsaturated carboxylic acids as a double centered nucleophilic system with alkenyl and aminokarbonile functions are convenient model objects for studying the reactions that lead to the formation of O- and N-containing heterocycles. Given the previously identified patterns of cyclization of N-arylstyrylacetamides, in this type of transformation we investigated thiophene analogues.

Cyclization N-thiophene amides of styrylacetic acids **1** under the action of arylsulfenyl chlorides and PPA was studied. It was established that the interaction of compounds **1** with arylsulfenyl chlorides undergoes with predominant formation thienoazepinones **2** and lactones **3** with high diastereoselectivity. Aryl substituents as well as the nature of arylsulfenyl chlorides not significantly affect the ratio of products. Cyclization of compounds **1** under the action of PPA leads to the formation thienoazepinones **4** and pyrolydine **5** in the ratio of 5 : 3.



R = H, F, Me

Ar = C_6H_5, 4-Me-C_6H_4, 4-O_2N-C_6H_4

The structure of the obtained compounds **2-5** was established by methods of mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy.

Simple Method for 2-Aminopyridine Chlorination

P-57

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Methods of halogenation aminopyridines used N-chlorosuccinimides [1], $Me_4NI^+Cl_2^-$ [2], H_2O_2/HCl [3, 4], Cl_2 and Br_2 [5]. Methods of radical halogenation have the deficiencies, namely 1) the difficult method of selection of yields, 2) present an impurity dihalogen derivant, 3) strict observance of requirements of reaction. We are updated metod of chlorination 2-aminopyridine, , used impurity unorganic salts. Product yield was not large of 30% in reaction condition [3]. At a variation of chemical composition of salts, under constant requirements we managed to enlarge an yield monohalogen derivative of aminopyridine to 65%. After hydrochloric acid neutralising 2-amino-5-chloropyridine does not demand the further purification. The structure is proved NMR ^1H and ^{13}C spectra.

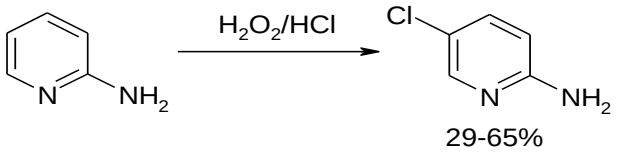

Table 1. Chlorination of 2-aminopyridine used impurity unorganic salts.

Time	Temperature	Salt	Yield
20 h	20 -25°C	-	29%
20 h	20 -25°C	NH_4Cl	41%
20 h	20 -25°C	NaCl	49%
20 h	20 -25°C	AgCl	55%
20 h	20 -25°C	KCl	65%

1. Gan, Zongjie; Hu, Bin; Song, Qiao; Xu, Yungen "Convenient Chlorination of Some Special Aromatic Compounds Using N-Chlorosuccinimide" *Synthesis* 2012, 44, 1074-1078;

2. Lesyna Yu.A., Tret'yakov A.N., Krasnokutskaya H.A. Iodination aminoderivatives nitrogencontained heterocycles using $Me_4NI^+Cl_2^-/AgNO_3$ in methanole. // *Bulletin of the Tomsk Polytechnic University*, 2009.- vol.315 - №3.- p. 65-68;

3. Svertylova I.A, Yutilov Yu.M., Kovaleva L.I. Abstr. coll. Reactants and especially pure substances (methods for the preparation of chemical reagents and high purity substances). Vyp. 3 (30). Moskow: NIITEChIM, 1976, p. 54;

4. Shapiro R. "Process for the manufacture of 2,3-dichloropyridine" WO/ 2005/070888 20050804 Sulfanilamidoheterocycles" *JACS* vol. 68,(1946) p.453.

P-58

Glycosides of Pyrazolo[3,4-C]isoquinoline

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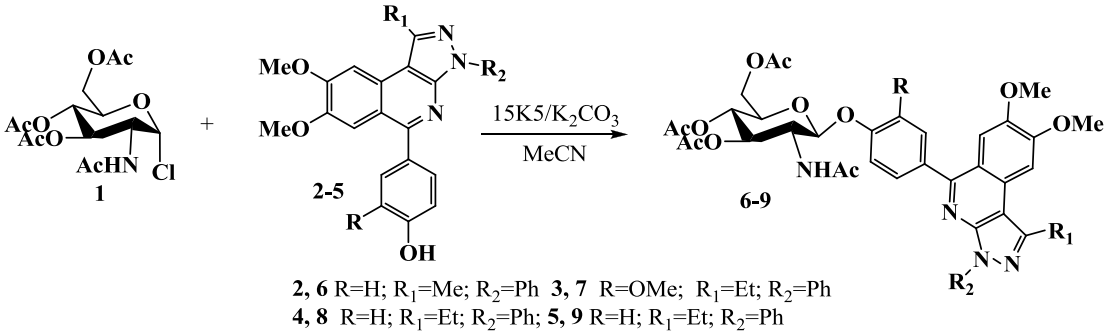
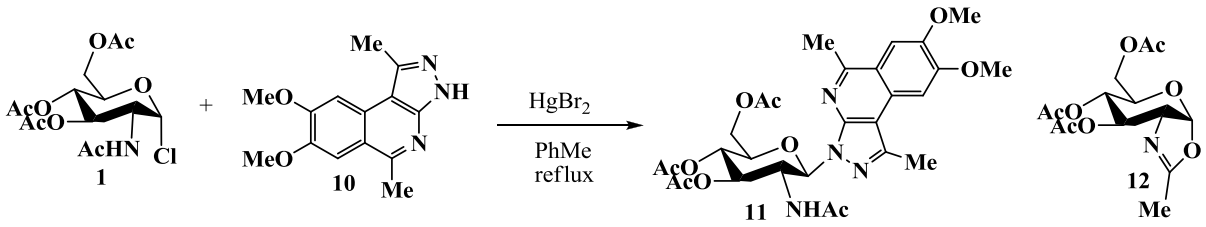
Recently extensively investigated the biological activity of pyrazolo[3,4-*c*]isoquinoline derivatives. They have become a new class of anaplastic lymphoma kinase inhibitors, also increase the effeciency of chemotherapy drugs and antibiotics and regulate the multidrug transport systems across the blood brain and placental barriers.

Unfortunately, pyrazolo[3,4-c]isoquinolines are poorly soluble. Therefore, the goal of our present work there preparation their glycosides.



2, 6 R=H; R_1=Me; R_2=Ph **3, 7** R=OMe; R_1=Et; R_2=Ph
4, 8 R=H; R_1=Et; R_2=Ph; **5, 9** R=H; R_1=Et; R_2=Ph



O-glycosides were prepared under phase transfer catalysis. N-Glycoside 11 were prepared by reaction glucosaminyl chloride and pyrazolo[3,4-*c*]isoquinoline in the presence of mercury bromide (II) excess.

Electronic Absorption Spectra of Benzimidazolic Chalcones Revisited: Quantum-Chemical Study

P-59

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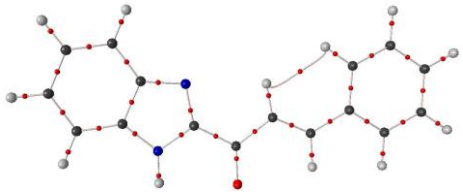
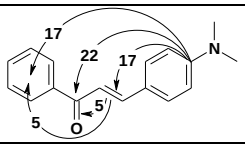
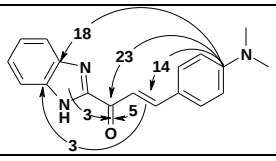
From the viewpoint of electronic spectroscopy chalcones are usually considered as bichromophoric systems with weak interaction between their chromophoric subunits – "*acetophenone*" and "*cynnamoyl*" ones [1,2]. However, introduction of benzimidazolic unit into the "*acetophenone*" part leads to significant bathochromic effect even in the case, when their long-wavelength band belongs to another chromophore. Absence of intramolecular hydrogen bond between the benzimidazolic N-H and carbonyl groups was approved by quantum–chemical modeling with application of Bader' AIM [3] theory (Scheme). That is why H-bond should not be responsible for the observed spectral behavior.



Application of ESSA approach [4] (b3lyp/cc-pvdz, Table) shows the reason for such behavior is definite increase of intramolecular donor-acceptor interaction of the chromophoric units involved and higher participation of the benzimidazolic unit in formation of LW electronic transition.

Electronic transition		Electronic excitation localization, %				Electronic density redistribution at excitation
Type	Energy, WL, intensity	Ph/Bi	C=O	CH=CH	Ph	
Chalcone, 4'-N,N-dimethylamino						
S_0-S_1 ($\pi\pi^*$)	26110 cm^{-1} 383 nm *f* = 0.786	14.5	**17.9**	**20.0**	**47.7**	
Benzimidazolic chalcone ananlog, 4'-N,N- dimethylamino						
S_0-S_1 ($\pi\pi^*$)	24540 cm^{-1} 408 nm *f* = 0.963	19.0	**18.3**	**18.3**	**44.4**	

[1] W.B. Black, R.E. Lutz. Ultraviolet absorption spectra of chalcones. Identification of chromophores // JACS.- 19555.- V.77.- P.5134-5140.

[2] D.N. Dhar, D.V. Singhal. Absorption spectra of some substituted chalcones // Spectrochim. Acta. A. – 1970. V. 26.- P. 1171-1172.

[3] R.F.W. Bader. Atoms in molecules // Acc. Chem. Res.- 1985.- V.18.- P. 9-15.

[4] A.V. Luzanov, O.A. Zhikol. Electron invariants and excited state structural analysis for electronic transitions within CIS, RPA, and TDDFT models // Int. J. Quant. Chem.- 2010.- V. 110.- P. 902-924.

