Plenary Lectures
SYNTHESIS OF PHARMACOLOGICALLY RELEVANT RING SYSTEMS BY NEW ONE POT CYCLIZATIONS

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In recent years, a number of one-pot cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes, 1,3-bis(silyl enol ethers), have been developed \cite{1}. This includes cyclizations with oxalyl chloride \cite{2}, 3-silyloxy- and 3-alkoxy-2-en-1-ones \cite{3}, benzopyrylium triflates \cite{4}, iminium salts \cite{5}, and various other electrophiles \cite{6} which provide a convenient access to highly functionalized alkylidenebutenolides, salicylates and phenols, carba- and heterocycles, bridged and nonbridged N-heterocycles, and wide range of arenes and heteroarenes, respectively. The synthesis of fluorinated arenes based on one-pot cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes and its fluorinated analogues with corresponding fluorinated, trifluoromethyl-substituted, and perfluoroalkyl-substituted enones have also been reported \cite{7}. In addition, organosulfur compounds can be readily prepared either starting from thio-substituted dienes or from sulphur containing dielectrophiles \cite{8}.

References
\begin{thebibliography}{99}
\bibitem{1} For a review of 1,3-bis(silyl enol ethers) in general, see: Langer, P. \textit{Synthesis} \textbf{2002}, 441.
\bibitem{7} Review: Langer, P. \textit{Synlett} \textbf{2009}, 2205.
\bibitem{8} Review: Nawaz, M.; Sher, M.; Langer, P. \textit{Synlett} \textbf{2010}, 2383.
\end{thebibliography}
TRANSFORMATIONS OF PORPHYRINOIDS TRIGGERED BY COORDINATION

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Insertion of boron(III), silicon(IV) or phosphorus(V) into N-confused porphyrin triggers the N-confused pyrrole inversion followed by a fusion step affording an 18 π-electron aromatic porphyrinoid with a fused tri-pentacyclic ring confined in the macrocyclic core: N-fused porphyrin. A template factor has been recognized as a driving force of fusion which allows a specific mode of the coordination core adjustment to the given small sizes of coordinated cations. In fact N-fused porphyrin and related porphyrinoids are geometrically adjusted to create a suitable coordinating center for phosphorus(V) \( \text{I} \) or silicon(IV) \( \text{II} \). The structural changes of the investigated complexes are easily triggered by two-electron reduction of N-fused porphyrin to yield N-fused isophlorin. Remarkably, the coordination allowed to identify new constitutional isomers of porphyrins which preserve the basic skeleton of maternal N-fused porphyrin. The template effect of phosphorous forcing contraction operates also for other porphyrinoids including tetraaryl-21-telluraporphyrin which converts to the complex of phosphorous(V) N-fused dihydrotelluraporphyrin containing an inverted tellurophenic ring \( \text{III} \). A cycle of direct transformations affords an elegant triangle of three mutually convertible N-fused porphyrinoids, with distinct spectroscopic features: antiaromatic, nonaromatic and aromatic. Alternatively to insertion, the silicon atom has been introduced into the porphyrin-like structure replacing one of pyroles with silole to form 21-silaphlorin \( \text{IV} \). An effort to trap 21-silaporphyrin resulted in the serendipitous discovery of a unique transformation of 21-silaphlorin \( \text{IV} \) into a non aromatic isomer of 2,3-diphenyl-5,10,15,21-tetrap(\( p \)-tolyl)-carbacorrole (\textit{iso}-carbacorrole) \( \text{V} \) which contains a cyclopentadiene ring embedded in the tripyrrolic framework. Coordination of silver(III) or copper(III) affords organometallic complexes of “true” carbacorrole \( \text{VI} \) in which the metal(III) ions are bound by three pyrrolic nitrogens and a tetrahedrally hybridized C(21) atom of the cyclopentadiene moiety. The inner-core reactivity of carbaporphyrinoids and metallo carbaporphyrinoids has been also explored affording appropriate hybrid ligands. The created coordination center provides a suitable environment allowing stabilization of organocopper(II) complexes.
A STEREOCONTROLLED AND FLEXIBLE ROUTE
TO OPTICALLY-ENRICHED OXABISPIDINES

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Over recent years, molecules possessing both the bispidine \(1; X = \text{CH}_2\) and oxabispidine \(1; X = \text{O}\) unit have been shown to display a range of biological properties that have made them attractive targets for the pharmaceutical industry.\(^1\) The lupine alkaloid, (-)-sparteine \(2\), also has the bispidine structure \(1; X = \text{CH}_2\) at its core, with this optically-enriched natural product having been employed as the key chiral ligand in an extensive array of enantioselective transformations.\(^2\) The imperfect stereoselectivity observed in some of these processes, together with the lack of a naturally occurring antipode has driven efforts to prepare and study analogous chiral bispidines, in particular those which may serve as surrogates for \((+)-2.\(^3\) In contrast, chiral oxabispidines \(1; X = \text{O}\) have been the focus of significantly less attention as ligands for use in enantioselective organic reactions, despite the potentially similar chiral environment. Although some stereoselective routes to oxabispidines have emerged recently, the available methods tend to be limited by (i) the requirement for more than one pre-formed chiral substrate, (ii) relatively lengthy synthetic pathways, and (iii) a lack of flexibility relating to the substituent groups that can be introduced around the oxabispidine core.\(^4\) Accordingly, pharmaceutical applications have been restricted to compounds containing the simplest core structure lacking substitution on the carbon skeleton.

We have developed a flexible and stereocontrolled route to oxabisidine acetics \(5\) proceeding from oxazine \(4\), which in turn is prepared in a short and efficient synthetic sequence from commercially available \((S)-(\text{\textsuperscript{\textast}})-2,3\)-epoxypropylphthalimide \(3\). The key reaction is an intramolecular Mannich cyclization of an imine (formed upon condensation of \(4\) with the appropriate aldehyde) and represents an attractively late point at which diversity is incorporated. The inherent flexibility imparted by the differentiated nitrogens of \(5\) has been exploited in the synthesis of a range of oxabispidines \(6\), exemplifying all combinations of \(R^1\) and \(R^2\) = H or Me.

\[\begin{align*}
\text{3} & \quad \text{4} & \quad \text{5} \\
\text{O} & \quad \text{CO}_2\text{Bn} & \quad \text{MeO} & \quad \text{O}_2\text{Bn} \\
\text{N} & \quad \text{H} & \quad \text{R}^1 & \quad \text{R}^2 \\
\end{align*}\]

\[\begin{align*}
1. \text{RCHO, MgSO}_4 & \quad 2. \text{TIOH, MeOH} \\
\end{align*}\]

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To cover a diverse set of heterocyclic frameworks and at the same time to make syntheses efficient and expeditious, we assembled diverse and structurally unrelated heterocycles from common solid-supported intermediates. This strategy allows to efficiently prepare compounds with different frameworks and skeletal disimilarity. Our approach will be documented on transformation of polymer-supported α-acylamino ketones. Syntheses involved known as well as novel chemical routes and comprised variety of chemistries (C-C, C=C, C-N, C=N, C-O bond formations). Different sizes of heterocycles (4-, 5-, 6-, and 7-membered rings) were prepared including dihydro-pyrrol-2-ones, pyrazin-2-ones, dihydro-triazepin-6-ones, morpholin-3-ones, imidazoles, β-lactams, and isoquinolin-1-ones [1]. Further elaboration to fused ring systems was also documented. In addition several unexpected synthetic routes leading to efficient syntheses of heterocycles will be presented [2].

References

Multicomponent reaction design in the quest for molecular complexity and diversity

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The main research interest of the Synthetic & Bio-organic Chemistry group focuses on sustainable (atom and step economy) synthetic method development employing domino (or tandem) processes. The methodology is applied to the diversity-oriented synthesis of small focused libraries of fine-chemicals with a high added value, like building blocks for medicines or ligands for catalysis. A powerful strategy involves the use of multicomponent reactions (MCRs), which combine at least three different simple reagents in a well-defined manner to form a single product. Smart design of our synthetic strategies based on the concepts of Diversity Oriented Synthesis (DOS) and Biology Oriented Synthesis (BIOS) take advantage of the potential of MCRs allowing molecular complexity and diversity to be created by facile formation of several covalent bonds in one-pot transformations. At the same time our reactions proceed with high atom economy and low E factors thus minimizing the number of functional group manipulations towards a given complex molecular target and avoiding the use of protective groups. This lecture focuses on the design, of novel MCRs for atom- and step efficient syntheses and discusses some asymmetric methodology for stereoselective MCRs employing biocatalysis. Both mechanistic aspects, stereochemistry using biocatalysis, optimization towards robust procedures and synthetic utility are discussed e.g. in the synthesis of potentially biologically active molecules (antitumor, antibiotics, hepatitis C) as well as ligands relevant to catalysis (N-heterocyclic carbene complexes, organocatalysts).
Unsaturated bicyclic vicinal diols can react with \( \text{Pb(OAc)}_4 \) or \( \text{PhI(OAc)}_2 \) acting as domino promoters in several ways, depending on the reaction conditions. When the angular position bears a functional substituent, such as an alkoxy, an ester or a carbonyl group, more than one domino reaction paths could be put in competition. Structurally different products can be reached selectively in a single synthetic operation, in spite of the similarities in the starting compounds, which differ only by the substitution pattern at the angular position (C11). The nature of substituent at C11 is responsible for the modular aspect of the domino process as well as the extent of the generated complexity, and therefore determines the regiochemical course leading to original scaffolds. Thus, it is possible to select either a ring-expanding [1], a hetero[4 + 2 + 2]cycloaddition [2], a hetero[4 + 3 +2]cycloaddition [3], an oxonium path [4] or simply to interrupt the process half the way through at the \([4\pi + 2\pi]\) stage [5], by varying the functional group at C11.

