TOWARD THE IDEAL SYNTHESIS AND TRANSFORMATIVE THERAPIES: THE ROLE OF STEP ECONOMY AND FUNCTION ORIENTED SYNTHESIS

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Studies in our laboratory are focused on the design, synthesis and evaluation of molecules that exhibit unique modes of action for unmet medical needs, new tools for real time cellular and animal imaging, and novel drug delivery strategies based on “guanidinium rich molecular transporters”. These programs all draw on the introduction and development of new reactions and synthetic strategies that would deliver designed or natural targets in a “step economical” if not “ideal” fashion (Nature 2009, 197; JACS 2012, 11012). “Function oriented synthesis” is a key concept used in achieving these combined synthetic and therapeutic goals (PNAS 2011, 6721; Accts 2008, 40). As will be presented in this lecture, representative synthesis-driven projects are directed at as yet unachieved but hugely important goals including the eradication of HIV/AIDS, the development of first-in-class strategies to treat Alzheimer’s disease, and a general strategy to overcome resistant cancer, the major cause of chemotherapy failure (Lead references include: Nature Chemistry 2012, 705; Science 2008, 649; PNAS 2012, 13171; PNAS 2012, 13225; Nature Chemistry 2011, 615; J. Amer. Chem. Soc. 2011, 9228; Gynecologic Oncol. 2012, 118; Nature Medicine 2000, 1253).
TRANSITION METAL CATALYZED SYNTHESIS OF AROMATIC HETEROCYCLES

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Several basic methods of transition metal catalysed cyclization will be considered.

1. Pd-catalysed intramolecular addition of E-H bond to triple bond (E=element) and its intermolecular version with internal alkynes.
2. Wacker-type intramolecular addition of E-H bond to double bond.
3. Cyclisation via intramolecular Heck reactions.
4. Intramolecular and intermolecular carbon-heteroatom cross-coupling cyclizations catalysed by Pd(0).
5. Cross-coupling via C-H activation.
6. Catalysis by Cu(I), Au(I), Au(III), Hg(II).
NEW ADVANCES IN TRANSITION METAL-CATALYZED SYNTHESIS AND FUNCTIONALIZATION OF HETEROCYCLES

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We have developed a set of new transition metal-catalyzed methodologies for synthesis of furan, pyrrole, and $N$-fused heterocycles. These methods operate via several types of novel cycloisomerizations, including migratory cycloisomerizations, and recently discovered transannulation reaction. Lately, we expanded the scope of these transformations, as well as performed more detailed mechanistic studies, toward better understanding of this chemistry.

We have also developed several new two- and tri-component coupling reactions toward synthesis of indolizines, indolines, indoles, and imidazopyridines. Some of these methods have been applied to a synthesis of focused and mid-sized libraries of small molecules for wide biological screening.

The scope of these and some other transformations will be demonstrated and the mechanisms will be discussed.
SYNTHESIS OF PHARMACOLOGICALLY ACTIVE HETEROCYCLIC COMPOUNDS

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Natural product chemistry has always been an inspiration for the search of novel lead structures for drug development and very often heterocyclic compounds have been in the focus. Carbazole alkaloids represent a rich source of novel bioactive compounds. Using a palladium-catalyzed oxidative cyclization, we developed a versatile route to carbazoles. Recent applications were directed towards the total synthesis of biscarbazole alkaloids.

We have reported the isolation of the maradolipids from the nematode *C. elegans* and their synthesis. A silver(I)-mediated oxidative cyclization of homopropargylamines to pyrroles was developed in our laboratories and has been applied to the synthesis of the pyrrolo[2,1-α] isoquinoline alkaloid (±)-crispine A. Using a silver(I)-catalyzed cyclization process, the total synthesis of pentachloropseudilin was achieved. The pentahalogenated pseudilins represent a novel class of isoform-specific inhibitors of myosin ATPase.

**References:**

THE DISCOVERY AND OPTIMIZATION OF INHIBITORS OF HEPATITIS C VIRUS

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Hepatitis C virus (HCV) chronically infects approximately 200 million individuals worldwide and is an insidious infection that progresses slowly over the course of decades to inflict serious liver damage. Therapy has progressed from a combination of pegylated interferon-α and the nucleoside analogue ribavirin, neither of which are specific antiviral agents, to include the recently launched HCV NS3 protease inhibitors telaprevir and boceprevir. However, side effects with these drug regimens and rates of cure are less than optimal, providing for a significant unmet medical need for improved therapeutic options. This presentation will describe two complementary approaches to drug discovery: a structure-based approach to the design of HCV NS3 protease inhibitors that led to the identification of asunaprevir and the implementation of a chemical genetics strategy to identify mechanistically novel HCV inhibitors that culminated in the discovery of the NS5A inhibitor daclatasvir. The optimization of both asunaprevir and daclatasvir illustrate some interesting examples of the application of bioisosterism in drug design. These two compounds are currently being evaluated in clinical trials as combination therapy with and without the HCV NS55 polymerase inhibitor BMS-791325 and the early clinical results will be discussed.

References:
DESIGN AND SYNTHESIS OF RING-FUSED 2-PYRIDONES & APPLICATIONS IN CHEMICAL BIOLOGY

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Highly substituted ring-fused 2-pyridones are excellent scaffolds for the development of novel antibacterial agents, pilicides and curlicides, that target bacterial virulence by inhibiting the formation of bacterial pili and curli.\textsuperscript{1,2} The heterocyclic central fragment (1) (Fig. 1) can be synthesized via an enantioselective acyl-ketene imine cycloaddition.\textsuperscript{3} In this reaction two substituents are independently introduced to the scaffold (R\textsubscript{1} and R\textsubscript{2}, Fig. 1) and methods to introduce substituents in all other positions on the scaffold have been developed.\textsuperscript{4} In addition, we have also shown that this synthetic platform could be directed to synthesize compounds that inhibit the formation of functional amyloids in bacteria, curli.\textsuperscript{2,5}

\textbf{Figure 1.} By fine-tuning the substitution pattern on the thiazolo ring-fused 2-pyridone scaffold 1, compounds that inhibit the formation of bacterial fibers (pili and/or curli) are obtained.

References:
HETEROCYCLES AS NOVEL DNA BASES
BEYOND WATSON AND CRICK

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I am going to discuss the latest results related to the function and distribution of the new heterocyclic nucleobases 5-hydroxymethylcytosine (hmC), 5-formylcytosine (fC), and 5-carboxycytosine (caC).[1] These nucleobases seem to play an important role in epigenetic reprogramming of stem cells and some of these bases are also detected at relatively high levels in brain tissues. I will present new synthetic routes that enable preparation of these compounds and of the corresponding phosphoramidites using modern metal organic chemistry. Finally I will discuss how chemistry leads to new insights into the biology of stem cell development processes. In particular mass spectroscopy in combination with the availability of the isotopically labeled heterocycles allows investigation of the distribution of these novel compounds in various tissues and during stem cell development. The recently discovered base formylcytosine for example, is present at relatively high levels in stem cells and its distribution varies during development in a wave like fashion. I am going to describe the distribution of carboxylytosine in somatic tissues and in stem cells and will provide new quantitative data derived from a detailed mass spectrometric analysis. In order to elucidate the function of the nucleobases we devised a new isotope tracing experiment that enables us to unravel the biochemistry of the heterocycles with high precision and accuracy. I will discuss the synthesis of double [15N]-labeled hmC, fC and caC and the preparation of DNA containing these isotopologes.[1]

Scheme 1. Depiction of the epigenetic bases hmC, fC, and caC.

1. Schiesser, B. et al. ACIE 2012, DOI: 10.1002/anie.201202583
The cis-decahydroquinoline (cis-DHQ) system constitutes a key structural framework occurring in a variety of both natural and synthetic bioactive compounds. The most abundant source of cis-DHQ alkaloids is found in the skin secretions of neotropical dart poison frogs. Additionally, the eight cis-DHQ members of the lepadin family have been isolated from various marine natural sources. However, the DHQ motif is rare in plant sources, being restricted to Lycopodium and Nitraria species. Due to the wide range of biological activities displayed by many of these derivatives and their ability to act as a testing ground for new synthetic methods, DHQs have attracted considerable attention from organic chemists over the years. Nevertheless, the number of synthetic methodologies reported in the literature for the efficient enantio- and stereoselective construction of this azabicycle with substituents at the carbocyclic ring is still limited.

In recent work we have explored cyclocondensation reactions between chiral aminoalcohols and cyclohexanone- or 2-cyclohexenone derivatives having a propionate chain at C-2, stereoselectively leading to tricyclic lactams bearing up to four stereocenters of well-defined absolute configuration. The synthetic potential of these chiral tricyclic lactams as precursors for the preparation of cis-DHQ alkaloids will be discussed.

Acknowledgements
Financial support from the Ministry of Economy and Competitiveness, Spain (project CTQ2012-35250) and the DURSI, Generalitat de Catalunya (Grant 2009SGR-1111) is gratefully acknowledged.
IODINE AND COINAGE METAL CATALYZED HETEROCYCLE SYNTHESIS

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Substituted quinolines and isoquinolines are often found as structural framework in a large number of biologically active natural products and pharmaceuticals. Because of their importance, much attention has been paid to development of efficient methods for the synthesis of substituted quinolines and isoquinolines. We recently reported metal-catalyzed or non-metal-catalyzed synthesis of substituted dihydroisoquinolines, and an entirely new method for the synthesis of substituted isoquinolines through iodine-mediated or gold-catalyzed cyclization of 2-alkynyl benzyl azides. This method was applied to a short synthesis of norchelerythrine.

FROM METAL-FREE COUPLINGS TO RADICAL CYCLIZATION CASCADES: NEW METHODS FOR TARGET SYNTHESIS

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A nucleophilic ortho-propargylation of aryl sulfoxides exploits intermolecular delivery of the nucleophile to sulfur followed by an intramolecular relay to carbon.1 The operationally simple, metal-free coupling is general, regiospecific with regard to the propargyl nucleophile, and shows complete selectivity for products of ortho-propargylation over allenylation.

The rerouting of carbonyl reduction through less-conventional intermediates allows new selectivity and reactivity to be exploited. Upon treatment with SmI₂–H₂O, unsaturated lactones undergo cascade processes that allow ‘one-pot’ access to biologically-significant molecular scaffolds.2

References:
INVITED LECTURE
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Investigation of complex catalytic systems requires rigorous real-time and global examination of the dynamics of the constantly changing environment of a catalytic reaction, such as critically important events, such as activation and deactivation of a catalyst, unproductive off-cycle pathways, and changes in the nature of the dominant species. A key lesson that emerged from our work during the last decade is highly dynamic mixtures of complexes that exist in rapid equilibria with each other can actually serve as exquisitely selective catalysts.

A single, well-defined catalyst is not always required and may, in fact, may be counterproductive when compatibility with many functional groups and conditions is the goal.

This approach will be exemplified using several case studies of the catalytic reactions of alkynes. Alkynes are among the most energetic hydrocarbons, and transition metals enable selective and controlled manipulation of the triple bond, opening the door to the wealth of reliable reactivity: transformations of alkynes into heterocycles and into a variety of molecules with new carbon–heteroatom bonds. The combination of catalytic alkyne functionalization followed by manipulation of the resulting products allows one to proceed from a system with high energy content to a system of lower energy in a stepwise fashion, thereby enabling controlled introduction of new elements of diversity in every step. Various architectures, including a range of bioactive heterocycles, prepared using these methods are finding increased use in organic synthesis, nano- and biotechnology, and materials science.
INDIRECT C–H FUNCTIONALIZATION OF ELECTRON-RICH HETEROCYCLES

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Development of methodologies for functionalization of heterocycles is of highest importance both in medicinal and in process chemistry, because heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances.

Our approach is based on functionalization of aromatic and heterocyclic C–H bonds by the in situ formation of unsymmetrical heteroaryl-\(\lambda^3\)-iodanes, followed by their regioselective fragmentation in the presence of transition metal (Pd, Cu) catalyst.

The developed methodology effects transformation of electron-rich heterocyclic C–H bonds into C–O bonds and C–N bonds in an operationally simple one-pot sequential multistep process.

References:
LINEAR ENCODING OF FUNCTIONAL GROUPS: THEORETICAL APPROACH AND APPLICATION IN BIOMASS CONVERSION

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The discovery of new chemical routes to poly-substituted heterocyclic compounds remains the area of wide research interest due to a number of natural products, pharmaceutical substances, and material science building blocks that utilize unique physical, chemical and biological properties of heterocyclic systems. Formation of heterocyclic core followed by incorporation of required functional groups using a series of substitution reactions is nowadays typical synthetic route to access poly-substituted heterocycles (Scheme 1).

In our group we have predicted new intramolecular cycloaddition reactions using a special computational approach with heteroatom scan along the linear structure of the initial reagent (Scheme 1).[1,2] A family of novel [4+2] cycloaddition reactions was studied to carry out efficient preparation of poly-substituted heterocyclic compounds in a single step from linear precursors.[1,2]

Practical application of the developed approach was demonstrated on the industrially important process of biomass conversion to platform-chemicals. A novel conversion system was developed in ionic liquids to accomplish transformation of carbohydrates into 5-hydroxymethylfurfural (5-HMF).[3] The involvement of “linear-encoded” intermediate was revealed in the reaction.

References:
(b) V. P. Ananikov, Chem. Rev., 2011, 111, 418.
CATALYTIC OLEFINATION REACTION. NEW APPROACH TO FLUOROORGANICS

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The importance of fluoroorganic substances is well-known, for instance, about 25% of currently used drugs contain at least one fluorine atom. A novel synthesis of alkenes has been discovered recently by our research group. It was found that N-unsubstituted hydrazones of carbonyl compounds can be smoothly transformed into various substituted alkenes by treatment with polyhaloalkanes in the presence of catalytic amounts of CuCl. This reaction was found to be a new general approach for the construction of carbon-carbon double bonds. A number of convenient and simple methods for the synthesis of various alkenes including fluorinated ones were developed. Fluorinated β-halostyrenes easily synthesized by this method are of special interest because of the possibility of their modification by nucleophilic vinylic substitution providing simple and general pathway to useful fluorinated building blocks. The latter compounds were successfully used in the synthesis of various carbo- and heterocyclic compounds.
NEW METHODS FOR CARBON-HYDROGEN BOND FUNCTIONALIZATION

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Transition-metal-catalyzed functionalization of C-H bonds is an efficient method for the formation of carbon-carbon bonds. While significant advances have been reported in the last decade, many challenges still remain. First, the generality of the methods usually is not high. Second, conversion of unactivated (not benzylic or alpha to heteroatom) sp3 C-H bonds to C-C bonds is rare. Most of such examples involve functionalization of t-butyl groups that is inherently easy due to lack of β-hydride elimination from metalated intermediates. Third, expensive palladium, rhodium, and ruthenium catalysts are routinely used for C-H bond conversion to C-C bonds. Use of less exotic metals such as copper, iron, or manganese is rare. This talk will describe our attempts to provide solutions to the problems stated above.
TRIFLUOROMETHYLATIONS WITH FLUOROFORM-DERIVED CUCF$_3$

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Selectively fluorinated organic compounds often exhibit biological activity and useful processing properties. Trifluoromethylated building blocks and intermediates are in particularly high demand for the synthesis of agrochemicals, pharmaceuticals, and specialty materials. Readily available fluoroform, CHF$_3$, a side-product of Teflon manufacturing, is by far the best CF$_3$ source for various trifluoromethylation reactions of organic compounds. However, the previously developed deprotonation methodology to activate fluoroform (pK$_a$ = 27 in H$_2$O) is cost-prohibitive on a large scale because of the necessity to use low temperatures in order to avoid the facile α-elimination leading to difluorocarbene.

The first reaction of direct cupration of fluoroform was discovered only recently in our laboratories. We have found that CuCl reacts with 2 equiv of $t$-BuOM (M = K, Na) in DMF to produce novel dialkoxyocuprates [M(DMF)$_n$]$^+ \left[ \text{Cu(OBu-}t\text{-)}_2\right]^{-}$ (X-ray) that readily metalate CHF$_3$ at room temperature and atmospheric pressure. The resultant CuCF$_3$ (>90% yield) can be used for highly efficient, low-cost trifluoromethylation reactions of a variety of organic and inorganic substrates, including metal complexes, aryl and heteroaryl halides, boronic acids, and α-haloketones.

References:
TRPV1 ANTAGONISTS FOR TREATMENT OF PAIN: TEMPERATURE EFFECTS, NEW OPPORTUNITIES AND RECENT PROGRESS

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TRPV1 channel is involved in the development and maintenance of pain and participates in the regulation of core body temperature. Clinical findings from first TRPV1 antagonist studies raised concerns as to whether the hyperthermia associated with TRPV1 antagonism could be overcome and led to studies to identify antagonists devoid of temperature effects. As a result, subseries of heteroaryl urea compounds were identified, which did not exhibit effects on core body temperature in preclinical models of thermoregulation.
The formation of new blood vessels sprouting from existing host capillaries (angiogenesis) is a necessary process for tumors to grow beyond a certain critical size. Specific inhibition of this tumor-induced angiogenesis prevents growth of many types of solid tumors and provides a novel approach for cancer treatment. Angiogenesis factors are key growth factors in tumor angiogenesis. Hypoxia-inducible factors (HIF) are heterodimeric ($\alpha/\beta$) transcriptional factors and major physiological stimuli for expression of angiogenesis factors. The levels of HIF-1$\alpha$ are low under normal oxygen conditions (normoxia) but increase in response to hypoxia. HIF-1$\alpha$ has been found in a wide variety of human primary tumors compared with corresponding normal tissue, thus considered to be a potential target for antineoplastic therapy.

We developed carborane-containing phenoxyacetanilides (1) as potent inhibitors of HIF-1$\alpha$ activation under hypoxic conditions.\textsuperscript{1} Furthermore we succeeded in the synthesis of multifunctional molecular probes of HIF-1 inhibitors (2) for combining photoaffinity labeling and click reaction moieties in the molecules in order to clarify the action mechanism of 1 against HIF inhibition. Using the probe molecules (2), we identified that heat shock protein (HSP) 60 is the target protein of 1, indicating that HSP60 might be a new molecular target for HIF inhibition.\textsuperscript{2}

![Figure 1. Structures of carborane-containing HIF-1$\alpha$ inhibitors and their probes](image)

References:


BIFUNCTIONAL AND DUAL CATALYSIS IN CHEMICAL SYNTHESIS

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The use of more than one catalytic functionality either in the same molecule (bifunctional catalyst) or as two separate catalytically active species (dual or synergistic catalysis) is a very common strategy in organocatalytic reactions. In this talk, recent examples from our research where the dual or bifunctional catalytic strategies have proved fruitful will be discussed.1-2

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References:
SYNTHETIC APPROACHES TO NOVEL ACYCLIC NUCLEOSIDE PHOSPHONATES

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Acyclic nucleoside phosphonates (ANPs) represent a recognized class of antiviral and anticancer agents. ANPs have originated from the successful collaboration between Antonín Holý (Institute of Organic Chemistry and Biochemistry, Prague, Czech Republic) and Erik De Clercq (Rega Institute for Medical Research, K.U. Leuven, Belgium). ANPs have gradually gained recognition in the pharmaceutical world, as 3 of them (cidofovir, adefovir, and tenofovir) have been approved by regulatory agencies worldwide for clinical use. Tenofovir disoproxil fumarate (TDF) has also been approved for the treatment of HIV infections in fixed-dose combinations with other anti-HIV agents (Truvada®, Atripla®, Complera®/Eviplera®, Stribild®). However, biological activity of ANPs is not restricted solely to the antiviral effects. Novel types of ANPs were designed and synthesized in our lab (e.g. compounds 1-4, Figure 1.) and some of them were shown to display important biological properties. An overview of the most recent achievements in the field of these nucleotide analogues will be outlined.

**Figure 1.** Examples of novel ANPs modified at the aliphatic moiety.

![Figure 1](attachment:figure1.png)

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ELECTROPHILIC ACTIVATION OF UNSATURATED SYSTEMS: APPLICATIONS TO THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Different electrophilic transformations are now recognized as powerful synthetic tools to accomplish the synthesis of useful heterocyclic scaffolds in an efficient and selective manner. Thus, this presentation will address different strategies that have been developed by our group to assist this purpose.

Thus, besides some examples touching early work on iodine-triggered heterocyclization reactions, recent approaches to building-block elaboration based on gold-catalyzed chemistry will be discussed. The presentation will be arranged according to the nature of the intermediate responsible for the key cyclization step. Eventually, differentiate procedures for the elaboration of carbo- and heterocyclic structures from unsaturated substrates upon reaction with nucleophiles are obtained.[1-4] Straightforward addition processes and, alternatively, “domino” reactions, which give rise to the formation of more elaborated products from simple precursors, are described.

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References:
HOW TO MAKE COMPLEX MOLECULES FROM SIMPLE STARTING MATERIAL: THE PALLADIUM, A POWERFUL TOOL

Jean Suffert

In addition to molecular complexity, the challenge of the chemist today is also the quest for efficiency of the synthetic route and maximization of structural complexity. Our laboratory investigations focus for several years on the study of an unprecedented cascade reaction involving a rare 4-exo-dig cyclocarbopalladation followed by a terminated cross-coupling with an organometallic reagent. A 6π- or 8π-electrocyclization can occur leading to new tricyclic structures. The seminar will show that we can offer an easy access to complex polycyclic molecules resulting from readily available simple starting materials. Eventually, it will be possible to propose the elaboration of a large collection of unprecedented structurally novel molecules based on recent promising results. Below are represented several complex structures that has been prepared through the powerful 4-exo-dig cyclocarbopalladation. Many other extension of this method have not been so far explored and can afford a multitude of new and original scaffolds.
SYNTHESIS OF HETEROCYCLES FUSED WITH ENEDIYNE SYSTEMS

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Heterocycles possessing an enediyne system are promising objects as analogs of naturally occurred enediyne antibiotics, displayed strong antineoplastic activity. Recently we proposed a new approach towards heterocycle-fused enediyne systems, based on the cyclization of ortho-functionalized buta-1,3-diynylarenes. In particular, 2-ethynyl-3-iodobenzofurans, -indoles, -benzothiophenes as direct precursors of enediyne systems fused to a heterocyclic core are easily accessed via electrophilic cyclization of ortho-functionalized buta-1,3-diynylarenes.

Proposed methodology enables obtaining the asymmetrically substituted enediyne systems with absolute regiocontrol which is very important for the further construction of macrocycles. For the synthesis of analogs of naturally occurring macrocyclic enediyynes two approaches were developed. The first one includes Richter-type cyclization of ortho-(buta-1,3-diynyl)aryltriazenes which affords cinnoline core and the Nozaki-Hiyama-Kishi reaction for the crucial macrocyclization step. In the second approach the electrophilic cyclization followed by ring-closing metathesis were used for the first time as key steps in the synthesis of a macrocyclic dienediyne fused with benzothiophenes.


References:
2. Vinogradova, O; Sorokoumov, V; Balova, I. Tetrahedron Lett. 2009, 6358;
MICROWAVE-ASSISTED SYNTHESIS IN P-HETEROCYCLIC CHEMISTRY

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The microwave (MW) technique is a useful tool in synthetic organic chemistry. We wish to show the potential of MW irradiation in the synthesis of P-heterocyclic derivatives.1,2

MW irradiation makes possible reactions that are otherwise impossible on conventional heating. Such reaction is the direct esterification of cyclic phosphinic acids (1) by reaction with alcohols (1).

Further derivatizations, such as thioesterification and amidation may also be carried out under MW conditions.

It is also possible that a reaction becomes simply faster and more efficient on MW irradiation. This may be exemplified by the Diels–Alder reaction of 1,2-dihydrophosphinine oxides (3) with dialkyl acetylenedicarboxylates. In turn, the resulted phosphabicyclo[2.2.2]octadiene derivatives (4) may be useful in fragmentation-related phosphorylations of nucleophiles, such as phenols (2).

Other reactions, such as inverse Wittig-type reactions, Michael-additions, transesterifications, the Arbuzov reaction and P–C couplings will also be discussed.

The third group of MW-assisted transformations embraces cases, when MW irradiation substitutes catalysts, such as in the Kabachnik–Fields reaction, or in the alkylation of P–O-functionalized CH acid compounds.

References:
COMBINATION OF HYDRAZINE POLYANION STRATEGY AND RING- CLOSING METATHESIS IN THE SYNTHESIS OF HETEROCYCLES

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Many of hydrazine derivatives show remarkable biological activities and were shown to be effective for treatment of tuberculosis, Parkinson’s disease and hypertension [1]. Therefore, there is a need in development of new efficient synthetic ways to hydrazine moiety containing heterocycles.

In our current work the synthesis of cyclic hydrazine derivatives using polyanion strategy and subsequent ring-closing metathesis is described. At the first step the alkylation of hydrazine with alkenyl bromides was performed. Then, RCM furnished the formation of the desired 6- to 9-membered heterocyclic products [2].

References:
STEREOSELECTIVE SYNTHESIS OF BARMUMYCIN VIA A BORON ENOLATE IRELAND-CLAISEN REARRANGEMENT

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Barmumycin was isolated in 2010¹ from an extract of the marine actinomycete Streptomyces sp. BOSC-022A and was found to be cytotoxic against various human tumor cell lines. Structurally Barmumycin contains one stereogenic center and an E-ethylidene substituent at 4-position of the proline fragment. Although a total synthesis of Barmumycin has been reported¹, efficient control of the olefin geometry has not been achieved.

Herein we disclose an efficient, stereoselective synthesis of (S,E) ethylidene proline derivative 2 via a boron enolate Ireland-Claisen rearrangement of 7-membered lactone 1, and the further elaboration of this building block into Barmumycin.