P-60

Benzimidazole Nucleus Containing 1,3,5-Triaryl-substituted 2-Pyrazolines and Pyrazoles

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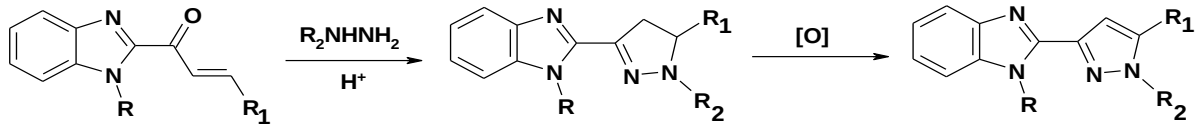
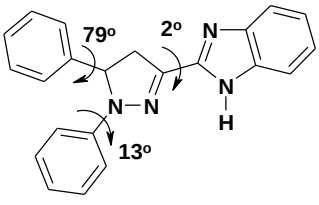
A series of 1,3,5-tryaryl-2-pyrazolines with benzimidazole nucleus in position 3 were synthesized with moderate yields (45-75%) from the corresponding chalcones by their condensation with phenylhydrazine in acidified ethanol solution. N-methylation of benzimidazole moiety was shown to have no influence on the yield of target products. Attempts of introduction of the nitro-substituted chalcones into the same reaction were unsuccessful: only intermediate hydrazones were obtained in such case.

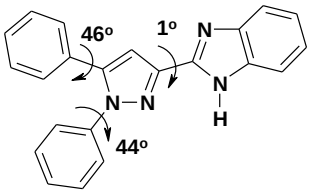


R = H, CH_3; R_1 = C_6H_5, 4-Cl-/4-Br-C_6H_4; R_2 = C_6H_5, 4-F/4-Cl-/4-Br-/4-OMe-/4-NMe_2-C_6H_4

Application of thiosemicarbazide except phenylhydrazine and subsequent reaction with α-bromoacetophenone results in obtaining of several 2-pyrazoline derivatives with 3'-phenyl-thyazole-2-yl moiety in position 1. All the synthesized pyrazolines were tested for the possibility of their conversion into corresponding pyrazoles via mild oxidation by freshly prepared nickel peroxide or magnesium dioxide in benzene. Surprisingly, N,N-dimethylamino group in pyrazolinic penyl-5 inhibits oxidation completely, thus, corresponding pyrazoles were not synthesized.

Quantum-chemical modeling of molecular structure of the synthesized compounds reveals absence of intramolecular H-bond between the benzimidazolic N-H and pyrazolinic/ pyrazolic nitrogen atom in position 2. Aryl radical in position 5, which was almost orthogonal to pyrazoline cycle, does not return to the plain of pyrazole cycle in the oxidation product. Analogously, dis-flattening with the heterocycle was observed also for pyrazolic phenyl-1.





Electronic absorption, fluorescence spectra and quantum yields were measured for all the investigated compounds in acetonitrile solutions. Conversion of pyrazolines into pyrazoles results in hypsochromic shift of both absorption/emission spectra and nearly doubling of fluorescence quantum yields.

P-61

Influence of Substituent at the Indolenine Moiety Nitrogen on the Synthesis, Photophysical and Photochemical Properties of Indodicarbocyanine dyes

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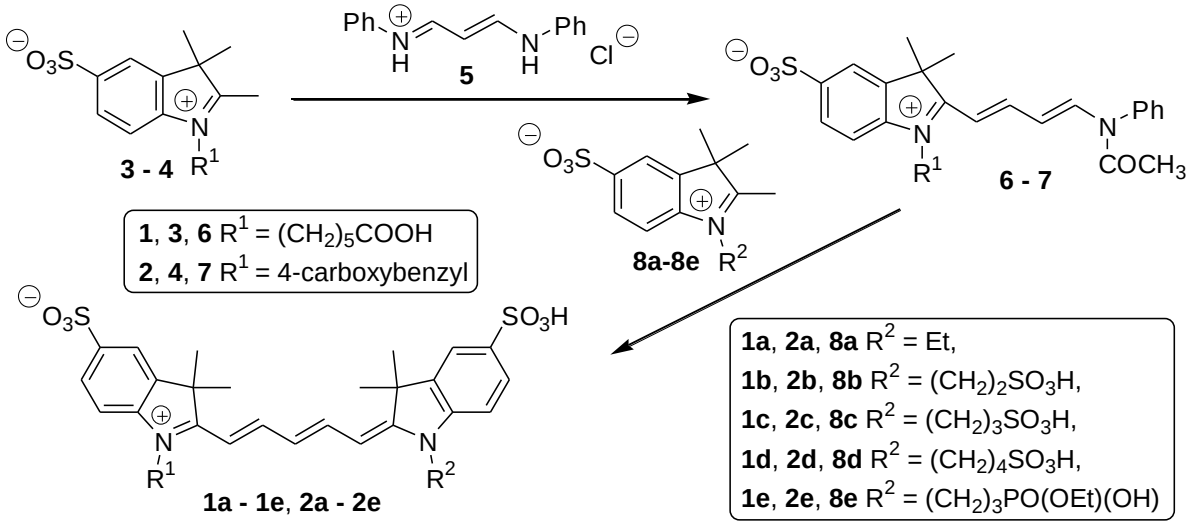
With the aim to investigate influence of *N*-alkyl and *N*-benzyl substituent in the indolenine moiety on the spectral and photophysical properties of indodicarbocyanines the series of dyes with *N*-carboxypentyl (**1a–1e**) and *N*-(4-carboxybenzyl) (**2a–2e**) were synthesized.

Indolenines with *N*-carboxypentyl (**3**) and *N*-(4-carboxybenzyl) (**4**) substituent demonstrate the same reactivity in the reaction with dianyl of malonic aldehyde (**5**) to form corresponding intermediates **6–7**, which react with the second indolenine **8** to give required unsymmetrical indodicarbocyanine dyes **1a–1e** or **2a–2e**.



It was found that substitution of *N*-carboxypentyl group with *N*-(4-carboxybenzyl) group do not affect much on the spectral properties of the obtained indodicarbocianine dyes. The maxima of absorption and emission wavelengths of the dyes in aqueous solution are found in the range of 645–648 nm and 665–668 nm, respectively. The spectra of these dyes exhibited negative solvatochromism and solvatofluorochromism: when aqueous solution is replaced by methanol the spectra are red-shifted to 2–7 nm. At the same time photostability of *N*-benzyl dyes **2a–2e** is almost 2 times higher as compared to their *N*-carboxypentyl analogs **1a–1e**.

The results of the study provide the rationale for the design of dicarbocyanine dyes with improved photophysical properties suitable as fluorescent labels for biomedical applications.

The work was supported by the Science and Technology Center in Ukraine (Projects P548) and the National Academy of Sciences of Ukraine (Project 0113U001410).

P-62

A Base-Promoted Domino Reaction of *N*-Cyanomethyl Iminium Salts for the Preparation on Annulated Chromenoimidazoles

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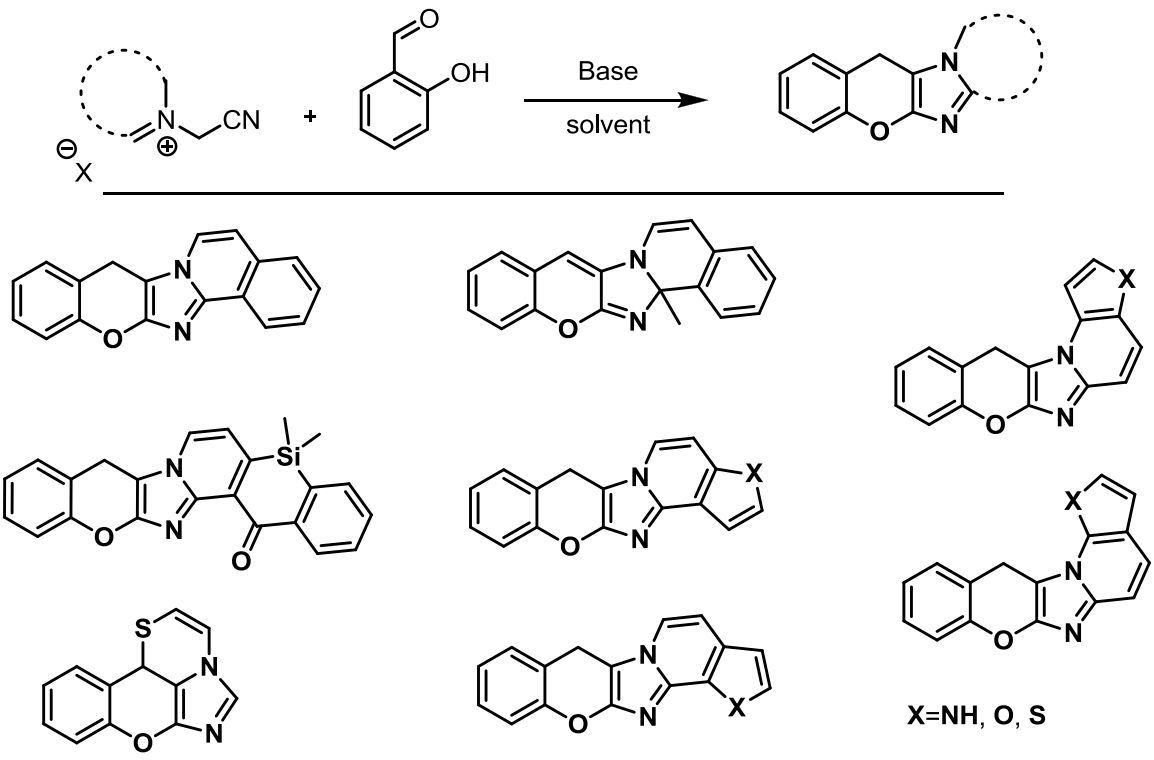
A route towards chromenoimidazoles, condensed with isoquinoline, pyridosilaazanthracene, thiazine, isomeric pyrrolo-, thieno- or furopyridine rings has been developed. It has been shown, that the interaction of cyanomethylium quaternary iminium salts of nitrogen-containing heterocycles with different *o*-hydroxybenzaldehydes proceeds in an effective atom-economical manner, creating two or three rings in one synthetic procedure.