The substrate-based modulation is derived from the mechanistic role of each functional group installed at the angular position; by inserting diverse reactivity, the ensuing domino
probe can be oriented to a different outcome. The presentation will focus on probing this class of domino reactions in an effort to define the origins of orienting factors and to develop a prognostic model for general use. A “where from to where” and a “what for” aspect will be discussed. Within the time limits, some applications to the construction of key building blocks for bioactive natural products which are likely to be major synthetic targets will be presented in reasonable detail.

References
CHEMO-ENZYMATIC SYNTHESIS OF NITROGEN HETEROCYCLES

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The use of enzymes in organic chemistry is well established nowadays, even in industry, because of their selectivity, high yields and mild reaction conditions. This presentation describes two applications of enzymes in the synthesis of nitrogen heterocycles.

The first example focuses on the use of *Sulfolobus* KDG aldolases as stereoselective catalysts for carbon-carbon bond formation. The enzyme couples two substrates, the natural ‘donor’ is pyruvate and the natural ‘acceptor’ is glyceraldehyde. The donor specificity is very strict, but the acceptor can be easily replaced by a wide range of aldehydes. We found that azido-aldehydes are surprisingly good substrates, giving rise to azido-functionalized products. In order to determine the stereoselectivity of the enzyme we reduced the azide group, leading (after ring closure and further reduction) to chiral hydroxyprolines and carboxyhydroxy-piperidines.

The second case relates to the biobased economy. Nitrogen heterocycles are important compounds in chemical and pharmaceutical industry, but they are all synthesized from fossil materials and ammonia. Since fossil materials will be scarce in the future, and because the production of ammonia is highly energy-intensive, we studied the use of natural compounds as feedstocks for nitrogen containing chemicals. In nature, nitrogen is fixed enzymatically by nitrogenase; the resulting ammonia mostly ends up in proteins and amino acids. We investigated the use of glutamic acid, the most abundant amino acid, as a starting material for the preparation of a number of nitrogen containing compounds, like the industrial solvent N-methylpyrrolidone and the monomer N-vinylpyrrolidone [1,2].

References
CROSS-COUPLINGS AND C-H ACTIVATIONS OF PYRIMIDINES, PURINES AND PYRROLO[2,3-d]PYRIMIDINES. FROM NEW NUCLEOSIDE CYTOSTATICS TO BASE-FUNCTIONALIZED DNA

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Novel methodologies of synthesis of modified nucleobases, nucleosides, nucleotides and oligonucleotides have been developed largely using modern organometal-catalyzed reactions (cross-couplings, C-H activations, etc.). An efficient two-step methodology of construction of functionalized nucleic acids was developed by a novel chemo-enzymatic approach using aqueous-phase cross-coupling reactions of nucleotides followed by incorporation by DNA polymerase. The methods are applied in the synthesis of derivatives for biological activity screening (two novel types of nucleoside cytostatics will be presented) and the use of functionalized oligonucleotide probes for electrochemical detection of DNA hybridization or for DNA bioconjugation.

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References:
HETEROCYCLIC SYNTHESIS FOR CHEMICAL INTERVENTION IN CELLULAR AGEING

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Accelerated cellular ageing and the phenotypic changes associated with cell senescence may have a dramatic role to play in the onset of age-related diseases. This presentation describes how new rapid methods for the synthesis of heterocycles, in combination with the use of an extremely rare autosomal recessive genetic disorder, can help us to understand the age-related biochemical triggers for cell senescence and how this process can be rescued using inhibitors of MAPK signal transduction [1-3]. The use of microwave heating has delivered a library of complementary mitogen-activated protein kinase (MAPK) inhibitors to understand the role of cell signalling in the pathology of WS. In particular, a range of different inhibitors of p38 MAPK and the downstream target (MK2) of this signal transduction cascade have been prepared and tested in Werner syndrome cells to understand their biochemical role and compare their effectiveness in Werner syndrome cells. Microwave irradiation was found to improve routes to the Vertex compound VX–745, Boehringer-Ingelheim’s BIRB 796, a library of pyrazolyl ketones related to Roche compound RO3201195, and Palau Pharma compound UR-13756 (Figure 1), amongst others. Furthermore, when some of these chemical inhibitors were added to Werner syndrome fibroblasts, their growth rate and cell morphology was restored. This opens the opportunity for using chemotherapeutic treatments for inflammatory conditions to combat rapid ageing in Werner syndrome patients, with relevance to the relationship between inflammation, ageing and disease progression in normal individuals.

References
DISCOVERY AND PRECLINICAL PROFILING OF NEW PYRAZOLO[1,5-a]PYRIMIDINE-BASED INHIBITORS OF CDK2 AND CHK1 KINASES

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Inhibition of cyclin-dependent kinases (CDKs) has emerged as an attractive strategy for the development of novel oncology therapeutics. The lecture will describe the synthesis, \textit{in vitro} and \textit{in vivo} profiling of numerous structurally diverse pyrazolo[1,5-\(a\)]pyrimidine-based CDK inhibitors, which resulted in the identification of SCH 727965 (dinaciclib), a potent and selective CDK inhibitor that is currently undergoing clinical evaluation [1].

![Chemical Structures]

Checkpoint kinase 1 (CHK1) is a serine/threonine kinase that controls the cellular response to DNA damage. Inhibition of CHK1 abrogates cell-cycle arrest resulting in genomic instability and ultimately progression into mitosis and cell death. Systematical variation of substituents on the pyrazolo[1,5-\(a\)]pyrimidine core combined with high-content cell-based screening lead to the discovery of the clinical candidate SCH 900776, which interacts synergistically with DNA antimetabolite agents to selectively induce cell death in tumor cell backgrounds [2].

![Chemical Structures]

References
A MULTIPLY CONVERGENT SYNTHETIC ROUTE TO TRIOXACARCINS

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Presented in this lecture will be the development of a highly convergent synthetic route to the trioxacarcins, a class of densely oxygenated, structurally complex natural products with potent antiproliferative effects in various human cancer cell lines. To address the chemical synthesis of natural and unnatural trioxacarcins broadly, a differentially protected trioxacarcin precursor was targeted. The trioxacarcin precursor was assembled in six steps from three components of similar structural complexity and was converted, in two additional steps, to the natural trioxacarcin DC-45-A2 \cite{1}. The highly convergent nature of the sequence, based on the plan in which strategic bond-pair constructions are staged at or near the end of the synthetic route, allows for rapid structural modifications of the trioxacarcin scaffold in order to explore the potential of the trioxacarcins for the development of small-molecule probes and drugs.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{DC-45-A2.png}
\caption{X-ray crystal structure of DC-45-A2}
\end{figure}

References
Short Lectures
**β-HALOGENATED N-(1-ACETOXYETHYL)- AND N-(1-TOSYLETHYL)UREAS IN HETEROCYCLIC SYNTHESES**

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In continuation of our work on synthesis of hydrogenated nitrogen-containing heterocycles using ureidoalkylation we report here application of readily available β-halogenated N-(1-acetoxyethyl)- and N-(1-tosylethyl)ureas (e.g., 1) to the preparation of functionalized 1,2,3,4-tetrahydropyrimidin-2-ones, hexahydropyrimidin-2-ones, 1,2-dihydropyrimidin-2-ones, 2,3-dihydro-1H-1,3-diazepin-2-ones, and dihydrofurans.

Starting compounds, ureas 1, were obtained in 1–2 steps from corresponding α-halogenated aldehydes and urea. Reaction of 1 with sodium enolates of β-oxoesters or 1,3-diketones 2 in acetonitrile at room temperature yielded the corresponding oxoalkylureas 3 (X = Cl) or hydroxypyrimidines 4 (X = F) in high yields. In the case of chloromethyl-substituted ureas 3 (n = 1), spontaneous cyclization of the obtained 3 was observed to give 5-ureido-4,5-dihydrofurans 5. Treatment of dichloromethyl- and trichloromethyl-substituted ureas 3 (X = Cl, n = 2–3) or trifluoromethyl-substituted pyrimidines 4 (X = F, n = 3) with TsOH in refluxing MeCN led to formation of the corresponding 4-dihalomethyl- and 4-trihalomethyl-substituted 1,2,3,4-tetrahydropyrimidin-2-ones 6.

We have shown that trichloromethyl-substituted pyrimidines 6 (X = Cl, m = 3) in the presence of bases (NaH, DBU) transform into previously hardly available 5-functionalized 1,2-dihydropyrimidin-2-ones 7 through elimination of chloroform. Treatment of dichloromethyl-substituted pyrimidines 6 (X = Cl, m = 2) with NaCN in DMF gave 2,3-dihydro-1H-1,3-diazepine-2-one (8) as a result of cascade reaction proceeding with ring expansion. Mechanisms of all above transformations will be discussed.
SYNTHESIS OF 2-SUBSTITUTED TETRAHYDROQUINOLINE ALKALOIDS

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A novel 2-substituted tetrahydroquinoline alkaloids, angustureine, galipinine, cuspareine, and galipeine were isolated from Galipea officinalis Hancock in 1999 [1]. Their tetrahydroquinoline alkaloids have been reported to exhibit anti-malarial and cytotoxic activities.

In this report, we are trying to modify above reaction for synthesis of racemic angustureine, galipinine and cuspareine.