References:
FURAN RECYCLIZATIONS AS A ROUTE TO NITROGEN HETEROCYCLES

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2-Aryl- and 2-benzylsubstituted furans bearing nucleophilic function at the ortho-position of the phenyl ring can be easily synthesized from furfural which is produced from waste of forest and agricultural industries. An acid-induced recyclization of 2-(2-aminophenyl)- and 2-(2-aminobenzyl)furan was utilized for the synthesis of a differently substituted indoles and quinolines:

Variation of the nucleophilic moiety and the spacer between it and the furan ring allowed for preparation of a variety of other nitrogen heterocycles:

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TOTAL SYNTHESIS OF BARINGOLIN

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Baringolin is a thiopeptide\textsuperscript{1} of marine origin extracted from \textit{Kocuria sp.} cultures which has been found to be active against Gram-positive bacteria. Although its structure had been previously suggested,\textsuperscript{2} it needed confirmation and also assignment of its stereochemistry. Our efforts have focused on the synthesis of suitable enantiopure fragments\textsuperscript{3} and the development of a new synthetic strategy to obtain baringolin in an efficient manner.

\begin{center}
\includegraphics[width=\textwidth]{baringolin.png}
\end{center}

\textbf{Baringolin}

References:


ASYMMETRIC CYCLOPROPA NATION OF
HETEROCYCLES

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While the asymmetric cyclopropanation of simple olefins like styrene has been well
developed, electron-rich heterocyclic substrates like N-protected pyrroles and furan
derivatives proved to be a challenging task.[1,2] Herein we report highly enantio- and
diastereoselective cyclopropanation reactions of aromatic, heterocyclic substrates
using diazoacetates toward multiple functionalized bicyclic compounds, which
proved to be versatile building blocks for natural product synthesis approaches,[2,3] as well as for the development of foldamer building blocks.[4,5]

References:
RECYCLIZATION OF EPOXYALANTOLACTONE (HET)ARYLETHYLAMINODERIVATIVES

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Natural sesquiterpene lactones which contain an exocyclic methylene group in the \( \beta \)-position of the lactone ring react readily with \( N \)-nucleophiles to give compounds having novel forms of biological activity when compared with the starting compounds [1]. When the reaction was carried out with 5\( \alpha \)-epoxyalantolactone (1) (a secondary metabolite of the plants of the genus *Inula L.*) and the (het) arylethylamines 2 we were able to show the formation of the novel heterocyclic system, namely the hydrogenated benzo[g]furo[4,3,2-cd]indolones 3.

Evidently the amines initially add to the activated double bond (Michael reaction) and then the dialkylamino group attacks the sterically most available carbon atom of the oxirane ring. The process occurs under mild conditions using an equimolar amount of the reagents which are held at room temperature in methanol. The reaction occurs stereospecifically to form only one spatial isomer. The structure of the compounds 3 obtained was proved using spectroscopic methods. The complete data for identifying the structure and the determination of the configuration of the new C-2a asymmetric center (analysis of the IR, \( ^1H \) and \( ^13C \) NMR spectra including COSY and NOESY experiments) together with the results of the X-ray structural analysis are discussed in this report.

References:
LOOKING AT NEW INHIBITORS OF VEGFR-2.

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Angiogenesis is the process of new blood vessels formation, creating new capillaries from existing vasculature. A dis-regulation of angiogenesis may be involved in the development and progression of various diseases such as tumor growth and metastasis.\textsuperscript{1} The vascular endothelial growth factor (VEGF) pathway provides several opportunities by which small molecules can act as inhibitors of endothelial proliferation and migration and thus as anticancer agents. Among VEGF receptor, VEGFR-2 or the kinase insert domain receptor (KDR) seems to play a key role in tumor angiogenesis. Molecular modeling based on Three-Dimensional Quantitative Structure-Activity Relationships (3-D QSAR),\textsuperscript{2} provides crucial information about the structure of potent inhibitors of VEGFR-2.\textsuperscript{3} A first study revealed that, with predicted IC\textsubscript{50} values reaching 5nM, thieno[3,2-d]pyrimidinones combined with urea and indole moieties or equivalent aromatic rings can afford promising VEGFR-2 inhibitors. Two synthetic strategies to access these compounds are presented and discussed.

SYNTHESIS, ACTIVITY AND INTERACTION OF NITRONE FUNCTIONALIZED PAH DERIVATIVES

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Polycyclic aromatic hydrocarbons (PAHs) are widely studied. Their carcinogenic properties are well known. In a sharp contrast to those effects the functionalized PAHs were recently identified as important candidates for cancer therapy.1 Mechanism of action is often simplified and studied at the DNA level. A lot of discussion has been held about groups being introduced to the PAHs structure. Novel approach to functionalized polycyclic aromatic hydrocarbons (PAHs) is presented. According to our experience in nitrone chemistry2 the synthetic design of new PAHs derivatives was achieved by a multicomponent reaction of compounds 1-3.

References:
HETEROCYCLIC BISARYL-METHANONES AS INHIBITORS OF FLT3 AND PDGFR KINASES

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FLT3 receptor tyrosine kinase is aberrantly active in many cases of acute myeloid leukemia (AML).[1] Recently, bis(1H-indol-2-yl) methanones[2] were found to inhibit FLT3 and PDGFR kinases. To optimize FLT3 activity and selectivity, modeling studies were implemented.[3] Novel derivatives of bis(1H-indol-2-yl)methanones or bisbenzofuranyl methanones with various substituents in the 5- or 6-position of an indole ring were synthesized and tested for inhibition of FLT3 und PDGFR autophosphorylation.

References:
RECENT TRENDS IN THE DESIGN, SYNTHESIS AND BIOLOGICAL EXPLORATION OF \(\beta\)-LACTAMS

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Since the discovery of penicillin, natural and synthetic \(\beta\)-lactams have aroused great interest not only as sources of effective antibacterial agents but also as specific inhibitors of proteases responsible for various non-bacterial pathological processes. Current presentation summarises recent achievements in this area dedicated to the design, synthesis and biological exploration of \(\beta\)-lactams, \(\beta\)-sultams, aza-\(\beta\)-lactams with anti-inflammatory, antiviral, anticancer and other activities. On molecular level these properties are based on the ability of mentioned heterocycles to form a stable covalent conjugate with a nucleophile in the active site of specific serine or cysteine proteases. Broad synthetic possibilities in the synthesis of variously substituted \(\beta\)-lactams in combination with the availability of X-ray crystallographic data for target enzymes and computational molecular modelling techniques create good prerequisites for new achievements in this field of medicinal chemistry.
POSTER PRESENTATIONS
Azide functional group is a valuable source of nitrogen atom in the synthesis of nitrogen-containing heterocycles. Azide nitrogen can enter into new ring through generation of either electrophilic nitrene or nucleophilic amino-group. Within the research project devoted to the chemistry of 2-(2-azidobenzyl)furans we elaborated the method of synthesis of the previously unknown ortho-aminodiarylfurylmethanes by the azide to amino-group reduction. Non-aqueous diazotization of the ortho-aminodiarylfurylmethanes gave rise to cinnoline derivatives bearing acylvinyl substituent in the 3rd position of the ring [1].

Acknowledgements: Financial support was provided by the Ministry of Education and Science of the Russian Federation (grant 3.3578.2011) and Russian Foundation for Basic Research (grant 13-03-01048 a).

References:
ENANTIOSEPARATION OF 1,4-DIHYDROPYRIDINE-6-MERCAPTOETHANOL

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The 1,4-dihydropyridine (1,4-DHP) nucleus serves as a scaffold for important cardiovascular drugs possessing stereoisomers. Therefore, it’s important to develop 1,4-DHP enantioseparation methods. Previously, we reported lipase-catalyzed hydrolysis of 6-methoxycarbonylmethylsulfanyl-1,4-dihydropyridines\(^1\). In this study, we describe the lipase Amano PS from *Burkholderia cepacia* catalyzed kinetically controlled acylation with vinyl acetate, which proceeds with formation of 6-acyloxyethylsulfanyl-1,4-DHP \(^2\) in 85% enantiomeric excess and 1,4-DHP-6-mercaptoethanol \(^3\) as unreacted substrate (98% ee).

Enzyme catalyzed acylation of 1,4-DHP-6-mercaptoethanol 1 by using vinyl acetate is a new method for enantioseparation of sulfur-containing 1,4-DHPs.

References:
Acknowledgements: study was supported by the State Research Programme „Biomedicine“
NATURAL SESQUITERPENE LACTONES FROM INULA BRITANNICA IN THE AMINATION REACTION

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In recent years, amino derivatives of natural sesquiterpene lactones are considered as prodrugs [1]. Lactones britanin (1) and inuchenolide C (2) from the plants *Inula britannica* L. contain exomethylene group in lactone ring and react easily with the N-nucleophilic reagents. We investigated the reaction of britanin (1) and various amines 3. It was found that the direction of the reaction depends on the structure of the reacting amine and process conditions (temperature, solvent). The aminoderivatives (4–6) were obtained with high yield in all cases. These substances are characterized by the presence and position of the acetyl group in the alicyclic fragment.

![Structural diagram](image)

The inuchenolide C amino derivatives (5) are formed easily by the reaction of suitable amine and compound 2.

References:
VARIATION IN LITHIATION SITES OF VARIOUS SUBSTITUTED PYRIDINES

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Smith’s group has developed several efficient lithiation procedures for preparation of various substituted aromatics and heteroaromatics that might be difficult to prepare by other means.1 As part of such studies we have shown that the lithiation and substitution of 2- and 4-substituted N-(pyridinylmethyl)amines provided easy access to various side-chain (methylene) substituted derivatives in high yields.2 Variations in the site of lithiation of N-acyl-3-(aminomethyl)pyridines with different N-substituents using different lithiating reagents has been investigated. Ring lithiation has been achieved by the use of t-BuLi at –78 °C followed by reaction with various electrophiles to give the corresponding 4-substituted products in high yields. On the other hand, the reaction was regioselective towards the side-chain when LDA was used as the lithium reagent at –20 to 0 °C. A mixture of ring and side-chain substitution products was obtained when n-BuLi was the lithium reagent.

Acknowledgements: We thank the Saudi Government for financial support.

References
ALLYLBORANES IN AN ENANTIOSELECTIVE SYNTHESIS OF FUROFURAN LIGNANS

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Allylboration now presents a classical method for new carbon-carbon bonds formation, and a wide number of allylboranes have been used in syntheses of natural compounds\textsuperscript{1}. Compounds containing two B-allylic fragments at the same time almost have not been studied but present promising starting materials for the tandem allylation of carbonyl compounds.

In this work we present an efficient method for the enanthioselective synthesis of furofuran lignans\textsuperscript{2} based on allylboration reaction of aromatic aldehydes\textsuperscript{3} with new chiral diboron derivatives prepared from hexa-1,5-diene and enantiomeric diisopinocampheyl-chloroboranes. The synthesis sequence involves allylboration, ozonolysis (construction of 3,7-dioxabicyclo[3.3.0]octane core) and dehydroxylation\textsuperscript{4}.

NOVEL 2-AMINO-PYRROLO[1,2-A]-PYRAZINE-1,3-DIONE DERIVATIVES

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Pyrrolo[1,2-a]pyrazine is known to be a fragment of biologically active compounds exhibiting proliferative, Vasopressin1b receptor antagonist, metabotropic glutamate receptors modulator and other activities [1,2]. For the last years alkaloid Peramine is of great interest too (Fig. 1) [3]. Agrochemists established that it is high effective natural insecticide produced by endophyte.

Fig. 1 - Alkaloid Peramine
We have managed to synthesize novel ethyl 2-amino-6,8-dimethyl-1,3-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-7-carboxylate and study its reactivity in the following reactions:

Scheme 1 – Reactivity of ethyl 2-amino-6,8-dimethyl-1,3-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-7-carboxylate

References:
N-(HALOPYRIDYL) DERIVATIVES OF ADAMANTANAMINES

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As adamantane-containing amines and their heterocyclic derivatives are of great interest as physiologically active compounds, we investigated the catalytic N-heteroarylation of some amines with adamantane fragment using dihalopyridines. We have found out that symmetrical 2,6- and 3,5-dihalopyridines successfully produce mono- and diamino derivatives depending on the stoichiometry of starting compounds. Generally, better results were obtained with 2,6-dichloropyridines in comparison with 2,6-dibromopyridines.

Unsymmetrical 2,3- and 2,5-dihalopyridines did not produce corresponding diamino derivatives even upon reacting with great excess of adamantanamines. However, the catalytic substitution of the halogen atom at α-carbon atom was in many cases successful, and again better results were achieved with less active dichloropyridines. The most interesting fact is the possibility to synthesize N,N-bis(5-halopyridin-2-yl) derivatives of adamantane-containing amines in yields up to 95% using 2,5-dihalopyridine taken in a 4-fold excess.

Acknowledgements: The work was supported by the RFBR grant 10-03-01108.
THE SYNTHESIS OF HETEROYCIC AMINOPHOSPHONIC AND AMINOPHOSPHINE DERIVATIVES

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α-Aminophosphonates and related derivatives are in the focus these days due to their versatile bioactivity. The most common approach to α-aminophosphonates is the condensation of an amine, oxo compound and dialkyl phosphate that is called the Kabachnik–Fields (or phospha-Mannich) reaction. Continuing our research in the field of microwave (MW)-assisted phospha-Mannich reactions,1,2 we have studied the condensation of 3-amino-6-methyl-2H-pyran-2-ones, paraformaldehyde and dialkyl phosphites or diphenylphosphine oxide. It was found that there is no need for any solvent and catalyst.3

\[
\text{Me} \quad \text{O} \quad \text{O} \quad \text{NH}_2 \quad R = \text{H, C(O)Me, C(O)Ph} \\
\text{Y} = \text{OMe, OEt, OBu, Ph} \\
\text{Y} = \text{OMe, OEt, OBu, Ph} \\
\text{Y} = \text{OMe, OEt, Ph} \\
\text{Y} = \text{OMe, OEt, Ph} \\
\text{Y} = \text{OMe, OEt, Ph} \\
\]

We also studied the double Kabachnik-Fields reaction of primary amines, paraformaldehyde and >P(O)H species, which provide bis(phosphonoalkyl)- or bis(phosphinoxido) products.4,5 After double deoxygenation of the bis(phosphinoxido) derivatives, we have synthesized P-metallocycles by complexation with Pt precursor. The ring metallocycles were tested as catalysts in the hydroformylation of styrene.

ENANTIOSELECTIVE HALOGENATION OF ENAMINE DERIVATIVES

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A highly stereoselective electrophilic α-bromination of enecarbamates allowing to access enantioenriched vicinal bromoamines has been developed.¹ Metal-free chiral phosphoric acids and chiral calcium phosphates both catalyze this transformation and either enantiomer can be formed in good yield with excellent diastereo- and enantioselectivity simply by switching the catalyst from the phosphoric acid to its calcium salt.²

The generality of the reaction has been further investigated to other halogen sources to allow the fluorination, chlorination and iodination of enamines derivatives. Details of our study will be presented in this communication.

References:

2,6-BIS-(1,2,3-TRIAZOLYL)PURINES IN REACTIONS WITH S-NUCLEOPHILES

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Recently, we have reported the synthesis and application of 2,6-bis-(1,2,3-triazol-1-yl)purine nucleosides [1]. The 1,2,3-triazolyl ring at C(6) position of purine has been shown as good leaving group in nucleophilic aromatic substitution reactions. In this study, we extended the range of nucleophiles with thioles. The latter produced products with general formulas 1 and 2. Triphenylmethyl mercaptan, thiophenol, dodecanethiol, benzylthiol, propane-1,3-dithiol, decane-1,10-dithiol were used for the substitution. For example, S-trityl protected 2-triazolyl-6-thiopurine derivative was obtained in reaction of 9-(2’,3’,5’-tri-O-acetyl-β-D-ribofuranosyl)-2,6-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-purine with triphenylmethyl mercaptan in good (80%) yield. Reactions of the same substance with thiophenol and dodecanethiol proceed equally smoothly in DMF in presence of dry K₂CO₃. After deprotection of sugar moiety with MeNH₂/H₂O target compounds were isolated in 82% and 62% yield.

References:
SYNTHESIS OF DEXTROMORPHANE DERIVATIVES

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Dextromethorphan (R\(^1\)=OMe, R\(^2\)=H) is a well-known cough suppressant\(^1\), which shows multiple activity: NMDA receptor antagonist, serotonin reuptake inhibitor (SRI) and voltage gated sodium channel blocker (VGSCB). We wanted to increase the SRI and VGSCB activity of dextromethorphan for the treatment of anxiolytic diseases, e.g. obsessive compulsive disorder (OCD). New functionalities (R\(^2\)=halogen, nitro or amino groups) were built up, to introduce further building blocks with VGSCB activity\(^2,3\) (Ar=aryl, heteroaryl, biaryl, X=O or H\(^2\) etc.) By the Suzuki cross coupling reaction of the halogenated dextrorphan, or by alkylation or acylation reaction of the amino group new derivatives could be synthesized. Varying the substituents we could overcome the hERG liability. Our best compound showed promising activity at the in vivo marble burying test.

![Chemical structure](image)

In course of O-alkylation of dextrorphan a rearrangement reaction by opening of the piperidine ring was observed similarly to N-methylation of N-desmethyl-dextromethorphan\(^4\).

References:
SYNTHESIS OF PHOSPHOROUS ANALOGS OF CYCLIC AMINOACIDS BY HYDROGENATION OF HETARYLPHOSPHONATES

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Aminophosphonates are very interesting candidates for exhibiting a wide range of biological activity as phosphorous analogs of naturally occurring amino acids and can be used as antibiotics, enzyme inhibitors with antiviral agents.1,2

The new efficient method of the synthesis of diethyl 2- and 3-piperidyl- and 3-tetrahydroquinolyl phosphonates by hydrogenation of corresponding hetarylphosphonates with molecular hydrogen in the presence of a palladium catalyst has been developed.

The method provides a phosphorous analogues of cyclic aminoacids in almost quantitative yields. Hetarylphosphonates have been obtained by improved method using Pd(OAc)₂-dppf catalytic system.

Financial support was provided by Russian Foundation of Basic Research (grant 12-03-92701-IND-a).

References:
SYNTHESIS OF NEW LEVOGLUCOSAN DERIVATIVES

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Levoglucosan (1,6-anhydro-β-D-glucopyranose) as the anhydrosugar is an important primary pyrolysis product of carbohydrates, such as starch and cellulose. Here we report a synthesis of new substituted levoglucosan derivatives with aryl and alkyl substituents. Procedure involves a reaction of levoglucosan with different acyl chlorides in an excess of base. Number of reaction products depends on the nature of acyl chloride, ratios of reagents and time of the reaction.

SYNTHESIS AND CRYSTALLIZATION FEATURES OF TIMOLOL PRECURSORS

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Enantiomeric $(S)$-timolol maleate $(S)$-1·$(\text{HO}_2\text{CCH})_2$ has gained a wide acceptance as an anti-hypertensive and anti-glaucoma remedy under a variety of trade names. The obtaining of the enantiopure 1 is complicated by the solid solution nature of its crystal phase. 4-[4-(Oxiran-2-ylmethoxy)-1,2,5-thiadiazol-3-yl]morpholine 2 and 3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-propane-1,2-diol 3 are valuable timolol precursors.

Jacobsen kinetic hydrolytic resolution of rac-epichlorohydrin 4 was used as a source of chirality for all the substances obtained. The oxiran $(S)$-2 was prepared from $(R)$-4 and thiadiazolol 5, and was transformed to $(S)$-1:

$$
\begin{align*}
(R)-4 &\quad 91\% \text{ ee} \\
(S)-2 &\quad (S)-1, 97.5\% \text{ ee}
\end{align*}
$$

The $(S)$-diol 3 was obtained from $(S)$-3-chloropropane-1,2-diol $(S)$-7 and was subsequently transformed to $(S)$-1 via cyclic sulfite $(4R)$-8:

$$
\begin{align*}
(S)-7 &\quad 95.0\% \text{ ee} \\
(S)-3 &\quad (S)-1, 99\% \text{ ee}
\end{align*}
$$

Investigation of IR spectra, thermodynamic and X-ray characteristics has shown that chiral molecules 2 and 3 prone to spontaneous resolution, but in the case of 2 racemic conglomerate transforms to continuous solid solution at elevated temperature. All the revealed crystallization properties were taken into account during the synthesis of target enantiopure compounds 1-3.

Acknowledgements: The authors thank the Russian Fund of Basic Research for financial support (grant number 13-03-00174).
PYRROLO[1,2-\(\alpha\)]PYRAZINES VIA FURAN RECYCLIZATION REACTION

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Within the research project towards synthesis of annulated pyrroles through intramolecular Paal-Knorr-like reaction employing furans as 1,4-diketone equivalents \([1,2]\), we proposed a new approach to pyrrolo[1,2-\(\alpha\)]pyrazines 4 via recyclization of 2-amino-\(N\)-(furan-2-ylmethyl)acetamides 2.

\[
\text{R} = \text{Me, Et, } t\text{-Bu}; \text{R}^1 = \text{H, Me, Ph}; \text{R}^2 = \text{H, Me}; \\
\text{R}^3 = \text{o-FC}_6\text{H}_4, \text{p-ClC}_6\text{H}_4, \text{p-FC}_6\text{H}_4, \text{p-OMeC}_6\text{H}_4, \text{p-CF}_3\text{C}_6\text{H}_4, \text{p-MeC}_6\text{H}_4
\]

Acknowledgements: Financial support was provided by Russian Foundation for Basic Research (grant 13-03-96024) and the Council of President of the Russian Federation (grant MK-442.2013.3).

References:
SYNTHESIS OF 4-SUBSTITUTED 1,2-BENZOXATHIINE-2,2-DIOXIDES

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Carbonic anhydrases (CA) are zinc containing enzymes which catalyze reversible hydration and transport of carbon dioxide and provide pH regulation in cells. In a search for new inhibitors of tumor associated CA IX, good inhibitory activities were demonstrated for coumarin derivatives [1, 2]. Therefore we were interested in synthesis of derivatives of 1,2-benzoxathiine 2,2-dioxide (2) which is consider to be the bioisostere of coumarin (1) and potential CA IX inhibitor.

![1](image1.png) ![2](image2.png)

In a search for new inhibitors we developed a synthesis of 4-substituted 1,2-benzoxathiine 2,2-dioxides 3 from salicylaldehyde (4) and Gringard reagent with following oxidation, mesylation and cyclization in presence of strong organic base.

![4](image3.png) ![3](image4.png)

References:
DIRECT TRIFLUOROMETHYLATION OF 1,3-DIMETHYLURACIL AND CONSECUTIVE C-H ARYLATION

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The introduction of fluorine containing groups into molecules plays an important role in organic chemistry because of the changes of molecular properties of modified compounds. The trifluoromethyl group is an important structural moiety present in diverse classes of pharmaceuticals, agrochemicals, liquid crystals, dyes, and polymers. Therefore, we decided to introduce the trifluoromethyl group to 1,3-dimethyluracil as a model compound for pyrimidine nucleobases and then to apply C-H arylation to the next position.

\[
\begin{align*}
\text{H}_3\text{C}&-\text{N}-\text{O} \\
\text{O} &-\text{N} - \text{CH}_3 & \text{H}_3\text{C}&-\text{N}-\text{O} \\
\text{O} &-\text{N} - \text{CH}_3 & \text{H}_3\text{C}&-\text{N}-\text{CF}_3 \\
\text{O} &-\text{N} - \text{CH}_3 & \text{H}_3\text{C}&-\text{N}-\text{Ar}
\end{align*}
\]

Acknowledgements:
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References:
Towards Synthesis of Heterocyclic Fused Dienediynes

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Enediyne antibiotics are one of the most active classes of natural products possessing antineoplastic activity [1]. Recently we have demonstrated that electrophilic cyclization of o-functionalized diacetylenic arenes is a useful tool for the synthesis of acyclic [2] and 12-membered cyclic [3] enediyynes fused to heterocycles. In order to obtain highly active synthetic analogs of enediyne antibiotics, 10- (1, 2) and 11-membered (3) dienediynes were chosen as targets.

The synthetic strategy towards these macrocycles involved electrophilic cyclization (EC) and ring closing metathesis (RCM) as two key steps. In that way using of EC on initial steps allowed to obtain substrates for RCM in rather good overall yields. Unfortunately, the final step – RCM – did not proceed regardless of the nature of catalyst and reaction conditions, while the same reaction for the formation of the 12-membered dienediyne proceeded smoothly [3]. The found reactivity was explained in terms of the isodesmic reaction approach based on DFT calculations at the B3LYP/6-31++G(d,p) level.

Acknowledgements:
N.D. is thankful to SPbSU (12.38.14.2011) and to the CFN.

References:
SYNTHESE OF ISOXAZOLES WITH PHOTOCHROMIC LABEL

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The development of new pathways for the modification of various bioobjects by the photochromic ligands led to the creation of the effective way for the photocontrol of their biological activity. Nowadays the modified spiropyran derivatives are the attractive photochromic probes for the labeling of different biological targets. It has been shown by us that 3,5-substituted isoxazoles are potent inhibitors of the human platelets aggregation process. For the purpose of the ligand-receptor binding investigation of these compounds we synthesized new 3,5-substituted isoxazole analogs with photochromic label – a spiropyran moiety at the 3- or 5-position of the isoxazole ring. We proposed several variants for direct modification of the spiropyran core at the C5'-position of the indoline cycle to introduce biospecific tag fragments. The key reaction involved a [3+2]cycloaddition of nitrile oxides with alkynes or alkenes. Spectral-kinetic properties of synthesized compounds were investigated in two solvents – ethanol and toluene. The specific binding of these compounds with human platelets was studied.

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SYNTHESIS OF SALTS OF GUARESCHI IMIDES

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Guareschi imides (2,6-dioxopiperidine-3,5-dicarbonitriles) are well known to exhibit anticonvulsive, sedative and analgesic activities [1-7]. The common approach to Guareschi imides is based on the reaction of NH$_3$, ethyl cyanoacetate and carbonyl compounds. As it was shown [6], the success in the synthesis of Guareschi imides strongly depends on the nature of carbonyl components – the reaction proceeds smoothly with unbranched ketones up to C$_3$–C$_4$ substituents. However, it fails when attempting to use arylalkyl ketones, branched ketones or aldehydes. In the case of aldehydes, the initially formed Guareschi products 1 undergo oxidation under reaction conditions to give pyridine-2-ones 2, and 4-monosubstituted Guareschi imides cannot be obtained by this way.

![Chemical structure of Guareschi imides](image)

To overcome the disadvantages of the classic approach, we had to develop a new method to the synthesis of Guareschi imides. We found that treatment of cyanoacrylamides 3 with 1-cyanoacetyl-3,5-dimethylpyrazole 4 in the presence of excessive Et$_3$N in cold acetone leads to triethylammonium salts 5. The free Guareschi imides 1 could be obtained after reaction with aq. HCl.

