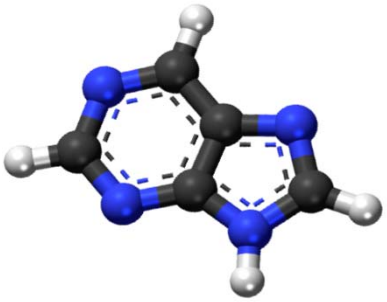
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Prezentace výsledků projektu CZ. 1.07/2.3.00/20.0009

Kombinatoriální chemie ve výzkumu i vzdělávání

KOMBICHEM



Přehled

- Cíle projektu
- Výzkumná činnost
- Grantová činnost
- Vzdělávací činnost
- Podpořené osoby v rámci zapojení do výzkumného týmu

Cíle projektu

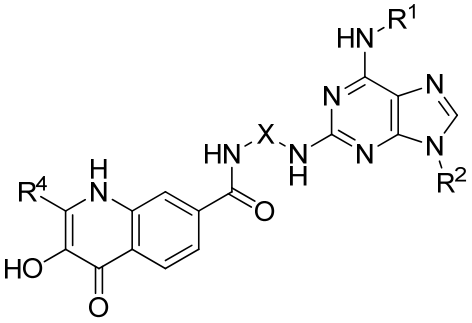
- Vytvoření výzkumných týmů na mezinárodní úrovni pod vedením
  - RNDr. Viktor Krchňák, CSc.
  - doc. RNDr. Jan Hlaváč, Ph.D.
  - doc. RNDr. Miroslav Soural, Ph.D.
- Výzkum v oblasti kombinatoriální chemie a organické syntézy na pevné fázi (SPOS)
- Zavedení vzdělávacích aktivit pro studenty/vědecké pracovníky

Výzkumná činnost

- Publikace v odborných časopisech (19)
- Publikace přijaté k tisku (3)
- Publikace v recenzním řízení (2)
- Kapitola v odborné zahraniční knize (2)
- Výsledky aplikovaného výzkumu (6)

Publikace v odborných časopisech

- Motyka, K; Vaňková B.; Hlaváč, J; Soural, M.; Funk, P. *J. Fluoresc.* **2011**, 21 (6), 2207-2212 (MZ_2)
  Purine Scaffold Effect on Fluorescence Properties of Purine-Hydroxyquinolinone Bisheterocycles

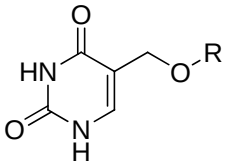


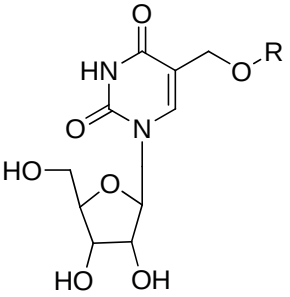
The fluorescence properties of bisheterocycliccompounds that contain purine and the 3-hydroxyquinolin-4(1*H*)-one skeleton connected with an aliphatic spacer of a different length/structure (3HQP) were examined. It wasfound that the introducing of the spacer-purine scaffold led in the comparison to 3HQs themselves to (1) the possibility of the effectual excitation in the wider range of excitation wavelengths, moreover, some derivatives can be excited at relatively high wavelengths around 400 nm, (2) the lowering of the quantum yield and (3) the slight longer wavelength shift of the dual emission spectra. Tested organicsolvents did not affect significantly the 3HQP fluorescence properties. The characters of emission spectra as well as the quantum yields of 3HQPs were notably influenced by the ratio of water and DMSO in their composed mixture applied as a solvent. With increasing water content in the mixture both I1/I2 and the quantum yield decreased.