Further synthetic study of optically active angustureine and other related 2-substituted tetrahydroquinoline alkaloids is currently underway.

References
MICROWAVE-ASSISTED SYNTHESIS IN ORGANOPHOSPHORUS CHEMISTRY INCLUDING P-HETEROCYCLIC CHEMISTRY

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A variety of reactions including esterifications, alkylations, additions, cycloadditions, fragmentations and condensations were carried out under microwave MW-assisted and solventless conditions, occasionally in ionic liquids (ILs).

Esterifications of phosphinic acids (1) and inverse-Wittig reactions (2) do not take place on traditional thermal heating, but maybe realized under MW conditions that is the consequence of a specific MW effect.

\[ \text{P} - \text{Ar} \overset{\text{OH}}{\underset{\text{CO}_2\text{Me}}{\longrightarrow \text{OR}}} \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{CO}_2\text{Me} \text{Me} \quad \text{Cl} \quad , \quad \text{Ar} = 2,4,6\text{-trialkylphenyl} \]

Diels–Alder cycloadditions (3) and fragmentation-related phosphorylations (4) became much faster and more efficient on MW irradiation.

\[ \text{RNH}_2 + 2\text{HCHO} + \text{P(O)H (EtO)}_2 \overset{\text{MW} \text{no solvent}}{\longrightarrow \text{PY}}_2 \text{O} \quad \text{R}^2 \quad \text{R}^1 \quad \text{R}^1 \quad \text{R}^2 \quad \text{Y} = \text{Ph}, \text{Bn} \quad \text{H} \quad \text{Me} \quad \text{Ph} \quad \text{Me} \quad \text{Ph} \]

The MW irradiation is an excellent tool to promote three-component condensations, like the Kabachnik–Fields reaction. We found that exotic and expensive catalysts suggested in the literature may be omitted if the condensation of simple oxo-compounds, primary amines and diethyl phosphite is carried out under MW conditions (5).

In a novel extension, the primary amines were reacted with two equivalents of formaldehyde and the >P(O)H species to provide bis(phosphonomethyl)- or bis(phosphinoxido) products (6) that, after double deoxygenation, may be used as bidentate P-ligands in ring Pt complexes.
SYNTHESIS OF FERROCYNL-1,2,3-TRIAZOLE-SUBSTITUTED CIS PENTACIN STEREOISOMERS

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Cyclic $\beta$-amino acids are key elements of many natural products, precursors of bioactive $\beta$-lactams. Several $\beta$-amino acid derivatives such as cispentacin, icofungipen, oryzoxymicin, or oxetin possess strong antifungal or antibacterial properties. The alicyclic, $O$- and $N$-heterocyclic conformationally rigid $\beta$-amino acids are building blocks in the synthesis of novel peptides. The enantiomerically pure $\beta$-amino acids and their derivatives are efficient chiral auxiliaries in asymmetric syntheses [1]. Recently the triazole-modified analogues of a series of antiviral compounds such as oseltamivir or zanamivir have been described as important derivatives with high pharmaceutical potential. The triazole skeleton is key component of the antiviral agent ribavirin, carbocyclic ribavirin, and of the biologically active modified nucleosides e.g. triazole-modified neplanocines [2]. During our present research work the synthesis of ferrocenyl-1,2,3-triazole-substituted aminocyclopentanecarboxylate stereo- and regioisomers has been accomplished from bicyclic lactams in 5 steps. The synthetic method was based on diastereoselective epoxidation, regioselective azidolysis and azide-ethynylferrocene dipolar cycloaddition reactions.

References
DOMINO RADICAL REACTIONS TOWARDS INDOLE-HETEROCYCLES OF BIOLOGICAL INTEREST

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Polycyclic (dihydro)indole derivatives are attractive synthetic targets due to their varying biological activities. The 1,3-dihyridindol-2-one (oxindole) ring is a key structural unit of numerous natural products[1] (horsfiline, spirotryprostaines, alstonisine…) and synthetic analogs of biological interest. Among the various powerful methods for the construction of such heterocyclic systems domino radical cyclization excelled in efficiency[2].

Herein we disclose a simple aryl radical induced 5-exo-trig/5-exo-trig type domino cyclization approach for the synthesis of 3-pyrrolidinone substituted oxindoles (2).

In a second series of experiments the same type of domino radical cyclization was combined for the first time with Smiles-rearrangement[3] affording 3-(2-arylacetamido)-substituted oxindoles (4) by a very efficient manner.

Both 3-substituted oxindoles (2, 4) could be considered as valuable intermediates for the synthesis of more complex indole derivatives by simple functional group transformations.

References
SYNTHESIS OF NATURALLY OCCURRING CHROMONE DERIVATIVES BY PALLADINIUM-CATALYZED CROSS-COUPLING REACTIONS

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Chromonoids and flavonoids are well known naturally occurring derivatives often having remarkable biological effects. Many of them have C-alkenyl units on their resacetophenone- or phloroacetophenone-type Ring A or a tricyclic furochromone or pyranochromone ring system which can be achieved by the ring-closure of these intermediates. Some representative examples are shown below.

We presumed that the key step, \textit{i.e.} the formation of the C-C bond can be performed by using the Heck or Sonogashira reactions which can provide a new approach to these important target molecules. Recently, we have presented the applicability of the Heck reaction in field of simple bromochromones \textsuperscript{[1]} and 6-bromo-7-hydroxychromones \textsuperscript{[2]}. In our contribution we will present our new results on the use of palladium-catalyzed cross-coupling reactions in the synthesis of alkenylated and alkynylated mono and dihydroxylated heterocycles and the also the ring closure of these products. Applications in the synthesis of naturally occurring structures and related systems will also be demonstrated.

References
SYNTHESIS OF A LIBRARY OF OLIGOTHIOPHENES AND THEIR UTILIZATION AS AMYLOID LIGANDS

Therése Klingstedt, Andreas Åslund, Rozalyn A. Simon, Leif B. G. Johansson, Jeffrey J. Mason, Sofie Nyström, Per Hammarström and K. Peter R. Nilsson.

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Herein we report the synthesis of a novel set of anionic LCO ligands and provide some insight of the basic molecular requirements for optimal performance of these dyes in the detection of amyloid protein aggregates.

The development of molecular dyes for the detection of proteinaceous deposits is of great importance, as the formation of extra- or intracellular protein aggregates, amyloid, is a common pathological hallmark associated with many diseases, including; Alzheimer’s; Parkinson’s; Huntington’s; and the infectious prion diseases.[1] These molecular probes are important to advance the understanding of molecular pathogenesis underlying amyloid diseases.

Luminescent conjugated polythiophenes (LCPs) have recently been introduced as a novel class of amyloid-binding fluorescent probes. In 2009, Åslund et al. improved on the concept, presenting defined structures termed luminescent conjugated oligothiophenes (LCOs) which could be utilized for in vivo imaging of protein aggregates.[2] 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 in contact with amyloid proteins.

An investigation of various length and arrangements of the thiophene backbone to influence the spectral difference between Aβ plaques and NFTs when binding to LCOs was undertaken. Furthermore, examination of the capacity to detect pre-fibrillar Aβ assemblies, as reported for the LCO p-FTAA, affected when changing the length of the thiophene backbone or the amount of anionic substituents.

References
NEW RING FUSED IMIDAZO[5,4-f]BENZIMIDAZOLEQUINONES: SYNTHESIS and ANTI-CANCER STUDIES

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This group has recently reported several classes of benzimidazolequinone anti-tumour agents.[1-4] Highly potent five to seven-membered alicyclic [1,2-\textalpha] ring fused benzimidazolequinones have been prepared via alkyl radical cyclizations.[4] The pyrido[1,2-\textalpha]benzimidazolequinone \(1\) was the most potent compound prepared being more than 300 times more cytotoxic than the clinically used drug mitomycin C (MMC) towards human hypoxic (low \(pO_2\)) cells. One-pot double radical cyclizations allowed the synthesis of alicyclic ring fused imidazo[4,5-f]benzimidazoles and imidazo[5,4-f]benzimidazoles.[5] Dipyridoimidazo[5,4-f]benzimidazolequinone \(2b\), and iminoquinone precursor \(2a\) showed selective toxicity towards cancer cell lines expressing high levels of the quinone reductase enzyme, NAD(P)H:quinone oxidoreductase (NQO1, also known as DT-diphorase). Synthesis of the new heterocyclic system: [1,4]oxazino ring fused imidazo[5,4-f]benzimidazoles \(3a-3b\) is now presented. The mechanism for cyclization via amine \(N\)-oxide intermediates, and anticancer activity of a library of imidazo[5,4-f]benzimidazolequinones is described.[6]

\[
\text{MMC} \quad \text{1} \quad 2a: \ X = \text{NH}, \ Y, \ Y = \text{CH}_2 \\
2b: \ X = \text{O}, \ Y, \ Y = \text{CH}_2 \\
3a: \ X, \ Y, \ Y = \text{O} \\
3b: \ X = \text{O}, \ Y = \text{CH}_2, \ Y = \text{O}
\]


The novel indoloquinoxaline derivatives (1 and 2) have, in preliminary studies, been demonstrated to have excellent inhibitory effects against Human cytomegalovirus (HCMV), Herpes simplex virus (HSV) and Varicella zoster virus (VZV) as compared with B-220 (3) and already established antiviral agents Cymevene® (Roche) and Foscavir® (AstraZeneca). The mechanism of anti-viral action is somewhat unclear but it appears to involve reversible non-covalent binding by intercalation into the DNA helix and, thus, disturbing the processes those are vital for viral uncoating [1]. We have performed extensive spectroscopic studies to investigate the interaction between a series of novel indoloquinoxaline derivatives and DNA by determining the binding constant, the binding geometry and the AT-specificity. The variation in structure, such as, the linker length, permanent/non-permanent nitrogen salt and introduction of substituents on the indoloquinoxaline moiety, are shown to have an immediate significant influence on the interaction between the ligands and DNA [2].