A number of the synthesized compounds were screened *in vitro* and showed a prominent antiproliferative activity.

The financial support of Russian Foundation for Basic Research (14-03-93001) and Ministry of Science and Education (project #2042) is gratefully acknowledged.

Search of Biologically Active Compounds on the Basis of Uracil and its Derivatives

P-63

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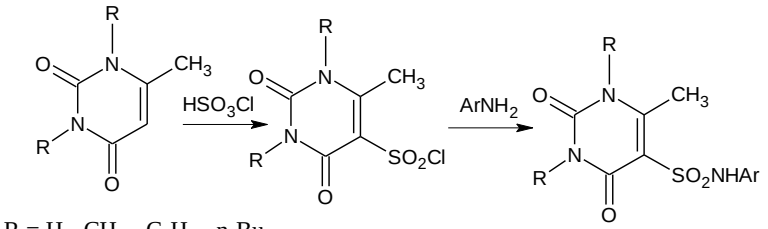
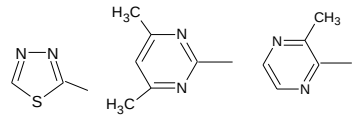
Uracil is a constituate component of nucleic acids and that is why it doesn't show Toxic properties while getting into the organism of human beings and animals. This bact enables to search for biologically active compounds on its basis. Among such compounds one can find those containing sulfonamide groups resembling (according to their structure) common sulfonamides which have wide application in medical practice as effective antiseptics (according to their structure) common sulfonamides which have wide application in medical practice as effective antiseptics (streptocide, etasol, sulfadimezin, sulfalen etc.).



R = H-, CH_3-, C_2H_5-, n-Bu

Ar = H-, R,



In the interaction of 6-methiluracil-5-sulfochloride with primary and secondary amines in the medium of pyridine or in acetic acid in the presence of sodium acetate the respective sulfonamides have been produced with high output. The preliminary toxically investigation carried out showed that the majority of them are several times less toxic in the comparison with streptocide. Sulfonamide, produced by the interaction of methyluracilsulfochloride with 4-aminoantipyrine, practically stops the growth of Staphylococcus and intestinal bacillus [1, 2].

Individuality of synthesized compounds and the end of the reaction were determined on the silufol using different suitable systems.

The Structure of compounds produced was determined with the help of IR- end PMR- spectroscopy.

1. I.P.Pogorelova, V.D.Orlov, A.D.Isak. *J. priklad. Chemii*, 2006, v. 79 № 4, P 639-641
2. I.P.Pogorelova, A.D.Isak, U.P.esipowa, L.A.Shemtchuk. *Westn. Pharmac*., 2004/ v/1(37), p/20-23

P-64

Interaction of Heterocyclic Compounds with Hydroxylamine in the Alkaline Medium in the Presence of Ferrum(II) Ions

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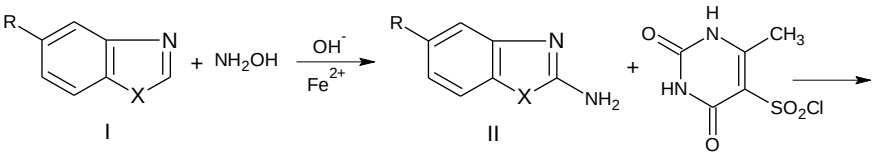
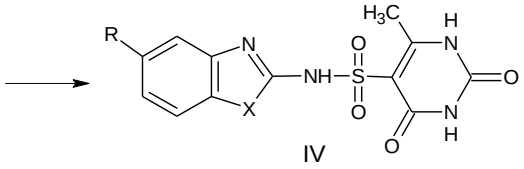
Heterocyclic compounds containing a primary aminogroup are widely used in manufacturing dyes of different types, biologically active compounds, agricultural preparations (herbicides, sprout preparations etc.). That is why, search of more reasonable method of producing compounds with a primary aminogroup is of great practical significance. In addition, this reaction is of great theoretical value. Using the interaction of hydroxylamine with aromatic and heterocyclic compounds one can study reactivity, interinfluence of groups and atoms on reactivity and turn of chemical reactions, and also investigate the mechanism of the changes, catalyst effect on the turn of substitution reaction. Chichibabin's was the first to investigate the reaction of direct introduction of a primary group into the nucleus of pyridine It was showed that on heating pyridine with sodamine in aqua-ammonium 2-aminopyridine was produced with high output.

At boiling benzoglyoxaline (X = NH, R = H) in the aqueous and alcohol solution alkali with hydroxylamine in the absence of ferrous(II) salt the reaction of ammonization does not practically take place, while the addition of catalyc quantities of ferrous sulfate makes the reaction vigorous with the formation of 2-aminobenzoglyoxaline (II) whit high output



I X = NH, S, O, Se; R = H, NO_2 II III



IV

On further heating on the vapous bath the compounds (II) with methyluracilsulfochloride in pyridine or dimethylaniline, the compound (IV) which had not been described before, was isolated.

According to forecasting the compound isolated should be biologically active.

P-65

Aziridine Photochroms Based on the Benzimidazole Analogues of Chalcone

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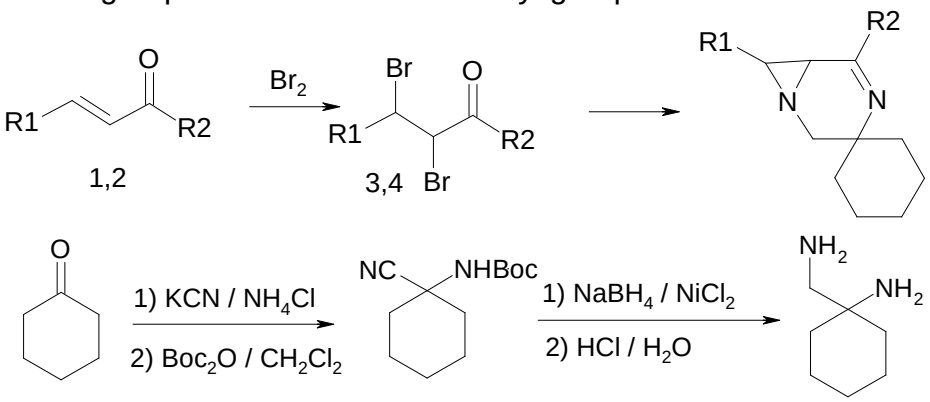
The polynuclear compounds with annelatedaziridine cycle (including cyclic aziridinylaniles)are highly sensitive crystalline photochroms, but their disadvantage is low speed of the reverse process.

That is why the problem of synthesis of new compounds with various substituents, affecting the rebuilding of the chromophoric system without taking part in this process directly, remains actual.

The synthesis of the aziridinylanileshas been carried out basing on the benzimidazole analogues of chalcone **1** and **2**. The formation of sparingly soluble salts because of high basicity of the heterocycle became a problem at the stage of bromination. We managed to obtain individual monobromides and dibromides **3**, **4** only after heating in glacial acetic acid with five-time excess of bromine. This difference is probably caused by the unequal influence of N-H and N-CH_3 groups on basicity of the molecules **1** and **2**. Both **3** and **4** are equally suitable for further transformations, because HBr elimination is the first stage in the next processes. O-phenylenediamine, 1,2-ethylenediamine and 1-amino-1-(aminomethyl)cyclohexane were taken as the second component in these reactions. The synthesis of 1-amino-1-(aminomethyl)cyclohexane is stated at the scheme. The reactions of bromides **3** and **4** with diamines were carried out in methanol with Et_3N as catalyst. All obtained compounds at solid state had strong photochromic effect, that along with element and spectral analysis data testifies to formation of the target aziridinylaniles. In the case of the diamine, by the model experiments involving x-ray crystallography, it was shown that aziridine cycle was formed by a less sterically charged aminomethylene group, and cyclohexane aminogroup condenses with carbonyl group.



P-66

d(GpGpG) DNA Minihelix Structure with Rare Base Pair Tautomer: the DFT Study with M06-2x Functional

Kukuiev M. A.[a], Zubatiuk T. A.[a], Luzanov A. V.[a], Gorb L. G.[b]

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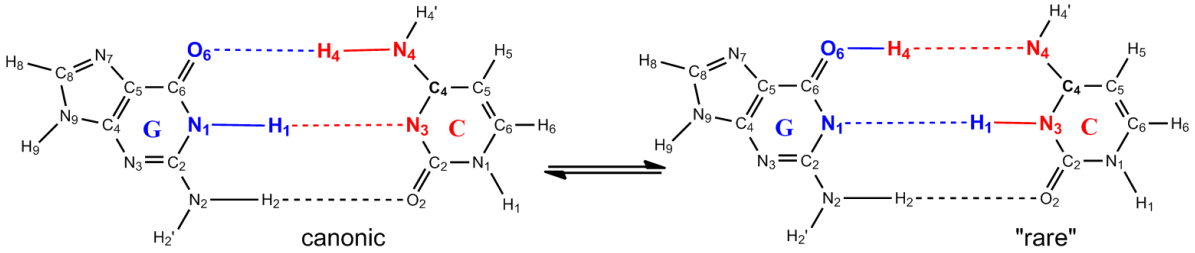
[b]Depatament for Nanotoxicity, Jackson State University, MP, USA

Rare tautomeric forms of the DNA base pairs are believed to be responsible for spontaneous point mutations in gene structure. Tautomers of this kind can be a result of protons exchange between bases of the single base pair. For instance, the scheme for this occurrence in GC base pair is shown on the figure below:



Cytosine loses its amine proton H4 to Guanine and accepts imine H1 proton from the latter.