![Chemical structure of salts of Guareschi imides](image)

References:
**SOME NUCLEOPHILIC REACTIONS WITH 4-HYDROXY-1-METHYL-3-[(2-OXO-2H-CHROMENE-3-YL)-CARBONYL]QUINOLIN-2(1H)-ONE**

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The reactivity of 4-hydroxy-1-methyl-3-[(2-oxo-2H-chromen-3-yl)carbonyl]-quinolin-2(1H)-one (1), as a new asymmetric diheterocyclic ketone, towards different nucleophilic reagents, was examined. The reaction of the ketone 1 with hydrazine led to pyrazolinone 2, and excess of hydrazine pyrazolinopyrazole 3 was obtained. Treatment of the ketone 1 with 2,2-dimethoxyethanamine gave pyrrolocoumarin 4, while cyanoguanidine afforded pyrimidinone 5. Under PTC conditions, the ketone 1 was reacted with chloroacetonitrile, diethyl malonate, ethyl cyanoacetate, malononitrile, and cyanoacetamide to give coumarinyl furoquinoline 6, pyranquinolines 7, 8, 9, and benzonaphthyridine 10, respectively.
A NEW RECYCLIZATION OF 2-SUBSTITUTED 4-OXO-PYRIMIDINES

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2-Substituted 4-oxo-pyrimidines are known for a number of unusual rearrangements catalyzed by acid agents. Upon treatment with strong acids (pTSA or polyphosphoric acid) at the temperatures of 220° or 135°C respectively, pyrimidine 1 produces octahydrophenanthridone 2. When boiled in toluene with 8 to 10-fold excess of POCl₃ for a long time (10 to 24 h), it produces 10-aminooctahydroacridine 3.

\[
\begin{align*}
\text{NH}_2 & \quad \xrightarrow{\text{POCl}_3} \quad \text{N} \\
\text{O} & \quad \xrightarrow{\text{H}^+} \quad \text{O} \\
\text{N} & \quad \xrightarrow{\text{CN}} \quad \text{N} \\
\text{H} & \quad \xrightarrow{\text{CHO}} \quad \text{H} \\
\end{align*}
\]

In our study, we established a new rearrangement of 2-substituted 4-oxo-pyrimidines by the formylation during soft conditions.

\[
\begin{align*}
\text{NH} & \quad \xrightarrow{\text{POCl}_3+\text{DMF}} \quad \text{N} \\
\text{O} & \quad \xrightarrow{\text{CN}} \quad \text{N} \\
\text{N} & \quad \xrightarrow{\text{NH}_2} \quad \text{N} \\
\text{H} & \quad \xrightarrow{\text{CHO}} \quad \text{H} \\
\end{align*}
\]

Unexpected reaction occurred at fomylation of thio-analog 11.

\[
\begin{align*}
\text{NH} & \quad \xrightarrow{\text{POCl}_3+\text{DMF}} \quad \text{N} \\
\text{S} & \quad \xrightarrow{\text{S}} \quad \text{N} \\
\end{align*}
\]

Some another model compounds were used at this formylation.
Unnatural amino acids play an important role in the structure of many natural peptides. In particular, biaryl amino acids are present in a wide range of naturally occurring peptides that display significant biological activity (1). Among them, 5-arylhistidines have been shown to be the central structures of cytotoxic and antifungal marine peptides (2). Moreover, the incorporation of unnatural amino acids into natural or synthetic sequences has led to peptides with comparable or improved biological profile. In this context, our research group has reported the synthesis of linear peptidotriazoles and linear biaryl peptides with potent activity against plant pathogenic bacteria and fungi, and low hemolysis (3,4).

In this work, we have extended our previous studies on the synthesis of linear peptides containing biaryl and triazolyl amino acids to the preparation of cyclic sequences incorporating these unnatural amino acids. The key step for the synthesis of the cyclic biaryl peptides was the formation of an aryl-aryl bond between the side-chain of two aromatic amino acids through a Suzuki-Miyaura cross-coupling. Cyclic peptidotriazoles incorporated a 1,2,3-triazole at the side-chain of a selected residue. This heterocycle was prepared through a copper-catalyzed azide alkyne cycloaddition. The structure of both families of cyclic peptides as well as their solid-phase synthesis will be presented.

**NOVEL HIGHLY FUNCTIONALIZED CYCLIC AMINO ACIDS**

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Dipolar cycloaddition of nitrile-oxides to an olefinic bond, followed by reduction of the formed isoxazoline ring represent a powerful selective synthetic strategy for the access of many highly functionalized cyclic amino acid derivatives such as *Peramivir* and other analogues with important biological properties [1]. Novel highly functionalized cyclopentane amino acid derivatives have been synthetized starting from bicyclic β- and γ-lactams by nitrile-oxide cycloadditions to the C-C double bond of the corresponding cyclopentane amino esters, followed by reductive isoxazoline opening. Synthetic aspects of the cycloaddition and isoxazoline opening related to their selectivity will be discussed [2].

References:
CAGED PROTON SPONGES
IN BASE-CATALYZED REACTIONS

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We reported a suitable synthetic approach to the preparation of compounds 1 with four fused five-membered rings and their acid-catalyzed rearrangement leading to bidentate caged secondary amines 2 in quantitative yields. Following alkylation reactions under basic conditions led to air nonsensitive highly stable substituted diazatetracyclo[4.4.0.1\(^{3,10}\).1\(^{5,8}\)]dodecanes (DTDs) 3 with properties of proton sponges. Their pK\(_{BH^+}\) values were determined by \(^1\)H NMR transprotonation experiments with known reference base. The molecular structures of free base and its conjugated acid 4 have been proved by X-ray structure analysis. Recently we performed several types of base-catalyzed reactions with one selected DTD (pK\(_{BH^+}\) (CD\(_3\)CN) = 21.7±0.1). Knoevenagel condensation and Pudovik reaction are two chosen candidates where we discovered good to excellent kinetic activity of our system in particular.

Acknowledgements:
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References:
SIMPLE ROUTE TO FURFURYLARYLGLIOXALS

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Simple furan derivatives are valuable synthons in the heterocyclic syntheses due to furan ring ability to serve as a 1,4-diketone equivalent. From this point of view carbonyl furan derivatives can be considered as hidden polyketones and can provide rich possibilities for recyclization reactions. Earlier we proposed a new method for the synthesis of phenacylfurans [1]. Now we wish to report the two-stage simple approach to the corresponding furan containing α-diketones [2].

\[
\begin{align*}
R = H, Me & \quad R' = H, F, Cl, Br, OMe, NO_2 \\
\text{(Et}_3\text{O)}_2P & \text{EtOH}
\end{align*}
\]

Acknowledgements: Financial support was provided by the Ministry of Education and Science of the Russian Federation (grant 3.3578.2011) and Russian Foundation for Basic Research (grant 13-03-01048 a).

References:
1,2-DIHYDROXYINDOLIZIDINES: 
A NEW APPROACH FROM 
1-(2-PYRIDYL)-2-PROPEN-1-OL

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The significant biological activities of polyhydroxylated indolizidine alkaloids promoted an intense synthetic work to afford these natural products and their nonnatural analogues. In particular, natural (+)-lentiginosine, isolated in 1990 from the leaves of *Astragalus lentiginosus*, was found to be a potent and selective inhibitor of the fungal $\alpha$-glucosidase, amyloglucosidase, while recent results showed that the nonnatural enantiomer (–)-lentiginosine acts as an apoptosis inducer on tumor cells of a different origin.1

1-(2-Pyridyl)-2-propen-1-ol, obtained by vinylation of commercially available picolinaldehyde, behaved as a good starting material for the synthesis of the indolizidine skeleton. A simple process involving bromination, reduction, and one-pot nucleophilic substitution (via elimination/addition) afforded (±)-lentiginosine, in ca. 27% overall yield, as well as the nonnatural diastereomer with inverted configuration at C-8a.2 Synthetic and mechanistic aspects of this new approach, able to afford variously functionalized indolizidines even in optically pure form, will be discussed.

NOVEL STEREOSELECTIVE ROUTE TO SYN AND ANTI AMINO ALCOHOLS

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Amino alcohols are valuable constituents of a wide range of biologically active natural products and pharmacologically important compounds. Besides, they serve as a versatile precursors for other building blocks, such as \(\beta\)-hydroxy-\(\alpha\)-amino acids, 2-hydroxyalkyl piperidines, 2-amino 1,3-diols, etc. Vinyloxazolines 2 are versatile amino alcohol precursors. Herein, we present an investigation of regioselectivity and diastereoselectivity in Lewis acid catalysed cyclization of bis-trichloroacetimidates 1 to the corresponding cis- and trans-\(E\)-oxazolines 2.

It was found that the double bond configuration of substrate determines the reaction diastereoselectivity. In the case of \(E\)-bis-imidates 1 the major reaction product was cis-\(E\)-oxazoline 2, while \(Z\)-bis-imidates 1 gave trans-\(E\)-oxazoline 2. It is demonstrated, that regioisomeric ratio varies depending on substrate used, as well as Lewis acid catalyst.
SYNTHESIS AND PROPERTIES OF NOVEL HETEROCYCLIC DERIVATIVES OF BENZANTHRONE

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The design of new fluorescent molecules is of continuing interest for many applications in research and industry. Especially donor–acceptor p-conjugated organic materials have attracted considerable interests owing to their potential wide applications for development of photoactive materials. Many derivatives of benzo[de]anthracene-7-one are known as effective luminescent dyes with emission in the spectral region from green to red-purple, depending on the structure [1]. Target benzanthrone derivatives are synthesized by condensation reaction of 3-amino–benzanthrone with appropriate heterocyclic aldehydes with following reduction of obtained imines by NaBH₄ in DMF solution:

\[
\begin{align*}
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} \\
\text{N} \\
\text{R} \quad \text{O} \\
\text{R} \\
\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{N} = \text{R} \\
\text{NaBH}_4, \text{DMF}
\end{align*}
\]

References:
SYNTHESIS AND ASYMMETRIC CATALYTIC ACTIVITY OF 4-PHENYLQUINAZOLINES

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The addition of phenyl acetylenes to aldehydes, particularly asymmetric version has been quite important study in the area of C-C-bond formation reactions in the past decade due to the synthesis of propargylic alcohols.\textsuperscript{1}

Quinazolinones (\textit{QH}) (1a-e) were synthesised from \(\alpha\)-hydroxy acids or \(\alpha\)-amino acids in 4-5 steps in high yields without a need of chromatography, following with the literature procedure.\textsuperscript{2} Subsequently, QH’s were converted into enantiopure 4-phenylquinazolines (2a-e) in additional 2 steps. After successfully synthesis of PhQ’s, were tested in catalytic enantioselective propargylic alcohol synthesis. Under the optimised reaction conditions, propargylic alcohols were then successfully accomplished by reaching up to \%91 ee and up to 98\% product yield.

\begin{align*}
\text{R} & \quad \text{O} \\
\text{X} & \quad \text{OH} \\
\text{Ar} & \quad \text{O} \\
\text{H} & \quad \text{Ph} \\
\text{L}^* (2a) & \quad 10\text{mol}\% \\
\text{Ti(OPri)}_4 & \quad 25\text{mol}\% \\
\text{Et}_2\text{Zn}, \text{THF}, -10^\circ\text{C} & \quad \text{up to 91 ee}
\end{align*}

References:
NOVEL RACEMIC AND OPTICALLY ACTIVE 1-ALKYL-3-PHOSPHOLENE PLATINUM(II) COMPLEXES

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Chiral transition metal-phosphine complexes form an important group within the organophosphorous compounds, as they may be used as enantioselective catalysts in homogenous catalytic reactions, such as hydrogenation and hydroformylation. As an extension of a resolution method developed by our research group, the resolution of 1-alkyl-3-phospholene 1-oxides (1) was accomplished using TADDOL derivatives (2-3) and Ca^{2+} salts of dibezoyl- and di-p-toluyl-tartaric acid (4) as resolving agents.

The racemic and optically active 1-alkyl-3-phospholene 1-oxides (1a-e) were converted to the corresponding novel racemic and optically active platinum(II)-complexes (6a-e), and they were tested in the hydroformylation reaction of styrene. Unexpectedly high regioselectivities towards the branched aldehyde were observed, and the enantioselectivities were significantly higher than in case of the phenyl-substituted derivative.

References:
FUNCTIONALIZED TETRAHYDRO-INDOLIZINES AS BUILDING BLOCKS FOR MEDICINAL CHEMISTRY

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New synthetic strategies for the construction of functionally diverse tetrahydroindolizines scaffolds are of importance to many areas of pharmaceutical and academic research.¹ Natural products featuring the tetrahydroindolizine framework often exhibit desirable pharmacological activities such as antibacterial, antihelmintic, and other properties. Rhazinilam 1 have attracted considerable attention in both the biological and synthetic communities.² Similar to taxol and vincristine, rhazinilam was found to interfere with tubulin polymerization dynamics, making it a promising starting point for the development of anticancer agents. Our laboratory has developed a new, multicomponent procedure for the synthesis of highly functionalized 5,6,7,8-tetrahydroindolizines rings through a selective hydrogenation of the indolizine nucleus. Starting indolizines synthesized under the Thorpe reaction conditions.³

References:
DESIGN OF CHIRAL PYRIDINES AS ORGANOCATALYSTS FOR ASYMMETRIC CYCLOPROPANATION REACTION

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Pyridine derivatives are widely used as organocatalysts and as ligands in transition metal catalysis. Herein we report synthesis and application of chiral pyridine organocatalysts in cyclopropanation reaction.

To find suitable conditions for pyridine 4a-c catalyzed cyclopropanation a range of solvents and bases was screened. It was found that the desired reaction proceeds smoothly without non-catalyzed background cyclopropanation reaction if K$_2$HPO$_4$·3H$_2$O or KOAc were used as base in dichloromethane.

Further investigation on pyridine derivative 4a-c structure showed that electron donating groups in para-position accelerate cyclopropanation. Notably, 4-methoxypyridine (4a) and N-pyridin-4-ylacetamide (4b) showed the best yields (80% and 78%, respectively), whereas 4-dimethylaminopyridine (4c) gave only trace amounts of cyclopropane 3.

Chiral organocatalysts (S,S)-7aa'-'cc' were synthesized by ortho-lithiation of pyridine 5 followed by quenching with aldehydes (S)-6a'-'c'.

When catalysts (S,S)-7aa'-'cc' were employed in cyclopropanation reaction best enantioselectivities (48.8% ee) were achieved with sterically large substiruent R$_3$ (Piv and Ts).
MICROWAVE-ASSISTED DIRECT ESTERIFICATION AND AMIDATION OF CYCLIC PHOSPHINIC ACIDS

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Phosphinic acids do not undergo direct esterification and other related derivatizations. The conventional methods for the synthesis of phosphinates involve P-chlorides that are not environmentally friendly. Therefore, we wished to study the MW-assisted direct esterification of cyclic phosphinic acids (1), such as 1-hydroxy-3-phospholene 1-oxides, 1-hydroxy-phospholane 1-oxides and a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine 1-oxide, resulting in the formation of the appropriate phosphinates (3). To our surprise, the esterifications did take place that may be due to the beneficial effect of the MW irradiation.

The energetics and mechanism of the direct esterifications were evaluated by B3LYP/6-31++G(d,p) calculations. Encouraged by the above results, we also studied the MW-assisted direct thioesterification and amidation of the cyclic phosphinic acids. However, these reactions could be performed in only lower conversions. This experience is the consequence of the thermodinamics of the reactions as suggested by high level calculations.

References:
THE SYNTHESIS AND USE OF 1-ALKOXY- AND 1-AMINO-3-PHOSPHOLENE 1-OXIDES

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Various 3-phospholene 1-oxides, such as 1-alkoxy and 1-amino derivatives that are available by the McCormack reaction and subsequent direct functionalizations, form a representative group of P-heterocycles.\textsuperscript{1,2}

1-Alkoxi-3-phospholene 1-oxides (1), obtained directly from the corresponding phosphinic acids by MW-assisted direct esterification, can be used in ring enlargement involving the addition of dichlorocarbene on the double-bond of the phospholene oxide (1) followed by the thermal opening of the cyclopropane ring of the dichlorocarbene adduct (2) so formed.

\[
\begin{align*}
1 & \xrightarrow{\text{CITEBA} / \text{NaOH/H}_2\text{O}} 2 \\
2 & \xrightarrow{\text{TEA / PhMe}} 3
\end{align*}
\]

We have found that higher carbon atom chain alkoxy groups promote the dichlorocarbene addition reaction.

The synthesis of 1-amino-3-phospholene 1-oxides (5) involves the reaction of the corresponding phosphinic chloride (4) with amines. However, the reaction results in a mixture containing the expected amino-phospholene oxide (5) and, surprisingly, its N-phosphinoyl derivative (6) as a by-product.

\[
\begin{align*}
4 & \xrightarrow{\text{RNH}_2} 5 + 6
\end{align*}
\]

It was found, that the product composition could be influenced (fine-tuned) and thus, either phosphinic amide 5 or the corresponding bis product (6) can be obtained selectively, and in high yields.

References:
DIRECT C-H SULFENYLATION OF 7-DEAZAPURINES

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Purines1 and their analogues show a great variety of biological activities. 7-Deazapurines (pyrrolo[2,3-d]pyrimidines) have been much less thoroughly studied but some examples display antibiotic2, antiviral3 and cytostatic4 effects. In our previous study, we have reported synthetic approach to 8-modified 7-deazapurines via a “one pot“ C-H borylation followed by Suzuki coupling.5 An analogy to C-H sulfenylation of indoles,6 we report here on sulfenylation of 7-deazapurines to position 7 by diverse disulfides using Cu catalysis in air. Optimized conditions (Scheme 1) allowed the synthesis of the target 7-alkyl- or -arylsulfanyl derivatives in nearly quantitative yields.

Scheme 1

Acknowledgement

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 b) La Regina, G.; Gatti, V.; Famiglini, V.; Piscitelli, F.; Silvestri, R. ACS Comb. Sci., 2012, 14, 258–262
A CONVENIENT SYNTHESIS OF IMIDAZO[1,2-C] QUINAZOLINES

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Variously hydrogenated 5-alkyl- and 5-arylimidazo[1,2-c]quinazolines have shown attractive pharmacological activities and insecticidal properties. However, the previous methods for synthesis of this tricyclic ring system were very limited and mostly relied on assembling of imidazole heterocycle onto quinazoline frame. In this communication we report a convenient approach to synthesis of 5-substituted imidazo[1,2-c]quinazolines 3-5 which based on a quinazoline ring closure.

\[
\begin{align*}
\text{CN} & \quad \text{EDA} \quad \text{NH}_2 \\
& \quad \text{NH}_2 \\
\text{RCHO} & \quad \text{RC(O)Me}_3 \\
& \quad \text{RC(NH)Me} \\
\text{K}_2\text{MnO}_4/\text{SiO}_2 & \quad 1 \text{ equiv}, \quad 2 \text{ equiv}
\end{align*}
\]

Thus, anthranilonitrile (1) smoothly reacted with EDA in the presence of P$_2$S$_5$ (0.02 equiv) to give aminoimidazoline 2 (93%). Acid-free condensation of the latter with aromatic and aliphatic aldehydes led to 2,3,5,6-tetrahydroimidazo[1,2-c] quinazolines 3 in high yield. Condensation of 2 with orthoesters or with iminoesters afforded 5,6-dihydroimidazo[1,2-c]quinazolines 4. Derivatives 3 were selectively dehydrogenated to 4 with K$_2$MnO$_4$/SiO$_2$ (1 equiv), while applying 2 equiv of the same reagent led to exhaustive dehydrogenations to 5. Additional variants of the ring closure and dehydrogenations will be also discussed.
CATALYTIC APPROACH TO STEROIDS BEARING HETEROCYCLIC MOIETY

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Development of new catalytic tools for modification of biologically active natural molecules is one of the most important challenges of modern organic chemistry. Vinyl iodides obtained from readily available ketosteroids have been involved in copper-catalyzed cross-coupling reactions. An efficient protocol for C-N bond formation between steroid fragment and various azoles have been developed.

Another type of hetaryl substituents have been introduced by means of Pd-free Sonogashira reaction followed by cyclization step.

Copper-catalyzed 1,3-dipolar cycloaddition reaction of azidosteroids with iodoacetylenes has afforded 5-iodotriazoles which can be converted to different functionalities by diverse cross-coupling methodologies.

We are grateful to RFBR (grant № 11-03-00265-a) for financial support.
REATIONS OF TETRACYANOETHYLENE WITH $N'$-ARYLBENZAMIDINES: A SHORT ROUTE TO 2-PHENYL-3H-IMIDAZO[4,5-$B$]QUINOLINE-9-CARBONITRILES

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Tetracyanoethylene (TCNE) is the simplest of the percyano alkenes (cyano-carbons).\(^1\) It is highly electron-deficient and therefore strongly electrophilic.\(^2\) TCNE reacts with a variety of bis-amino-nucleophiles to give after the initial addition to the double bond intramolecular cyclisations typically on the vicinal nitrile that lead to various heterocyclic systems.\(^3\) Here we report our complementary study on the reaction of tetracyanoethylene (TCNE) with the readily available $N'$-arylbenzamidines\(^4\) which affords 2-[1-aryl-5-imino-2-phenyl-1$H$-imidazol-4($5H$)-ylidene]malononitriles 2 in good yield. Dimroth rearrangement\(^5\) of which, affords the isomeric (Z)-2-[4-(arylimino)-2-phenyl-1$H$-imidazol-5(4$H$)-ylidene]malononitriles 3 in near quantitative yield. Subsequent thermolysis in biphenyl ether yielded 2-phenyl-3$H$-imidazo[4,5-$b$]quinoline-9-carbonitriles 4 again in near quantitative yields. Single crystal X-ray structures for 2-[5-imino-1,2-diphenyl-1$H$-imidazol-4($5H$)-ylidene]malononitrile 2 ($Ar = Ph$) and (Z)-2-[2-phenyl-4-(phenylimino)-1$H$-imidazol-5(4$H$)-ylidene]malononitrile 3 ($Ar = Ph$) are presented.

\[\text{References:}\]
CONTROL FORMATION OF 3,3’- AND 3,4’-PYRAZOLINYL-PYRAZOLES ON THE BASE OF UNSATURATED OXIRANYLKETONES

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New bipyrazoles heterocycles have been synthesized due to their complex-forming ability. Unsaturated oxyranylketones 1 were used as starting substances owing to convenient polyfunctionality. The diazole cycle formation has been obtained by variation in the sequence of 1,3-dipolar diazomethane cycloaddition to double bond and hydrazines cyclocondensation with oxyranylketone moiety. These two routes allowed to realise target synthesis of pyrazolinlypyrazoles with heterocyclic rings bonded in 3,3’- and 3,4’-positions.

Bipyrazoles with 3,3’-coupled rings 2-5 can be obtained by both synthetic routes. While the synthesis of 3,4’-coupled pyrazolinlypyrazoles 6,7 can only be achieved by the route 2 and the regioselectivity of the 1,3-dipolar cycloaddition stage in this case is controlled by the introduction of electron-withdrawing substituent in the styryl moiety.
REACTION OF 6-HALOGENOPYRIMIDINE CARBOXYLATES WITH N-, O-, S-NUCLEOPHILES

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Dihydropyrimidines, obtained via a three-component Biginelli reaction are thoroughly studied these days due to the wide spectrum of their biological activity. Over the years various synthetic approaches towards Biginelli compounds were developed. However, there was a lack of study on the reactivity of Biginelli reaction products towards various nucleophiles. In present work we developed synthetic approaches towards 6-methyl substituted pyrimidine carboxylates 2 where the substituents at C6 are N-, O-, S-nucleophiles that were introduced into the dihydropyrimidine molecule via reaction of 1 with biologically active nucleophilic reagents. Therefore, we were able to link the residues of substituted amines, sulfanilamides, aminoacids, phenols, thiophenol and 2-mercaptobenzimidazole to the pyrimidine core of 2.

Synthesis of products 3 where X = N, O, S has been provided by the change of both the reaction conditions and reagents. The reaction products of both types 2 and 3 were isolated with the yields of 38-94 % depending on the nature of the substituent introduced into the pyrimidine molecule.

SYNTHESIS AND THERMOLYSIS OF 4-(2-THIENYL CARBONYL)-5-(TRIFLUOROMETHYL)-2,3-FURANDIONE

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4H-pyran-4-one derivatives constitute an useful class of heterocyclic compounds which are widely distributed in nature. These compounds display diverse biological activities [1-3]. On the other hand, polyfluoroalkyl- substituted heterocyclic compounds are of particular interest owing to their biological activity, specific properties and chemical reactivity [4]. Therefore, there is a need for development of available and convenient methods of synthesis polyfluoroalkyl-substituted 4H-pyran-4-one.

We showed for the first time that the reaction of 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione 1 with oxalyl chloride give to 4-(2-thienylcarbonyl)-5-(trifluoromethyl)-2,3-furandione 2, whose thermolysis leads to 3,5-bis(2-thienylcarbonyl)-2,6-bis(trifluoromethyl)-4H-pyran-4-one 3.

The structure of compound 3 was established by elemental analysis, IR, 1H-NMR, 13C-NMR, 19F-NMR and single-crystal X-ray diffraction..

References:

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ISOXAZOLE-LINKED OLIGOSACCHARIDES

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Modification of C(3) and C(5) position in glucose leads to discovery of new previously unknown conjugates. Here we report a novel approach for synthesis of sugar clusters which is based on Michael addition/1,3-dipolar cycloaddition reaction sequence. We have identified glucose-derived nitroalkene 1 as a suitable structural motif which is capable to link a molecule possessing nucleophilic center and a molecule possessing terminal alkyne. Using different O-, S-, N- sugar nucleophiles it is possible to build carbohydrate cluster of type 2 and 3.

Acknowledgements: The authors thank JSC Olainfarm for kind donation of diacetone-β-glucose and for scholarship.