Additional studies for compounds 1 and 2 and similar derivatives are currently being tested in the EU funded project I-CARE: Integrative nano-Composites And Regeneration of the Eye. The objective of this project is to develop a regenerative-based treatment for Corneal Herpes Keratitis (HSK) [3].

References
DNA ADDUCTS DERIVED FROM BENZENE: THEIR SYNTHESIS,
METABOLIC TRANSFORMATION, AND EXCRETION

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Benzene is a proven human and animal carcinogen present almost ubiquitously in the environment. However, the mechanism by which it exerts the carcinogenic effect is not well understood. Three reactive intermediates in the metabolism of benzene, benzene oxide (BO), \textsuperscript{o}-benzoquinone (\textsuperscript{o}-BQ), and \textsuperscript{p}-benzoquinone (\textsuperscript{p}-BQ) react with nucleosides, nucleotides and the DNA yielding numerous adducts described in the literature. Surprisingly, only one of them, \textsuperscript{N\textsubscript{2}}-(4-hydroxyphenyl)-\textsuperscript{2\prime}-deoxyguanosine-\textsuperscript{5\prime}-phosphate (N\textsubscript{2}HPDGP), was found in living cells whereas none has been detected \textit{in vivo}.

We synthesised a complete series of known nucleobase and nucleoside adducts derived from BO, \textsuperscript{o}- and \textsuperscript{p}-BQ for use as analytical standards. Urine of mice exposed to benzene vapours at the concentration levels of 900 and 1800 mg/m\textsuperscript{3}, 6 h daily for 14 days, were analysed by LC-ESI-MSMS for DNA adducts, namely, 7-phenylguanine (7-PhG), 3-phenyladenine (3-PhA), \textsuperscript{N\textsubscript{2}}-(4-hydroxyphenyl)guanine (N\textsubscript{2}HPG), 3-hydroxy-3,\textsuperscript{N\textsubscript{4}}-benzethenocytosine (CBQ), 7-hydroxy-1,\textsuperscript{N\textsubscript{2}}-benzethenoguanine (GBQ), 7-(3,4-dihydroxy-phenyl)guanine (DHPG) and 3-(3,4-dihydroxyphenyl)adenine (DHPA). Detection limits ranged from 50 to 400 pg/mL. Only DHPA, an adenine adduct derived from \textsuperscript{o}-BQ, could be identified in the urine of mice exposed to the higher level of benzene. However, DHPA belongs to rapidly depurinating adenine adducts, which can reflect only a short time exposure. Its applicability in biological monitoring is therefore very limited. Absence of BO adducts (7-PhG, 3-PhA) in urine is consistent with the observed very low reactivity of BO with DNA. In vitro, conversion to these adducts at physiological pH was about 0.001 % and 0.003 % for the DNA adenine and guanine adducts, respectively.

To explain the discrepancy observed between reported DNA adduct formation \textit{in vitro} and their absence in the urine, we hypothesised that they could undergo efficient biotransformation \textit{in vivo}. Indeed, after administration of N\textsubscript{2}HPG or benzetheno adducts to rats, extensive biotransformation was observed, indicating that only minor fractions of the administered dose could be recovered unchanged from urine.

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Pyrazoles are small heterocyclic molecules which can be found in many natural products and biologically active compounds [1]. Our research group recently disclosed simple and general route to pyrazol-3-ones, also typical pyrazole derivatives [2]. Starting from commercially available aldehydes and acetic acids the synthesis pathway enables the isolation of acrylic acids 1, hydrazides 2 and pyrazolones 3, 4 where diazenes 5 act as key intermediates.

We explored the application of pyrazol-3-ones 4 and their precursors 1, 2, 3 as an attractive gateway for the synthesis of different types of biologically active compounds.

In past years there has been an intense effort to develop anti-cancer drugs that damage the tumor vasculature, obstruct blood flow and ultimately kill the tumor while leaving normal cells intact [3]. Combrertastatins have proven to be exceptional for such an approach, especially combretastatin A-4 (6) [4]. In recent publication we described synthesis and biological activity of pyrazolone-fused combretastatins and their precursors with some excellent anti-cancer activity [5]. The pyrazolone-fused combretastatin A-4 analogue (7) and the hydrazide 8 are highly cytotoxic against various tumor cell lines including cisplatin resistant cells. Details and some recent efforts to increase biological activity will be presented.

References
Posters
MICROWAVE-ASSISTED REACTIONS OF SOME P- AND N-HETEROCYCLES

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These days, the utilization of the microwave (MW) technique in organic synthesis has become widespread [1,2]. There is already some application in industrial scale, however, the real breakthrough is expected in next years. Phase transfer catalyst (PTC) is also a good tool in environmentally friendly chemistry. The combination of MW with solventless conditions and PTC offers also attractive possibilities [3].

During of our research work, first we have studied the alkylating esterification of cyclic phosphinic acids and then the N-alkylation of 5-membered N-heterocycles by alkyl halogenides under MW conditions. Our aim was to examine what will happen if the PTC and the MW techniques are combined. Control experiments were carried out under conventional heating. Besides, our aim was to find the optimum conditions of these reactions and to identify the products. We proved the efficiency of the MW irradiation in case of the model reactions studied, and we found that in most cases the PTC enhanced the reaction. We have also explored the optimum reaction conditions.

$$\text{R'O} + \text{R'X} \xrightarrow{\Delta \text{ or MW}} \text{R'O'P}$$

PTC $\text{K}_2\text{CO}_3$

$$\text{R} = \text{H, Me or Me, Me}$$
$$\text{R'X} = \text{EtI, nPrBr, iPrBr, nBuBr, BnBr}$$

$$\text{N}$$
$$\text{H}$$

$$\text{carbazole, imidazole, benzimidazole, indole-3-carbaldehyde}$$

Finally, we have studied the phospha-Michael addition of $>\text{P(O)H}$ species to maleimide derivatives under MW conditions. We have succeed in carrying out these reactions in good yields without the use of any solvents and catalysts.

$$\text{N-Y} + \text{R}_1\text{P(O)H} \xrightarrow{\text{MW}} \text{(RO)P}$$

no solvent

$$\text{Y} = \text{Me, Ph}$$
$$\text{R}_1 = \text{Et, Me, Et, Ph}$$
$$\text{R}_2 = \text{Et, Me, Ph, Ph}$$

References
THE SYNTHESIS AND GLYCOSIDASE INHIBITORY EVALUATION OF CHIRAL POLYHYDROXYCYCLOPENTA[c]ISOXAZOLIDINES

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The chiral pool is a valuable renewable source of starting materials, with carbohydrates being the most abundant representatives. The use of carbohydrates has its pros and cons and the chemical industry mostly refrained from its widespread use. There are, however, some distinct classes of compounds where the application of these substances is beneficial. One example is the synthesis of highly functionalized chiral carbocycles. The ω-unsaturated D-glucose-derived oxime (1) can be transformed into single diastereomer (3) according to Dransfield et al. Bicycles (3) can be easily cleaved into cyclopentanes (4). We have elaborated a stereoselective route to single diastereoisomers of polyhydroxylated chiral 9-oxa-1-azabicyclo[4.2.1]nonanes (5) through an intramolecular 1,3-dipolar cycloaddition involving nitrone (2). The core structures served as starting points for the generation of combinatorial libraries with the objective to obtain glycosidase inhibitors. To this end, carbocycles 3-5 have been derivatized in (a) acylation, (b) urethane and (c) urea formation reactions. The resulting compounds have been deprotected and their yeast α-glucosidase inhibitory activity has been assessed. Some of these compounds had inhibitory effect comparable with that of acarbose, an antidiabetes drug.

References
C-Nucleosides are an important class of compounds which are characterized by replacement of the labile C-N bond by a chemically and enzymatically more stable C-C bond, thus they exhibit in vivo stability against nucleosidase enzymes. These artificial aryl C-nucleosides could serve as new building blocks in chemical biology due to their capability of π-stacking and self pairing within DNA duplex. C-Nucleosides also have applications in medicinal chemistry, as the inhibitors of purine nucleosides phosphorylase or IMP dehydrogenase. There are several approaches for the synthesis of C-nucleosides, but all suffer from poor yields and/or insufficient anomeric selectivity.\[1\] We are currently involved in the development of modular methodologies based on the synthesis of various key intermediate C-nucleosides and their further use for a generation of series of diverse derivatives. In our novel modular approach we have synthesized several new types of various hetaryl C-nucleosides in two key steps.\[2\] The first step was the preparation of haloaryl-C-nucleoside intermediate which was subsequently submitted to palladium-catalyzed reactions to introduce the various types of substituents.

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References
ISOCYANIDE-BASED MULTICOMPONENT SYNTHESIS OF BIOLOGICALLY INTERESTING HETEROCYCLES

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Isocyanide-based multicomponent reactions (IMCRs) are particularly interesting as they are more versatile and diverse than other MCRs [1]. The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in IMCRs. MCRs involving isocyanides have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [2]. In this context, N-heterocyclic molecules show interesting features that make them attractive for use in IMCRs.

Heterocyclic compounds occur widely in Nature and are essential to life. N-heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life [3]. Herein, we report novel isocyanide-based multicomponent methods for the preparation of new N-heterocycles.