Rare tautomeric forms of DNA bases are relatively thoroughly explored including numerous computational works. The vast majority of these studies focuses upon the structure of individual base pairs free from the rest of DNA structure. Only few works take into account surrounding structural elements of DNA up to considering of the couple of nucleosides [1].

To investigate influence of rare base pair on DNA structure we use the approach similar to that employed in [2]. We consider the model of three base pairs including one in the rare form within DNA sugar-phosphate backbone. Bearing in mind a possible biological role of rare bases we choose the conditions that mimics living cell environment (water solution modeled with the conventional PCM, charge of backbone countered with sodium cations etc).

The proton exchange (see the figure) leads to shortening of corresponding hydrogen bonds which reduce r(O6–N4) by almost 0.4 Å, also reduce r(N1–N3) and increase r(N2–O2) slightly. This minor change in the base-pair mutual orientation leads to greater values of opening and buckle parameters, and lowers the propeller twist parameter of DNA. Rare base pair causes a slight increase of helical twist of minihelix, and produces some other less notable changes. Nevertheless, such a minihelix still closely preserves the main conformational features of B-DNA.

[1] Poltev, V. I. *et al.* DFT Study of B-like Conformations of Deoxydinucleoside Monophosphates Containing Gua and/or Cyt and their Complexes with Na^+ Cation. *Journal of Biomolecular Structure and Dynamics* **25,** 563–571 (2008).

[2] Zubatiuk, T. A., Shishkin, O. V., Gorb, L., Hovorun, D. M. & Leszczynski, J. B-DNA characteristics are preserved in double stranded d(A)3·d(T)3 and d(G)3·d(C)3 mini-helixes: conclusions from DFT/M06-2X study. *PCCP* **15,** 18155 (2013).

Synthesis of (1-Aryl-4-chloro-1*H*-imidazole-5-yl)acetic Acids

P-67

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[2]*Bukovinian State Medical University, 2, Theatralna sq., Chernivtsi, Ukraine; 58000; e-mail: vchornous@gmail.com*
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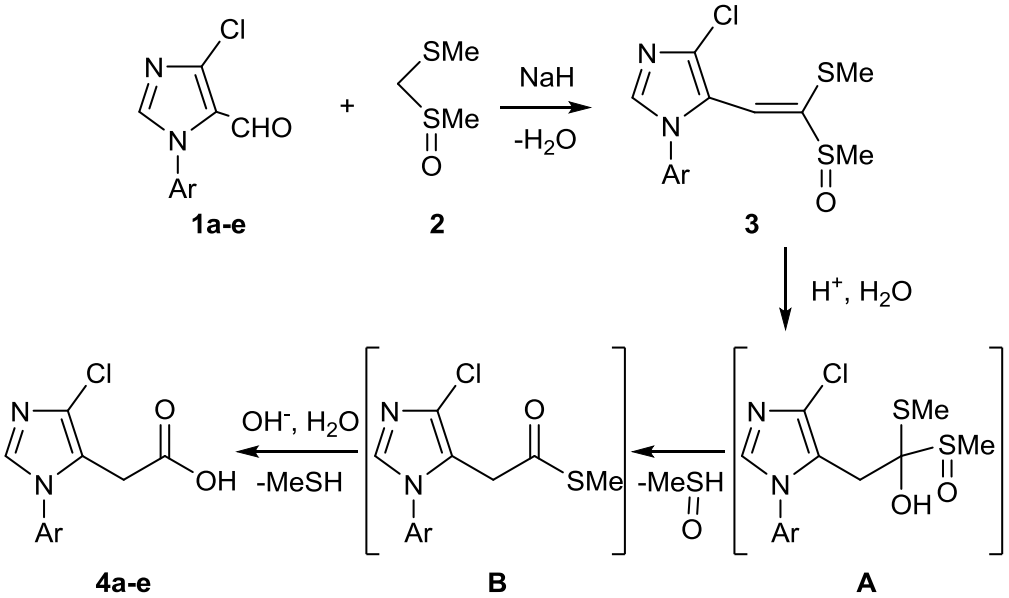
5-Imidazolylacetic acids are important building blocks for molecular design of various bioactive systems.

Take into account the strong biophoric potential of 5-carbofunctional 4-chloroimidazoles, was advisable preparing its new members that have combined 4-chloroimidazle and acetic acid fragments. We have developed an effective approach to synthesis of the imidazolylacetic acids **4a-e**, which is based on the interaction of 5-formyl-4-chloroimidazoles **1a-e** with accessible (methylsulfinyl)(methylthio)methane **2** and performed through intermediates A and B.



1, **4**, Ar = 4-BrC_6H_4 (**a**), 3-MeC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-MeOC_6H_4 (**d**), 1-$C_{10}H_7$ (**e**).

The structure of imidazolylacetic acids **4a-e** was prove by results of measurements IR, ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectra of imidazolylacetic acids **4e** the protons of the methylene group have diastereotopic character which is evidence of atropoisomeric effect of molecule due to the restricted rotation of volumetric 1-naphthyl substituent.

P-68

The Cyclization of Enamino Ketones of Neoflavones with *N,O*- and *N,N*-Binucleophiles – an Effective Approach to Neoflavones with *N,O*- and *N,N*-Heterocycles

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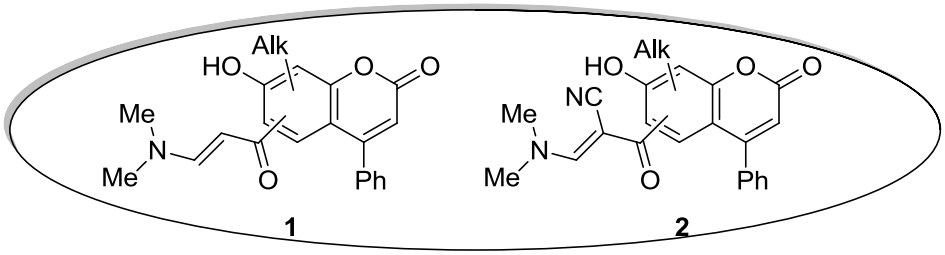
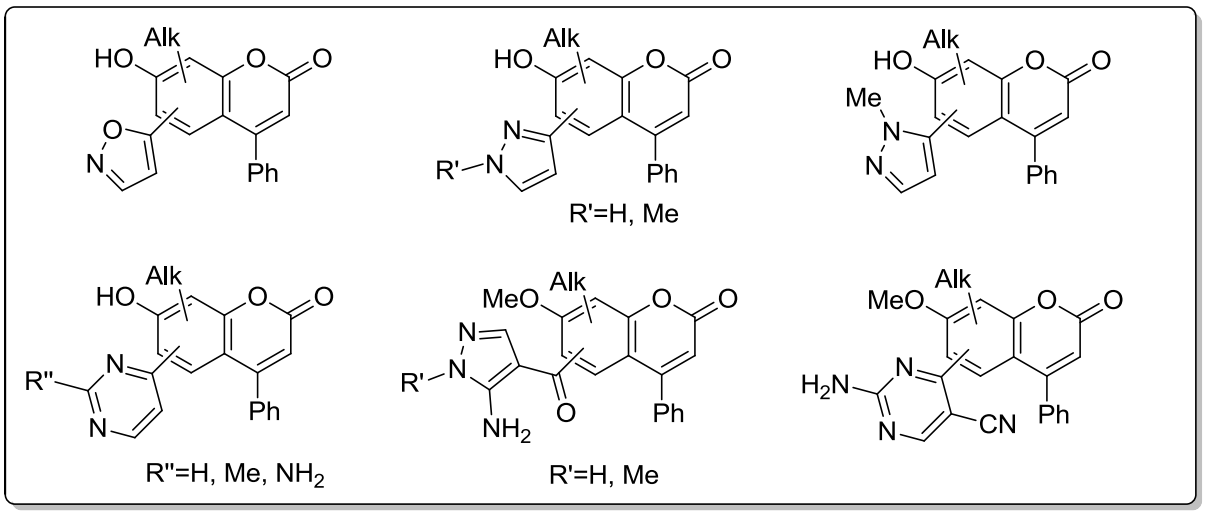
Derivatives of neoflavones (4-phenyl-2*H*-1-benzopyran-2-ones) are widespread in nature and posess a wide spectrum of biological activity. On the other hand, compounds with isoxazole, pyrazole, pyrimidine moieties are of significant interest due to their diverse biological activity.

Hereby we present a new convenient method for the synthesis of neoflavones containing the aforementioned biogenic fragments, using the corresponding enamino ketones **1**, **2** as key intermediates.



The interaction of enamino ketones **1**, **2** with hydroxylamine hydrochloride , hydrazine hydrate, methylhydrazine, amidine salts led to corresponding neoflavones with isoxazoles, pyrazoles, *N*-methylpyrazoles, 5-aminopyrazoles, pyrimidines moieties.



The use of the presented synthetic methodology has allowed to obtain 6(8)-hetaryl-substituted neoflavones for the first time.