References:
1,3-DIPOLAR CYCLOADDITION OF NITRONES TO SUBSTITUTED ALLENES

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1,3-Dipolar cycloaddition is known as one of the most powerful tools to create N,O–five-membered heterocycles. In particular, dipolar cycloaddition of nitrones to carbon-carbon double bonds of different alkenes allows access to a variety of isoxazolidines. These cycloadducts attracted considerable attention due to their potential biological activities. Isoxazolidines have also been used as precursors of such natural products as β-lactam antibiotics and alkaloids. In this work reactions of arylallenes with C-carbamoyl- and C,C-bis(methoxycarbonyl)nitrones were investigated and regio- and stereoselectivity of the reaction was shown. It was found that in some cases initial products undergo the further transformations.

\[
\begin{align*}
\text{Ar} &= \text{Ar}, \text{R}_1 = \text{Ar, Me;} \quad \text{R}_2 = \text{C(O)NHAr, R}_3 = \text{H;} \quad \text{R}_2 = \text{R}_3 = \text{COOMe}
\end{align*}
\]

The structure of obtained products was established by spectral and X-ray methods. The mechanism of the reactions is discussed. So, the reaction of allenes with nitrones afford isoxazolidines with additional functionalities, that may be transformed in some new heterocyclic systems.
A CONVENIENT ROUTE TO 4-ARYL-3,4-DIHYDRO-1H-QUINOLIN-2-ONES

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3,4-Dihydro-1H-quinolin-2-ones containing hydroxyl group in benzene ring are starting compounds for synthesis of phosphodiesterase inhibitor Cilostazol and atypical antipsychotic and antidepressant Aripiprazole. Our studies were devoted to synthesis of 4-aryl-3,4-dihydro-1H-quinolin-2-ones 1, mainly substituted with methoxy groups in both aromatic rings. It is well known that compounds 1 can be obtained by internal cyclization of cinnamoyl anilines.\(^1\) We found out that anilides 2 also can be successfully used for synthesis of target compounds 1. Taking this into account, we developed a new convenient method: one pot direct preparation of quinolinones 1 by heating of malonanilic acids 3 and aromatic aldehydes in trifluoroacetic acid without isolation of cinnamoyl anilines 2. The crude products of this procedure contained up to 90% of 1H-quinolin-2-ones 1. The antiradical properties of obtained compounds 1 have been tested.

\[ R - \text{CHO} \xrightarrow{\text{TFA, reflux}} \begin{array}{c}
\begin{array}{c}
\text{Ar} \\
\text{OH}
\end{array}
\end{array} \]

\[ \begin{array}{c}
\begin{array}{c}
\text{Ar}
\end{array}
\end{array} \xrightarrow{TFA, reflux} \begin{array}{c}
\begin{array}{c}
\text{OH}
\end{array}
\end{array} \]

\[ \begin{array}{c}
\begin{array}{c}
\text{OH}
\end{array}
\end{array} \]

\[ \begin{array}{c}
\begin{array}{c}
\text{Ar}
\end{array}
\end{array} \]

Acknowledgements. Authors thank JSC Olainfarm for scholarship to A. Stikute.

References
SYNTHESIS OF ACYCLIC AND MACROCYCLIC MULTIURACILS

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Earlier we’ve shown that pyrimidine containing macrocycles (pyrimidinophanes) possess high antimicrobial activity. We suggested that a compound, consisting of several “monomeric” pyrimidinophanes linked together in some way, can demonstrate higher activity and/or selectivity. We used azide-alkyne cycloaddition and coupling of acetylenes with copper acetate to obtain nanosized structures containing pyrimidinophanes.

We also synthesized a series of acyclic analogues of macrocyclic multiuracils. Among them we consider uracil containing dendrimers to be the most promising. We managed to synthesize several uracil containing dendrimers, including the 3rd generation dendrimers, which consists of 15 uracil units.

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SYNTHESIS OF N⁶-SUBSTITUTED-2-TRIAZOLYL-ADENINE DERIVATIVES

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A novel class of 2,6-bis-triazolylpurine nucleosides 2 were obtained from 2,6-diazido precursors 1 via copper (I) catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction. These intermediates appeared to be very reactive towards N-nucleophiles and thus selectively gave C(6)-substituted analogs 3 with triazolyl moiety at C(2)-position. Thereby, 1,2,3-triazoles act as good leaving groups in regioselective nucleophilic aromatic substitution reactions [1].

Photophysical properties of the obtained products have been studied. Products 3 exhibit interesting fluorescence properties.

References:
DIASTEREOSELECTIVE SYNTHESIS OF 1,2-DIHYDROARENOFURANS

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The dihydroarenofurans belong to an important class of heterocycles, principally because this ring-system constitutes the core skeleton of an increasing number of biologically active natural products and pharmaceuticals. We have developed a simple, general route to the 1,2-dihydroarenofurans, substituted in position 2 by an acyl or aryl group, starting from phenolic Mannich bases, 2-acetoxybenzyl acetates or quaternary ammonium salts and the carbonyl-stabilized pyridinium ylides generated \textit{in situ} from pyridinium salts. The mechanism of the reaction is believed to involve the formation of the \(\text{o-quinone methide} \) intermediate, Michael-type addition of the ylide to the \(\text{o-quinone methide} \) followed by intramolecular nucleophilic substitution.

This method can be also widespread on N-benzylpyridinium salts. The advantages of this approach include the use of readily available starting materials, simple experimental steps and product isolation, and chromatographic purification is not usually required.
NOVEL METHOD FOR SYNTHESIS OF 2-NITROARENOFURANS

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Synthesis of 2-nitroarenofurans has drawn extensive and enduring attention because of their varied biological activities. Many of these compounds exhibit antibacterial, antiparasitic and mutagenic properties. Besides, 2-nitrobenzofurans are useful intermediates for the preparation of 2-halogenobenzofurans, dibenzofurans and benzofuro[2,3-c]pyrroles. Herein, we report a simple, efficient, TEA catalyzed method for the synthesis of 2-nitroarenofurans from quaternary ammonium salts, phenolic Mannich bases or 2-acetoxybenzyl acetates and potassium trinitromethanide in moderate-to-good yields using acetonitrile or ethanol as the reaction medium.

In some cases, trinitromethyl derivatives and 2,2-dinitro-2,3-dihydrobenzofurans were isolated.

The mechanisms of these reactions are believed to involve the formation of the \( \sigma \)-quinone methide intermediate.
SYNTHESIS OF FLUORINATED 3,4-DIHYDRO-PYRIDINES

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Fluorine emerged as a “magic element” in Drug Discovery and the develop of synthetic methods for the preparation of fluorinated building blocks with biological activity have attracted a great deal of attention in recent years [1]. Furthermore, α,β-unsaturated imines are a versatile family of compounds with a wide range of applications in preparative organic chemistry. We described the preparation of the first stable N-unsubstituted α,β-unsaturated imines [2]. These fluorinated imines are used as intermediates for synthesis of vinylogous fluoroalkylated amino nitrile derivatives (3) and for the regioselective synthesis of fluorine containing trans-3,4-dihydropyridin-2-ones [3]. Continuing with our interest in the design of new fluoroalkyl substituted building blocks, we report here a simple and regioselective synthesis of fluorine containing 3,4-dihydropyridines (2) by conjugate addition (1,4) of nitriles to α,β-unsaturated imines (1).

R1R2CN  \xrightarrow{TMSCN}  R1R2NH2

(1,2-Ad)

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References:
SYNTHESIS OF 10-METHYL-8,10-DIAZABICYCLO[4.3.1]DECANE RING SYSTEM

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A convenient method for the synthesis of 10-methyl-8,10-diazabicyclo[4.3.1]decane \textit{6} as a new important synthetic organic chemistry scaffold was developed using octanedioic acid as a starting material. The key transformation in the 5-step synthesis sequence involved a chemoselective reaction of dimethyl 2,7-dibromooctanoate \textit{2} with methylamine, which resulted in the formation of cis-dimethyl 1-methylazepan-2,7-dicarboxylate \textit{3}. The latter was further transformed into bicyclic 8-benzyl-10-methyl-8,10-diazabicyclo[4.3.1]decane-7,9-dione \textit{4} under heating with benzylamine. Reduction of the formed bicyclic dione with LiAlH$_4$ resulted in 8-benzyl-10-methyl-8,10-diazabicyclo[4.3.1]decane \textit{5}, and hydrogenolysis efficiently yielded the target product.
SYNTHESIS OF ADAMANTYL-SUBSTITUTED ISOXAZOLES

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Isoxazole derivatives are of interest as objects for pharmacology. They are active principle of some drugs differ in their functions. On the other hand, the introduction of lipophilic adamantyl radical to some molecules provides a significant increase in the pharmacological activity of the compound. It seems promising to modify the biological activity of isoxazoles with adamantyl radical.

A simple method for the synthesis of adamantyl-substituted 5-chloroisoxazoles has been proposed via heterocyclization reaction of 1,1-dichlorocyclopropanes with NOCl•2SO$_3$ under nitrosation conditions affording a mixture of regioisomers and their monochlorinated derivatives. The yield and the ratio of the products depend on the reaction conditions.

In the case of 2-adamantyl-1,1-dichloro-3-methylcyclopropane only chlorination of the adamantly fragment was observed obviously due to the steric hindrance.

This work was supported by the RFBR (pr. no. 11-03-00707-a) and the program of the Presidium of the RAS ‘Development of Methods for Synthesizing Chemical Compounds and Creating New Materials’.
SELECTIVITY IN THE CROSS-COUPLING REACTIONS OF 6-BROMO-7-TRIFLYLOXYCHROMONES

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In continuation of our work in the cross-coupling reactions of chromones and flavone\textsuperscript{[1]} we have investigated the Suzuki-Miyaura and/or Sonogashira transformations of 6-bromo-7-triflyloxychromones.

C-arylation/alkynylation of 6-bromo-7-triflyloxychromone performed exclusively in position 7 due to the electronic effect. This selectivity allowed the synthesis of unsymmetrically substituted products. \textit{bis}-Arylated or alkylated products have also been prepared. These reactions allow the synthesis of various hitherto unknown derivatives including compounds available from natural sources.

6-Bromo-8-methyl-7-triflyloxychromone was completely unreactive under these conditions.

SYNTHESIS OF 2,6-DIAZA-BICYCLO[2.2.2]OCTANE 3,5-DIONES

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Zinc containing enzymes (ZCE), such as histone deacetylase (HDAC) and matrix metalloproteinases (MMP), play a major role in both cancer initiation and progression. It has been shown that some of these enzymes can be inhibited by cyclic amides as zinc-binding groups [1], therefore bicyclic diamides 2,6-diazabicyclo[2.2.2]octane 3,5-diones could be used for ZCE inhibition. A simple one-pot three-component method for synthesis of these compounds has been previously reported [2], but the scope of this reaction hasn’t been investigated. 2,6-Diazabicyclo[2.2.2]octane 3,5-diones are synthesized in a reaction between an aromatic aldehyde 1, a ketone 2 and malonic diamide 3 in presence of base.

We have discovered, that asymmetric methylketones, both aliphatic and aromatic, could be used in a regioselective reaction to form only 1,8-disubstituted 2,6-diazabicyclo[2.2.2]octane 3,5-diones. Aromatic aldehydes with both electron donating groups, as well as weak electron withdrawing groups, were successfully used, however aldehydes with strong electron withdrawing substituents did not afford the bicyclic product. We achieved yields up to 85% in the regioelective reactions.

References:
SYNTHESE OF GABA DERIVATIVES FROM CHIRAL POOL

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We present an approach to synthesis of enantiomerically enriched 3-substituted γ-aminobutyric acid derivatives. This class of compounds includes well-known CNS drugs baclofen, phenibut and pregabalin.

\[
\begin{align*}
\text{baclofen: } & R = -C_6H_4-pCl \\
\text{phenibut: } & R = \text{Ph} \\
\text{pregabalin: } & R = i-\text{Bu}
\end{align*}
\]

The proposed key reaction is diastereoselective Michael addition on α,β-unsaturated lactone 2 which contains sugar moiety as chiral auxiliary. The latter is obtained in a three-step synthesis from diacetone-α-glucose 1, an inexpensive and commercially available compound.

Diastereoselectivity of the reaction \(2 \rightarrow 3a+3b\) and its optimization will be discussed.
SYNTHESIS OF 1-(3-NITROPHENYL)-5,6-DIHYDRO-4H-[1,2,4]TRIAZOLO[4,3-a]-[1,5]BENZODIAZEPINES

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Through the various molecules designed and synthesized in recent years, active research has been initiated on heterocycles and the chemistry of 1,2,4-triazoles has received considerable attention owing to their wide range of biological activities. Benzodiazepines and their polycyclic derivatives also exhibit a broad spectrum of useful properties. It was therefore of interest to prepare tricyclic 1,2,4-triazolo derivatives as the combination of different pharmacophores frame which may lead to compounds with interesting biological profiles.

Thionation of the corresponding cyclic lactams with P₂S₅ afforded thiolactams 1. The alkylation of less reactive thioamides 1 led to the desired imidothioethers 2 which were converted to N’-(2,3-dihydro-1H-1,5-benzodiazepin-4-yl)-3-nitrobenzohydrazide derivatives 3. The tricyclic 1-(3-nitrophenyl)-5,6-dihydro-4H-[1,2,4]triazolo[4,3-a]benzodiazepines 4 were prepared by the thermal cyclization of compounds 3. Compounds 4 were obtained in 65-81 % yield. The IR, ¹H, ¹³C NMR spectral data of new compounds correspond to their structure.

STEREOSELECTIVE SYNTHESIS OF 2-VINYLSERINOL DERIVATIVES

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2-Vinylserinol derivatives 1 are structural elements of a number of biologically active natural products including isoleucyl tRNA synthetase inhibitor SB203207, 20S proteasome inhibitor omuralide, and sphingolipid mycestericin E.

[Structural formulas of SB203207, Omuralide, and Mycestericin E]

Herein we report novel stereoselective synthesis of protected 2-vinylserinols – oxazolines 3 by Lewis acid catalyzed cyclization of chiral bis-trichloroacetimidates 2. The best diastereoselectivity (d.r. 99:1) for oxazoline 3 formation was achieved with O-TBS protected substrate (R1=iPr) and AlCl3 as a catalyst.
SUGAR BASED SPIROOXAZOLIDINONES

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N-Acyl-oxazolidinones have found extensive applications in the asymmetric synthesis as chiral auxiliaries. Present work describes an optimized protocol for the synthesis of carbohydrate derived spirooxazolidinones (1).¹ Commercially available diacetone-d-glucose was chosen as a convenient starting material² for the preparation of spirooxazolidinones in seven steps with a combined yield of 36% on a 10 g scale. The method of N-acylation with acylchlorides for both types of spirooxazolidinones was developed to study the diastereoselective alkylation at α-position. To explore the scope and reactivity of the obtained compounds, a small combinatorial library of novel N-alkyl-spirooxazolidinones derivatives was generated with individual product yields reaching up to 88%.

[Chemical structures are shown]

Acknowledgements: The authors thank JSC Olainfarm for kind donation of diacetone-d-glucose and for scholarship.

References:

SYNTHESIS OF NEW FUNCTIONALIZED PYRAZOL-5-ONE DERIVATIVES

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The derivatives of pyrazol-5-one exhibit various biological activities which in fact depend on the nature of functional groups and its position in the molecule. Here we present the synthetic route to diaminomethylidene derivatives of 1-aryl-3-methylpyrazol-5-one based on the chelate assisted methodology developed in our group [1].

\[ \text{Ar} = \text{Ph}, \ 4-\text{ClC}_6\text{H}_4, \ 4-\text{MeC}_6\text{H}_4 \]

Such an approach makes it possible to construct biheterocyclic systems connected by C-C bond. Thus, compounds 1 were further used as N,N-dinucleophyles in the heterocyclisation reactions, and the new corresponding pyrazolon-5 derivatives 2 and 3 with N-containing heterocyclic substituent in position 4 were obtained.

\[ \text{Ar} = \text{Ph}, \ 4-\text{ClC}_6\text{H}_4, \ 4-\text{MeC}_6\text{H}_4; \ R^1 = \text{Me}, \ R^2 = \text{H}, \ R^3 = \text{OH}; \ R^1 = \text{H}, \ R^2 = \text{CN}, \ R^3 = \text{NH}_2 \]

Acknowledgements: This work was financially supported by the Russian Academy of Sciences (Program for Basic Research of the Presidium of the Russian Academy of Sciences “Development of a Methodology of Organic Synthesis and Creation of Compounds with Valuable Applied Properties).

References:
SYNTHESIS OF MACROCYCLIC SYSTEMS DERIVED FROM DI-(2-INDOLYL) HETEROARENES

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Indoles are an important class of heterocyclic compounds whose derivatives occur widely as natural products in plants, fungi and marine organism. More complex indoles, such as bis-indoles are very important biologically active scaffolds as they are found in many pharmacologically active alkaloids. Bis-indole alkaloids are heterocyclic compounds, which consist of two indoles connected to each other via linking units. In our current synthetic study, a novel range of bis-indoles 2,2'-linked with heterocyclic units such as carbazole and dibenzofuran have been prepared. Imine cyclic systems were subsequently produced from these precursors via condensation of the corresponding of dialdehydes with various diamines (Figure 1). In particular, the desired indole macrocyclic systems were successfully produced from aliphatic diamino compounds such 1,4-diaminobutane and 1,6-diaminohexane.

![Figure 1: Macrocyclic bis-indole systems](image-url)
SYNTHESIS OF 2-ETHYNYL GLYCINOLS BY LEWIS ACIDS CATALYZED CYCLIZATION OF BISTRICHLOROACETIMIDATES

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2-Ethynyl glycinol derivatives belong to the class of β-aminoalcohols which are important building blocks for the synthesis of natural products and pharmaceuticals.

Herein we report novel method for the synthesis of ethynyl glycinols 4 from butyne-1,2-diols 1. The synthetic route involves transformation of diol 1 to bis-trichloroacetimidate 2 which undergoes cyclization in the presence of Lewis acids to give oxazolines 3 as precursors of ethynyl glycinols 4. Cyclization of bistrichloroacetimidates 2 is regioselective leading to 3 as major product. In the case R = Me cyclization of 2 proceeds with complete inversion of configuration at the chiral center suggesting $S_N^2$ mechanism of the reaction. In the case of R = Ph, cyclization of 2 proceeds with racemization indicating $S_N^1$ mechanism in the case of carbenium ion stabilizing substituent.
**β-EXOMETHYLENE δ-AMINO ALCOHOLS BY INTRAMOLECULAR AMINATION OF NON-CLASSICAL CYCLOPROPYL METHYL CATION**

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β-Exomethylene δ-amino alcohols 4 are multifunctional building blocks that can be transformed to amino acids, γ-butyrolactams, pyrrolidine derivatives etc.

![Chemical structure](image)

Herein we present Lewis acid catalysed intramolecular amination of non-classical cyclopropyl methyl cation as a novel, late transition metal-free route to β-exomethylene δ-amino alcohols 4. We have demonstrated that bis-imimates 1 give 6-methylene oxazepines 3 in moderate to good yield, if R is carbocation stabilizing group. In addition, we have shown that oxazepines 3 can be readily transformed to N-protected β-exomethylene δ-amino alcohols 4.
SYNTHESIS OF NEW TYPE OF BICYCLIC NITROSOACETALS BY FORMAL [3+3]-CYCLOADDITION OF NITRONATES WITH CYCLOPROPANES

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Cyclic nitronates 1 are well-known 1,3-dipoles in [3+2]-cycloaddition chemistry and their reactions with olefins have been intensively investigated. Here we report formal [3+3]-cycloaddition and the first synthesis of bicyclic nitrosoacetals 3, possessing two annelated 6-membered rings. The transformation utilizes donor-acceptor cyclopropanes (DAC) 2 as 1,3-dipole equivalents under Lewis acid (Yb(OTf)₃, Sc(OTf)₃) catalysis. For 3-unsubstituted nitronates (R⁵ = H) good yields with good to excellent diastereoselectivity are achieved, while 3-substituted (R⁵ = Me) ones failed to react. The conformational preferability of adducts 3 is also discussed.

\[
\begin{align*}
\text{R}^2 \text{R}^1 \text{R}^6 \text{R}^5 & + \text{E} \hspace{2cm} \text{Yb(OTf)}_3, \text{MS 4Å,} \text{CH}_2\text{Cl}_2, \text{rt,} \text{3 d} \\
\text{E} = \text{CO}_2\text{Me} \\
& \text{for} \text{ R}^5 = \text{H;} \\
& \text{61-92%}, \\
& \text{dr} = 2:1 - \text{single isomer}
\end{align*}
\]

Acknowledgements: The work was supported by RFBR (grant №12-03-00278).

References:
DIHYDROPYRROLO[1,2-b]PYRAZOLES WITH POTENTIAL BIOLOGICAL ACTIVITY

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Many compounds with dihydropyrrolo[1,2-b]pyrazole skeleton appeared as very interesting for their biological activity. Beside alkaloid withasomnine, known since 1966,[1] there are some recently published papers where compounds with this skeleton act as inhibitors of TβR-I or p38 MAPK kinases.[2]

Herein, we report a synthesis of dihydropyrrolo[1,2-b]pyrazoles starting either from γ-butyrolactone or ethyl-4-chlorobutyrate. Our target compounds have various substitution R on the pyrazole ring (phenyl, 4-pyridyl, 5-isochinolinyl, etc.) and another amino or alkoxy substitution at the position 4 of the pyrrole ring.

References:
UNUSUAL FURAN RECYCLIZATION IN THE INDOLE SYNTHESIS

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Earlier, we reported an acid-catalyzed reaction of 2-(tosylamino)benzyl alcohols with N-tosylfurfurylamine affording 2-(2-acylviny1)indoles 1 [1]. Indoles are formally formed through the oxidative furan ring opening despite the absence of any oxidant. Effect of “oxidation” is achieved due to the elimination of tosylamine under acidic conditions.

\[
\begin{align*}
\text{Ts} & \quad \text{NH} \\
\text{Y} & \quad \text{R} \\
\text{OH} & \\
\text{R} & \\
\end{align*}
\]

[3]

\[
\begin{align*}
\text{Ts} & \quad \text{NH} \\
\text{Y} & \quad \text{R} \\
\text{O} & \\
\text{N} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ts} & \quad \text{NH} \\
\text{Y} & \quad \text{R} \\
\text{O} & \\
\text{N} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ts} & \quad \text{NH} \\
\text{Y} & \quad \text{R} \\
\text{O} & \\
\text{N} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ts} & \quad \text{NH} \\
\text{Y} & \quad \text{R} \\
\text{O} & \\
\text{N} & \\
\end{align*}
\]

In this report, we present the results of our careful investigations of this reaction, namely, the effect of the reaction conditions and the nature of the leaving group on the recyclization process. In particular, we found that the reaction of N-furfurylphthalimide with benzhydryl alcohols 3 produces indoles 2 via a protolytic furan ring opening.

Acknowledgements: Financial support was provided by Russian Foundation for Basic Research (grant 13-03-00463-a) and Ministry of Education of the Perm Krai.

References:
**FACILE SYNTHESIS OF TRIAZOLES AND BENZOTRIAZOLE DERIVATIVES USING NANOPARTICLES OF ORGANOSILANE-BASED NITRITE IONIC LIQUID IMMOBILIZED ON SILICA DICATIONIC NITRITE IONIC LIQUIDS**

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Nanoparticles of organosilane-based nitrite ionic liquid immobilized on silica, 1-butyl-3-methylimidazolium nitrite and 1-(3-Trimethoxysilylpropyl)-3-methylimidazolium nitrite, were used as effective reagents for the preparation of benzotriazole derivatives from the 1,2-diaminobenzenes at room temperature under mild solvent-free conditions. 1,5-Bis(3-methylimidazolium-1-yl)pentane nitrite and azide was used as dicationic task-specific ionic liquid (DTSIL) for the efficient, fast, straightforward and one-pot synthesis of 1,2,3-triazoles under mild conditions.
ENAMINONES BORON CHELATES IN THE SYNTHESIS OF N-CONTAINING HETEROCYCLES

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Enaminones (1) easy form stable in air and under heating diphenyl boron complexes 2 and 3. The latter were used for the synthesis of new CF₃-containing heterocyclic compounds: 4-amino(4-hydroxy)pyridines and 1,6-naphtyridin-4-ones. Interaction of 2 with primary amines results in yield 4-amino(alkylamino)-3-trifluoroacetimidoylpent-3-en-2-one – new building blocks for the construction of N-containing heterocycles. Several ones, synthesized on the base of chelates 2 and 3, are presented on the scheme.

References:
THE BROMINATION OF 4-PHENYL-2-PYRROLIDONE DERIVATIVES

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During past decade there was observed steady interest in the structure activity relationship (SAR) investigations aimed at the search of new agents for the treatment of central nervous system (CNS) disorders: impairment of cognition/memory, epilepsy and seizure, neurodegenerative diseases, stroke/ischaemia, stress and anxiety. At present the key role in their treatment belong to drugs sharing pyrrolidin-2-one pharmacophore 1a-d. That is why in the frame of synthetic studies aimed at the targeted preparation of new biologically active pyrrolidin-2-one derivatives by regioselective formation of new C-C bonds we have developed new methodology for the insertion of bromine in various derivatives of this heterocycle.

It was unexpectedly found that 1-acetyl-4-phenylpyrrolidin-2-on 2a and its variously substituted derivatives 2b-e could be easily converted into appropriate 1-acetyl-penyl-pyrrolin-2-ones 3a-e by radical bromination using NBS in the presence of AIBN catalyst or UV-irradiation, which was accompanied by the spontaneous dehydrobromination of unstable halogenated intermediate. In the case of the excess of brominating agent there was observed allylic bromination in the position 5 of pyrrolin-2-ones 3a-d with the formation of 5-brom and 5,5-dibrom substituted heterocycles 4a-d and 5a,c. Specifically dibrominated compound 6d, which structure was confirmed by X-ray analysis, was isolated after analogous treatment of 3d with the excess of brominated agent.
SYNTHESIS OF PYRROLOPYRIMIDINE DERIVATIVE

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We earlier investigate interaction of methyl N-{4(3)-[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)acetyl]phenyl}carbamates with ethyl-3-aminocrotonate upon heating in mixture of toluene - ethanol, 2:1 resulting to formation of 3-pyrrol-3'-yloxindoles with carbamate function [1]. It is found, that heating of chalcone (I) and 6-amino-2-(methylthio)pyrimidin-4(3H)-one (II) in [bmim]Br during 1 h results in formation of methyl N-{4-[2-(methylsulfanyl)-4-oxo-5-(2-oxo-2,3-dihydro-1H-indol-3-yl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl} carbamate (III) in 69% yield.

\[
\begin{align*}
\text{I} & \quad \text{NHCO}_2\text{Me} \quad \text{O} \quad \text{NH}_2 \\
\text{MeS-N} & \quad \text{O} \quad \text{NH}_2 \\
\text{II} & \quad \text{MeS-N} \quad \text{O} \\
\text{III} & \quad \text{NHCO}_2\text{Me} \\
\end{align*}
\]

The structure of compound (III) has been confirmed by IR, \(^1\text{H}, \text{\textsuperscript{13}C} \) NMR spectra.