- Brulikova, L.; Dzubak, P.; Hajduch, M.; Hlavac, J. *Carbohydr. Res.* **2011**, 346, 2136-2144.(MZ_2)

Synthesis of Various 5-Alkoxymethyluracil Analogues and Structure-Cytotoxic Activity Relationship Study

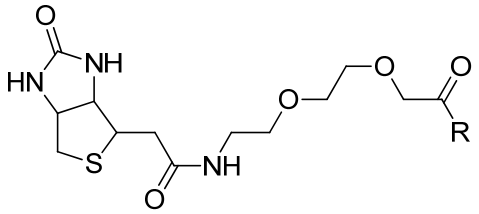
A number of 5-alkoxymethyluracil analogues were synthesized in order to evaluate their cytotoxic activity. 5-Alkoxymethyluracil derivatives 1 were prepared via known nucleophilic substitution of 5-chloromethyluracil 5 and subsequently transformed to their corresponding nucleosides 2. All prepared compounds were submitted to cytotoxic activity testing against drug sensitive and drug resistant leukemia cells and solid tumor derived cell lines. In addition to this, the cytotoxic activity of 5-alkoxymethyluracil analogues 1,2 was compared with the previously published 5-[alkoxy(4-nitrophenyl)methyl]uracil analogues 3,4. Extensive structure-cytotoxic activity relationship studies are reported.





Publikace v odborných časopisech

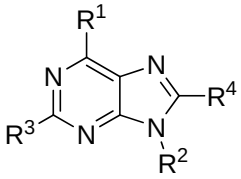
- Cankařová, N.; Funk, P.; Hlaváč, J.; Soural, M. *Tetrahedron Lett.* **2011**, 52 (44), 5782-5788(MZ_2)
  Novel preloaded resins for solid-phase biotinylation of carboxylic acids



Use of solid-phase synthesis for the derivatization of carboxylic acids with biotinylated spacers consisting of ethylenoxy units is described. An aminomethylated resin provided with an acid-labile aldehyde linker is used as the polymer support and three different systems with a reactive amino group are introduced. Acylation of each system was tested with a set of model carboxylic acids and afforded crude products of excellent purity. The preloaded resins are similar to the Biotin-PEG-NovaTagTM resin but offer several advantages including simple elongation of the spacer arm. The protocols described represent a very efficient way of modifying compounds to obtain ligands for affinity chromatography studies.

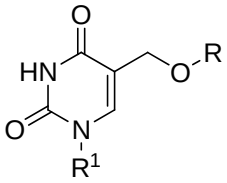
- Vaňková, B.; Krchňák, V.; Soural, M.; Hlaváč, J.
  Direct C-H Arylation of Purine on Solid Phase and Its Use for Chemical Libraries Synthesis
  ACS Combinatorial Science **2011**, 13 (5), 496-500n (MZ_2)

C8-H direct arylation of purine derivatives immobilized on Wang resin is described. The purine skeleton was immobilized via C6-regioselective substitution of 2,6-dichloro-purine with polymer-supported amines. After N9-alkylation with two different alkyl iodides and C2 substitution with two selected amines, reaction conditions for C8-H arylation were developed and optimized. Various aryl bromides and aryl iodides were used for the reaction affording the target 2,6,8,9-tetrasubstituted purines in very good purity. The same reaction conditions were also applied for the synthesis of 2,6,8-trisubstituted purines, however, yields were lower. The methodology is applicable for high throughput synthesis of chemical libraries comprised of purine scaffold.



Publikace v odborných časopisech

- Brulíková, L.; Hlaváč, J. *Beilstein Journal of Organic Chemistry* **2011**, 7, 678-698 (MZ_2)
  Synthesis, reactivity and biological activity of 5-alkoxymethyluracil analogues



This review article summarizes the results of long-term investigation of 5-alkoxymethyluracil analogues and is aimed at methods of syntheses in particular. Most of the presented compounds were synthesized in order to evaluate their biological activity, therefore, the brief survey of biological activity, especially antiviral, cytotoxic and antibacterial is also reported.