P-69

Quaternization of 2,3-Dimethyl-3*H*-indoles and 2,3-Dimethyl-1*H*-benzo[e]indoles and Their Use for Synthesis of Water-soluble Monosquaraines

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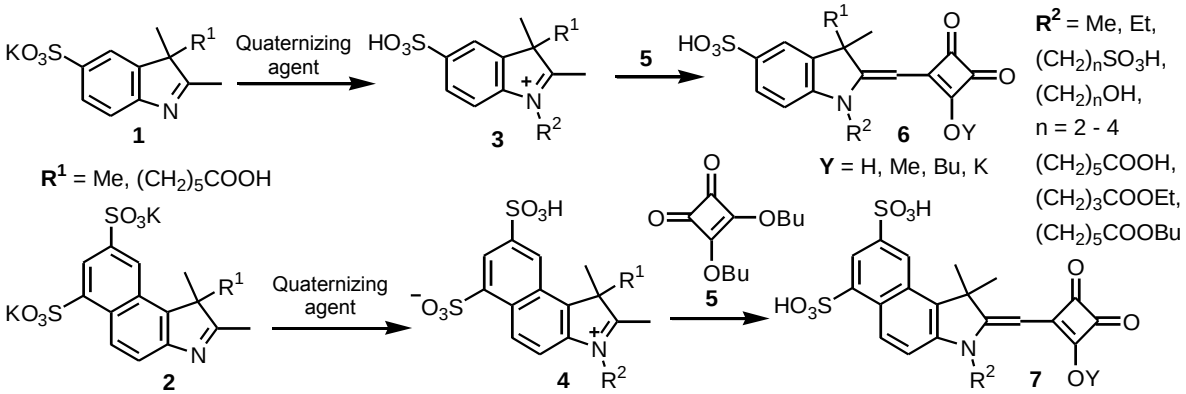
2,3-Dimethyl-3*H*-indole (**1**) and 2,3-dimethyl-1*H*-benzo[*e*]indole (**2**) derivatives are the important intermediates for the synthesis of polymethine, squaraine and styryl dyes, which are widely used due to their spectral and photochemical properties.

We examined the quaternization reaction of indoles **1** and **2** with sodium bromosulfonate, propane and butane sultones, methyl and ethyl iodide, but also with alkyl halides containing carboxyl and hydroxyl groups. Boiling of indoles **1** or **2** with the quaternizing agent in a suitable organic solvent or fusing at 140–150 °C results in the quaternized products **3** and **4**.



It was found that the quaternization reaction rate decreases with the extension of the aliphatic chain of quaternizing agent. Esterification of the carboxyl group in 6-bromohexanoic and 4-bromobutyric acid leads to increase of yields in reaction of quaternization from 50% to 75%. Indoles **1** and **2** with the free sulfogroup (-SO_3H) does not react with the investigated quaternizing agents, while their potassium salts (-SO_3K) give products **3** and **4** with satisfactory yields. Introduction of carboxypentyl group in the position 3 of indoles **1** and **2**, as well as benzoannulation of indole (indole **2** compared to **1**) results in a decrease of their reactivity and reduction in the yield of the desired products.

The obtained salts **3** and **4** by the reflux with an excess of dibutylsquarate (**5**) in pyridine or methanol in presence of potassium *tert*-butylate give monosquaraines **6** and **7**, respectively, with the yield of 15% – 48%. These monosquaraines are high water-soluble compounds, which can be utilized for synthesis of a series of practically important water-soluble red- and NIR-emitting squarylium dyes.

P-70

Halogenated Indolenines: Synthesis and Application as Terminal End-Groups of Heptamethine Cyanine Dyes

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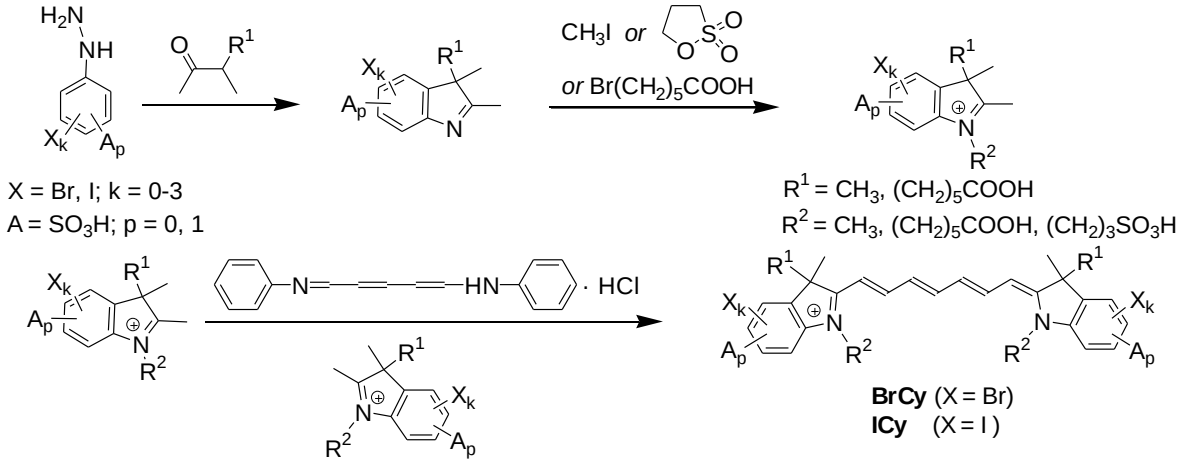
Indolenine based heterocyclic systems are widely used moieties to build a variety of organic dyes, luminophores, photosensitizers, and many other practically important compounds. However, these heterocycles containing halogen atoms as a substituent have only moderately been explored. This work is to synthesize brominated and iodinated indolenines and heptamethine cyanine dyes **BrCy** and **ICy** containing these halogenated heterocycles and to investigate effect of these heterocycles on the spectral, photophysical and photochemical properties of the dyes.

The syntheses were done according to the scheme:



The spectral properties, fluorescent quantum yields, extinction coefficients, brightness photostability, and photosensitizing efficiency were measured and compared to those for non-halogenated heptamethine dyes.

We found that the introduction of heavy bromine and iodine atoms surprisingly increases not only photosensitizing efficiency, as was expected, but also fluorescence quantum yield and photostability of heptamethine cyanine dyes, which makes them advantageous for reporting, diagnostics, and/or photodynamic therapies, among other applications.

The work was supported by the Science and Technology Center in Ukraine (Projects P384 and P542) and the NAS of Ukraine (Project 0113U001410).

P-71

Multicomponent Reaction of α-Aminopyrazoles, Malononitrile, and Arylglyoxals

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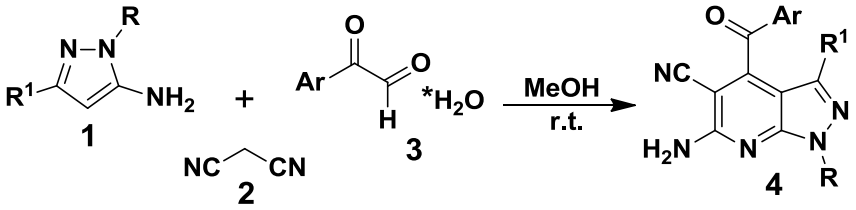
N-Heterocycles are a special type of organic compounds due to a wide spectrum of their biological activity. In particular, pyrazolopyridine derivatives often act as hypoglycemic, antiinflammatory, antipyretic, analgesic and hypotensive agents [1,2]. Therefore, the development of efficient methods for the synthesis of such compounds is the actual goal.

A series of novel pyrazolo[3,4-*b*]pyridine derivatives (**4**) were synthesized via a three-component condensation of α-aminopyrazoles (**1**), malononitrile (**2**), and arylglyoxales(**3**) in methanol at room temperature (Scheme). The formation of pyridine cycle was observed both in the case of N-substituted and N-unsubstituted aminopyrazoles.



R = H, Ph; R^1 = Me, 4-$CH_3OC_6H_4$;
Ar = : 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-IC_6H_4

The structure of the compounds (**4**) has been found by spectral data (^{1}H NMR, ^{13}C NMR spectra and mass-spectra).

[1] A. Straub, J.-P. Stasch, C. Alonso-Alija, J. Benet- Buchholz, B. Ducke, A. Feurer, C. Furstner. NO-Independent stimulators of soluble guanylate cyclase // Bioorg. Med. Chem. Lett. – 2001. – V. 11, № 6. – P. 781-784.
[2] W. Yanfang, Y. Limin, W. Xinsheng, Z. Heming, Y. Yanyan, CN Pat. Appl. 101955480; Chem. Abstr., 154, 207602 (2011).

P-72

Polymorphic Forms of 5,14-Dihydrodibenzo[b,i][1,4,8,11]tetraaza[14]annulene in Thin Films

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5,14-Dihydrodibenzo[b,i][1,4,8,11]tetraaza[14]annulene (TAA) and its various derivatives including metal complexes are organic semiconductors with a high thermal and chemical stability suitable for thin film technology processing. These promising materials are widely used in optical and electronic devices, e.g. field effect transistors, gas sensors, recordable laser optical disk, spin electronics devices [1,2]. The interest in electronic applications of organic semiconductors, in particular TAA, stimulates efforts to understand and model the charge transport in this class of materials and to determine the limits of their utility. In the case of small-molecule organic semiconductors, as TAA, the charge transport is closely related to their crystal-packing and, therefore, depends on polymorphic transformations. The molecular packing of organic thin films can be controlled by the substrate type and temperature, as well as thickness of films.

We have performed the X-ray study of TAA films vacuum deposited on different dielectric substrates; the thickness varied from several tens to several hundreds of nanometers. At the initial stage of deposition mainly one polymorphic form is observed (space group P21/c). After the thickness of films exceeds 100 nm both known polymorphic forms of TAA registered in the Cambridge Crystallographic Data Centre (space group P21/c and space group P21/a) are detected. Also, highly ordered textures are observed for TAA films of various thicknesses. Physical and chemical mechanisms of the formation of above thin film structures are discussed.

1. В. Д. Орлов, В. Г. Удовицкий Свойства и применение веществ и материалов на основе дибензотетрааза[14]аннулена // Физическая инженерия поверхности.- 2014.-№3.-С.372-385.
2. Q. H. Wu, P. Zhao, Y. Su et all. Spin transport of dibenzotetraaza[14]annulene complexes with first row transition metals // RSC Advances, Issue 65, 2015, 5, 52938-52944.