**Acknowledgements:**
The authors thank the professor of Voronezh State University Kh.S. Shikhaliev, who provided sample of enamine for research.

**References:**
THE PREPARATION AND BIOLOGICAL INVESTIGATION OF STEREOISOMERIC 2-(5-METHYL-4-PHENYL-2-OXOPYRROLIDIN-1-YL)-ACETAMIDES

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Individual enantiomers of 2-(5-methyl-4-phenyl-2-oxopyrrolidin-1-yl)-acetamide 5a-d were synthesized using following chemical scheme. Diastereoisomeric mixtures of diethyl (1R)- and (1S)-2-(2-nitro-1-phenylpropyl)-malonates 1a,b were prepared by asymmetric Michael addition of diethyl malonate to 2-nitroprop-1-enylbenzene in the presence of (3aR,3'aR,8aS,8'aS)-2,2'-cyclopropylenebis-[3a,8a]-dihydro-8H-indeno-[1,2-d]-oxazole or its optical antipode.

\[
\begin{align*}
1a, b & \quad \text{Me} \quad \text{NO}_2 \\
R^1 & = \text{Ph}, R^1 = \text{H}; b \quad R = \text{H}, R^1 = \text{Ph} \\
2a, b & \quad \text{Me} \quad \text{NO}_2 \\
R^1 & = \text{H}, R^1 = \text{Ph}
\end{align*}
\]

\[
\begin{align*}
3a-d & \quad \text{Me} \quad \text{NO}_2 \\
R^1 & = \text{Ph}, R^1 = \text{H}; c \quad R = \text{H}, R^1 = \text{Ph}; d \quad R = \text{H}, R^1 = \text{Ph}
\end{align*}
\]

\[
\begin{align*}
4a-d & \quad \text{Me} \quad \text{CONH}_2 \\
R^1 & = \text{Ph}, R^1 = \text{H}, R^1 = \text{H}, R^1 = \text{H}, R^1 = \text{H}, R^1 = \text{Me};
\end{align*}
\]

Obtained compounds were converted into methyl (3R)- and (3S)-4-nitro-3-phenylpentanoates 2a,b and separated by chromatography on silica gel, affording four erythro- and threo isomers 3a-d. Each enantiomer was transformed into individual 5-methyl-4-phenylpyrrolidin-2-one 4a-d by reductive cyclisation and afterward into target compound 5a-d by the attachment of the acetamide group to the heterocyclic nitrogen in 4a-d.
SYNTHESIS OF TRIAZOLYL DERIVATIVES OF 2-SULFONAMIDO THIOPHENE

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Zinc-containing enzymes Carbonic anhydrases (CA) are playing an important role in metabolic processes of bicarbonate and carbon dioxide. Presently are known 16 α-CA isoforms with various physiological functions. Among inhibitors of CA drugs with clinical applications as diuretics, antiglaucoma, antiobesity and antitumor are found.¹ Acetazolamide (AAZ), a common antiglaucoma drug and CA inhibitor, contains [1,3,4]thiadiazole scaffold. Driven by medicinal chemistry needs we were interested to replace thiadiazole ring with thiophene to obtain structures 3. Here we report synthesis of thiophene-2-sulfonamide triazolyl derivatives 3. Since bromide 1 with free sulfonamide group did not participate in Sonogashira reaction, we have developed synthetic pathway where as a core intermediate role plays protected sulfonamide 2. In subsequent Sonogashira and click-reactions desired compounds 3 were synthesized.

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SYNTHESIS OF PYRROLO[1,2-α]-QUINAZOLINE DERIVATIVES

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Fused quinazoline derivatives such as pyrrolo[1,2-α]quinazolinones can be found both in natural and in synthetic pharmaceutically active substances.

One approach to the pyrrolo[1,2-α]quinazolinone synthesis is reactions of aminobenzoic acid (anthranilic acid) amides with α-ketoacids.

We present here anthranilic acid hydrazides (3a-j) prepared from isatoic anhydride (1) and aromatic (2a-e) or cyclohexene dicarboxylic acid hydrazides (2f-j) that are useful instead of amides.

\[ R^1 = \text{a) H; b) F; c) Cl; d) Br; e) NO}_2 \]

\[ 4, 6 R^2 = \text{COOH; 5, 7 R^2 = CH}_3 \]
NEW SELENIUM SUBSTITUTED IMIDAZOLYL IMINES AND THEIR COMPLEXES WITH COPPER(II)

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High biological activity made selenium-containing organic compounds an attractive class of ligands for studying of coordination properties in the reactions with transition metals. Such complexes can be used as cytostatic agents [1]. In view of the recent increased interest in effects of selenium rapid expansion of our understanding of the roles of this trace element in biology can be expected [2]. We have obtained the novel selenium containing organic ligands N-(ω-phenylseleno)ethyl)-N-(imidazolylmethylene)amines, and their complexes with copper(II) chloride:

\[
\begin{align*}
R \quad \text{CHO} + \quad H_2N \quad \text{SePh} & \quad \xrightarrow{\text{EtOH} \atop t^\circ C} \quad R \quad \text{N} \quad \text{NH} \quad \text{SePh} \\
R \quad \text{CHO} + \quad H_2N \quad \text{SePh} & \quad \xrightarrow{\text{EtOH} \atop t^\circ C} \quad R \quad \text{N} \quad \text{NH} \quad \text{SePh}
\end{align*}
\]
\( R = \text{H, CH}_3, \quad n = 1, 2 \)

\[
\begin{align*}
L + \quad \text{CuCl}_2 \quad 2\text{H}_2\text{O} & \quad \xrightarrow{\text{EtOH/CH}_2\text{Cl}_2} \quad L\text{CuCl}_2
\end{align*}
\]
\( 3-10 \)

The X-ray analysis of copper complex with 2-(phenylseleno)ethyl)-N-(imidazol-4-ylmethylene) amine revealed that the copper(II) ion assumes a tetracoordinated square–planar geometry with an \( \text{N}_2\text{Cl}_2 \) donor set. Cyclic voltammetry experiments showed a quasi-reversible behavior of the \( \text{Cu}^{II}/\text{Cu}^I \) redox couple.

References:
The copper complex 4 was characterized by X-Ray analysis. Both copper atoms of the binuclear cluster have almost equivalent metal coordination geometries and are located in a tetrahedral environment (disregarding the neighboring Cu atom) bound by one bridging chlorine atom. Apparently, methanol acts as a reducing agent in the process of complex 4 formation.
SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,5-NAPHTHYRIDINES

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Nitrogen-containing heterocycles are important compounds widely employed in the fields of biochemistry, pharmaceuticals, and materials science. Consequently, reactions, including hetero-Diels-Alder reactions of azadienes have attracted special interest because of its utility on the synthesis of nitrogen containing heterocycles, both chemo- and stereoselectively. Recently, we have reported the synthesis of nitrogen-containing heterocyclic compounds, as 1,5-naphthyridines, in a regio- and stereoselective way by a cycloaddition reaction (see Scheme). Several different derivatives have been obtained by this strategy modulating both aldehyde and dienophile nature. Moreover, in some cases, oxidation of methylene groups of polycyclic compounds has yielded corresponding carbonyl derivatives. Biological activity of all obtained heterocyclic compounds has been studied in order to inhibit COLON cancer cells proliferation as inhibitors of Topoisomerase I. The docking studies have also indicated the intercalation of these heterocycles in the TOP I/ADN complex.

Scheme

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References:
PYRROLO[2,3-a]CARBAZOLES AS PIM KINASE INHIBITORS

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The Pim family of protein kinases is composed of three isoforms (Pim-1, Pim-2 and Pim-3) involved in survival pathways in cancer cells. These recent findings gave rise to a growing interest in the development of Pim kinase inhibitors as antitumor agents. We recently reported pyrrolo[2,3-a]carbazole-3-carbaldehydes, such as compound 1, as potent Pim inhibitors. As part of our ongoing studies aiming at developing new inhibitors of these kinases, we carried on our structure-activity relationship studies by the synthesis of novel substituted pyrrolo[2,3-a]carbazoles.

The synthesis of these new analogues will be presented, as well as their evaluation toward Pim kinases. Molecular modeling studies identifying interactions between newly synthesized compounds and their biological target will also be discussed.

References:
Microwave-Assisted Synthesis of Pyridines, Pyrazoles, Pterins and the P38 MAPK Inhibitor RO3201195

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The Bohlman–Rahtz synthesis of various substituted pyridines has been modified to be simple, involves mild conditions and high yielding. We have shown that substituted pyridines could be synthesis efficiently and high yields under microwave condition for a relatively short reaction time. The process was also successful for the production of a range of fused heterocycles containing pyridine moiety in high yields (e.g. pyrido[2,3-d]pyrimidin-4(3H)-ones and pyrido[2,3-d] pyrimidine-2,4(1H,3H)-diones) (Structure 1).

The synthesis of chemotherapeutic agent RO3201195, has been investigated in a highly selective inhibitor of P38α, in seven steps under microwave conditions. The procedure provides high yield of the desired product and all other intermediate involved in all steps compared with conventional heat methods (Structure 2).
1,4-DIHYDROPYRIDINES POSSESSING ANTI-VIRAL EFFICACY

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Most of the anti-viral compounds known in the art are nucleoside derivatives. In turn, 1,4-dihydropyridines (1,4-DHP) are well known as a class of calcium channel blockers, but there are only few patent data on the anti-viral action of 1,4-DHP related compounds. Recently we have found that disodium 2,6-dimethyl-1,4-dihydropyridine-3,5-bis-carbonyloxyacetate (carbatone) possesses anti-herpes activity [1]. In this report the results of the study of anti-viral activities of new type of water-soluble 1,4-DHP – analogues of carbatone – are presented.

All the synthesized 1,4-DHP were evaluated in in vitro experiments as potential anti-viral compounds using virus infected mammalian cell lines. The research was performed with various groups of viruses – group V: (-)ssRNA viruses (influenza A(H3N2) virus), group IV: (+)ssRNA viruses (Dengue virus type 2) and group I: dsDNA viruses (HSV2). These investigations have confirmed the anti-herpes activity of carbatone and have revealed several perspective lead compounds possessing remarkable activity concerning influenza A(H3N2) virus.

Acknowledgement:
The study was partially supported by the State Research Programme “Biomedicine”

References:
SYNTHESIS AND BIOACTIVITY OF 1,2-DIHYDROXYINDOLIZIDINES

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(+)-Lentiginosine, a hydroxyindolizidine alkaloid found in the leaves of Astragalus lentiginosus, is a selective inhibitor of amylglucosidases and a potent inhibitor of Heat shock protein 90 (Hsp90) a therapeutic target for some diseases including cancer.\(^1\)
Non-natural (–)-lentiginosine is a caspase-dependent apoptosis inducer on different strains of human cancer cells, but with very low cytotoxicity.\(^2\)
The interesting biological profile of lentiginosine in both its enantiomeric forms encourages the collection of variously functionalised derivatives to modulate bioactivity and study the interaction of 1,2-dihydroxyindolizidines with bioreceptors.

In this communication, some aspects of the stereoselective synthesis of 7-substituted and benzo-fused lentiginosine derivatives such as 1-3 and the effect of the structural modifications on bioactivity will be presented.

SYNTHESIS AND ANTICANCER ACTIVITY OF
3-(2,4-DICHLOROPHENOXYMETHYL)-6-ARYL-7H-[1,2,4]
TRIAZOLO[3,4-b][1,3,4]THIADIAZINES DERIVATIVES

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It is known that condensed 4-aminotriazoles exhibit a wide spectrum of biological activity. A range of 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 4 was obtained in high overall yields.

Anticancer activity for these compounds was studied at the United States National Cancer Institute (NCI, Bethesda, Maryland, USA). Results obtained show that these compounds are promising for creating of a new drug for the treatment of melanoma on their basis. It was found that anticancer properties of compounds 4 increase with increasing of electron-donor properties of the substituent in the para position. Thus, compound 4 (R = F) inhibits the development of melanoma cells LOX IMVI to 36.73% better than 5-fluorouracil, 4 (R = OCHF₂) - to 80.29%, and 4 (R = OCH₃) - to 90.79%, respectively. This trend is observed in all 8 varieties of cancerous melanoma cells.
SYNTHESIS OF NEW 2-BENZAZEPINO-
NAPHTHALENE DERIVATIVES
VIA 1,7-ELECTROCYCLISATION

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For many years 1,3-dipoles have been used extensively for the construction of five-
membered heterocyclic rings via their cycloadditions with suitable dipolarophiles
and by the 1,5-electrocyclization reactions of \( \alpha,\beta \)-unsaturated 1,3-dipoles. More
recently, the electrocyclization of diene-conjugated 1,3-dipolar intermediates has
provided a powerful general synthetic route to seven-membered heterocyclic ring
systems. As a continuation of these studies our aim was to show the generality of
these methods as useful tools for the annelation of benzazepine ring to different
napththalene derivatives in a single step.\(^1\) In this communication we describe the
synthesis of some unknown 2-benzazepino[4,5-a]napthalene derivatives (1, 2, 3
and 4) via 1,7-electrocyclisation of nonstabilized azomethine ylides. The starting
material 3,4-dihydro-aryl-napthtalene derivatives 5 were prepared in two steps
starting from the corresponding \( \alpha \)-tetralone 6, through intermediate 7 and 8. Our
studies applied the generation of non-stabilised azomethine ylides from various
amino acids 9 and 10 by the decarboxylation method.\(^1\) In some cases, surprisingly,
pyrrole derivs. were isolated. A mechanism for the formation of the pyrrole 11
byproduct is proposed.

References:
\(^1\)Novak, Tibor; Mucsi, Zoltan; Balazs, Barbara; Keresztely, Laszlo; Blasko, Gabor;
Nyerges, Miklos Synlett 2010, 16, 2411-2414.
SYNTHESIS OF GLYCOSYLATED PORPHYRIN-OLIGOTHIOPHENE CONJUGATES

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Porphyrrins and porphyrin-based compounds are of great interest in a vast variety of scientific areas due to their unique photophysical and biochemical properties. We have recently reported a porphyrin-oligothiophene conjugate that selectively binds to amyloid fibrils associated with Alzheimer’s disease which shows enhanced fluorescent properties as compared to the previously used probes.\textsuperscript{1} A prerequisite to use these conjugates for intracellular applications, e.g., real time imaging and photodynamic therapy, is that the cellular uptake of the conjugates is adequate. Glycosylation offers the means to meet this requirement.\textsuperscript{2} We herein present the synthesis of novel glycosylated porphyrin-oligothiophene conjugates for the improved water-solubility and cellular uptake.

References:
\textsuperscript{1}Arja, Sjölander \textit{et al.} \textbf{In Press.} Macromolecular Rapid Communications
\textsuperscript{2}Hirohara \textit{et al.} Bioconjug. Chem. \textbf{2012}, 23 (9), 1881-1890
NITROGEN HETEROCYCLES CONTAINING 1,2-BENZOXATHIINE 2,2-DIOXIDES

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Carbonic anhydrases (CA) are zinc containing enzymes which catalyze reversible hydration and transport of carbon dioxide and provide pH regulation in cells. In a search for new inhibitors of tumor associated CA IX, good inhibitory activities were demonstrated for coumarin derivatives [1, 2]. Therefore we were interested in synthesis of derivatives of 1,2-benzoxathiine 2,2-dioxide (2) which is considered to be the bioisostere of coumarin (1) and potential CA IX inhibitor.

After a primary CA inhibition screening of several previously synthesized 1,2-benzoxathiine 2,2-dioxides it was observed, that higher selectivity towards CA IX exhibit 6-substituted 1,2-benzoxathiine 2,2-dioxides. Therefore it was of our interest to develop synthesis of 6-substituted 1,2-benzoxathiine 2,2-dioxides 3 and 4 containing triazole and tetrazole cycles.

Acknowledgements: This project was financed by European Social Fund (No. 2009/0203/1DP/1.1.1.2.0/09/APIA/VIAA/023)

References:
Highly cytotoxic amino derivatives of 2-thienylgermacyclanes (LC₅₀ 1-6 µg/ml) have been prepared by hydrogermylation reaction of heterocyclic N-allylamines with corresponding hydrogermane in the presence of platinum catalysts. The effects of the amines and the germacycle were examined to establish structure-activity relationships. The starting 2-thienylhydrogermanes 3 have been synthesized from the 2-bromothiophene by two consecutive Grignard syntheses followed by conversion of bromo derivatives 1 into ethoxy derivatives 2 by alcoholysis and subsequent reduction by LiAlH₄ under phase transfer catalysis conditions. Next, Pt-catalyzed hydrogermylation of different allylamines with hydrogermanes 3 allowed for efficient preparation of a series of 2-thienyl-aminopropylgermacycles:

\[
\begin{align*}
\text{a)} & \quad \text{Mg/} \text{Et₂O/GeCl₃} & \text{b)} & \quad \text{BrMg(CH₂)₃} & \text{MgBr/} \text{Et₂O/THF} & \text{c)} & \quad \text{EtOH/} \text{Et₃N/hexane} & \text{d)} & \quad \text{LiAlH₄/18-crown-6/hexane} & \text{e)} & \quad \text{R²/H₂PtCl₆/6H₂O}
\end{align*}
\]

In order to reveal the effect of heterocyclic amino group and size of germanium cycle in compounds 4 on their antitumor activity we have studied their cytotoxicity (IC₅₀) on two cell tumour lines: HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma). The investigations showed that most of germacyclohexyl derivatives (n = 1) exhibited high antitumor activity against mouse hepatoma MG-22A (IC₅₀ 1-4 µg/ml) and less cytotoxicity for normal fibroblasts NIH 3T3 (IC₅₀ 19-37 µg/ml). All of the studied compounds possessed moderate toxicity; lethal doses for them are in the range 338-782 mg/kg.
NOVEL DERIVATIVES OF 5-ETHYNYL-2’-DEOXYURIDINE AND THEIR BIOLOGICAL INVESTIGATIONS

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Nucleosides are basic building blocks of ribonucleic (RNA) and deoxyribonucleic (DNA) acids. They also play many important functions as themselves or in phosphorylated form (nucleotides) in conjugation with other biomolecules. Because of their crucial role in many metabolic pathways their derivatives and analogues are often used as chemotherapeutics, mainly as antiviral and anticancer agents\textsuperscript{1}. Among the vast number of nucleoside derivatives, boronated nucleosides constitute an attractive subfamily. Boron containing nucleosides are considered to be potential boron carriers for the boron neutron capture therapy (BNCT) of tumors\textsuperscript{2}.

\begin{center}
\begin{tikzpicture}
  \node (1) at (0,0) {\includegraphics[width=4cm]{figure}};
  \node (2) at (2.5,0) {\includegraphics[width=4cm]{figure}};
  \node (3) at (5,0) {\includegraphics[width=4cm]{figure}};
  \node (4) at (7.5,0) {\includegraphics[width=4cm]{figure}};
  \node (5) at (10,0) {\includegraphics[width=4cm]{figure}};
\end{tikzpicture}
\end{center}

Now we would like to present synthesis of novel derivatives of 5-ethynyl-2’-deoxyuridine with \textit{closo}-dodecaborate and cobalt-\textit{bis}-dicarbollide. At the first step of our investigation new 5-ethynyl-2’-deoxyuridine modification (1) was effectively synthesized. Then, desired conjugates were prepared by the reaction of 1 with a range of cyclic oxonium adducts of \textit{closo}-dodecaborate and cobalt-\textit{bis}-dicarbollide boron clusters. Cytotoxicity of these new conjugates in several cell lines was examined. These compounds can be used as potential boron delivering drugs for the boron neutron capture therapy (BNCT) of tumors.

Authors thank grants RFBR 12-03-31146 and POIG.01.01.02-10-107/09.

SYNTHESIS OF 2-ARYL-6-SULFAMOYL-SACCHARIN DERIVATIVES

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The aim of this project was to develop a method of synthesis of 2-aryl-6-sulfamoylsaccharin derivatives.

In a search for new zinc binding groups as potential inhibitors of zinc containing enzymes carbonic anhydrases (CAs), we focused our attention on saccharin derivatives because of saccharin’s promising ability to inhibit tumor associated isoform of carbonic anhydrase CA IX.1

During our investigation we concluded that it’s impossible to arylate 6-sulfamoylsaccharin using Cu, Fe and Ni catalysts.

Here we report successful 5 step synthesis of 2-aryl-6-sulfamoylsaccharins starting with 2-amino-4-nitrobenzoic acid.

References:
PO 087 / Poster presentations

XVth Conference on Heterocycles in Bio-organic Chemistry - 2013

PEPTIDIC $\alpha$-KETOAMIDES WITH GLUTAMINE $P_1$ SIDE CHAIN

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As a part of the program for design & synthesis of malarial protease PfSUB1 inhibitors, $\alpha$-ketoamides based on the substrate nonprime sequence KITAQ were targeted [1]. Ketoamide containing protected glutamine side chain 1 was prepared as a model compound and subjected to deprotection conditions. Formation of cyclic tautomer 3 was observed as a major product while expected compound 2 was present in a trace amount (ca 5 %). This was obviously due to strong electron withdrawing $\alpha$-keto group in ketoamide 2.

These results suggest that biosteric replacements for the glutamine side chain are necessary to prepare analogues of $\alpha$-ketoamides based on KITAQ sequence.

References:
NEW BIOACTIVE SULFONYLAMIDE DERIVATIVES OF AZOLES

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The high bioactive potential and combinations sulfonyl amide pharmacophore with a low-molecular structural core causes interest to search new sulfonyl amide derivatives of azoles.

We have elaborated the synthesis consisting in creation azole-containing biheterocyclic systems on the basis of various acetyltiophene or acetylfuran and the subsequent introduction of sulfonyl amide component in a molecule.

The resulting combinatorial series of structural analogs were tested for cytotoxicity to cancer cells of different origin (MDA-MB-231, Du145) and normal liver cells to assess the prospects of these substances and their impact on the safety of the human liver. Based on these results, we have selected the most promising compounds in the search for new anticancer drugs.
SYNTHESIS AND BIOCONVERSION OF NEW 1,5-BENZODIAZEPINE OXIMES

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Recent studies on the degradation of some benzodiazepines catalyzed by laccase in the presence of mediator in aqueous solution prompted us to investigate the ability of *Polyporus pinsitus* laccase (rPpL) to oxidize new 1,3,4,5-tetrahydro-2H-1,5-benzodiazepine oxime derivatives without mediator. The new 1,3,4,5-tetrahydro-2H-1,5-benzodiazepine oximes (IIa-c) were obtained by refluxing 1,5-benzodiazepinithiones (Ia-c), hydroxylamine hydrochloride and sodium acetate in anhydrous ethanol.

![Chemical Structures](image)

Synthesized derivatives have similar absorbance spectra in UV region with a maximum at 290 nm. (Fig. 1a). Oxidation potentials and pKa of the derivatives of these compounds were determined.

![Absorbance Spectra](image)

Fig. 1. IIa-c absorbance spectra (a) and IIC absorbance spectra change during oxidation catalyzed by rPpL laccase (b).

During the oxidation process the increase of absorbance was observed in all 280-700 nm region (Fig. 1b). The absorbance increased at 290 nm and new absorbance maxima at 360 and 550 nm were observed. Absorbance increasing as well as reaction rate depended on laccase and derivatives concentrations, structure and buffer solution pH. During the biocatalytic process derivatives were completely converted according to the LC-MS analysis.
SYNTHESIS OF NEW WATER SOLUBLE PHTHALOCYANINES

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Phthalocyanines are an important class of non-natural organic pigments which find applications in different technological areas (e.g., photodynamic therapy (PDT) and organic photovoltaics). Last decades uses of phthalocyanines for therapy and diagnosis of cancer and some other diseases are intensively studied [1]. According to, photophysical and photochemical characteristics such as solubility in water, photostability under light irradiation, quantum yield lifetime, phthalocyanines are candidate for further investigation for application in photodynamic therapy [2, 3].

Here we present the synthesis of new water soluble phthalocyanines. As starting material we chose 4-nitrophthalodinitrile, which in reactions with 3-pyridinemethanol and 3-pyridinepropanol gave 4-(3-pyridylmetoxy)- and 4-(3-pyridylpropoxy)-phthalodinitriles. Synthesis of phthalocyanines was accomplished in penthanol in the presence of strong base DBU. Synthesis of pyridinium salts was accomplished with methyl iodide in DMF. Tetrakis-[3-(N-methyl)pyridylmethoxy]phthalocyanato tetraiodide and tetrakis-[3-(N-methyl)pyridylpropoxy]phthalocyanato tetraiodide are soluble in water, and show good photostability under light irradiation. Physical and physicochemical properties of new phthalocyanines were investigated.

References:
THE NEW BUILDING-BLOCKS ON THE BASIS OF 4,4,4-TRIFLUOROCROTONONITRILE, INDOLE AND PYRROLE DERIVATIVES

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The new method of choice for selective functionalization of indoles and pyrroles using 4,4,4-trifluorocrotononitrile in the presence Lewis acids is proposed. The compounds obtained are successfully converted to the valuable building-blocks for construction more complicated structures with useful properties.

Synthetic utility of the new compounds and their biological activity are discussed.
DIASTEREOMERIC ATROPISOMERS OF 1,4-DIHYDROPYRIDINES

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Potentially biologically active diastereomeric 1,4-dihydropyridine (1,4-DHP) atropisomers are synthesized and investigated by spectroscopic and electrochemical methods at variable temperatures.

Rotation barrier of the C(4)-C(1’) bond between naphthyl and 1,4-DHP ring are compared for symmetrically (1a) and unsymmetrically substituted dihydropyridine derivatives (1b, 2a, 3a). Obtained results are compared with the 4-aryl-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine whose the rotation of C(4)-C(1’) bond has been "frozen-out" already at room temperature [1].

In aprotic media electrochemical oxidation of the 1,4-DHP (4-6) proceeds in one irreversible step, while 1,4-DHP (1a-3a, 1b) undergo two step irreversible oxidation (Table 1). During the anodic oxidation of 1,4-DHP (4-6) dimethoxy-methyl group is eliminated, while the 4-(3-ethoxy-naphthalen-2-yl) substituted pyridine derivatives were the products of the first oxidation step of 1,4-DHP (1a-3a). Mechanism and products of anodic oxidation have been studied.