- Cagno, M.; Stein, P.C.; Stýskala, J.; Hlaváč, J.; Skalko-Basnet, N.; Brauer-Brandl, A. Eur. J. Pharm. Biopharm. **2012**, 80, 657-662.(MZ_3)
  Overcoming instability and low solubility of new cytostatic compounds: A comparsion of two approaches

The pharmaceutical use of some 3-hydroxyquinolinone derivatives with high cytotoxic and cytostatic activities (under in vitro conditions) as well as potential immunosuppressive properties is seriously limited by their low solubility in water accompanied by instability in oxidative environment, like physiological fluids. In an attempt to improve the bioavailability and the stability of four of these derivatives, we propose here two different approaches: complexation with β-cyclodextrin derivatives and incorporation of these substances inside antioxidant micelles. The comparison of the two different methods is the focus of this work, as well as the investigation of some physicochemical properties of the micellar aqueous dispersions. Antioxidant micellar dispersions appear to be suitable for increasing the apparent solubility and stability for all the compounds studied, most probably because of the antioxidant activity of the specific surfactant used, combined with the low amount of water present in the center of the micelles. On this regard, 1H NMR and UV–vis spectroscopy result as efficient tools to verify that the drug molecules are indeed placed in the core of the micelles. Moreover, freeze-drying provides a very easy and powerful technique to obtain solid formulations starting from micellar dispersions. On the contrary, cyclodextrins could potentially be used as solubilizing agents, but the drawback connected to degradation in aqueous media could not be overcome with this type of solubilizer.

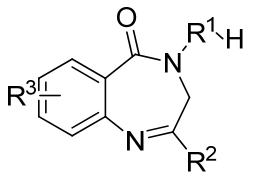
Publikace v odborných časopisech

- Brulíková, L.; Hlaváč, J.; Hradil, P. *Current Medicinal Chemistry* **2012**, 19 (3), 364-385 (MZ_3)
  DNA interstrand cross-linking agents and their chemotherapeutic potential

DNA interstrand cross-linking (ICL) agents are an important group of cytotoxic drugs with the capability of binding covalently between two strands of DNA, thereby preventing vital processes such as replication or transcription in dividing cells. In anticancer therapy however, their potential is limited due to the resistance by various mechanisms. In order to develop highly effective antitumor drugs it is necessary to study both effective ICL formations and their subsequent repair mechanisms. This review presents an overview of development over the past decade and the use of both well-known and new DNA interstrand cross-linking agents. Their potential in applications especially as anticancer chemotherapeutics in the framework of current knowledge of repair mechanisms and development of combined chemotherapy is discussed.

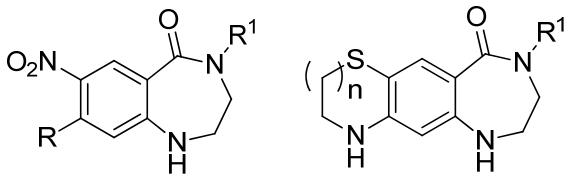
- Fülöpová, V.; Gucký T.; Grepl, M.; Soural, M.
  Solid-Phase Synthesis of Trisubstituted Benzo[1,4]-Diazepin-5-one Derivatives
  ACS Combinatorial Science **2012**, 12, 651-656(MZ_4)

Solid-phase synthesis of 3,4-dihydro-benzo[e]diazepin-5-ones with three diversity positions is described. Various primary amines were used as the starting material and immobilized on the polystyrene resin equipped with different acid-labile linkers. Polymer supported amines were converted to □-aminoketones with the use of their sulfonylation with the 4-nitrobenzensulfonylchoride (4-Nos-Cl) and subsequent alkylation with α-bromoketones. After the cleavage of the 4-Nos group the corresponding □-aminoketones were acylated with various o-nitrobenzoic acids. Reduction of the nitro group followed by spontaneous on-resin ring closure gave the target immobilized benzodiazepines. After acid-mediated cleavage the products were obtained in very good, crude purity and satisfactory yields which makes the developed method applicable for simple library synthesis of the corresponding derivatives in a combinatorial fashion.