Functionalization of 4,7-Dihydroazolo[1,5-*A*]pyrimidines

P-73

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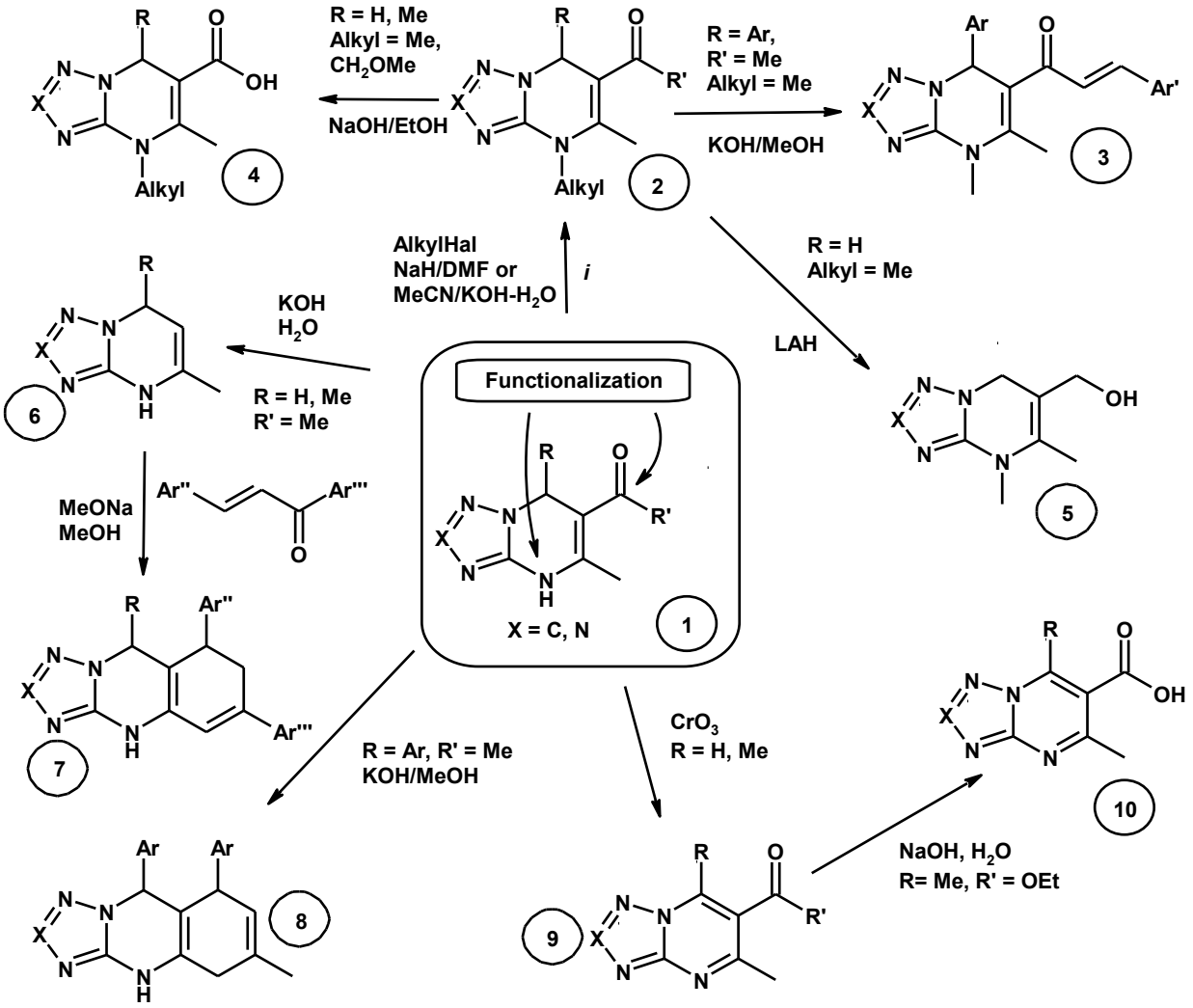
7-Aryl-4,7-dihydroazolo[1,5-*a*]pyrimidines, including 6-EWG-substituted, are popular objects for investigation. Nevertheless, their 7-alkyl and 7-unsubstituted analogs, despite of their usability as building-blocks, are poorly known. Here we demonstrate the synthesis and applicability of several compounds of mentioned type.



The starting compounds type **1** give 4-alkylderivatives **2**, which are the key intermediates to cinnamoyl derivatives **3**, acids **4** and alcohols **5**. Deacylation of compounds **1** leads to building blocks **6**, which are promising 1,3-C,N-binucleophile reagents. In contrast, deacylation of 7-arylanalogs of **1** results in cascade process of the compound **8** formation. Aromatic acids type **10** may be synthesized by oxidation of compounds **1** to azolo[1,5-*a*]pyrimidines **9** with subsequent hydrolysis. All the worked-up procedures may be used in large-scale processes.

P-74

Bis(2,5-diphenylfuryl)-R-methanes

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[c]State Scientific Institution "Institute for Single Crystals" of NAS of Ukraine
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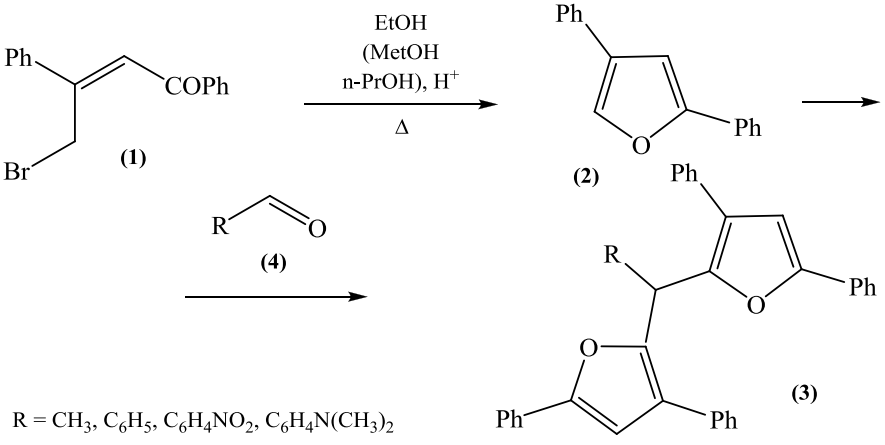
Furan relates to a number of electron-abundant heterocycles, and it easily reacts with electrophilic agents. However, due to its acidophobia, processes catalyzed with acids are running regularly by resin formation. In the same time, there is a number of methods of synthesizing the furan range compounds, where the acid environment appears in the process itself duration, and so it favors the process. An example is formation of 2,5-diarylfurans based on 4-brom-1,3-diarylbutene-2-ones-1 (γ-Br-β-dypnones).

γ-Br-β-dypnones are multifunctional and pretty reaction-capable compounds. This lets synthesize on their basis different mono- and bis-heterocyclic compounds. Exploring the γ-brom-β-dypnone (**1**), we paid attention at that while it is boiled within ethanol by the enzymatic technology with adding catalytic quantity of hydrochloric acid, we observe the main product 2,4-diphenylfuran (**2**) along with insignificant quantity of a new compound (**3)**, whose outcome was increasing as the boiling duration was being prolonged. It was successfully extracted and identified by NMR ^{1}H spectrum (doublet and quartet of protons of CH_3 and CH groups, characteristic signals of a diphenylfuryl fragment doubled by intensity) as 1,1-bis(3,5-diphenyl-furyl-2)ethane (**3**) – a product of interaction of compound (**2)** and acetaldehyde (**4**) (R = CH_3), which is permanent impurity of enzymatic alcohol. That was confirmed also by direct experiments: by interaction of the compound (**1)** or (**2)** with the reactive (**4)** within alcohols (methanol, ethanol, n-propanol) by acid catalysis; outcomes of ethane (**3)** reached those quantitative ones. Finally, structure of 1,1-bis(3,5-diphenylfuryl-2)ethane (**3**) was confirmed by X-ray crystallography. This reaction was carried out by involving a series of other aldehydes (see the scheme). In all cases, the outcome appeared close to quantitative one.



P-75

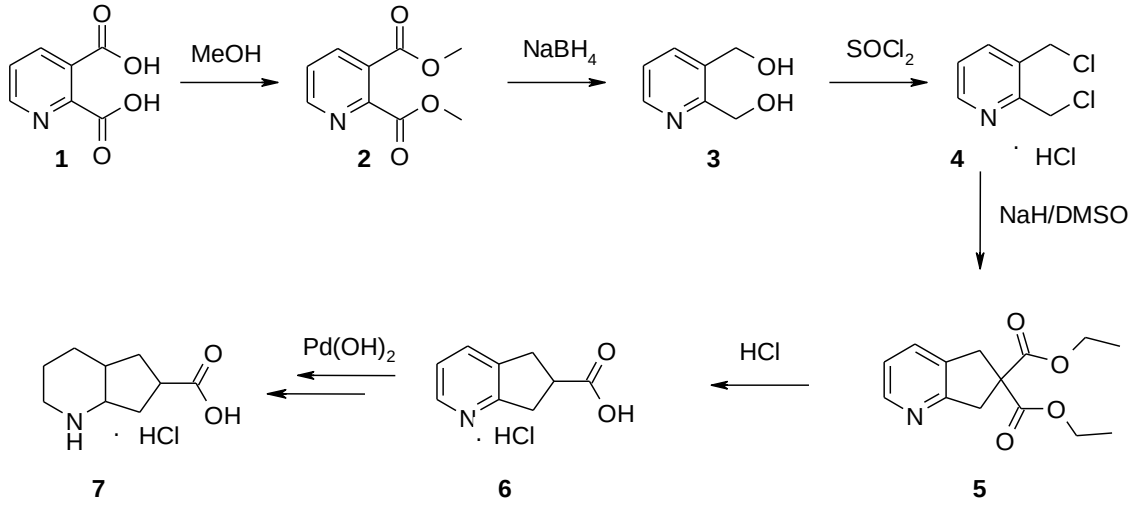
Conformationally Restricted GABA Analogues Based on Octahydro-1*H*-cyclopenta[b]pyridine Scaffold

Kostyantyn P. Melnykov,[1,2] Oleksandr O. Grygorenko,[2] Sergey V. Ryabukhin,[2] Oleksiy S. Artamonov,[1] Dmitriy M. Volochnyuk[1]

[1]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine*
[2]*National Taras Shevchenko University of Kyiv*

Conformationally restricted molecules are promising building blocks for the synthesis of efficient ligands for biological targets, catalysts (including enantioselective), and compounds of interest for the coordination, supramolecular, and other fields of chemistry. Molecular rigidity is inherent in a significant number of drugs and natural compounds. Therefore, design of compound libraries with potential biological activity based on bicyclic systems with pre-defined positions of the functional groups is interesting and relevant task of organic synthesis.