<table>
<thead>
<tr>
<th>Cpd</th>
<th>$E_{1}^{ox}$, V</th>
<th>$E_{2}^{ox}$, V</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>+1.09</td>
<td>+1.68</td>
</tr>
<tr>
<td>1b</td>
<td>+1.19</td>
<td>+1.74</td>
</tr>
<tr>
<td></td>
<td>+1.44</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>+1.03</td>
<td>+1.67</td>
</tr>
<tr>
<td>3a</td>
<td>+1.12</td>
<td>+1.68</td>
</tr>
<tr>
<td>4</td>
<td>+1.17</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>+1.05</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>+1.09</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1.
Cyclic voltammetry program:
CH$_3$CN / 0.1 M NaClO$_4$,
working electrode – glassy carbon, counter electrode – Pt wire, reference electrode – Ag/Ag$^+$.  

Towards the synthesis of THF-containing marine polyketides

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Marine organisms produce structurally diverse secondary metabolites with important biological activities, providing excellent candidates for the investigation of new bioactive molecules. Polyketide macrolides containing tetrahydropyran (THP) or/and tetrahydrofuran (THF) units have shown interesting pharmacological profile, some of them reaching the clinical trial stage or the market. The determination of full bioactivity, mechanism of action, and further medical application are usually unfeasible because their isolation from natural sources furnishes small sample amounts. Thus, synthesis is a must for further development of these macrolides as pharmacological leads in terms of their supply and for structural and stereochemical assignments.

The synthesis of the THF-containing macrolactone of a new group of secondary metabolites with important cytotoxic activity against various human tumour cell lines will be discussed. Our efforts towards a strategy based on a RCM to form a trisubstituted double bond provided only small amount of product. Finally, a strategy based on a Julia-Kocienski olefination led to the desired macrocycle.

References:
Recyclizations of 1H-pyrrole-2,3-diones via their interaction with bifunctional nucleophiles represent a convenient construction method towards previously inaccessible or hardly accessible heterocyclic systems of condensed, bridge and spiro-types. The interactions described here present rare examples of the regioselective synthesis of spiro heterocyclic systems embedding different functional substituents in both heterocyclic fragments. Structurally all the products are the polycarbonyl compounds suitable for further elaboration. High yields, simplicity of reaction and purification procedures are the key advantages of this synthetic approach. The structures of compounds were confirmed by X-ray analysis.

Multicomponent reactions of 1H-pyrrole-2,3-diones is an effective technique for creation of spiroheterocyclic systems by upbuilding of the pyrroledione cycle.

Thus, the new synthetic strategy to produce biologically active heterocycles has been developed and it will be discussed.

Acknowledgements: The study was financially supported by the RFBR (Grants 12-03-00696 and 12-03-31157), the Ministry of Education and Science of Russian Federation, the Ministry of Education of Perm Region.
SYNTHESIS OF TRIARYL PYRROLES
AS CANNABINOID RECEPTOR LIGANDS

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Cannabinoid receptor ligands show clinical efficacy in the treatment of obesity and obesity-related disorders and improved cardiovascular and metabolic risk factors. The present study is devoted to the synthesis of new aryl pyrrole derivatives, which are analogues of known CB1 receptor antagonist – Rimonabant (SR141716), and their binding affinity and selectivity towards CB1 and CB2 cannabinoid receptors were evaluated. Triaryl substituted epoxy alkanoyl dihydropyrroles 1a–f were obtained as individual diastereomers by cycloaddition nitrile ylide 2 to epoxy enones 3a–f reaction.

\[
\begin{align*}
\text{3a-f} & \quad + \quad \text{2} \\
\text{CH}_2\text{Cl}_2 & \quad \rightarrow \\
\text{1a-f}
\end{align*}
\]

\( a \) \( X = H \), \( b \) \( X = Cl \), \( c \) \( X = Br \), \( d \) \( X = Me \), \( e \) \( X = OMe \), \( f \) \( X = OEt \)

Among these compounds, dihydropyrrole 3f exhibited similar values of binding affinity towards both subtypes of cannabinoid receptors (Ki CB1 = 0.54 μM, Ki CB2 = 0.27 μM). Dihydropyrrole 3c displayed high CB2 receptor selectivity, in contrast to the CB1 ligand Rimonabant. Compound 3c showed slightly lower CB2 activity value (Ki CB1 > 10 μM, Ki CB2 = 0.061 μM) as compared with the natural cannabinoid (-)-Δ⁹-THC (Ki CB2 = 0.036 μM). The results of this research indicate the expediency of further investigation of selective CB1 and CB2 ligands in series of triaryl substituted pyroles and confirm the fact that minor structural changes in the analogs of known ligands can substantially to respond to the specificity and efficiency of their interactions at the receptor level.
SYNTHESIS OF POLYQUINOLINES: NEW BCL-2 FAMILY PROTEIN MODULATORS

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Bcl-2 family members are important regulators of apoptosis that are divided in three groups comprising anti- and pro-apoptotic members. Overcoming altered apoptosis leading to resistance of tumor cells to conventional chemotherapy is an attractive therapeutic approach that could be achieved by modulation of the Bcl-2 family protein-protein interactions (PPI). Thus, the development of small molecules able to mimic the α-helix of pro-apoptotic proteins that interact with the hydrophobic groove of their anti-apoptotic counterparts has lately attracted great interest. Consequently, we recently developed a research program concerning the synthesis and biological evaluation of quinolines that mimic the helicoidal structures involved in PPI regulating cellular apoptosis.

The synthetic work and the results of the structure-activity relationship studies performed in the series will be described.

References:
SYNTHESIS AND BIOLOGICAL EVALUATION OF AZIRIDIN-1-YL OXIMES AS POTENTIAL ANTITUMOR AGENTS

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In our effort to discover and develop potential anticancer agents, we synthesized a series of aziridin-1-yl oximes 1 derivatives. A preliminary study of SAR of 1 suggested that substitution on $p$-position of aniline core increases the cytotoxic activity.

For this reason and also in order to obtain SAR of $p$-substitution at aniline core we have extended the range of analogues of 1 and evaluated their cytotoxic activity on several cancer cell lines. The results obtained allowed us to provide a hypothesis for further structure optimization of aziridin-1-yl oximes 1.
Tuberculosis is a major health problem worldwide. In 2008, there were an estimated 8.9–9.9 million incident cases of TB, 9.6–13.3 million prevalent cases of TB, 1.1–1.7 million deaths from TB among HIV-negative people and an additional 0.45–0.62 million TB deaths among HIV-positive people (classified as HIV deaths in the International Statistical Classification of Diseases), with best estimates of 9.4 million, 11.1 million, 1.3 million and 0.52 million, respectively [1]. The development of effective chemotherapy for the treatment of tuberculosis began in the 1940s and has been reinvigorated recently due to concern regarding the emergence of highly drug-resistant TB strains [2]. Today, procedures being at the stage of clinical trials or preclinical development several compounds such as diarylquinolines (TMC207). They show promising activities against sensitive and resistant \textit{Mycobacterium tuberculosis} strains [3]. We applied lithiation method with some modification using cerium chloride (III) to chemical synthesis of some derivatives of diarylquinolines. The results of our studies of this reaction are reported.

References:
SELENIUM ANALOGUES OF RALOXIFENE: SYNTHESIS AND ACTIVITY

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Raloxifene is selective estrogen receptor modulator (SERM) already used for treatment of osteoporosis and reduction of invasive breast cancer incidence in postmenopausal women. On the other hand, selenium has attracted a great interest as an essential element and certain diseases have been eradicated by dietary supplementation of this element. Furthermore, selenophene–based derivatives exhibit potent \textit{in vitro} and \textit{in vivo} antitumoral activity which involves DNA damage. With the aim to develop new drugs for treatment of estrogen dependant cancers we have elaborated convenient synthetic pathway for preparation of selenium analogues of \textit{Raloxifene} as a key step using cyclization of diarylalkyne under two–phase selenobromination conditions.

A series of selenium analogues have been obtained and characterized. Structure and cytotoxic activity relationship on various cancer cell lines including estrogen-positive and estrogen-negative will be discussed.
SYNTHESIS AND STUDIES OF AMPHIPHILIC 1,4-DHP DERIVATIVES WITH STYRYLPYRIDINIUM MOIETIES

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1,4-Dihydropyridine (1,4-DHP) derivatives possess a wide variety of pharmacological activities. According to Triggle, 1,4-DHP nucleus is a privileged structure which is intrinsic characteristic for many pharmacologically active compounds and commercial drugs. Polyfunctional pyridinium amphiphiles based on 1,4-DHP structures possess self-assembling properties and some of them are very efficient in gene delivery experiments into many cell lines in vitro. The aim of our work - synthesis of new cationic amphiphilic 1,4-DHP derivatives containing styrylpyridinium moieties, studies of self-assembling, fluorescent and antioxidant properties.

Establishing of structure-activity relationships for polyfunctional pyridinium 1,4-DHP derivatives is a promising tool for design and developing of more potent and efficient physiologically active compounds. Obtained styrylpyridine 1,4-DHP derivatives could be promising fluorescent probes with specific biological activities for biochemical experiments.

Acknowledgements: EURONANOMED Project “ChemTherDel”
NEW 2-OXINDOLE CONTAINING ANTIPROLIFERATIVE AGENTS

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Two new basic molecules containing 2-oxindole fragments as potential inhibitors of the ATP-binding sites of GSK-3\(\beta\)/CDK kinases family have been designed. QSAR and molecular docking methods were used for this. Evidently that Erlenmeyer-Plöchl reaction is optimal for the synthesis of compounds designated as 3 and 6. The above mentioned reactions were carried out successfully using the activation by ultrasonic irradiation. This procedure is the first successful application of ultrasound supporting for Erlenmeyer-Plöchl reaction \(^1\).

\[
\begin{align*}
\text{Ar} = \text{C}_6\text{H}_5; & \quad \text{b} \quad \text{Ar} = 4-\text{FC}_6\text{H}_4; & \quad \text{c} \quad \text{Ar} = 4-\text{ClC}_6\text{H}_4; & \quad \text{d} \quad \text{Ar} = 3-\text{BrC}_6\text{H}_4; \\
\text{e} \quad \text{Ar} = 2-\text{CH}_3\text{C}_6\text{H}_4; & \quad \text{f} \quad \text{Ar} = 4-\text{CH}_3\text{C}_6\text{H}_4; & \quad \text{g} \quad \text{Ar} = 4-\text{tert}-\text{butylC}_6\text{H}_4.
\end{align*}
\]

The compound 4 inhibits proliferation of human lymphoma cell culture Jurcat cells and non-toxic to human fibroblasts in concentrations of 10-50 \(\mu\text{mol/l}\).

PREPARATION AND CYTOTOXICITY OF SELENOLOTHIOPHENES

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In the last years, fused heterocyclic systems have attracted considerable attention both from a theoretical standpoint and in view of their various practical applications. This interest is evidenced by a sharply increasing number of publications devoted to various aspects of the chemistry of fused thiophenes. However, much less is known about selenolothiophenes. Motivated by the importance of developing direct and facile methods for the preparation of various selenolothiophenes we examined interaction of 2- and 3-ethynylthiophenes with various selenium (I), (II) and (IV) chlorides and bromides in aprotic solvents as well in aqueous media.

As a result desired aminomethylselenolo[2,3-b]- and -[3,2-b]thiophenes were obtained in good to almost quantitative yields. Molecular structures of selenolothiophenes have been unambiguously confirmed by X-ray analysis. Structure and cytotoxic activity relationship on HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), and NIH 3T3 (normal mouse fibroblasts) will be discussed.
Molecular Modeling, Synthesis and Biological Evaluation of New Potent Pyrazolo[1,5-\textit{a}]-Pyrimidine Inhibitors of CDK2

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Despite the fact that the structures of many protein kinases have been characterized by X-ray crystallography, molecular modeling of new kinase inhibitors remains a significant challenge. Recently, we successfully applied a refined quantum mechanics-based scoring protocol to reproduce the binding affinities of known pyrazolo[1,5-\textit{a}]pyrimidine inhibitors of CDK2 kinase and their bioisosteres. Utilizing the same scoring function, we have modeled new, previously unknown inhibitors bearing properly substituted biphenyls at the 5-postion of the pyrazolo[1,5-\textit{a}]pyrimidine core. The predictive power of the in silico methodology has been verified by subsequent synthesis and biological evaluation of the compounds. The most potent compounds in this series exhibit activity against CDK2 kinase in the single-digit nanomolar range.

\textbf{References:}
SYNTHESIS OF NOVEL TRIAZOLE-QUINAZOLINONE DERIVATIVES

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Quinazolines play important role in the field of drug discovery. Coupling quinazolines to biologically active molecules like triazoles might be a way for the synthesis of novel and significant derivatives. Considering our research interests related to the synthesis of new quinazolinone derivatives with potential antioxidant application, we now report the synthesis of novel triazole-quinazolinone derivatives.

\[
\begin{align*}
\text{OH} & \quad \text{HC(OEt)}_3 \\
\text{NH}_2 & \quad \text{H}_2\text{NC}_2\text{H}_4\text{OH} \\
\text{O} & \quad \text{Cu(I)} \\
\text{R} & \quad \text{TsCl}
\end{align*}
\]
STABILITY AND DEHYDRATION KINETICS OF PEMETREXED HYDRATES

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Pemetrexed disodium (Fig. 1.) is a heterocyclic compound containing pyrrolo[2,3-d]pyrimidine bicyclic core and is used in chemotherapy mainly for lung cancer treatment.

![The structure of pemetrexed disodium](image)

It is highly water-soluble white crystalline solid that may form two hydrates and metastable amorphous form [1].

Preparation conditions of hemipentahydrate, heptahydrate and amorphous form were clarified and obtained solid phases were investigated with powder X-ray diffraction. The stability of pemetrexed hydrates over controlled relative humidities and temperature was studied. Thermogravimetric and differential thermal analysis showed that dehydration of heptahydrate occurs at 60 °C and proceeds stepwise by forming hemipentahydrate followed by further dehydration. Dehydration kinetic parameters and most appropriate kinetic model for hemipentahydrate was calculated.

References:
SYNTHESIS AND CYTOTOXIC ACTIVITY OF FURYLSILYLAMINES

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The heterocyclic amines are important building blocks for the creation of anticancer drugs\(^1\). To further extension of our investigations on the biologically active organosilicon compounds we have prepared new 2,5-bis(3-aminopropylidimethylsilyl)furans. The starting furylhydrosilanes 1, 2 have been synthesized from the furan by consecutive metallation and hydrosilylation reactions:

\[
\begin{align*}
&\begin{array}{c}
\text{O} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \text{Me} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} & \begin{array}{c}
\text{Me} \\
\underset{\text{Si}}{\text{H}} \\
\end{array} \\
\end{align*}
\]

The transformation afforded a series of silylamines 3-11 containing two or three different heterocycles in good yield (51-59%). The cytotoxicity of amines on tumour cells HT-1080, MG-22A and normal mouse fibroblasts 3T3 have been investigated *in vitro*. All studied compounds exhibited high cytotoxic activity (IC\(_{50}\) 0.3-3 μg/ml). Compound 8 with piperidine and N-methylpiperazine rings in one molecule is the most promising compound in this series of amines: moderate toxicity (LD\(_{50}\) 380 mg/kg), high cytotoxicity on both cancer lines (IC\(_{50}\) 0.3-2 μg/ml) and lower cytotoxicity on normal fibroblasts (IC\(_{50}\) 11 μg/ml).

\[^{1}\text{Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*. Thieme: Stuttgart-New York, 2009; pp 1332.}\]
SYNTHESIS AND STUDIES OF NOVEL 1,4-DIHYDROPYRIDINE DERIVATIVES

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Introduction. 1,4-Dihydropyridine (1,4-DHP) derivatives are compounds which play an important role in synthetic, medicinal and bioorganic chemistry [1].

The aim of work. New N-propargyl and/or cationic pyridine moieties-containing 1,4-DHP’s and their structure-related parent compounds were synthesized to study: 1). structure-activity relationships in cell viability test in SH-SY5Y human neuroblastoma cells in the absence/presence of mitochondrial toxin (MPP⁺); 2). 1,4-DHP’s influence on calcium overload in SH-SY5Y and A7R5 rat aorta smooth muscle cells; 3). total antioxidant activity using phosphomolybdenum method.

Results. Novel N-propargyl substituted and N-unsubstituted 1,4-DHP’s have been synthesised according to Scheme.

Tested 1,4-DHP’s possessed moderate antioxidant activity. Analyses of structure-activity relationships shows that addition of N-propargyl substituent to 1,4-DHP cycle did not affect any protective activity in MPP⁺ cytotoxicity model in SH-SY5Y cells, however slightly increased the Ca²⁺ channel blocking activity in SH-SY5Y cells, but not in A7R5 cells.

Acknowledgements: EURONANOMED Project “ChemTherDel” and ESF Project Nr. 2009/0217/1DP/1.1.1.2.0/09/APIA/VIAA/031.

STABILITY OF ISONIAZID–CARBOXYLIC ACID COCRYSTALS

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Isoniazid is an anti-tubercular drug used to treat the *Mycobacterium tuberculosis* bacterial infection. Isoniazid tablet formulations are known to undergo degradation. Possible solutions for the stability problem are alternative crystal forms of isoniazid. For instance, cocrystals are crystalline single phase materials composed of different molecular compounds. New isoniazid cocrystals with selected carboxylic acids have been prepared and their properties have been investigated to explain stability of these cocrystals.

The melting points of isoniazid–dicarboxylic acid 2:1 cocrystals decrease with an increasing length of the acid chain. However, conformation change of compounds introduces instability to the system.

Isoniazid–dicarboxylic acid cocrystal solubility tends to increase with an increasing solubility of the coformer. The solubility may be influenced by the stability of a cocrystal.

The stability of isoniazid–carboxylic acid cocrystals was evaluated at accelerated climatic conditions (30 °C, 75% RH). Decomposition of isoniazid–benzoic acid and isoniazid–malonic acid cocrystals was observed after 2-4 week storage. The poor stability of isoniazid–benzoic acid cocrystal is explained by similar hydrogen bonding motifs in crystalline isoniazid and isoniazid–benzoic acid cocrystal.

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TARGETED CONJUGATE OF ISONIAZID WITH MAGNETIC NANOPARTICLES

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At present, isoniazid (isonicotinoyl hydrazide, INH) represents a medical drug of first choice to be used for prevention and treatment of tuberculosis.¹ This serious infectious disease represents a considerable threat to humankind and affects up to one third of world population, however, mostly people with decreased immunity (e.g., HIV).¹ The present article describes preparation and characterization of isoniazid conjugate (INH) with magnetic nanoparticles (~ 60 nm) with a core-shell structure (Fe₃O₄@SiO₂).² The isoniazid molecules were attached to the surface of the nanoparticles Fe₃O₄@SiO₂ by means of covalent pH-sensitive amidine bond.

The conjugate was characterized by means of microanalysis, IR spectroscopy, powder X-ray diffraction, TEM and dynamic light scattering. The release of INH from the carrier was monitored under the in vitro conditions with the use of UV-Vis spectroscopy. In a solution of 1·10⁻² mol·¹⁻¹ HCl at the temperature of 37 °C, INH is released from the carrier with the half-time t₁/₂ = 65 s. In a model medium with the pH value equal to 5.3, which is characteristic of a pathological tissue, isoniazid is released with the half-time t₁/₂ = 115 s (phosphate buffer 2·10⁻² mol·¹⁻¹; 37 °C). The synthesized potential slow-acting¹ conjugate of INH with biocompatible magnetic nanoparticles Fe₃O₄@SiO₂ enables a targeted effect of isoniazid in the affected tissue by application of external magnetic field.²

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References:
SYNTHESIS, STRUCTURE AND BIOLOGICAL PROPERTIES OF 1-(THIAZOL-2-YL)- AND 1-(BENZO THIAZOL-2-YL)PYRROLIDIN-2-ONES

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Novel effective synthetic pathway has been developed for the preparation of N-hetaryl substituted 2-oxo-pyrrolidine based structures through intramolecular alkylation of 4-chloro-N-(hetaryl)butanamides. To adjust the bis-cyclic products formation in presence of K₂CO₃, NaOH, NaI, amines or silica gel in different solvents, acetone, ethanol and toluene, in order to assess the possibility of thermal induced cyclization of 4-chloro-N-(1,3-thiazol-2-yl)butanamide and 4-chloro-N-(1,3-benzothiazol-2-yl)butanamide, the reaction process was controlled by HPLC-MS method. The reaction products have been identified using various physico-chemical methods, including HSQC and HMBC two-dimensional NMR spectroscopy. We found that in contrast to literature data for similar compounds, regiospecific alkylation took place not at the endocyclic, but at the exocyclic nitrogen atom and proceeded with the formation of 1-[(benzo)thiazol-2-yl]pyrrolidin-2-ones. The optimal conditions for the regioselective alkylation have been proposed and tested for the analogous intramolecular cyclization of 3-chloro-N-(1,3-thiazol-2-yl)propanamide.

\[
\begin{align*}
\text{Het} & \quad \text{Het:} \\
\text{N} & \quad \text{S} \\
\end{align*}
\]

It had been established that the synthesized compounds were non-toxic substances and exhibited selective inhibitory activity against the test gram-positive bacterial (Staphylococcus aureus and Bacillus cereus) and fungal (Candida albicans and Aspergillus niger) strains. 1-(Benzothiazol-2-yl)pyrrolidin-2-one displayed a specificity of the cytotoxic effect towards mouse hepatoma cell line MG-22A in microgram range. The nootropic activity of the synthesized N-substituted 2-oxo-pyrrolidines has been examined.

Acknowledgement: We thank the Latvian Council of Science (Joint Project 10.0030) for financial support.
NOVEL ANTIMICROBIAL TETRAHYDROISOQUINOLINES: SYNTHESIS AND IMMOBILIZATION ON THE SURFACE OF MAGNETIC NANOCARRIERS

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A series of new N,O-alkyl derivatives of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline has been synthesized under PTC conditions and subsequent N-alkylation. Various PTC systems and catalysts have been examined in order to investigate the reaction regioselectivity. The synthesized compounds revealed good inhibitory activity concerning Gram-positive and Gram-negative bacterial strains and fungi with MIC and MBC of 0.5–32 μg/ml for the most active ones, which were recommended for further investigation on enzymes involved in process of DNA replication.

\[
\begin{align*}
\text{R}^1 \text{H, Alk, SiR'R''R'''; R}^2 \text{Alk}
\end{align*}
\]

Some of the obtained compounds of different structure were selected for the synthesis of iron oxide/oleic acid based nanoparticles to evaluate their efficacy as antimicrobial agents. Superparamagnetic nanoparticles with iron oxide core diameter of 6.4–10.5 nm were synthesized using our earlier developed methodology [1]. To explore the possibility of extending the range of biologically active compounds used for synthetic magnetosomes preparation, the procedure for their synthesis was improved. XRD analysis, DLS measurements, method of magnetogranulometry and some others have been employed to determine the structure and size and investigate the properties of the nanoparticles synthesized.

Acknowledgement: We thank the Latvian Council of Science (Gr.09.1321 and Joint Project 10.0030) and EU COST Action CM 0902 for financial support.

References:
HETEROCYCLOPHANES BASED ON URACIL DERIVATIVES

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Herein a method for preparing heterocyclophanes which consist of uracil derivatives and five- and six-membered heterocycles bridged to each other with polymethylene chains is reported. The starting material for the introduction of uracil constituents were 1,3-bis(ω-bromoalkyl)-5(6)-substituted uracils 1. Reactions of the dibromides with 2-mercaptobenzimidazole afforded macrocyclic isomers 2a,b and heterocyclophane 3. Substitution of Br in 1 with NH₂Et followed by the reaction with cyanuric chloride gave heterocyclophanes 4. Macrocycles 5 have been prepared by click-chemistry method. Acyclic counter-parts of the heterocyclophanes have been synthesized with the same approach.

Some of the acyclic and macrocyclic compounds showed activity towards gram-positive bacteria and yeast fungus.

Acknowledgements: RFBR (projects #12-03-31862 and 13-03-00709), Federal goal-oriented program (contract #8432)

References:
DESIGN AND SYNTHESIS OF METAL-BINDING PEPTIDES

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A promising approach for the design of novel potential antitumor agents consists on the conjugation of a metal complex to a peptide sequence in an effort to improve its activity and bioavailability. Active research has been focused on the use of complexes of non-toxic metals such as Fe, Cu or Mn. In fact, complexes of these metals containing the tetradeinate ligand $\text{Me}_2\text{PyTACN}$ have been described as excellent oxidation catalysts on a wide range of substrates (1-3). Moreover, these $N_4$ ligands are emerging as versatile catalysts for oxidative processes with biomedical applications. These properties prompted us to study the conjugation of a $\text{Me}_2\text{PyTACN}$ ligand to the undecapeptide $\text{BP16}$ (4). This sequence has been identified from a library of antimicrobial peptides and has been shown to exhibit excellent cell-penetrating properties.

Herein we report a useful methodology for the solid-phase synthesis of peptides bearing a $\text{Me}_2\text{PyTACN}$ ligand either at the N-terminus or at the $N^e$-amino group of a Lys residue. The strategy involves the preparation of a peptide sequence followed by incorporation of a pyridine derivative as the anchor binding point. Next, the corresponding secondary amine ligand is attached affording the metal-binding peptide. The solid-phase synthesis of a range of metal-binding peptides will be described and discussed.

Zinc-containing enzymes Carbonic anhydrases (CA) are playing an important role in metabolic processes of bicarbonate and carbon dioxide. From presently known 16 CA isoforms, the highest attention is paid to tumor associated CA IX. The waste majority of known CA inhibitors contain sulfonamide moiety as Zn-binding group. Expanding research on new anti-cancer agents we paid our attention to derivatives of thiophene-2-sulfonamide.