Publikace v odborných časopisech

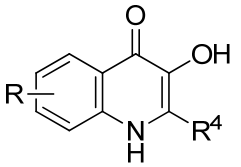
- Lemrova, B.; Soural, M. *ACS Combinatorial Science* **2012**, 14, 645-650(MZ_4)
  Solid-Phase Synthesis of 4,7,8-Trisubstituted 1,2,3,4-Tetrahydro-benzo[e][1,4]diazepin-5-ones



Solid-phase synthesis of 1,2,3,4-tetrahydro-benzo[e]diazepin-5-ones with use of polystyrene resin is described. The starting material was polymer supported 1,2-diaminoethane and as a key synthon, 4-chloro-2-fluoro-5-nitrobenzoic acid was used. The synthetic approach allows the preparation of derivatives with variable substitution at positions 4 and 8. Additionally, a skeletal diversity was increased when the nitro group was reduced and some benzene fused heterocycles were prepared. An expansion of a diazepinone to a benzodiazocinone scaffold was also successful although some limitations in a diversity of target derivatives were observed.

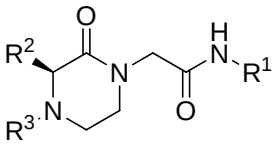
- Soural,M.; Hradil P.; Křupková S.; Hlaváč J. *Mini-Reviews in Organic Chemistry* **2012**, 9 (4), 426-432(MZ_4)
  An Interesting Synthetic Pathway to Some Quinolin-4(1H)ones: Phenacylanthranilates Rearrangement – Limits and Scopes

Rearrangement of some anthranilic acid esters, thioesters or amides under particularly acidic conditions gives derivatives of 2-aryl-3-substituted-quinolinon-4(1*H*)-ones. The reaction represents undoubtely the most efficient method for the preparation of derivatives bearing hydroxy and amino group at position 3. Furthermore, the target compounds comprise organic molecules with very interesting biological properties that have been reviewed quite recently. This mini-review summarizes information about limits and scopes of the unprecedent reaction that became extremely useful and revolutionary in area of flavonoids analogues research.



Publikace v odborných časopisech

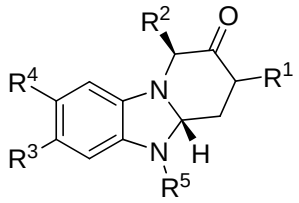
- Vaňková, B.; Brulíková, L.; Wu, B.; Krchňák, V. *Eur. J. Org. Chem.* **2012**, 26, 5075-5084(MZ_4)
  Synthesis of Piperazinones, Piperazines, Tetrahydropyrazines, and Dihydropyrazinones from Polymer-Supported Acyclic Intermediates via N-Alkyl- and N-Acyliminiums



Trisubstituted piperazinones, piperazines, tetrahydropyrazines, and dihydropyrazinones were prepared in a one-step procedure from easily accessible polymer-supported acyclic precursors containing either a masked aldehyde or ketone group. Acid-mediated unmasking of the aldehyde triggered cyclic iminium formation followed by reduction with triethylsilane present in the cleavage cocktail. The effect of the substituent at the iminium-forming nitrogen was evaluated: whereas complete conversion to the target compounds was observed with N-alkyl, aryl, and phenylsulfonamido derivatives, the N-acyl compound suffered from a partial reduction of the aldehyde to an alcohol. Similarly, ketones readily provided cyclic iminiums with N-alkyl compounds, whereas their cyclization with N-acyl precursors proceeded unwillingly. Interestingly, cleavage of the resin-bound acyclic precursor at 60 °C in the presence of triethylsilane resulted in the decomposition of the amide bond and formation of a lactone. An analogous synthetic route was also successfully used for the preparation of piperazines and tested as an alternative route for the synthesis of diazepanones.