SYNTHESIS OF ARYLOXY-ALKYLAMINES WITH SODIUM CHANNEL BLOCKING ACTIVITY

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Company Gedeon Richter is very active in the field of voltage gated sodium channel blockers. The centrally acting muscle relaxant tolperisone (Mydeton) and the neuroprotective agent vinpocetine (Cavinton) have long been used as drugs. Their action on sodium channels may contribute to their pharmacological effect. Searching the follow-up compound of tolperisone several aryloxy-alkylamines were synthesized. Modifying the aromatic (heteroaromatic) moiety, the spacer, the amine function we could establish structure-activity relationships. The sodium channel blocking activity of our new compounds was tested by BTX binding and/or fluorometric membrane potential measurement.

\[
\begin{align*}
X & = \text{Br, Cl, F, CN, Ph, Me, etc.} \\
Y & = \text{O, S} \\
R & = \text{alkyl, substituted alkyl, cycloalkyl, etc.}
\end{align*}
\]

NEW N-YLIDES AND THEIR METAL COMPLEXES AS POTENTIAL INHIBITORS FOR GLUTAMATE RACEMASE

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Ylides are bipolar organic compounds in which the carbanion is covalently bound to a positively charged heteroatom [1]. Nitrogen ylides can coordinate metal ions forming complexes [2]. Glutamate racemase (GR) is a source of D-glutamate in bacteria [3] which is an essential component of the peptidoglycan layer of bacterial cell walls and it is a target for antibacterial drug development since many clinically used antibiotics act on this pathway [4-5].

We report here the synthesis and complexation properties of new stable disubstituted 4-(4-pyridyl)pyridinium ylides with the general formula shown in the figure below:

\[
\begin{align*}
\text{N} & \text{N} \\
\text{O} & \\
\text{Ar} & \\
X & \\
\text{X} & = \text{O, S} \\
\text{NH} & \\
\text{C} & _6 \text{H} & _4 & R & (p) \\
\text{CdH}_2 & R & (p)
\end{align*}
\]

Physical methods (NMR, IR, UV-VIS, MS, XRD) were used for establishing the structures of the new ylides and their complexes with cobalt, nickel, copper. Interaction of some ylides and some metal complexes with the RacEa peptide (the catalytic site from Glutamate racemase) was studied using Affinity-MS, and some of the tested compound showed to bind to the synthetic RacEa peptide. The peptide (LGCTHY) from Glutamate Racemase RacEa was synthesized by solid phase peptide synthesis (Fmoc-SPPS). This peptide is part of the catalytic site of the enzyme, therefore our preliminary Affinity-MS study is of interest for development of N-ylides-based Racemase inhibitors.

References
EFFICIENT METHODS FOR THE SYNTHESIS OF PYRAZOLES AND OXAZEPINES

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Heterocyclic compounds are highly ranked among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. Heterocyclic derivatives such as pyrazoles and oxazepines are just a few examples from various pharmaceuticals featuring a heterocyclic component.

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds [1], among them such prominent drug molecules as Celecoxib, Pyrazofurine, and many others. Herein, we report a novel one-pot method for the preparation of biologically important amino pyrazoles.

The modification of the oxazepine nucleus synthesis is a versatile research area due to its presence in some natural products and biologically active substances [2]. There are many methods for the synthesis of oxazepine ring systems. However, new, simple, and efficient ways for constructing oxazepine rings are still in great demand [3]. Therefore, due to the biological importance of oxazepines, we report a simple synthesis of dibenz[b,f]-1,4-oxazepines by intramolecular nucleophilic displacement of chloro group under microwave irradiation.

SYNTHESIS OF SOME NOVEL NEW S- AND N,S-SUBSTITUTED NITRODIENES

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As a part of our consecutive studies, we now report the some new S- and N,S-substituted nitrodiienes. Nitro-substituted polyhalogeno-1,3-butadienes can react with nucleophiles such as amines, alcohols, and thiolalcohols. The synthesis of some thiosubstituted 2-nitrodiene compounds has been reported [1-3].

It is known some mono- and di-substituted piperazine derivatives are significant for clinical chemistry,  gen transfer studies and posses high biological activity for multidrug resistance in cancer. In this study, the mono(thio) substituted nitrodiene compound was synthesized from nitrodiene and thiol. In the following step, reactions of piperazine derivatives with the mono(thio) substituted nitrodiene compound were studied.

Reaction products were purified by column chromatography. Structures of these novel products were determined by microanalysis and spectroscopic methods (IR, ¹H-NMR, ¹³C-NMR, UV and MS).

![Chemical structures](image)

R¹: -(CH₂)₆-CH₃

R²: ![Chemical structures](image)

References
INTRAMOLECULAR CYCLYSATION OF 
O$^6$-HYDROXYALKOXYPURINES

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2-Amino-6-chloropurine activated in the 6 position with DABCO is known to readily undergoes reactions with divers nucleophiles. Thus, its reaction with primary or secondary alcohols in the presence of a base leads to O$^6$-alkylated guanines [1,2,3]. With ethylene glycol, propan-1,3-diol and butan-1,4-diol the reaction performed in dry DMF with NaH as a base gave smoothly corresponding O$^6$-hydroxyalkyl guanines. After transformation of the hydroxy group to a suitable leaving group (halogen or activate ester) O$^6$-hydroxalkylpurines underwent intramolecular cyclisation yielding corresponding tricyclic products. Best results were achieved with PPh$_3$/CBr$_4$ as a reagent for transformation the OH group. The ring closure reaction proceeded exclusively at N1 nitrogen of guanine. The same reaction sequence performed with 6-chloropurine as the starting material yielded corresponding series of tricyclic purine derivatives. No ring closure reaction at N7 was observed. A regio-selective and efficient synthetic method for tricyclic purine derivatives was developed. The products may find applications as biologically active compounds [4,5]. Reaction conditions and other synthetic approaches to tricyclic purines will be discussed.

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References
THE SYNTHESIS and CHARACTERIZATION OF NOVEL CYCLIC HALOQUINONE DERIVATIVES

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Quinones are well known in biologic systems. The synthesis of benzo- and naphthoquinone compounds as a new biologically active agents in medicinal chemistry have received a considerable attention [1-3]. The aim of this study is the synthesis of the novel oxygen containing benzoquinone compounds as a potential biologic active agents and characterize them with spectral methods.

In this study the novel crown ethers with haloquinone group were synthesized. The structures of novel compounds were characterized by using Micro analyses, $^1$H-NMR, $^{13}$C-NMR, FT IR, MS, UV-vis.

References
NEW HETEROCYCLIC DERIVATIVES OF BENZIMIDAZOLE WITH
ANTICANCER ACTIVITY

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Benzimidazoles and their derivatives are well documented in the literature to exhibit a wide range of biological activities [1]. The position and type of substituents in the benzimidazole are responsible for the variety of their biological activities. Taking into consideration the information gained from the literature analysis of known anticancer drugs and the fact that silylation (germylation) increases lipophilicity of the compounds and can change their metabolism [2], we decided to synthesize silicon- and germanium-containing benzimidazoles 1 and their N-substituted derivatives 2, and to test the cytotoxicity against cancer cell lines HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma) and normal mouse fibroblasts NIH 3T3.

\[
\text{R} \text{NH}_2 + \text{R'}\text{M} \text{CHO} \xrightarrow{\text{NaHSO}_3, \text{DMF, 80}^\circ\text{C}} \text{R'}\text{M} \text{N} \text{R} \text{X} \text{C} \text{HOR'3M X} \text{N} \text{R'3M} \text{R} \xrightarrow{\text{R''Br/18-Crown-6/C}_6\text{H}_6} \text{M = Si, Ge; X = O, S; R = H, Me, Cl, Br; R' = alkyl, phenyl; R''M = 1-methyl-1-silacyclopentyl-, 1-methyl-1-silacyclohexyl-; R'' = alkyl, alky, propargyl}
\]

A preliminary analysis of the structure–activity relationship for the benzimidazole derivatives clearly indicates that the introduction of silyl(germyl) substituents into furan or thiophene ring of 2-furyl(thienyl)benzimidazoles 1 significantly increases the cytotoxicity of the compounds. IC\textsubscript{50} for the most active benzimidazoles 1 are in the range 0.08-1.0 \(\mu\)g/ml (for R'\textsubscript{3}M = H, IC\textsubscript{50} = 8–100 \(\mu\)g/ml). Introduction of the certain silyl group (1-methyl-1-silacyclopentyl- or 1-methyl-1-silacyclohexyl-) at the furan rings improves the cytotoxicity against cancer cells MG-22A (IC\textsubscript{50} = 1 \(\mu\)g/ml) and suitably decrease cytotoxicity to normal cells NIH 3T3 (IC\textsubscript{50} = 100–427 \(\mu\)g/ml). Furthermore, these groups greatly reduce the toxicity of new furyl-benzimidazoles (LC\textsubscript{50} = 763–1452 mg/kg). Alkylation of benzimidazoles 1 leads to new compounds 2, they also possess a high cytotoxic effect on cancer cells (IC\textsubscript{50} = 1–3 \(\mu\)g/ml).