In this work, bifunctional derivatives of octahydro-1H-cyclopenta[*b*]pyridine substituted at position 6 were chosen as the targets for synthesis. In the scheme shown below, an approach to the synthesis of compound **7** – conformationally restricted analogue of γ-aminobutyric acid (GABA) – is described.



The compound **7** was synthesized in 6 steps and 24% overall yield. The compound prepared has two functional groups which can be modified selectively, this in turn can significantly increase the diversity of the potential compound libraries.

P-76

Synthesis of Trans-Disubstituted Pyrazolylcyclopropane Building Blocks

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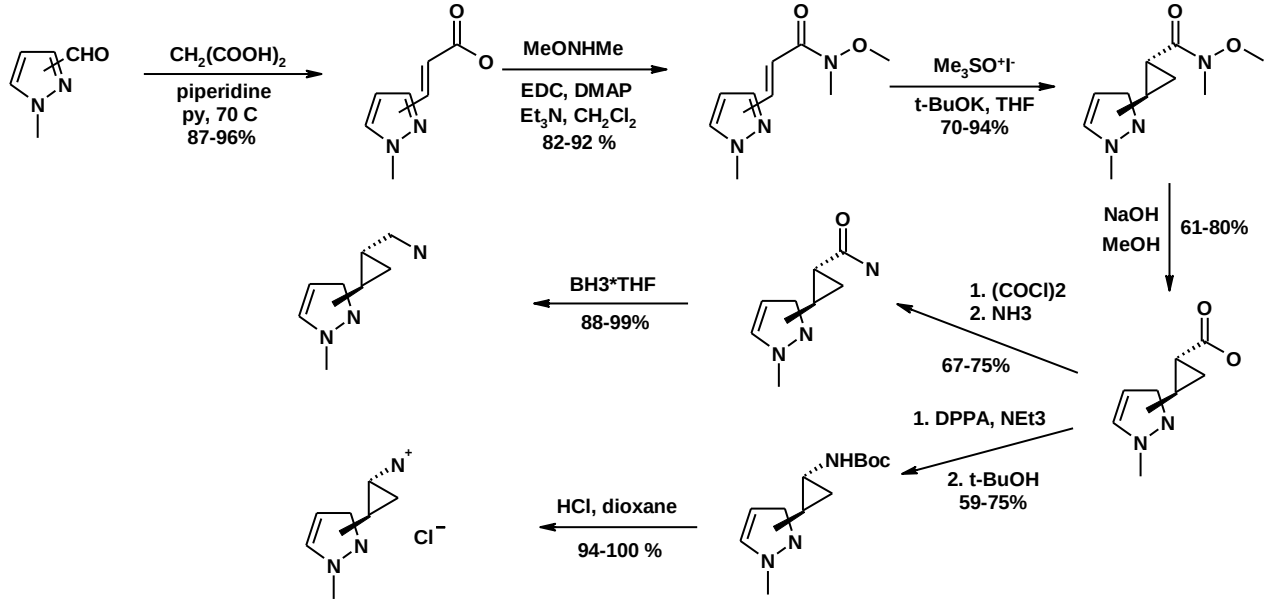
[1]National Taras Shevchenko University of Kyiv
[2]Institute of Organic Chemistry, National Academy of Sciences of Ukraine

Development of novel “good chemotypes” for drug discovery is a challenging task for organic chemists. Hydrophilic, sp^3-enriched, conformationally restricted building blocks of low molecular weight are considered as advantageous to address this challenge effectively. Small alicyclic scaffolds e. g. cyclopro¬panes can be used for design of such molecules.

Diastereoselective synthesis of trans-disubstituted pyrazolylcyclopropane building blocks (i. e. carboxylic acids and amines) is described starting from easily available pyrazole carbaldehydes. The key step of the synthesis was Corey–Chaikowsky cyclopropanation of the corresponding α,β-unsaturated Weinreb amides. The title compounds were prepared in 4 or 6 steps and 32–60% and 17–40% overall yields, respectively, on up to 50 g scale. The building blocks obtained are good starting points for the design of lead-like libraries; they themselves can be considered as isosteric analogues of CNS-active drug tranylcyclopropamine. It was showed the proposed approach to the synthesis of the target compounds on the scheme below:



Besides, we performed search for optimal reaction conditions by varying base, reagent ratio, and temperature. We have found that using t–BuOK in THF, as well as increasing temperature of the reaction to 40 °C improved the yield of the product significantly, so that the corresponding cyclopropanes were obtained from amides as single diastereomers (70–94%). The trans relative configuration for the compounds was confirmed using NOESY experiment.

Regio- and Stereoselective Aminomethylation of a Resorcin[6]arene

P-77

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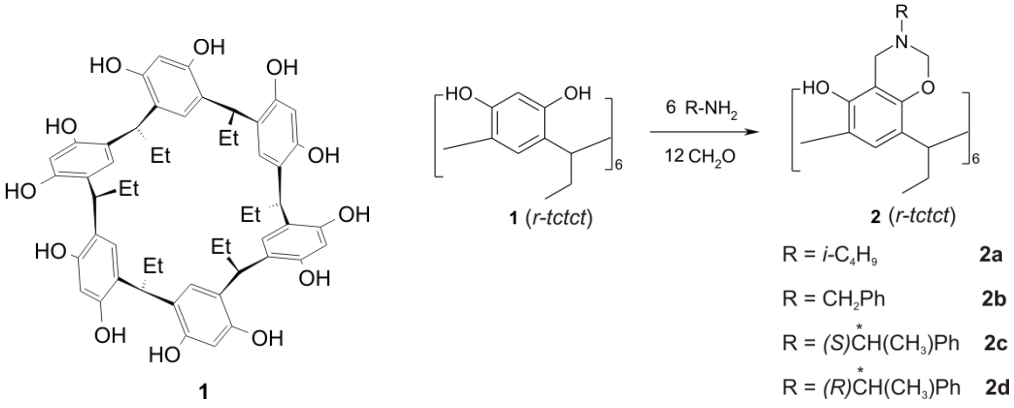
[1]*National Taras Shevchenko University of Kyiv*
[2]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine*

Resorcin[6]arenes are promising building blocks for rational design of widened container molecules, ion receptors, self-assembling molecular capsules and hollow crystal structures. Selective functionalization of resorcin[6]arenes is an effective method of modification of the structure and receptor properties of the obtained macrocyclic entities.

The present research was undertaken in order to develop a method for a regioselective aminomethylation of resorcin[6]arene **1**. Mannich-type condensation of *r-tctct* resorcin[6]arene **1** with primary amines and formaldehyde in ethanol gives hexaoxazines **2** in a 40% yield. Compounds **2** precipitate from the reaction mixtures and can be easily purified by simple recrystallization. Unlike the parent dodecaol **1**, hexaoxazines **2** are very soluble in nonpolar solvents, such as chloroform, dichloromethane, benzene, toluene, and insoluble in polar DMSO and methanol.



NMR experiments reveal that reaction of **1** with achiral primary amines results in S6-symmetrical hexadihydro-1,3-oxazine derivatives **2a** and **2b**, which are mesoforms. While condensation with individual enantiomers of α-phenylethylamine leads to C3-symmetrical enantiomeric hexaoxazines **2c** and **2d** with clock- and counterclockwise orientation of dihydro-1,3-oxazine cycles. An 'asymmetric unit' of **2c** and **2d** contains two diastereomeric fragments giving double set of signals for the protons at the 5-positions of the resorcinol rings and N-acetal methylene protons of the dihydro-1,3-oxazine rings in ^{1}H NMR spectrum.

Molecular mechanics calculations suggested that the *r-tctct* wreath-like conformation of molecule **2** is likely to be stabilized by six intramolecular OH---O hydrogen bonds. Accordingly, the protons of the OH groups of compounds **2** emerge in ^{1}H NMR spectra as slightly broadened singlets whose shape and position do not considerably depend on the concentration.

Described procedure can be used for synthesis of wreath-like *r-tctct* resorcin[6]arenes bearing six functional groups attached to the 5-positions or (and) to the oxygen atoms of the resorcinol rings.