- Cankařová, N.; Krchňák, V. J. Org. Chem. **2012**, 77 (13), 5687-5695(MZ_4)
  Polymer-Supported Stereoselective Synthesis of Benzimidazolinopiperazinones

Stereoselective synthesis of benzimidazolinopiperazinones on solid phase was described. The synthetic route involved iminium ion cyclization - nucleophilic addition. We have prepared a set of those derivatives from commercially available building blocks. The synthesis proceeded with full stereocontrol.

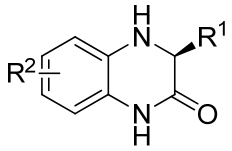


Publikace v odborných časopisech

- Hlavac J.; Soural M.; Krchnak V.
  Practical Aspects of Combinatorial Solid-Phase Synthesis (in Solid-Phase Organic Synthesis: Concepts, Strategies and Applications)
  kapitola v knize, Wiley & Sons, Inc., 2012(MZ_4)

- Neagoie, C.; Krchnak, V. *ACS Comb. Sci*. **2012**, 14(7); 399-402 (MZ_5)
  Piperazine Amide Linker for Cyclative Cleavage for Solid Support: Traceless synthesis of dihydroquinoxalin-2-ones

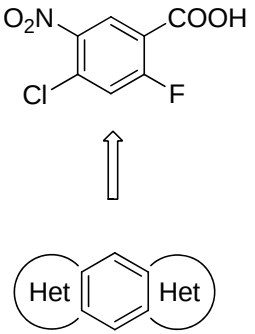
  A piperazine amide linker for cyclative cleavage from solid support and its use in the traceless solid-phase synthesis of dihydroquinoxalinones are described. Piperazine was attached to Wang resin via a carbamate linkage and acylated with Fmoc-amino acids. Following Fmoc group removal, resin-bound amines were reacted with 1-fluoro-2-nitrobenzenes. The nitro group of the resulting 2-nitroanilines was reduced, and acyclic precursors, in contrast to traditional ester-type linkage, remained attached to the resin. Target dihydroquinoxalinones were obtained either by acid- or microwave-mediated cyclative cleavage. The synthesis provided crude compounds of high purity and enabled the preparation of stable immobilized linear intermediates. The linker is suitable for combinatorial synthesis of compound libraries.



Publikace v odborných časopisech

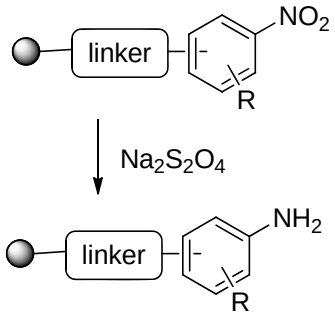
- Křupková, S.; Funk, P.; Soural, M.; Hlaváč, J. *ACS Comb. Sci*. **2013**, 15, 20-28 (MZ-5)
  4-Chloro-2-Fluoro-5-Nitrobenzoic Acid as a Possible Building Block for Solid-phase Synthesis of Various Heterocyclic Scaffolds

4-Chloro-2-fluoro-5-nitrobenzoic acid is a commercially available multireactive building block that can serve as a starting material in heterocyclic oriented synthesis (HOS)leading to various condensed nitrogenous cycles. This work describes its ability for the preparation of substituted nitrogenous heterocycles having 5–7-membered cycles via polymer-supported o-phenylendiamines. Immobilization of this compound on Rink resin followed by further chlorine substitution, reduction of a nitro group and appropriate cyclization afforded benzimidazoles,benzotriazoles, quinoxalinones,benzodiazepinediones and succinimides. The method developed is suitable for the synthesis of diverse libraries including the mentioned types of heterocycles, which have significant importance in current drug discovery. In this paper, we also report limitation of these method and unsuccessful attempt to prepare an 8-membered benzodiazocine cycle.