References
Synthesis of a Functionalized Multifunctional Amyloid Ligand

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The formation and accumulation of protein aggregates, amyloid, give rise to distinct pathological conditions known as amyloidoses. Alzheimer’s disease and Parkinson’s disease are both examples of neurodegenerative conditions resolving on local amyloid accumulation in the brain. To be able to study these diseases, molecular probes that selectively identify the amyloid are needed as a research tool. Luminescent conjugated oligothiophenes (LCOs) have been proven to be utilized for in vivo imaging of protein aggregates by using fluorescence microscopy.[1]

Herein we report the synthesis of an asymmetric functionalized thiophene tetramer. This will provide the possibility to use other techniques than fluorescence, such as SPR, MRI and PET for detecting the interaction between the LCO and amyloid fibrils. Additionally, the functionalized LCO might also be implemented as an amyloid capturing reagent in novel sensitive assays for detection of amyloid and serve as a molecular scaffold for novel therapeutical inventions towards protein misfolding diseases.

References
DIELS–ALDER REACTION OF ELECTRON DEFICIENT 2H–PYRAN-2-ONES WITH ELECTRON RICH VINYL MOIETY CONTAINING DIENOPHILES AND CHARACTERIZATION OF THE INTERMEDIATE PRODUCTS

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Diels–Alder reaction is still one of the most intensively studied reactions in organic synthesis [1]. 2H-Pyran-2-ones 1 are, because of their intrinsic cisoid conformation, potent dienes for variety of dienophiles. In the past we showed that cycloaddition between ethyl vinyl ether (2, R^4 = Et) and 2H-pyran-2-on 1 led to the substituted anilines 6 [2]. It was also established that an appropriate base (DABCO) tremendously affects the formation of the aromatic product 6. Our main goal was to isolate both intermediate products 4 and 5 and to determine the role of acidic (Dowex) or basic (DABCO) catalyst on the outcome of the reaction [3]. When the reaction was conducted thermally or under microwave assisted heating not even traces of 2-oxabicyclo[2.2.2]oct-5-enes 4 were detected. On the other hand, we were able to prepare them under high pressure (13−15 kbar), which is widely known to accelerate the reactions with the negative activation volume. We also found out that regioselectivity of high pressure promoted cycloadditions was the same in all cases studied, but their stereoselectivity (ratio endo/exo stereoisomers 4) was highly affected by the type of dienophile. Semiempirical calculations (methods AM1 and PM3) were in agreement with experimental results. Dihydrobenzene derivatives 5 could be synthesized thermally without addition of any catalyst that usually affects the elimination step toward final aromatic product 6. It is worth to mention, that this type of compound is impossible to obtain in pure form as the aromatization proceeds spontaneously even in pure crystalline state.

Treatment of 2-(4-chloro-5\textit{H}-1,2,3-dithiazolylideneamino)benzonitrile \textbf{1} with Ph$_3$P gave unexpectedly 3-aminoindole-2-carbonitrile \textbf{3} [1]. The reaction was shown to proceed via the 2-cyano cyanothioformanilide \textbf{2} [2][3]. Although of mechanistic interest this route was not suitable for the synthesis and isolation of 3-aminoindole-2-carbonitrile \textbf{3} on a gram scale that would allow a study of its chemistry. As such a Thorpe-Zeigler cyclization was pursued and optimized that gave the desired indole in high yield without the need of chromatography [4][5]. Subsequent Friedländer cyclizations of 3-aminoindole-2-carbonitrile \textbf{3} with various cyclic ketones gave a range of interesting new fused carbazoline scaffolds \textbf{4}.

\begin{center}
\textbf{Scheme 1}
\end{center}

References
C-linked nucleosides analog pseudoisocytidine (1), shows activity against cytarabine-resistant leukemia and is stable toward deamination by cytidine deaminase [1]. Unfortunately, hepatotoxicity of unknown origin in humans led to discontinuation of its clinical trials [2].

We have developed synthesis of carbocyclic analogs of 1 that are represented by general formula 2. The compounds are envisioned to possess greater chemical and metabolic stability toward degradation in the cell. Namely, the cyclopentane analogs should not undergo ring opening and anomerization processes. As their tetrahydrofuran counterparts, properly functionalized carbocyclic compounds 2 may inhibit important enzymes (e.g. DNA polymerases, ribonucleotide reductase [3] etc.) while their biological and toxicological profiles may be superior.

Starting from methyl propiolate and cyclopentadiene, we prepared key cyclopentane intermediate 3 (Scheme 1), which was subsequently converted into the target molecules 2a-c with differently substituted pyrimidine base.

Scheme 1

Furthermore, intermediate 3 is to be used for preparation of other analogs with different heterocyclic systems and carbocyclic variants.

References
α,β-UNSATURATED ACIDS AS STARTING MATERIALS FOR THE SYNTHESIS OF FUMARAMIDES AND QUINOXALINONES

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Diazenes are an interesting group of compounds and a longtime interest of our research group [1]. Diazenedicarboxamides in particular have been shown to inhibit an essential bacterial enzyme D-alanine:D-alanine ligase [2]. Due to their reactive nature, we wanted to synthesize structurally similar compounds by replacing the reactive N=N moiety with a C=C double bond, resulting in fumaramides 5. The synthetic route involves the synthesis of monoamides of maleic acid 1 by opening of maleic anhydride with an appropriate amine (R¹R²NH) and consequent coupling with EDC·HCl to give the corresponding maleamides 4. We optimized the isomerization of maleamides 4 under focused microwave irradiation in the presence of different bases. A catalytic amount (8 mol%) of a heterocyclic amine – piperidine, has shown the best results, giving 5 in high yields and purity [3]. The starting monoamides of maleic acid 1 were also used for the synthesis of N-substituted 2-(3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)acetamides 2. The reaction directly from 1 proceeds poorly (MW, CH₃CN), but the yields are increased by utilizing methyl esters of 1 and/or catalyzing the reaction with a base in polar solvents. Since 2 and benzodiazepines 3 are indistinguishable by NMR techniques it remains to be confirmed by X-ray crystallography which isomer is formed by this reaction.

SYNTHESIS OF (–)-HYPEROLACTONE C FROM (S)-STYRENE OXIDE

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Hyperolactone C was originally isolated from the leaves and stems of Hypericum chinese L. (1995)[1] as a part of a small family of related lactones. Hyperolactone C and ent-zingiberene are precursors of biyouyanagin A (3),[2] a new anti-HIV agent.[3] Quite recently, Xie and co-workers reported a new 6-step catalytic asymmetric synthesis of (–)-hyperolactone C.[4]

Our current work was based on the 7-step rac-hyperolactone C synthesis from ethyl acetoacetate.[5] We developed new asymmetric route starting from (S)-styrene oxide (1).[6] The key step of the synthesis was Rh$_2$(OAc)$_4$ catalyzed oxonium ylide formation–rearrangement of silylated diazoalcohol 2 followed by acid work-up to give, as a major diastereomer, lactone 3. Lactone 3 was successfully oxidized to give (–)-hyperolactone C.

Acknowledgment
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References
REACTIONS OF BENZENE OXIDE WITH DNA AND MODEL NUCLEOPHILES

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Benzene oxide (BO) is a reactive metabolic intermediate of benzene. Its capability of binding to biologically important thiols, such as glutathione and cysteine units in proteins and to nucleophilic centres in the DNA was studied in model reactions with 2-deoxyadenosine, dA and 2'-deoxyguanosine, dG, nucleotides (2'-deoxyadenosine-5'-monophosphate, dAMP and 2'-deoxyguanosine-5'-monophosphate, dGMP) and with the DNA itself. Reactions were performed in aqueous TRIS buffer solutions (pH 7.4) at 37°C. Reaction products were analysed by LC/MS. Primary 6-hydroxycyclohexa-2,4-dien-1-yl derivatives were converted to corresponding phenylguanines and phenyladenines by acidic hydrolysis and these products were identified and quantified using authentic standards. Reaction of BO with 2-deoxyadenosine yielded 0.3, 1.0 and 10.7 % of the adduct at pH 5.5, 7.4 and 11.4, respectively. The primary adduct formed, N-Acetyl-S-(6-hydroxy-2,4-cyclohexadien-1-yl)cysteine was completely converted to N-acetyl-S-phenylcysteine (phenylmercapturic acid) after standing 1 h at pH 2 at room temperature. On the other hand, reactions benzene oxide with dA or dG afforded only traces (not more than 0.006 %) of corresponding adducts. So, 2'-deoxyadenosine gave two products before acidic hydrolysis (6-hydroxycyclohexa-2,4-dien-1-yl)-2'-deoxyadenosines and major ribosylated adducts (6-hydroxycyclohexa-2,4-dien-1-yl)adenines. After acidic treatment (pH 1, 100°C, 1 h) these peaks disappeared and two other peaks co-eluting with authentic 3-phenyladenine (3-PhA) and N6-phenyladenine (6-PhA) were detected, the latter being the predominating one. Similarly, dG gave only 7-(6-hydroxycyclohexa-2,4-dien-1-yl)guanine, which under the same acidic conditions gave 7-phenylguanine (7-PhG).

Reactions of BO with the DNA afforded only traces (not more that 0.7 %) of adenine and guanine adducts. They were identified after complete acidic hydrolysis of DNA as 7-PhG, 6-PhA and 3-PhA. Surprisingly, their yields increase with the reaction time even after 4.5 h, i.e., after BO had disappeared from the reaction mixture its half life in neutral aqueous solution being about 30 min. Similarly, a significant increase in the adduct yields with reaction time was observed in model reactions with dGMP and dAMP.

Very low reactivity of BO with the DNA as well as with purine nucleosides and nucleotides was observed indicating that BO can hardly be responsible for the DNA damage caused by benzene. Low DNA reactivity of BO also explains negative findings of corresponding DNA adducts in experimental animals or humans exposed to benzene.