Here we report thiol-free procedure for the synthesis of thiophene-2-sulfonamide thioethers 2 based on derivatives of thiouronium salt 1.
SYNTHESIS AND CYTOTOXICITY OF NEW 6,6-DIMETHYL-2-OXO-4-{2-[5-ALKYL-SILYL(GERMYL)]HETARYL-2-YL}VINYL-5,6-DIHYDRO-2\textit{H}-PYRAN-3-CARBONITRILES

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New 6,6-dimethyl-2-oxo-4-{2-[5-alkylsilyl(germyl)]thiophen-2-yl}-5,6-dihydro-2\textit{H}-pyran-3-carbonitriles have been prepared by condensation of corresponding silicon(germanium) containing furyl(thienyl)-2-carbaldehydes with 3-cyano-4,6,6-trimethyl-5,6-dihydropyran-2-one using pyridine acetate as the catalysts:

\[ \text{O} \overset{\text{NH, CH}_3\text{COOH}}{\text{C}_6\text{H}_6} \text{O} \quad \text{R} \]

\[ = \text{Me}_3\text{Si}, \text{Et}_3\text{Si}, \text{Me}_3\text{Ge}, \text{Et}_3\text{Ge}, \text{Me}_2\text{Bu}S\text{i}, \text{Me}_2\text{Ph}S\text{i} \]

\[ \text{X} = \text{O}, \text{S}; \quad n = 1,2 \]

The structure of 6,6-dimethyl-2-oxo-4-{2-[5-trimethylsilyl]thiophen-2-yl]-5,6-dihydro-2\textit{H}-pyran-3-carbonitrile (1a) was studied by X-Ray diffraction method. The molecule of 1a is characterized by \textit{E}-conformation: the torsion angle of C4-C10-C11-C2' is equal 178.4(2)°. The effects of the heterocycle and the substituent at the heterocyclic ring on the cytotoxicity (two tumour cell lines HT-1080, MG-22A and normal mouse fibroblasts NIH 3T3) of the compounds have been studied \textit{in vitro}. Introduction of the certain triethylsilyl(germyl) group at the thiophene ring improves the cytotoxicity against cancer cells MG-22A (IC\textsubscript{50} = 2-6 μg/ml) and suitably decreases cytotoxicity to normal cells NIH 3T3 (IC\textsubscript{50} = 201-362 μg/ml). Furthermore, these groups greatly reduce the toxicity of new compounds (LD\textsubscript{50} = 1296-1569 mg/kg).
SYNTHESIS, STRUCTURE AND MOLECULAR MODELING OF 2’-\{[(E)-ANDROST-5-EN-17-YLIDENE]-METHYL\}OXAZOLINES

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Three step synthesis of 2’-\{[(E)-androst-5-en-17-ylidene]-methyl\}oxazolines 3 – new probes for investigation target macromolecules and key compounds for development of potential therapeutics is presented. Interaction of 20-ketosteroid-17,21-dihalide 1 with amines led to Favorsky type rearrangement\cite{2}; cyclization of obtained amides 2, followed by removal of protective groups and/or transformations of substituents in oxazoline ring results in target 17(20)\textit{E}-oxazolines 3, particularly to compounds with \textit{C}4’ chiral atom\cite{2,3}. Oxazolines 3\textit{f} and 3\textit{g} were successfully docked to ligand-binding site of nuclear receptor LXR\textit{β}.

\begin{center}
\begin{tikzpicture}
\node (start) at (0,0) {1};
\node (intermediate) at (2,0) {2};
\node (product) at (4,0) {3};
\draw[->] (start) -- (intermediate);
\draw[->] (intermediate) -- (product);
\end{tikzpicture}
\end{center}

\begin{center}
\textit{a}, \textit{X}=\textit{Y}=\textit{H}  \\
\textit{b}, \textit{X}=\textit{Y}=\textit{CH}  \\
\textit{c}, \textit{X}=\textit{C4’-Y}=\text{cyclohexyl}  \\
\textit{d}, \textit{X}=\text{COOCH}_3; \textit{Y}=\textit{H}  \\
\textit{e}, \textit{X}=\textit{H}; \textit{Y}=\text{COOCH}_3  \\
\textit{f}, \textit{X}=\text{CH}_2\text{OH}; \textit{Y}=\textit{H}  \\
\textit{g}, \textit{X}=\textit{H}; \textit{Y}=\text{CH}_2\text{OH}
\end{center}

\textbf{Acknowledgement}: This study was supported by RFBR (grant 12-04-31075 mol\textunderscore a).

SYNTHESIS OF SUBSTITUTED PYRIMIDO[4,5-b]INDOLE RIBONUCLEOSIDES

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Some 7-hetaryl-7-deazaadenosines showed cytostatic activity against multiple cell lines in nanomolar concentrations. Based on these results, the goal of this work was to synthesise a series of 4-amino-5(6)hetaryl as well as 4-substituted pyrimido[4,5-b]indole ribonucleosides to investigate their biological activities.

Synthesis started from previously prepared benzoylated 4-chloro nucleosides which were converted to free 4-aminopyrimido[4,5-b]indole nucleosides or directly to 4-substituted derivatives. (Het)aryl substituents were introduced into positions 5 or 6 by Pd-catalysed Suzuki or Stille cross-coupling reactions using X-Phos ligand in DMF. Target nucleosides were tested for biological activities.

![Scheme 1](image)

Acknowledgements:
This work was supported by the Academy of Sciences of the Czech Republic, Czech Science Foundation (P207/11/0344) and by Gilead Sciences, Inc.

References:
SYNTHESIS OF NOVEL BIOACTIVE ANTHRA[2,3-b]FURAN-5,10-DIONES

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Heterocyclic derivatives of anthraquinone are promising compounds to search for the new anticancer drugs. Previously, we have reported the method of synthesis of 2-methylanthra[2,3-b]furan-5,10-diones and shown that some of them are able to inhibit topoisomerase I and have a high anti-proliferative activity [1]. For further structure-activity studies, we have developed a scheme for the synthesis of anthra[2,3-b]furan-5,10-diones with carboxamide group at the position 2. Anthra[2,3-b]furan-5,10-dione-2-carboxamide was obtained from 4,11-di-methoxy-5,10-dioxoanthra[2,3-b]furan-2-carboxylic acid 1 [2]. Nucleophilic substitution of methoxy groups by ethylenediamine and the following introduction of the guanidino-residues at side chains produce the final compound 2. Biotesting established that 4,11-bisguanidine derivative 2 selectively inhibits a growth of prostate tumor cells (DU-145) and shows a high activity against telomerase and topoisomerase I – potential targets of cancer therapy. Moreover, the novel derivative 2 has an antiviral activity against Coxsackie B4 virus and resistant Herpes simplex virus-1.

References:
Flavonoids, arilbenzo-[b]-pyrans, are large and widespread group of natural compounds, which have an unusually wide range of biological activity. Dihydroquercetin (1) - trans-2R3R-2,3-dihydro-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-on (C\textsubscript{15}H\textsubscript{12}O\textsubscript{7}, M 304) is one of the representatives of this group. The oxygen atoms can coordinate metal ions to form aquacomplexes of dihydroquercetin of various types. We report here the synthesis and properties of new stable mono- and biligand zinc (2), copper (3) and calcium (4) aquacomplexes, shown in the figure below:

Physical methods (NMR, IR, UV-vis, EPR, RSEDMA) were used to establishing the structure and properties of new complex compounds. Results indicate that the chelation sites are different for zinc, copper and calcium compounds. The content of bound water in the zinc, copper and calcium complexes of dihydroquercetin was established by differential scanning calorimetry and thermogravimetry. It is described; there are two types of bound water in the zinc complex: weakly and strongly bound. There is only one kind of bound water in copper and calcium complexes. The study of the biological activity of the new compounds showed their potential as candidate molecules for development of medicines.
POLYMORPHISM OF THE NEW QUINOLONE DIURETIC CARBOQUINOL

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Since polymorphism of drugs can greatly affect their biological characteristics [1], any serious pharmaceutical manufacturer can not ignore this problem at present. By the same reason the government regulatory agencies pay attention to the issues of obtaining, identification, description, purity and properties of crystalline forms of products used in pharmacy. As a result, nowadays the registration of a new medicinal substance became impossible without such information in many countries of the world. Taking into account these circumstances we have studied crystal modifications of 6-hydroxy-N-(4-methoxyphenyl)-4-oxo-1,2-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxamide (1) proposed under the name of Carboquinol as a new diuretic.

Thus, it has been found that depending on the solvent used for crystallization anilide 1 can actually form some polymorphic modifications, which are different by their diuretic properties. The conditions, which according to the data of X-ray powder and single-crystal X-ray structural analysis, NMR $^1$H and $^{13}$C spectroscopy in solution, solid-state $^{13}$C NMR-spectroscopy, as well as high performance liquid chromatography allow to obtain the crystal modification of Carboquinol required with a high chemical and polymorphic purity, have been suggested.

References:
2,1-BENZOTHIAZINE-3-CARBOXAMIDES AS POTENTIAL NEW ANALGESICS

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Oxicams are an integral part of the range of modern non-steroidal anti-inflammatory drugs [1]. Piroxicam (1, R = 2-Py) became the first commercially successful drug of this group. Later its more effective analogs – Isoxicam, Meloxicam, etc., appeared at the pharmaceutical market. Today they are widely used by practical medicine in treating numerous rheumatic and autoimmune human diseases under the common name of selective inhibitors of cycloxygenase-2. It is interesting that isomeric oxicams of 4-hydroxy-1-R-2,2-dioxo-1H-2λ6,1-benzothiazine-3-carboxamides (2), which are different only by reverse mutual arrangement of atoms of nitrogen and sulfur in the thiazine cycle, remain completely unstudied at present. The cause of the existing situation is known – it is the absence of preparative methods for the synthesis of compounds of this chemical group.

We have developed a simple and effective method for obtaining of alkyl 4-hydroxy-1-R-2,2-dioxo-1H-2λ6,1-benzothiazine-3-carboxylates (3, R = H, Alk, All, Ph); on their basis a large series of anilides and hetarylamides 2 have been synthesized. To confirm their structure NMR spectroscopy (1H and 13C), mass spectrometry and X-ray structural analysis have been used. According to the results of pharmacological trials the substances, which exceed significantly the known drugs of the oxicam series by their analgesic properties and are of interest for further profound research, have been found among amides 2 synthesized.

References:
The carbonic anhydrases (CA) are metalloenzymes, containing zinc ion in the active site of enzyme. These enzymes catalyze a very simple reaction – interconversion of carbon dioxide and the bicarbonate ion. Many of CA isoizymes are important targets for the design of inhibitors with the clinical applications. Two main classes of carbonic anhydrase inhibitors are known: the metal complexing anions and unsubstituted sulfonamides, which bind to the Zn\(^{2+}\) ion of the enzyme. Coumarin derivatives were shown to constitute a totally new class of inhibitors of the zinc metalloenzyme carbonic anhydrase\(^1\).

In our work, we synthesized coumarin sulfonamides 2 via Pechman condensation and coumarin sulfonylation. Tricylic coumarins 3 were synthesized from ethyl-2-oxocyclopentanecarboxylate and phenols 1. Inhibition of hCA with coumarins were shown.

**Acknowledgements:** This project was partially financed by European Social Fund (No. 2009/0203/1DP/1.1.1.2.0/09/APIA/VIAA/023).

**References:**
REDOX LABELLING OF NUCLEIC ACIDS FOR ANALYZING NUCLEOTIDE SEQUENCES

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Nucleobase labelling of DNA for electrochemical sensing was attained through enzymatic incorporation of nucleotide conjugates with redox-active moieties (anthraquinone, benzofurazane and azidophenyl) using labelled deoxynucleoside triphosphates. An efficient two-step methodology for construction of base-modified DNA was developed based on aqueous-phase cross-coupling reactions of halogenated nucleoside triphosphates (dNTPs) with arylboronic acids (the Suzuki-Miyaura reaction) or terminal acetylenes (the Sonogashira reaction) followed by polymerase incorporation. 5-Substituted pyrimidine dNTPs and 7-substituted 7-deazapurine dNTPs are good substrates for some DNA polymerases and can be incorporated into DNA by primer extension which is suitable for construction of short DNAs with a few modifications in one strand.

Acknowledgements:
This work was supported by the Academy of Sciences of the Czech Republic (RVO: 61388963), Grant Agency of the Academy of Sciences of the Czech Republic (IAA400040901), Czech Science Foundation (203/09/0317 and P206/12/G151) and by Gilead Sciences, Inc. (Foster City, CA, U. S. A.).

References:
OPTIMIZATION OF THE LEAD MD77

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The investigation which led to the identification of our lead MD77 began from a screening (dual-luciferase assay system) of chemical libraries, performed in collaboration with our colleagues of the Korean Research Institute of Bioscience and Biotechnology (KRIBB). MD77 exerted positive results in the dual-luciferase assay, showing 20% inhibition at 5 μM. It was also able to significantly interact with STAT3-SH2 domain, with a dose-dependent profile and an IC50 of 17.7 μM (AlphaScreen-based assay). Moreover, it displayed a significant growth inhibitory activity evaluated on a panel of tumor cell lines with a GI50 around 2 μM for most of them. Modeling, docking and crystallographic studies were also performed and they gave a key support in understanding the binding mode of MD77 to the STAT3-SH2 domain. In light of these results, MD77 became our starting point for the development of new direct STAT3 inhibitors. Initially, the optimized derivatives were designed following the classical methodologies of medicinal chemistry, in which the molecule undergoes a gradual modification on the basis of SAR studies and with the support of molecular modeling studies. In particular, the substitution of the amide functionality with a bioisosteric thioamide group and the nature of the substituent at position 5 were considered. In detail, alkyl groups or halogens were introduced in the aromatic ring. In addition, since docking studies on MD77 suggested that in the binding mode of its favoured conformation to the SH2 domain, which is comparable to that of phosphorylated Tyr-705, the trifluoromethyl group could play an important role by establishing three hydrogen bond interactions with the guanidine moiety of Arg-595 residue, we synthesized the analogue lacking the substituent to verify this hypothesis. The main results from the biological screening will be displayed in the poster.

Acknowledgements: The financial support by PUR 2008 and PRIN 2010-2011 is acknowledged

NOVEL FPEP NUCLEOTIDE ANALOGUES AS INHIBITORS OF THE PLASMODIAL HG(X)PRTS

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The causative agents of malaria are protozoan parasites from the Plasmodiidae family. Hypoxanthine-guanine-(xanthine) phosphoribosyltransferase, HG(X) PRT, has been suggested as a target for the development of new anti-malarial therapeutics. Acyclic nucleoside phosphonates (ANPs) are potent and selective inhibitors of plasmodial HG(X)PRTs.¹ A new series of ANPs, bearing the [3-fluoro-(2-phosphonoethoxy)propyl] (FPEP) and [3-fluoro-(2-phosphonomethoxy)propyl] (FPMP) moiety has been prepared and tested towards human and plasmodial HG(X) PRTs (Fig. 1). Some of the FPEPG analogues were found to be potent inhibitors of human HGPRΤ, PfHGXPRT, and PvHGPRT with Ki's ranging from 0.1 to 29 µM.

Target ANPs

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References:
PREPERATION AND CHARACTERIZATION OF BENPERIDOL SOLVATES AND POLYMORPHS

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Benperidol (1-{1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl}-1,3-dihydro-2H-benzimidazol-2-one) is butyrophenone derivative, an antipsychotic, which can be used for the treatment of schizophrenia [1]. In the literature it is described that benperidol exists in three polymorphic forms, hydrate and ethanol solvate [2]. However, only crystal structure of polymorphic form I is reported [3]. In this study we examined the possibility of formation and the stability of various crystal forms of benperidol.

Benperidol was crystallized from various organic solvents. Crystallization from ethanol, methanol and acetonitrile resulted in formation of solvates with corresponding solvents, while from other solvents polymorph I was obtained. The only exception was isopropanol from which polymorph II was obtained in case of slow crystallization. Crystallization form water resulted in formation of the dihydrate. Crystal structure of polymorph II, dihydrate and all three solvates was determined.

Desolvation process of all solvates was studied and obtained results were associated with crystal structures of solvates and polymorphous forms. Dehydration kinetics of benperidol dihydrate was studied in isothermal mode and dehydration activation energy and kinetic model was determined.

References:
CLICK IMMOBILIZATION OF CALIX[4]AREN E IONOPHORES ON AZIDE-MODIFIED PVC MATRICES

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The Cu$^+$ catalyzed alkyne-azide 1,3-dipolar cycloaddition (CuAAC) yielding 1,2,3-triazoles is the premier example of ‘click’ reactions that has been frequently applied in bioconjugation, drug discovery and materials science. This method was lately utilized in the development of a new, PVC-based ion-selective electrode (ISE) in which the sensing molecule was anchored to the polymer matrix, thereby eliminating the disadvantage of the traditional ISEs (leakage of the membrane components), a longer electrode lifetime was achieved.

Now our current results concerning the synthesis of K$^+$-selective alkyne-modified calix[4]crown-5 ionophores (I) and coupling thereof to PVC-azide via CuAAC (Fig.), along with the potentiometric ion-selectivity of ISEs fabricated from the covalently immobilized ionophores (II) are presented.

Acknowledgements: Financial supports by the Hungarian Scientific Research Fund (OTKA No. K 67585) are gratefully acknowledged. The project is co-financed by the European Union and Hungary and implemented in the framework of the Hungarian ‘Social Renewal Operational Programme’ fellow sponsorship (TÁMOP 4.2.4.A/1-11-1-2012-0001).
**Zn AND Pd PYRAZOLE COMPLEXES AS PHOTOLUMINESCENT MATERIALS**

**MP. Cornago**

**Poster presentations / PO 128**

Self-assembly of transition metal complexes is a domain of increasing interest for the design of supramolecular structures. New pyridine-functionalized pyrazole N,N,N-tridentate ligands \([\text{pypz}^{\text{R(n)py}}] (R^{(n)}) = C_6H_4OC_{2n+1}; n = 1, 12, 14, 16, 18 (I)\) and their corresponding zinc and palladium complexes \([\text{MCl}_2(\text{pypz}^{\text{R(n)py}}}) \) (M = Zn; Pd) \((\text{II, III})\), have been synthesized and studied. Multinuclear NMR spectroscopy (\(^1H, ^13C\) and \(^15N\)) in solution as well as in the solid state is used to quantify the coordination effects induced by Zn and Pd on the chemical shifts of the substituted pyrazole ligand and allows establishing the coordination modes in each case.

The \(^{13}C\) and \(^{15}N\) CPMAS NMR results are in agreement with the X-ray structures. Furthermore, the analysis of the optical data of these complexes pointed out the luminescent behavior of complexes \((\text{II}) \ n = 12 \ and \ 18\).

**Acknowledgements:**

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**References:**
3-ALKENYL INDOLES AS TRYPTOPHAN 2,3-DIOXYGENASE INHIBITORS FOR THE ENHANCEMENT OF CANCER IMMUNOTHERAPY


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Recently, our group has shown that tryptophan 2,3 dioxygenase (TDO), a hepatic enzyme catalyzing the first step of tryptophan degradation, is expressed in many tumors, thereby contributing to tumoral immune resistance.1 The complementary role of tryptophan catabolites has been demonstrated by others.2 We set out to develop new, improved TDO inhibitors using as the starting point the only (unoptimized) series previously known in the literature.3

Herein, we describe the syntheses and structure-activity studies around a series of 3-alkenyl indoles and their derivatives.4 The TDO inhibitory potency was evaluated and rationalized by molecular modeling studies, while solubility, stability and oral bioavailability were determined for selected compounds. The most promising candidate was evaluated in a preclinical model in mice where, upon systemic treatment, it indeed reversed TDO-mediated tumoral immune resistance.5

References:
EFFECTS OF ALKYL SULFANYL PYRIDINES AND PYRIDOTHIAZINES ON P-GP MEDIATED MULTIDRUG RESISTANCE

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P-glycoprotein (P-gp) mediated multidrug resistance (MDR) is recognized as major type of MDR in various kinds of cancer cells. The dihydropyridine (DHP) derivatives were one of the first class of drugs which was identified as MDR inhibitors, but their advancement to clinical applications has been restricted due to their cardiovascular side effects. As part of our ongoing project to design new MDR modulators, we represent the synthesis and biological activity of alkylsulfanylpyridines 2-3 and pyridothiazines 4.

Compounds 2-3 having arylpiperazine moiety variously linked to DHP or pyridine nucleus were synthesized and selective P-gp modulating activity was revealed. When chloroalkylsulfanyl-1,4-DHP 1 were treated with NaOH or NaOEt, intramolecular alkylation at N-1 atom occurred. Various substituents were introduced by acylation or alkylation of hydroxyl group at the position 3.
**NOVEL CLASS OF ACYCLIC NUCLEOSIDE PHOSPHONATES: (S)-3-HYDROXY-2-(PHOSPHONOETHOXY) PROPYL ANALOGUES**

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Acyclic nucleoside phosphonates (ANPs) are nucleotide analogues well-known for the wide range of biological activities, especially antiviral, antiparasitic, and cytostatic. In the present study, an efficient synthesis of the (S)-3-hydroxy-2-(phosphonoethoxy)propyl (HPEP) analogues has been developed. Biological properties of the prepared HPEP derivatives and of their bis-amidate prodrugs have been evaluated. None of the prepared compounds 1-4, bearing the 6-oxopurine nucleobases, was active at subtoxic concentration against the viruses tested (HIV-1, HIV-2, MSV, HSV-1, HSV-2, CMV, VZV) but all of them revealed interesting inhibitory effects on human and/or *Plasmodium* hypoxanthine-guanine-(xanthine) phosphoribosyltransferases (HG(X)PRTases). HG(X)PRTase is the key enzyme of the purine metabolism of *Plasmodium* species, protozoan parasites causing malaria, and thus represents a potential drug target to combat this serious infectious disease.

This work was supported by the Grant Agency of the Czech Republic (grant No. P207/11/0108), National Health and Medical Research Council, Australia (grant No. 1030353), and by Gilead Sciences, Inc. (Foster City, U.S.A.).

**References:**
USE OF SESQUITERPENE LACTONES IN MEDICINAL CHEMISTRY

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Natural products are the inexhaustible source of chemical diversity that can be compared only with the powerful combinatorial chemistry techniques [1]. Plant secondary metabolites cause active interest in connection with their authentic influence on development of new drugs with outstanding properties. The object of our work - sesquiterpene lactones are widespread among higher plants. Biological activities of sesquiterpene lactones are well known and documented, since their use in national medicine and numerous scientific researches in recent years [2].

In the present report data on biological activity of sesquiterpene lactones of plant family Asteraceae for last 20 years are summarized, the basic biochemical targets are considered. The structure-activity relationship, the molecular mechanisms and the potential application are considered. Special interest is represented with complex researches in which interaction of sesquiterpene lactones with enzymes and receptor structures and role of these interactions in development of disease are considered with the most in detail emphasis on the use of sesquiterpene lactones as potential antineoplasts. Examples of their influences on development of a tumor growth are shown and discussed, as well as specific biochemical targets. The potential of sesquiterpene lactones in anticancer drug development lays down in their complex action on different biochemical targets and that is why sesquiterpene lactones are emerging as promising multitarget anticancer agents with potential applications in both cancer chemotherapy and chemoprevention.

References:
IN SITU POWDER X-RAY DIFFRACTION INVESTIGATION OF XYLAZINE HYDROCHLORIDE PHASE TRANSITION FROM X TO A FORM

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Xylazine hydrochloride (2-(2,6-xylidino)-5,6-dihydro-4H-1,3-thiazine hydrochloride) is an adrenergic α-agonist used as a sedative, analgesic, and muscle relaxant in veterinary medicine [1]. It is known to exist in four polymorphs (A, M, Z and X) and several pseudopolymorphs. It has been reported that the polymorph X is thermodynamically the least stable of these polymorphs, while the form A is the most stable at temperatures above 50 °C [2, 3].

Most commonly during the examination of solid phase transformation each time it is necessary to analyse the sample it should be removed from the conditions where transformation is studied. This perturbation can introduce error into experimental data and alert the transformation process; therefore to collect the accurate data it is better to analyse the sample in situ and in real time.

In this study the phase transition from xylazine hydrochloride polymorph X to A was investigated with powder x-ray diffractometer in in situ mode. Phase transition was studied in temperature interval 80-120 °C. Obtained results were compared with data obtained in traditional manner.

References:
COMPLEXES BASED ON THE OCTATHIOTETRAPHOSPHETANE AMMONIUM SALTS. STRUCTURE AND PROPERTIES

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Modern stage of development of organometallic and co-ordinated chemistry is characterized by the wide use of polyfunctional ligands. Cyclic octathiophosphetanes, namely their ammonium salts pertain to the novel heterocyclic ligands of such type. To study their complexation with transition metals, the reaction of piperidinium and triethylammonium salts of octathiotetraphosphetane with Cu(I), Ag(I), Co(II), Fe(II) halides was performed. Complexes obtained were characterized by the X-ray diffraction and IR/Raman spectroscopy combined with DFT calculations.

As heterocyclic compounds bearing a various functional groups in molecules these compounds are expected to possess wide set of useful properties, including biological activity. They were systematically assessed for their anti-fungal properties. Some of the tetraphosphetane derivatives have been identified as potent and promising anti-fungal (Candida albicans) agents whose activity are comparable to that of Amphotericin B, the fungicidal activity of metal derivatives exceeding twice that of initial ammonium salts of octathiotetraphosphetane.

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The bezo[c][1,2]oxaboroles heterocycles as active fragments for transformation of clarithromycin

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It is known that 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaboroles (BB) interact with bacterial Leu-tRNA of Gram-negative strains. Clarithromycin (CLA) is the ligand of bacterial rRNA of Gram-positive microbes. We made computer models and elaborated two synthetic approaches for conjugates CLA and BB. The first pathway explored the substitution of the C-9 carbonyl group of CLA, the second direction used the addition to the 4″-OH group of cladinose via formation of carbamates of BB. Antibiotic 1 was as a mixture of syn- and anti-isomers. All final products (1, 2) had just one peak in ESI-MS. The main side reaction of second direction was deboration of 2. Antibiotics 1 and 2 showed no broad efficacy simultaneously on Gr- and Gr+ strains. Antibiotic 2 was more active than CLA.
1,2-BENZOXATHIINE 2,2-DIOXIDES AS INHIBITORS OF CA

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Carbonic anhydrases (CA) are proteins which catalyze the hydration of CO₂ and dehydration of bicarbonate in vivo [1]. There are 15 different isoforms of CA, which are expressed in different cell types. Recently in Latvian Institute of Organic Synthesis coumarin bioisosters - 1,2-benzoxathiine 2,2-dioxides (sulfocoumarines) were synthesized [2]. Sulfocoumarines (1) act as CA IX inhibitors.

We used 1D (¹H, STD, WaterLOGSY and T1ρ) and 2D (¹⁵N-¹H HSQC) NMR experiments to study the hydrolysis, Z/E isomerisation and possible interactions of these compounds with CA.

![Fig.1](image)

Fig.1. CA catalyzed hydrolysis of sulfocoumarines.

Based on protein backbone amide chemical shift perturbation data, we modeled the 3D structures of the protein-inhibitor complex using molecular docking (OPLS 2005 force field). Chemical shift changes of the inhibitor suggested that sulfocoumarines bind in an opened form and the SO₃ group interacts with the zinc ion of CA.