- Kaplanek, R. ; Krchnak, V. *Tetrahedron Lett*. **2013** 54 (21); 2600-2603.(MZ_5)

Fast and effective reduction of nitroarenes by sodium dithionite under PTC conditions: application in solid-phase synthesis



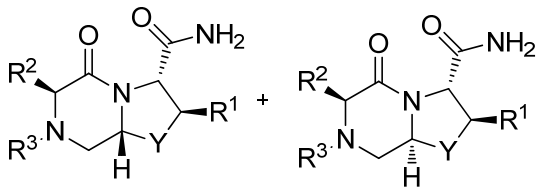
Herein, conditions for the fast and effective reduction of aromatic nitro groups bound to hydrophobic polystyrene-based Wang and Ring resins utilizing sodium dithionite in dichloromethane–water under PTC conditions are reported. Tetrabutylammonium hydrogen sulfate (TBAHS) was found to be an effective phase-transfer catalyst for this reaction. This method allows for the reduction of nitro groups to amino groups under mild conditions with complete conversion and is tolerant of other functional groups. This method is a superior alternative to tin(II) chloride-based reduction, which is known for its shortcomings.

Publikace v odborných časopisech

- La Venia,A. ; Dolensky, B.; Krchnak, V. *ACS Comb. Sci*. **2013;** 15 (3); 162-167. (MZ_5)

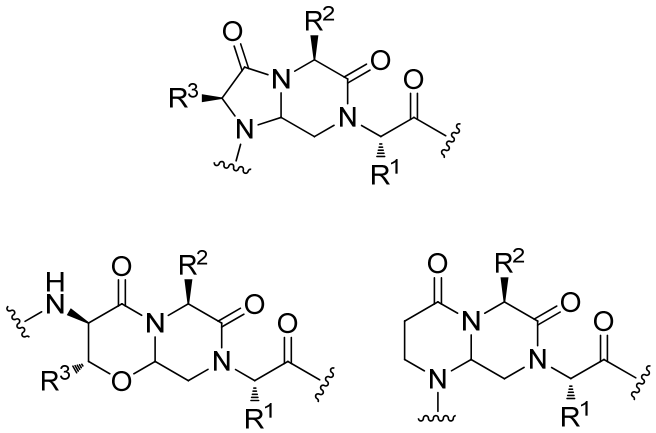
Polymer-Supported Stereoselective Synthesis of Tetrahydro-2H-oxazolo[3,2-a]pyrazin-5(3H)-ones from N-(2-Oxo-ethyl)-Derivatized Dipeptides via Eastbound Iminiums

Polymer-supported N-(2-oxo-ethyl)-derivatized Ser/Thr/Cys-containing dipeptides were synthesized and subjected to acid-mediated tandem N-acyliminium ion cyclization – nucleophilic addition to yield tetrahydro-2H-oxazolo-pyrazin-5(3*H*)-ones. The reaction conditions and building-block combinations for stereoselective synthesis of the newly formed asymmetric carbon were developed. The synthesis was fully compatible with solid-phase peptide synthesis, and the products serve as conformationally constrained peptidomimetics. The traceless synthesis of bicycles is also reported as part of this work.



- La Venia, A.; Lemrova, B.; Krchnak, V. *ACS Comb. Sci*. **2013**; 15 (1), 59-72. (MZ_5)

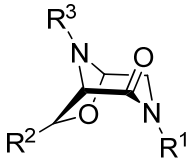
Regioselective Incorporation of Backbone Constraints Compatible with Traditional Solid-Phase Peptide Synthesis

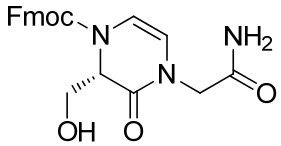


A protected aldehyde was attached via a two-carbon spacer to a peptide backbone amide nitrogen during a traditional Merrifield solid-phase synthesis. Acid-mediated unmasking of the aldehyde triggered the regioselective formation of cyclic N-acyliminiums between the aldehyde and the neighboring peptide amide nitrogen. In the absence of an internal nucleophile, the cyclic iminiums formed dihydropyrazinones, a six-membered peptide backbone constraint between two peptide amides. In the presence of an internal nucleophile, tetrahydropyrazinopyrimidinediones or tetrahydroimidazopyrazinediones were formed via tandem N-acyliminium ion cyclization-nucleophilic addition. The outcome of this nucleophilic addition was dependent on the substituent on the nitrogen nucleophile.