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Within the past decade, the resurgence of interest in multicomponent reactions (MCRs) has been driven, not only due to their convergent nature, superior atom economy, and straightforward experimental procedures but also because of their value to the pharmaceutical industry for construction of low molecular weight compound libraries through combinatorial strategies and parallel synthesis [1].

Ferrocene derivatives find an ever growing application in many fields, from chiral catalysis to material science, to medicinal chemistry [2]. A number of reasons may be enumerated to explain the success of ferrocenes, among which, its unusual stability for an organometallic species: ferrocenes can be handled in the air when solid and often in solution also. Ferrocenes are reactive aromatic compounds, but they are sensitive to oxidizing agents – as most electrophilic reagents are – as well as to acids [3]. Thus, formation of ferrocenyl amidoesters or ferrocenyl triamides via MCRs is useful in functionalizing ferrocenes, because oxidation can be easily avoided, reaction conditions are mild, and ester or amide groups may be transformed into a variety of functional groups.

Herein, we describe an efficient synthetic approach to ferrocenyl amidodiesters and ferrocenyl triamides by an isocyanide-based four-component reaction.

SYNTHESIS AND IN VITRO ANTIBACTERIAL ACTIVITIES OF NOVEL 3-(PHENYL AMINO) QUINAZOLIN-4(3H)-ONES

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Quinazolinone derivatives have drawn much attention due to their broad range of pharmacological activities such as antibiotic, antidefibrillatory, antispermatic, vasodilatory, and analgesic ability [1]. Several methods have been reported for the synthesis of quinazolinones [2].

As per our ongoing work to synthesize privileged-class bioactive nitrogen-containing heterocyclic compounds [3], and in view of our interest in the KAl(SO₄)₂·12H₂O catalyzed reaction [4], we have designed the three-component one-pot synthesis of novel 3-(phenyl amino) quinazolin-4(3H)-one 4 from isatoic anhydride 1, orthoester 2, and phenylhydrazine 3 using non-toxic and easily available KAl(SO₄)₂·12H₂O (Alum) as a heterogeneous catalyst (Scheme 1).

![Scheme 1](image_url)


TOWARDS N²,8-DISUBSTITUTED GUANINES, HAPTONS FOR IMMUNOCHEMICAL ANALYSES OF DNA ADDUCTS WITH ARYLAMINES AND NITROARENES

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Modified purines often show significant biological activity because of structural similarity with important endogenous compounds. They are also formed by reactions of electrophiles or free radicals with DNA. These lesions of DNA can be detected in biological fluids or tissues using sensitive analytical methods including immunochemical methods [1, 2].

Our aim was to develop synthetic methods for 8-arylamino guanines bearing an \( \omega \)-carboxyalkyl link at the \( N² \) position. These compounds could be used as haptons for the development of immunochemical methods to analyse 8-arylamino adducts formed from numerous carcinogenic arylamines and nitroarenes.

Esters of \( N²-(\omega\text{-carboxyalkyl}) \)guanines, namely, \( N²\)-carboxymethyl-, \( N²\)-(2-carboxyethyl)- and \( N²\)-(3-carboxypropyl)guanine were prepared by reactions of 2-bromhypoxanthine with corresponding amino acid esters to give \( N² \)-substituted guanines. Reactions were performed in anhydrous DMF with pyridine as a base. Three \( N² \)-substituted guanines were obtained in 90, 55, and 57 % yields for ethyl 2-aminoacetate, ethyl 3-aminopropanoate and ethyl 4-aminobutyrate, respectively. However, our attempts to brominate these unprotected derivatives by \( N \)-bromosuccinimide at C-8 position were unsuccessful.

Therefore, another approach to C8-substituted purines was tested based on the condensation of vicinal diaminoypyrimidine with \( N \)-arylcarbamates followed by appropriate modification of the C2 position. 4,5,6-Triaminopyrimidine was chosen as a model compound for condensation with \( N \)-arylcarbamates. When melted with methyl \( N \)-phenylcarbamate at 180°C 4,5,6-triaminopyrimidine gave \( N,N' \)-diphenylurea and 8-oxoadenine but not the expected product. Nevertheless, addition of \( N,N' \)-dicyclohexylcarbodiimide (DCCI) as a coupling reagent to the reaction mixture changed the course of reaction so that the requested product, 8-phenylaminoadenine. Two intermediate phenylcarbamoylated derivatives of 4,5,6-triaminopyrimidine were identified by LC/MS analysis. The condensation reaction will be optimised using other carbodiimides as coupling reagents.

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References
SYNTHESIS OF NATURALLY OCCURRING 6- OR 8-ALKENYLATED HYDROXYFLAVONES

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Chromonoids and flavonoids are well-known naturally occurring derivatives often having remarkable biological effects. In the last decades the palladium-catalyzed arylation and vinylation of alkenes (Heck reaction) has become a versatile tool in organic chemistry. Since only sporadic reports were found in the literature, our research group initiated a systematic survey on the use of palladium-catalyzed cross-coupling reactions of chromones, flavones and coumarins. The usefulness of this methodology was demonstrated in the case of bromochromones1 and 6-bromo-7-hydroxychromones2.

Iodination of phloroacetophenone derivatives was studied and optimized followed by their transformation to iodinated chromones. These substrates were submitted to Heck reactions to give the expected alkenes in moderate to good yields. The investigations were extended to various iodinated 5,7-dimethoxy- and 5-hydroxy-7-methoxyflavones.

Our results proved the synthetic value of this approach in the field of alkenylated polyhydroxyflavones. Two natural products such as trans-tephrostachin and trans-anhydrotephrostachin were synthetized. Studies on the deprotection and ring-closure of the obtained products into tricyclic systems are in progress.

References
Highly functionalized cyclic amino acids as important bioactive derivatives have been the focus of the organic and medicinal chemistry over the past ten years. The multifunctionalized cyclohexane amino acids such as the antibiotic oryzoxymycin [1], the antiviral agents tamiflu [2], zanamivir and 2,3-didehydro-2-deoxy-N-acetylneuraminic acid (DANA) [3] are important derivatives with high pharmacological potential. Also their modified derivatives [4] exhibit strong antiviral, antifungal or antibacterial activities. The synthesis of highly functionalized β-aminocyclohexanecarboxylate regio- and stereoisomers from bicyclic β-lactam has been developed by regioselective iodolactonization, stereo- and regioselective nitril oxide cycloaddition followed by lactone and isoxazoline ring opening reactions.

References
SYNTHESIS AND TRANSFORMATIONS OF ALICYCLIC 2-AMINO- 
AND 2-HYDROXYSULFONIC ACIDS

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2-Aminoalkanesulfonic acids, especially taurine and substituted taurines, are not only very important sulfur analogues of naturally occurring aminocarboxylic acids, but also one class of important naturally occurring amino acids, which have been found in many mammalian tissues and in marine algae, fish [1]. They play an important role in several essential biological processes, such as development of the central nervous system and the retina, calcium modulation, membrane stabilization, reproduction, and immunity [2]. As part of our program to synthesize structurally diverse β-amino acids our aim was to prepare alicyclic 2-aminosulfonic acid. Our present aim was also to examine the transformation of newly prepared taurine analogues, and to develop the synthesis of alicyclic 2-hydroxysulfonic acids.

$$\begin{align*}
1a & : \text{cyclopentene} \\
1b & : \text{cyclohexene} \\
1c & : \text{cycloheptene} \\
1d & : \text{cyclooctene} \\
1e & : 1,3-\text{cyclohexadiene} \\
1f & : 1,4-\text{cyclohexadiene} \\
1g & : 1,5-\text{cyclooctadiene} \\
1h & : \text{norbornene} \\
1i & : \text{norbornadiene}
\end{align*}$$

We now report some examples of a practical two-step conversion of cycloalkenes $1a-i$ into 2-aminocycloalkanesulfonic acids $3$, based on the use of the commercially available, solid, and easily handled SO$_3$/DMF complex [3]. A stoichiometric amount of trifluoromethanesulfonic acid was added to the aminosulfonation mixture (cycloalkene, SO$_3$/DMF complex, acetonitrile) to accelerate the reaction and prevent the competitive formation of by-products. After deprotection of the N-acetyl-aminosulfonic acid $2$, microwave irradiation in water or heating in aqueous HCl, resulted in the corresponding 2-aminocycloalkanesulfonic acids $3$ in good yields. 2-Hydroxysulfonic acids $7-9$ were synthesized by the ring opening of epoxides $4-6$ with aqueous Na$_2$SO$_3$. Amino- and hydroxysulfonic acids are useful synthons providing possibilities for further transformations, which will also be discussed.

References
1,4-naphthoquinone derivatives have been found to possess high biologic activity profile such as antimycobacterial, anti-inflammatory, antiallergic and antimalarial. The incorporation of sulfur atom in 1,4-naphthoquinone derivatives has led to antifungal, anticancer and antiviral activities.[1]. Some of the sulfur containing 1,4-naphthoquinone derivatives have been synthesized in literature before. [2-3] The aim of this study is the synthesis of the novel 1,4-naphthoquinone derivatives containing sulfur atom and characterize them with spectral methods.

The structures of novel compounds were characterized by using Micro analyses, $^1$H-NMR, $^{13}$C-NMR, FT IR, MS, UV-vis.

References
SYNTHESIS OF MAYOTLIDE

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Mayotlide is a heterocyclic peptide isolated recently by PharmaMar from a sample of *Spongia sp* with cytotoxic activity in three human cancer cell lines (MDA-MB-231, A549, HT29) at micromolar concentration. The first key feature present in its intriguing structure is the tricyclic unit, 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (HPIC), formed by internal cyclization of a Trp residue. The structure of this natural product was determined by mass spectroscopic techniques, nuclear magnetic resonance, and degradation [1].