References
BIOACTIVE MACROCYCLIC CARBENOIDS OF AZOLE SERIES

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A series of carbene complexes of transition metals as well as some azolium salts and carbenederivatives of azoles have been studied for antimicrobial activity recently [1, 2]. However the structural influence of anions and bridges in carbened compounds has been less studied up to now. The goal of our research was studying antimicrobial activity of crown-azolium salts: 1,1’,3,3’-bis(3-oxa-1,5-pentylene)bisimidazolium and 1,1’,3,3’-bis(3-oxa-1,5-pentylene)bisbenzimidazolium chlorides, isothiocyanates, thiosulfates 1; cyclophane-azolium derivatives - 1,1’,3,3’-bis(1,12-dodecamethylene)bisimidazolium salts 2; polymeric copper(I) and nickel biscarbene complexes 3. The antimicrobial and antifungal activities were studied on test-cultures of the bacteriums *E. coli, S. aureus, M. luteum* and the mushrooms *C. tenuis, A. niger* using the diffusion into agar and serial dilution methods. The highest antimicrobial activity of 1,1’,3,3’-bis(1,12-dodecamethylene) bisimidazolium salts 2 was found *in vitro*: chloride – for *S. aureus* (MBSC 31.2 and MBCC 62.5 mg/l), *M. luteum* (MBSC and MBCC 3.9 mg/l); thiocyanate – for *S. aureus* (MBSC 3.9 and MBCC 7.8 mg/l), *M. luteum* (MBSC 1.9 and MBCC 3.9 mg/l).

**Acknowledgement:** Financial support - grant № 83/09.02.12, NAS of Ukraine.

**References:**
THE BIOLOGICAL ACTIVITY OF HETARENO[ε] PYRROLE-2,3-DIONES

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Reactions of polycarbonyl derivatives of pyrrole-2,3-diones provide a wide opportunities of molecular design of compounds, containing groups of pharmacophores. Substances exhibiting antimicrobial, analgesic, anti-inflammatory and antihypoxic activity were detected among hetareno[ε]pyrrole-2,3-diones and their derivatives [1-3].

Compounds I-IV showed analgesic activity and substances with pronounced analgesic activity comparable with effect of Voltaren were found. Compound V (B=OH) showed high activity against St.aureous. Compounds VI have a good percentage of inhibition (~ 75%) on carrageenan-induced rat paw edema model. Expressed antihypoxic activity was found for compounds V (B=SCH₂COOH).

References:
UTILIZING EPRI AS A IN-VIVO DETECTION METHOD FOR AMYLOIDOGENIC PROTEINS

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Herein we report the synthesis of a novel set of biomarkers which utilize luminescent conjugated oligothiophenes (LCOs), containing stabilized radicals, to provide insight into the detection of amyloidogenic protein aggregates through the used of electro-paramagnetic resonance imaging (EPRI) for in-vivo detection of amyloid diseases.

Luminescent conjugated polythiophenes (LCPs) have recently been introduced as a class of amyloid-binding fluorescent probes. In 2009, Åslund et al. improved on the concept, presenting defined structures (LCOs) which could be utilized for postmortem imaging of protein aggregates.[1] LCPs and LCOs are comprised of a conjugated thiophene backbone, giving a combination of flexibility and rigidity, which results in conformation-sensitive spectral signatures when coordinated with amyloid proteins. This concept was further expanded upon where a library of oligothiophenes of defined lengths (4-7 thiophene units) displayed variations in their spectra. Some LCOs were also shown to be spectrally discriminative between two different types of amyloid proteins (Aβ and Tau) present in the tissue samples [2].

The introduction of stabilized radical moieties, as spin labels, to the LCOs for imaging in-vivo samples of amyloid proteins is the next evolution in our investigations. This study explores optimization between selected LCOs and suitably stabilized EPRI spin labels including the establishing the relationship between spacers to observe any changes in response between the binding of spin-LCOs.

References:
FURODIHYDROQUINOLINES –SENSITIZERS FOR PUVA THERAPY

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PUVA therapy, the method based on combined action of psoralen preparations and long-wavelength UV irradiation (UVA), is widely used for medical treatment of skin diseases. The formation of the cycloaddition adducts of psoralens to thymine bases of DNA upon UVA irradiation is the main factor causing the therapeutic efficacy of these compounds. The disadvantage of psoralens is the possibility of cross-linking of two DNA molecules with a psoralen molecule that causes the genotoxicity and may provoke cancer. That is why novel photosensitizers for PUVA therapy deprived of this disadvantage are examined. Several angular furodihydroquinolines (FDQ) with different positions of the furan ring and different substituents in the aromatics were synthesized.

\[
\begin{align*}
R & = H, NO_2, \text{NHCO(CH}_3\text{)}
\end{align*}
\]

The FDQ displayed very low total toxicity on cell cultures without irradiation, toxicity under UVA irradiation by the mechanism of apoptosis and the antioxidation activity. FDQ have a yield of the triplet state. The monoadducts of photocycloaddition reaction between FDQ and thymidine monophosphate (TMP) were identified in the photolysate of the FDQ + TMP mixture. Our results show that FDQ can be considered as potential photosensitizers for PUVA therapy.

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NEW ORGANOPHOSPHORUS ACIDS 
WITH HETEROCYCLIC FRAGMENTS 
AS PERSPECTIVE ANTIOXIDANTS AND 
CYTOPROTECTORS

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Functionalized organophosphorus acids and their derivatives with heterocyclic and aromatic fragments are of great interest as effective chelating ligands and perspective bioactive substances with various properties. These acids are well-known analogs of hydroxyl(amino)carbonic acids and natural pyrophosphates. We have developed the convenient methods of synthesis of new functionalized organophosphorus acids and their derivatives including heterocyclic, aromatic and unsaturated fragments as well as hydroxyl, amino, and carboxyl groups using as starting compounds the trimethylsilyl esters of several trivalent phosphorus acids and functionalized alkenes, aldehydes, and carbonic acids\(^1\,^2\). The new water soluble organophosphorus acids or their salts which are presented here.

\[
\begin{align*}
\text{HO}_2\text{PCH(OH)Ar} & \quad [(\text{HO}_2\text{P})_2\text{CHNAr}]_2 \quad \text{Ar Alk} \\
\text{X} \quad \text{Ar} & \quad \text{Ar} \quad \text{Y} \quad \text{O} \\
\text{R} = \text{MeCH=CH, Me(CH=CH)}_2, \text{PhCH=CH, Me(CH=CH)CH=CH(CH_2)_{2}}, \text{Py (2-, 3-, 4-), Ar;} \\
\text{Ar} = \text{Ph, } & \quad \text{HO}_2\text{PCH(OH)Ar} \\
\text{Y} = \text{OH, (CH_2)_{2}Ph, (CH_2)_{2}Py, (CH_2)_{2}COOH, (CH_2)_{3}N, n = 1,2;} \\
\end{align*}
\]

Multifactor antioxidative activity of these acids was investigated on homogenates of rat liver, fish sperm (Asipenser gueldenstaedti B.), and rat liver mitochondria. Also the influence of these compounds was studied on functional characteristics of rat liver mitochondria and on tert-BHP- and Fe\(^{3+}\)- induced toxicity in cerebellar granule cells of rats. This work was supported by RFBR, grants 12-03-00003 and 12-03-00003.

DISCOVERY AND HIT-TO-LEAD OPTIMIZATION OF TETRAHYDROQUINOLINES AND TETRAHYDRO[1,6]NAPHTIRIDINES AS NOVEL mGluR5 POSITIVE ALLOSTERIC MODULATORS

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The therapeutic potential of metabotropic glutamate receptor 5 (mGluR5) as a drug target, has recently been explored and expanded. It is considered that mGluR5 receptor agonists have treatment potential for both positive and negative, as well as cognitive symptoms of schizophrenia.1 Positive allosteric modulators (PAMs) of mGluR5 receptor have several important advantages over orthosteric agonists, including increased subtype selectivity and much better brain penetration.

Herein, we report the discovery of novel, selective mGluR5 positive allosteric modulators based on an earlier identified hit2. The synthesis, in vitro studies and structure-activity relationships of the newly identified lead series will be presented.

References:
2. WO2012/52451A1
BIOLGICAL ACTIVITY OF PYRROLO-[1,2-\(a\)]
THIENO[3,2-\(e\)]PYRIMIDINES

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Earlier we proposed a simple method for the production of a series of \(N\)-substituted 5-aryl-3-imino-3\(H\)-furan-2-ones by the intramolecular cyclization of \(N\)-substituted 2-amino-4-aryl-4-oxobuten-2-oic acids in the presence of acetic anhydride [1]. At the same time, the rare type of 2-furanone derivatives seemed extremely promising from the standpoint of high reactivity and the possible presence of biologically active compounds in series of furan derivatives. Moreover, the introduction of a thiophene substituent into the structure at the imine nitrogen atom increases the prospects of these compounds even further. The Gewald reaction products are widely employed in drug discovery as an important biological entity, which were actively employed in synthesis of a variety of target family classes [2].

We synthesized ethyl 2-(2-oxofuran-3(2\(H\))-ylideneamino)thiophene-3-carboxylates \(1\) and investigated their recyclization reactions.

\[
\begin{align*}
&\text{R}^1=\text{Ar, Het; R}^2,\text{R}^3=\text{Alk, Ar; R}^4=\text{COOAlk, CONH}_2
\end{align*}
\]

It was found that \(2\), in the presence of derivatives of cyanoacetic acid, undergo smooth cyclization into tricyclic compounds \(3\).

The mechanism of reactions and biological activity of compounds \(2,3\) will be discussed.

Acknowledgements: The work was carried out with support from the Russian Fundamental Research Fund (11-03-00882 and 12-03-31739) and Ministry of Education Perm Region.

References:
Recombinant DNA technology allows the production of proteins in large quantities and supplies them as needed for genomics and proteomics research. However, heterologous proteins can form aggregates, which are called inclusion bodies. To recover biologically active protein, inclusion bodies have to be isolated and solubilized, and the target protein has to be refolded to its native structure. However, the renaturation process of proteins deals with their aggregation [1]. Imidazole 1 and its derivatives, i.e., 2-(1H-imidazol-4-yl)ethanamine (histamine) 2 and N-(1H-imidazol-5-yl)guanidine 3 were tested as anti-aggregatory additives in the protein refolding process from Escherichia coli inclusion bodies.

Veterinary growth hormones were used as model proteins. It was found that imidazole and its derivatives inhibit protein aggregation, and the effect is dependent on the concentration of additive.

**Acknowledgements:** This research was funded by a grant (No PRO-12/2012) from the Research Council of Lithuania.

**References:**
NEW 5-ARYLMINO-2,5-DIHYDRO-ISOTHIAZOLE DERIVATIVES

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Isothiazoles (1,2-thiazoles) are known since 1950-s as biocides, antiviral and anti-inflammatory agents [1]. However partially hydrogenated, especially 2,5-dihydroisothiazole derivatives were studied to a much lesser extent [2]. Conventional synthetic approach for these compounds includes oxidative cyclization of the available amides of 3-amino-2-propenthioic acid.

\[
\text{R} = \text{Alk}; \text{R}^1 = \text{Alk, Ar}; \text{R}^2 = \text{H, acyl, aroyl, ester, amide}; \text{R}^3 = \text{Alk, OAlk, Hal}
\]

The best results were obtained by using \( \text{Br}_2 \), \( \text{I}_2 \), DEAD and \( \text{H}_2\text{O}_2 \) in acidic media, giving products 2 in good to excellent yields. The obtained derivatives have shown high cytotoxic activity towards cancer HT-1080 and MG-22A cell lines and induced NO generation (up to 400–700 %) in these cells while causing no mutagenic effect and/or morphological changes.

Compounds 2 could be studied either themselves, or as useful starting materials to obtain fully hydrogenated 1,2-thiazolidines (tetrahydroisothiazoles), sulfonamides (sultams, sulfa drugs, used as antibacterial agents and diuretics), 1,2,4-thiadiazoles (sphingosine receptor agonists, neuroprotectors, anti-inflammatory agents), and other biologically active heterocyclic derivatives.

References:
3,4-DIHYDRO-2(1H)-PYRIDONE LINKED CATIONIC AMPHIPHILES

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Dihydropyridones are important intermediates for the synthesis of natural products, particularly alkaloids and they have been extensively investigated as valuable building blocks for the construction of piperidines, perhydroquinolines, indolizines, quinolizidines and other alkaloid systems, with a wide range of biological and pharmacological activities.

There is only one published work [1] of 3,4-dihydro-2(1H)-pyridone being used as a linker in cationic amphiphile synthesis. The dihydropyridone scaffold (Figure), provides an opportunity for a single cation to be placed on the methyl group at carbon 6 and also long chain alkyl or perfluoro alkyl ester groups at carbon 5.

The cationic amphiphiles self-assemble in aqueous solutions forming aggregates in the 50-200 nm range as observed by atomic force microscopy and dynamic light scattering. These amphiphiles may find use in gene transfection and drug delivery applications in addition to their own inherent pharmacological activity.

\[
\begin{align*}
\begin{array}{c}
\text{R}^1 \quad \text{O} \\
\text{O} \\
\text{N} \\
\text{H} \\
\text{Br}^- \\
\end{array}
\end{align*}
\]

\[\text{R}^1: \text{Ar, H} \quad \text{R}^2: \text{alkyl or perfluoroalkyl} \quad \text{R}^3: \text{Py, PPh}_3, \text{or alkylammonium}\]

Acknowledgements:
The study was partially supported by the State Research Programme “Biomedicine”

References:
PYRIDO[1,2-\textit{a}]BENZIMIDAZOLES WITH POTENTIAL ANTITUMOR ACTIVITY

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One of the most promising chemical compounds for cancer chemotherapy are pyrido[1,2-\textit{a}]benzimidazoles. Their anti-tumor activity is based on the ability to intercalation into the double helix of DNA of cancer cells and suppress them in the replication process. Known methods of the synthesis of these heterocyclic compounds are ineffective. Disadvantages include the use of inaccessible reagents, formation of the desired compounds in low yield and the presence of by-products. Previously, we have proposed the method for the synthesis of pyrido[1,2-\textit{a}]benzimidazole is based on reductive cyclization of \textit{N}-(2-nitrophenyl) pyridinium salts in acidic aqueous-alcoholic medium using SnCl$_2$. This method has shown good results (yield $>$ 90\%), but the widespread use of the new approach for the synthesis of polycyclic condensed imidazole derivatives requires to simplify the isolation of products and solve the problem of Sn$^{+4}$ compounds disposal. Both of these problems can be eliminated by using electric current as an electron source in reduction.

\[
\begin{align*}
\text{R} & = \text{CF}_3, \text{CN}, \text{COOCH}_3, \text{COOC}_2\text{H}_5 \\
\end{align*}
\]

There have been studied features of electrochemical synthesis of pyrido[1,2-\textit{a}]benzimidazoles. The influence of the structure of the substrate, temperature, the reaction media and the cathode material were investigated in the process of reductive cyclization. The best results were observed when the reaction was carried out in acidic-aqueous medium in galvanostatic mode with diaphragm, on lead cathode, with a current 0.2 A. Anolyte was 15\% sulfuric acid, the anode - platinum. The yields were 77-94\%.

During cytological experiments on chromosomes was found that the new pyrido[1,2-\textit{a}]benzimidazoles have high intercalating activity, is superior analogs.

\textbf{Acknowledgements:}
The study was supported by The Ministry of education and science of Russian Federation, project 14.B37.21.0823
INTERACTION OF BODIPY WITH ALBUMIN AND ITS BILIRUBIN COMPLEX

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Boron-dipirrolylmethene complexes (BODIPY), which are used as limiters of intensive laser radiation, already known to be effective fluorophores. There was described a large number of BODIPY-labeled compounds, many of them are widely used in biological research, especially in photodynamic therapy. Being injected into the body BODIPY can bind with blood plasma proteins like albumin (BSA). Universal transport function of BSA can be used as a convenient model for the study of even weak intermolecular interactions. Emerging interactions causing corresponding changes in protein molecules can be traced through its own or induced fluorescence. The high sensitivity of the spectra fluorescence changes the polarity of molecule environment allows making important conclusions about the interaction mechanisms of small molecules to the protein molecule. The intrinsic fluorescence quenching of BSA under the influence of substances with different nature is the basis for the development test systems to specify the type and ability of small molecules to interact with proteins. There is an interesting fact about albumin to have the ability to form macromolecular complexes with bilirubin (BR), bile pigment formed from the decay of heme. BODIPY accession to the protein in the nature of things will lead to the changes in the properties of both molecules. In connection with this, the present study aimed to determine the characteristics of the interaction of BODIPY with BSA and BR•BSA using fluorescence and absorption spectroscopy.

Acknowledgements: This study was financially supported by the Russian Foundation for Basic Research (Project No. 12-03-31309).
DIVERSITY OF FURAGIN POLYMORPHS AND SOLVATE CRYSTAL FORMS

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Furagin, 1-[(3-(5-nitro-2-furyl)allylidene)amino]hydantoin, or Furazidin, an anti-infective agent for treating urinary tract infections was developed in Latvian Institute of Organic Synthesis. Despite of its long-term use the crystal structure of Furagin, its polymorphism and solvatomorphism have not been studied.

Search for polymorphs was performed in 12 solvents. Three stable polymorphs and four solvates were found and characterized by powder X-ray diffraction, Raman spectroscopy and DTA/TG. For two polymorphs and all solvate forms the crystal structure was determined by a single crystal X-ray structure analysis. Polymorphic forms differ in molecular packing. There are molecular chains formed by hydrogen bonds in 1 and dimers in 2. Furagin molecule is planar in all crystals, except 4. Solvate molecules in 3 and 6 are connected to Furagin molecules via water molecules by hydrogen bonds making planar systems.
THE FLAVONOIDS OF *LOPHANTHUS ANISATUS*

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With the help of HPLC method in aqua-ethanol extraction of leaves *Lophanthus anisatus Benth.* identified flavonoids, coumarin, phenolic compounds and found immunotrophic activity.

<table>
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<th>Flavonoids</th>
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<th>Koumarin</th>
<th>%</th>
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<tr>
<td><img src="image" alt="Luteolin" /></td>
<td>3.05</td>
<td><img src="image" alt="Umbelliferone" /></td>
<td>0.85</td>
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<tr>
<td><img src="image" alt="Quercetin" /></td>
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<td><img src="image" alt="Gallic acid" /></td>
<td>2.15</td>
</tr>
<tr>
<td><img src="image" alt="Apigenin" /></td>
<td>1.22</td>
<td><img src="image" alt="Chlorogenic acid" /></td>
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</tr>
<tr>
<td><img src="image" alt="Rutin" /></td>
<td>0.95</td>
<td><img src="image" alt="trans-Caffeic acid" /></td>
<td>0.52</td>
</tr>
<tr>
<td><img src="image" alt="Rutinosa" /></td>
<td></td>
<td><img src="image" alt="p-Coumaric acid" /></td>
<td>0.33</td>
</tr>
</tbody>
</table>

As a result activation of cell-mediated immunity was recorded, which was expressed by the increased index of the HRT local reaction by more than 35% and the increased number of the leucocytes by more than 20%.
SELENOLOCOUNARINS: SYNTHETIC DESIGN AND ACTIVITY

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Since the coumarin system is found in the composition of many natural compounds, derivatives of coumarin have excited considerable attention. On this basis medicinal preparations have been obtained and developed with a wide range of biological activities (Psoralen, Angelicin, Xanthotoxin, Bergapten, Nodakenetin, etc). On the other hand, the synthesis and studies of a series of organic and inorganic selenium compounds in many cases revealed a wide spectrum of biological activity. We developed a straightforward method for the preparation of a new heterocyclic systems, namely selenolocoumarins, via reaction of in situ prepared selenium(IV) bromide with ethynylcoumarins.

![Chemical structures]

In most cases, the cyclization proceeds smoothly and desired selenolo[2,3-c], [3,2-c] and [2,3-f]coumarins were obtained in good yields. Molecular structures of selenolocoumarins have been unambiguously confirmed by X-ray analysis. Structure and cytotoxic activity relationship on various cancer cell lines will be discussed. It was found that selected coumarines exhibit high inhibiting activity selectively on matrix metalloproteinase MMP-2.
NEW ORIGINAL ADAPTOGEN AND IMMUNOMODULATOR - 2- (METHYLPHENOXYACETOXY) PROTATRAN, ITS APPLICATION IN MEDICINE AND IN AGRICULTURE

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Long-term preclinical and clinical trials of the biological activity of 2-(methylphenoxyacetoxy) protatran (trecrezan, crezacyn) [(2-MeC₆H₄O)CH₂COO]⁺N⁺H(CH₂CH₂OH)₃, developed under the leadership of Academician M.G. Voronkov, found to have strong adaptogenic and immunostimulating effects. Trecrezan both as an adaptogen and prophylactic agent exhibits a positive effect on the human body at overstressed physical and mental loads, especially under extremal conditions of climate (high and low atmospheric pressure and temperature, stresses in emergency situations, etc.), but it also is affective as prophylactic and medicinal remedy for many diseases. Particularly, it is already being used for the rehabilitation of the patients with acute myocardial infarction and chronic heart failure, for the correction of pulmonary tuberculosis patients states, against hyperlipidemia and atherosclerosis, coronary disease and diabetes, at treatment of septic wounds and pneumonia, as anti-alcohol drug in the periods of abstinence and remission, and as the strengthening agent of the adaptive human responses in extremal situations. The medicine administration to herpes patients resulted in depressing of the objective disease signs for 5-6 days earlier than that for the control patient group. It is also used as an immunopoiesis and cytostatic modulator, as well as during the process of tissue formation in embryonic stem cells. The study of possible mechanisms of trecrezan action shows that trecrezan activates protein synthesis in the organism of patients with cardiovascular pathology. It activates all tryptophanyl synthetases i.e. transport, matrix and information ones. Trecrezan inhibits A1 and A2 phospholipases.

In agriculture trecrezan is often used under crezacyn name. In animal experiments trecrezan is found to have heparin-like and antihypoxic action, significantly improve the state animals in the sexual deprivation, the memory and trace processes that positively affect the manifestation of the maternal instinct. Its administration results in increasing the amount of globulins, especially gamma globulins that are responsible for the immune status of the animal body. The special theoretical and practical interests are the crezacyn’s stimulations of fertilities (productivity, number of litters and its viability) of mammals. This medicine stimulates the ovo- and spermatogenesis, accelerating the maturation of primordial ovarian follicles and the sperm motion intensity within 72-100 hours. Meanwhile, crezacyn has a positive effect on the natal development of the embryo. The productivity of hydrocoles, the viability of hatchlings is increased even in the presence of trecrezan traces in water. It accelerates the increases of live fish weight: fry peled at 10-27%, crucian carp at 15%, carp at 35-40%. Crezacyn adds the average weight of silkworm and oak bombyx cocoons by 5-10%, mainly due to the silk shell production that is the target sericulture product. The productivity increasing leads to the improvement of quality of the silk cocoon shells as well as the multipication of high grade cocoons, the average weight increment for silkworm is 16.5%.

Trecrezan and its analogues are also the effective stimulators of microbiological synthesis. When Trecrezan used as a stimulant of microbiological protein synthesis of yeast of the genus Candida (C. sake, C. tropicalis, C. guiliermondii, C. parapsilosis, C. caemonica, S. utieis, C. boidinii), Hansenula, Torulopsis, and others, as well as bacteria of the genus Pseudomonas, Methylomonas, Acetobacter, etc., it exhibits the increase of the biomass yield at 15-20%, the average productivity at 50-65%, and the protein content at 5-20%. Being added to milk at the production of Bifidobacterium and other cultured milk foods it multiplies the number of beneficial bifidus bacteria at 2-4 orders and reaches 10¹⁰ cells per ml of the product (Control is 10⁶). At the same time the contents of B1 (thiamine) and C vitamins are increased by 3 times and 1.5-2.8 times, respectively.
BENZO-1,3-DIOXOLANES POSSESSING BIOLOGICAL ACTIVITY

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As a result of accomplishing of biological activity of different cyclic acetals and ketals according to program PASS [1] we have found out that benzo-1,3-dioxolanes (on the base of catechol and substituted cyclopropanes) shows the high potential antibacterial and antivirus properties.

Synthesis of compounds representative the most interest was accomplished by condensation of the substituted catechols with gem-dichlorocyclopropanes.

Phenil- and vinyl-gem-dichlorocyclopropanes, possessing the high selectivity, generate ketals whereas chloromethyl-gem-dichloropropanes react as exo- as endo-cyclic atoms of chlorine in DMSO and the main products are vinyl ketals. The last are more biologically active than saturated benzo-1,3-dioxocyclanes.

The same result was achieved in an interaction tetrachloroderivative with phenol. However linear ketals have lower antivirus and antibacterial activity than cyclic.

It should be noted that monosubstituted catechols have exactly signified antioxidant properties and their using for inhibition of free-radical processing in polar bioorganic objects is very prospective.

References:
STRUCTURE DETERMINATION OF PIMOBENDANE FORM B AND DIOXANE SOLVATE

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\textsuperscript{b}Latvian Institute of Organic Synthesis, Riga, LV-1006, Latvia
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Pimobendane, 2-(4-hydroxy-phenyl)-5-(5-methyl-3-oxo-4,5-dihydro-2H-6-pyridazinyl)benzimidazole, is a drug with both inotropic and vasodilatory properties and is widely used for the treatment of heart failure in dogs. It is a benzimidazole-pyridazinone derivative that exerts its inotropic and vasodilatory effects through a combination of calcium sensitization and phosphodiesterase inhibition.

Data for structure determination were collected on a Bruker D8 Advance using Sol-X detector. The pattern indexing was performed with DICVOL06. Structures were determined with EXPO2009 and FOX 1.9.5.0. Determinations were performed from different initial conditions by changing cost function, cooling rate and other conditions of simulated annealing or parallel tempering. Final structures were refined using Rietveld method.

Pimobendane form B crystalizes in \( P2_1/c \) and dioxane solvate in \( P2_1/a \) space goup. For both structures \( Z'=1 \) and \( Z=4 \). In a both structures there is observed \( \pi \) stacking between pimobendane molecules.

Acknowledgements: This work was supported by the European Regional Development Fund (No. 2011/0014/2DP/2.1.1.1.0/10/APIA/VIAA/092).
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