P-78

β-Enaminoketones and Arylglyoxals in Synthesis of Azaheterocycles

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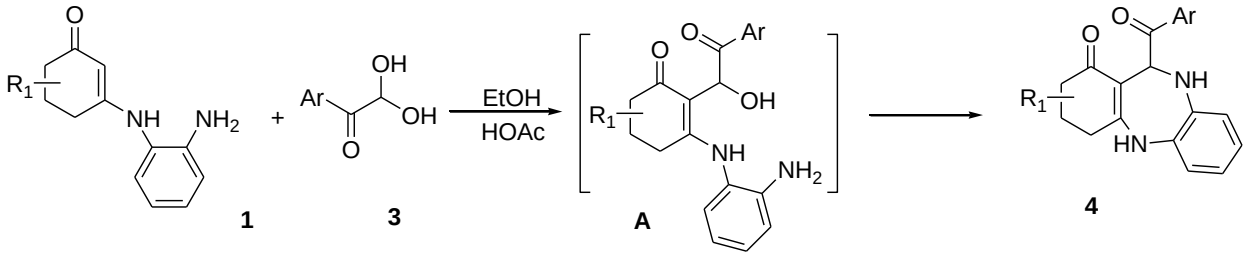
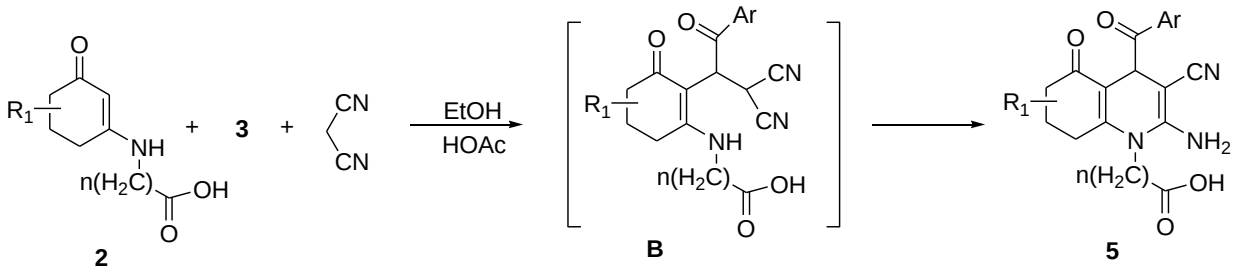
Recently, we and other researchers developed a number of domino reactions involving hydrates of arylglyoxals, which allow easy access to functionalyzed ring structures and are interesting in organic and medicinal chemistry [1]. Approaches to the synthesis of dibenzo[b,e][1,4]diazepin-1-ones **4** and polyfunctionalyzed tetrahydro-quinolines **5** were suggested in this work. It was shown that the reactions of N-arylenamines **1** (R_1 = H or R_1 = Me) with hydrates of arylglyoxals **3** in the system of EtOH/HOAc lead to endo-tetragonal cyclization of the intermediate hydroxyketone **A** and products **4** are formed. Substituting N-arylenamines with analogs of N-aminoacids (enaminoketone **2**) and using malonodinitrile in three-component condensations allows to obtain quinolines **5**.





The influence of the substitute in the aryl nucleus on the reaction rate and yield was investigated. We carried out the functionalization of diazepines **4** (acylation, alkylation, nitrosation) via the N-10 atom. It is shown that compounds **4** are stable in basic conditions, but can easily be transformed into 2-arylquinoxalines by heating in the presence of strong acids.

Compounds **4**, **5** were identified by NMR (1H, 13C), IR, mass-spectroscopy and elemental analysis. The structure of one of the substances **4** was confirmed by X-ray diffraction data.

1. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* 2013, 113, 2958.

Author Index

O-27

Dynamical flexibility and dynamical aromaticity of some six-membered nitrogen containing heterocycles

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Benzene and its highly aromatic heterocyclic analogues are commonly considered to be strongly conformationally rigid. However, the assumption of the strict planarity of such molecules contradicts some experimental observations and theoretical investigations. It was recently found that the energy of out-of-plane deformation of aromatic molecules is comparable of the energy of their thermal motion at the room temperature [1]. In the present work, the effect of thermal motion on conformational flexibility and aromaticity of benzene, pyrimidine, and 1,2,4-triazine was examined using Car-Parrinello molecular dynamics simulation.

The important feature of this method is considering of the molecule as a totality of its non-equilibrium states that makes a remarkable difference from classical quantum chemical methods that examine equilibrium states. It was found that all mentioned aromatic molecules are substantially non-planar at the room temperature (percentage of planar configurations is less than 30%), and the benzene molecule is the less planar (>7%). The average puckering degree is 0.13 – 0.16, and the main conformation of all those molecules is boat and twist boat [2,3].

The aromaticity of benzene and azines at room temperature also strongly differs from their aromaticity at equilibrium state. Thermal motion reduces aromaticity on 15-28%, and substantial portion of configurations can be treated as completely non-aromatic. The Bird aromaticity index shows decreasing of dynamical aromaticity from benzene to 1,2,4-triazine that corresponds to its change in the equilibrium geometry. The HOMA index reveals that dynamical aromaticity of benzene is the less among all molecules under study. It agrees with the conformational flexibility changes and can be explained by the interplay of enthalpy and entropy factors that change in different way during vibrational motion of molecules.

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DESIGN AND SYNTHESIS OF NEW [1,2,4]TRIAZOLOPYRIDINE DERIVATIVES

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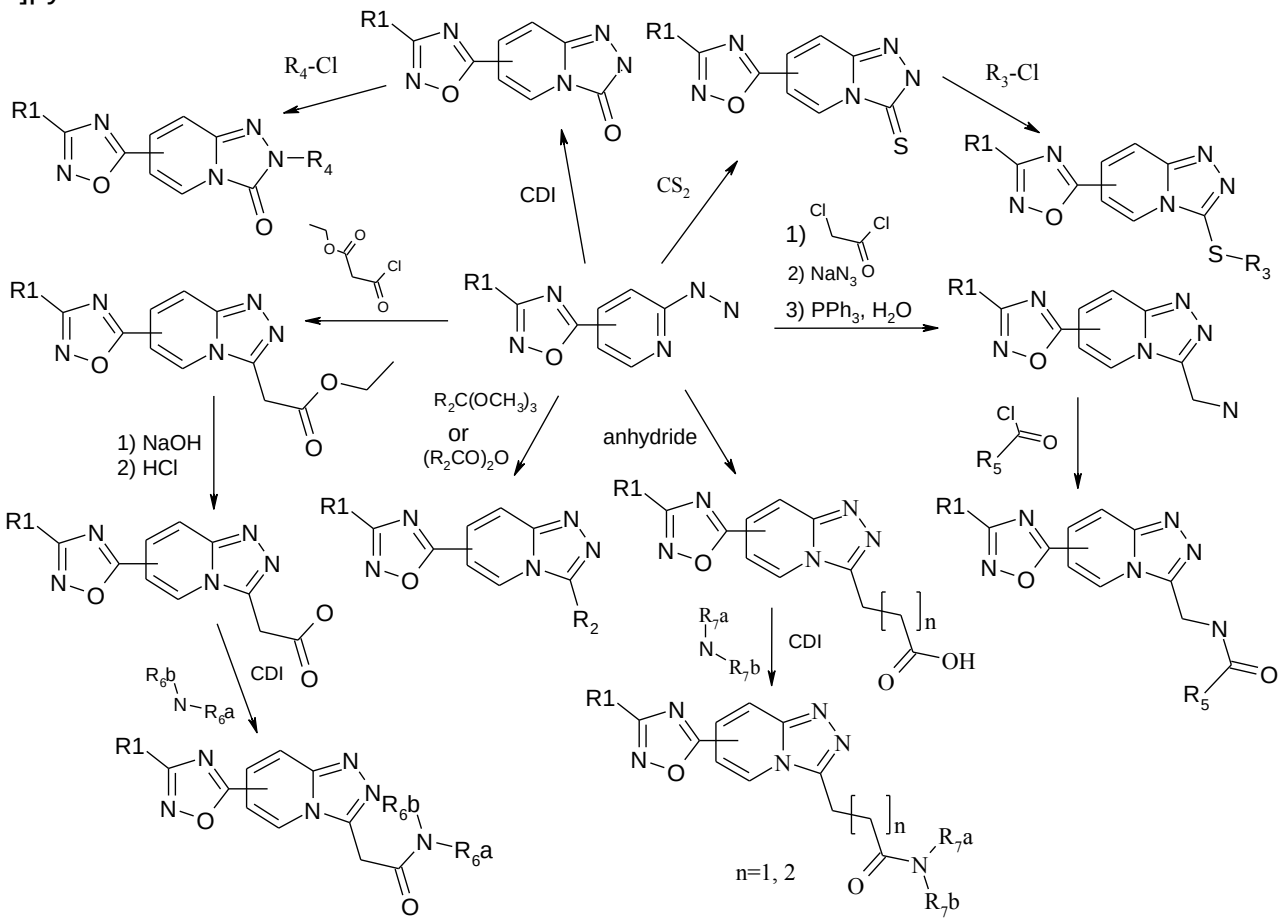
[1,2,4]Triazolopyridines are an important class of heterocycles with broad utility in the pharmaceutical industry. It is known that the compounds with triazolopyridine-fragment possess a wide range of pharmaceutical and biological activities. There are known antibacterial, antithrombotic, anti-inflammatory, anti-proliferative, herbicidal, antifungal, anticonvulsant, and anxiolytic activities. Trazodone (antidepressant drug) is the most well-known representative of compounds which contain 1,2,4-triazolo[4,3-a]pyridine core.



We have generated chemical space for new [1,2,4]triazolopyridine derivatives with a 1,2,4-oxadiazole cycle in different positions of pyridine core. The designed libraries are intended to be used for different targets to treat different diseases. Some derivatives were synthesized in order to validate the chemistry. They were described by several techniques including ^{1}H NMR, ^{13}C NMR, mass-spectrometry to confirm their structural characteristics. Further advances of this strategy in the synthesis of small molecules and medicinal chemistry programs will be reported.

ЗАПРОШУЄМО НА РОБОТУ

хіміків-органіків з досвідом роботи в лабораторіях, та випускників ВНЗ профільних спеціальностей

Науково-виробниче підприємство «Єнамін» (м. Київ) – це найбільша українська організація, що займається синтезом сполук для потреб медицини та агрохімії. За 20 років існування компанія «Єнамін» стала світовим лідером у своїй галузі, активно співпрацюючи з такими відомими фармацевтичними компаніями як Abbot, Bayer, GlaxoSmithKline, Merck, Pfizer та інші. В компанії сформований злагоджений колектив синтетиків, до складу якого входять більше 40 докторів і кандидатів наук та понад 200 кваліфікованих спеціалістів – професіоналів в галузі органічної та медичної хімії.

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