In the literature are described few natural products with related structures, whose members exhibit numerous bioactivities, including antitumor, antimicrobial, antinematodal and cytotoxicity. Notable members include the chetomin, chaetocochins A, B and C; all isolated from the solid-state fermented rice culture of the fungus *Chaetomium cochliodes* [2].

Natural products with HPI or HPIC unit bound through C3a to the N of a tryptamine or Trp. An extra degree of complexity is shown in kapakahines C and D, which are macrocyclic peptides formed through a bond between the N8 of an HPIC located at the N-terminal of the linear structure and the C4a of an α-carboline unit, located close to the C-terminal [3]. Synthetic approximations to this Trp-Trp system have been studied by several groups and only few total synthesis of natural compounds with that feature have been described [4]. The synthetic results in the preparation of mayotlide will be presented.

References

TARGETED CONJUGATES OF PREDNISOLONE BASED ON α-CYCLODEXTRIN-PEG-POLYPSEUDOROTAXANES

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The reaction of α-amino-ω-methoxypoly(ethylene glycol) [M = 5 kDa] or star α-amino-poly(ethylene glycol) [M = 20 kDa] with hemiesters of prednisolone dicarboxylic acids (succinic, glutaric, adipic, phthalic acid) has been used to prepare the corresponding conjugates. The synthesized conjugates form polypseudorotaxanes with α-cyclodextrins which were characterized by 2D NOESY NMR spectra, powder X-ray diffraction patterns and in one case also by STM microscopy. The rate of prednisolone release from the carrier can be controlled by three factors: character of the linker between the polymeric carrier and prednisolone, the molecular mass of PEG and complex formation with α-cyclodextrin [1].

![Principle of release of prednisolone from polypseudorotaxanes.](image)

We also prepared and characterized pH-sensitive conjugates and their polypseudorotaxanes [2]. Another methods of achieving goal-directed anti-inflammatory drug action is based on the fact that a number of pathogen processes induce lowering of pH value (≈ 5). For the pH-sensitive bond between prednisolone and PEG-carboxylic acid hydrazide, we have selected imino group, which is stable at pH values 7.4–7.6. On the other hand, the bond should be very easily hydrolyzed at lowered pH value. The synthesized polypseudorotaxanes represent new promising transport systems intended for targeted release of prednisolone in transplanted liver a) [1] or in the inflammatory tissues b) [2].

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References
SYNTHESIS AND SOME APPLICATIONS OF PHENACYLFURANS

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Recently we have shown that the reaction of xanthates 1 with 2-methylfuran under Fenton conditions leads to phenacylfurans 2 [1]. The transformation proceeds at very mild conditions and represents a new convenient method of the phenacylfuran synthesis.

\[
\begin{align*}
\text{R}_2\text{S} \quad \text{O} \quad \text{Et} \quad \text{O} & \quad \text{H}_2\text{O}_2 \quad \text{DMSO} \quad \text{FeSO}_4 \\
1 & \quad \text{R}_1 \quad \text{R}_3 \quad \text{R}_1 \quad \text{R}_3 \quad \text{R}_1 \quad \text{R}_3 \quad \text{R}_1 \quad \text{R}_3 \quad \text{R}_1 \quad \text{R}_3 \\
\text{2 (24-65%)}
\end{align*}
\]

(a) R\textsubscript{1}=H, R\textsubscript{2}=Br, R\textsubscript{3}=H
(b) R\textsubscript{1}=H, R\textsubscript{2}=OMe, R\textsubscript{3}=H
(c) R\textsubscript{1}=H, R\textsubscript{2}=NO\textsubscript{2}, R\textsubscript{3}=H
(d) R\textsubscript{1}=R\textsubscript{2}=OMe, R\textsubscript{3}=H
(e) R\textsubscript{1},R\textsubscript{2}=OCH\textsubscript{2}CH\textsubscript{2}O, R\textsubscript{3}=H
(f) R\textsubscript{1}=H, R\textsubscript{2}=R\textsubscript{3}=Cl

The obtained phenacylfurans can be used as starting compounds for the preparation of new carbo- and heterocycles. Thus, stirring of the compounds 2 in the mixture of acetic acid/ hydrochloric acid gives isomeric cyclopentanone derivatives 3 and 4 in good yields [2].

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References
Total synthesis of crispine A enantiomers through a *Burkholderia cepacia* lipase-catalysed kinetic resolution

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The plant *Carduus crispus* has been used for a long time in Chinese folk medicine for the treatment of colds, stomach problems and rheumatism. 8,9-Bis(methyloxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline (crispine A) \([1]\) was isolated in 2002 by Zhao from this plant. In recent years extensive investigations have been carried out on the chemistry of tetrahydroisoquinoline alkaloids \([2]\) in view of their potential pharmaceutical activity. We developed a new total synthesis of both enantiomers of the antitumour-active alkaloid crispine A. This alkaloid was synthesized through a *Burkholderia cepacia* lipase-catalysed acylation of the primary hydroxy group of \(N\)-Boc-protected 1-(3-hydroxypropyl)-6,7-bis(methyloxy)-1,2,3,4-tetrahydroisoquinoline \((\pm )-1\) and enantioselective hydrolysis of the corresponding \(O\)-decanoate \((\pm )-2, R = (\text{CH}_2)_8\text{Me}\) with a remote, four-atom distant stereogenic centre. High enantioselectivities were observed for \(S\) -selective \(O\)-acylation with vinyl decanoate in the presence of Et\(_3\)N and Na\(_2\)SO\(_4\) in \(t\)-BuOMe at 45 °C \((E = 68)\), and for \(S\)-selective hydrolysis with H\(_2\)O in \(t\)-BuOMe at 45 °C \((E = 52)\).

The enzymatic resolutions performed in two steps, afforded the key alcohol and ester enantiomers with high enantiomeric excesses \((ee \geq 94\%)\). Ester enantiomers \((+)-2\) and \((-)-2\) \([R = (\text{CH}_2)_8\text{Me}\)] were hydrolysed to the corresponding alcohols \((+)-1\) and \((-)-1\) in K\(_2\)CO\(_3\)/MeOH without loss of enantiopurity. Ring-closure reactions of alcohol enantiomers \((+)-1\) and \((-)-1\) with thionyl chloride afforded the desired crispine A enantiomers \((ee \geq 95\%)\).

References

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF NEW NAPHTH[1,2-e][1,3]OXAZINO[3,4-c]QUINAZOLINE DERIVATIVES

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The Betti reaction is a convenient method for the preparation of \( \alpha \)-aminobenzyl napthol derivatives. In previous studies, the synthesis and conformational analysis of napth[1,2-e][1,3]oxazino[3,4-c][1,3]benzoxazine\textsuperscript{1} and 8-substituted 10,11-dihydro-8\textsuperscript{H},15b\textsuperscript{H}-napth[1,2-e][1,3]oxazino[4,3-a]isoquinoline\textsuperscript{2} derivatives have been achieved. Since quinazoline and quinazolinone derivatives exhibit a wide range of biological activities and in order to extend the series of naphthoxazino-fused heterocyclic ring systems our primary present aim was to synthesize naphthoxazinoquinazolines. A further aim was the conformational analysis of these polycyclic compounds by NMR spectroscopy and accompanying molecular modelling.

For the synthesis of the proposed naphthoxazinoquinazoline derivatives, the preparation of 1-(amino(2-aminophenyl)methyl)-2-naphthol as starting material was achieved by the reaction of 2-naphthol, 2-nitrobenzaldehyde and \textit{tert}-butyl carbamate or benzyl carbamate, followed by reduction and/or removal of the protecting group. The aminonaphthol derivative thus obtained was converted in ring-closure reactions with formaldehyde, benzaldehyde and/or phosgene to the corresponding napth[1,2-e][1,3]oxazino[3,4-c]quinazoline derivatives. The conformational analysis of some derivatives by NMR spectroscopy and accompanying molecular modelling were also done.

References
Formation of aromatic amidoximes with hydroxilamine and scale-up in microreactor

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Application of microreactors is new trend in chemistry. Microreactors have several advantages compared to batch technology. Small volumes (few ml or µl) and high surface/volume ratio enable their safe application for highly toxic or explosive reactants and for dangerous reactions, too. Quick, and efficient optimization is a valuable advantage of a microreactor for process chemists in early development phase, while low amounts of materials are being used. Nowadays, more and more reactions are accomplished in microreactor in the fine-, and pharmaceutical industry [1, 2, 3].

Amidoximes are commonly used for synthesis of heterocycles in pharmaceutical chemistry, such as oxadiazoles. Amidoximes can be prepared from the corresponding nitriles in reaction with hydroxylamine. Hydroxylamine is considered as a toxic and a dangerous reagent, since even metal traces at ppm level can catalyze its decomposition [4]. Temperature of process has to be lower than decomposition temperature of hydroxylamine, and it can be higher through precise temperature control and high pressure in microreactor than in batch.

Batch mode preparation of this molecule was not robust and safe during development, therefore continuous mode synthesis of amidoximes was targeted as an alternative technology to reach the desired reproducibility and process safety. Replacing hydroxylamine hydrochloride 50% water solution of hydroxylamine was used in microreactor to ensure the homogeneity of the reaction mixture. During the formation of various aromatic amidoximes, microreactor and continuous process technologies were screened and applied to have considerable benefit on safety aspects of the process.

References