Publikace v odborných časopisech

- Schütznerova, E.; Oliver, A. G.; Zajicek, J.; Krchnak, V. *Eur. J. Org. Chem.* **2013,** 3158-3165. (MZ_6)
  Polymer-Supported Stereoselective Synthesis of (1S,5S)-6-oxa-3,8-iazabicyclo[3.2.1]octanes.



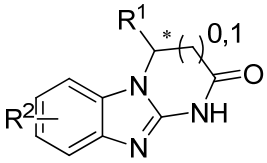


We describe a polymer-supported stereoselective synthesis of the (1S,5S)-6-oxa-3,8-biazabicyclooctane-bridged scaffold by tandem iminium ion cyclization/nucleophilic addition reactions. A series of resin-bound acyclic intermediates bearing different substituents were prepared, and the scope and limitations of the chemical route leading to the bridged scaffold were evaluated. The Thr-derived bridged scaffold was found to be substantially more stable in acid than the Ser-derived scaffold, which was partially transformed into dihydropyrazinones. Substitution at the iminium-forming nitrogen was critical for acid stability, and the N-arylsulfonamides with electron-withdrawing groups yielded the highest purity of the crude products prepared by acid-mediated cleavage. The acid-labile target compounds were synthesized by nucleophile-mediated cleavage from the esterified Wang resin and cyclization in formic acid.

- Cankařová, N.; Krchňák, V.
  Solid-Phase Synthesis Enabling Chemical Diversity. In Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis
  Kapitola v knize, Drug Discovery, and Chemical Biology, Trabocchi, A., Ed.; Wiley: 2013; pp 201-252. (MZ_6)

Publikace v odborných časopisech

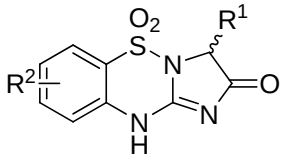
- Messina, I.; Popa, I.; Maier, M.; Soural, M. *ACS Comb. Sci.* **2014,** *16* (1), 33-38 (MZ_7)
  Solid-Phase Synthesis of 5-Noranagrelide Derivatives



Solid-phase synthesis of 1*H*-benzo[d]imidazoimidazol-2(3*H*)-one derivatives employing Fmoc-α-amino acids and nitroaryl fluorides as key building blocks has been developed. The Fmoc-α-amino acids immobilized on Wang resin, equipped with a piperazine carbamate linker, were transformed to o-nitroanilines in two steps. After reduction of the nitro group, the corresponding o-phenylenediamines gave the 2-aminobenzimidazole scaffold by reaction either with cyanogen bromide or Fmoc-NCS. Cleavage from the polymer support and further cyclization afforded the target compounds. The developed methodology represents a versatile and simple approach for the preparation of various corresponding 1H-benzo[d]imidazoimidazol-2(3H)-ones from large number of commercially available building blocks.

- McMaster, C., Fülöpová, V., Popa, I., Grepl, M., Soural, M. ACS Comb. Sci. (ID: co-2013-00119c.R)
  High Throughput Synthesis of Anagrelide Sulfonyl Analogues – ***v tisku***

Simple solid-phase synthesis of 3,10-dihydro-2H-benzo[e]imidazothiadiazin-2-one 5,5-dioxides is described, with Fmoc- α-amino acids and 2-nitrobenzenesulfonylchlorides (2-NosCls) being the key building blocks. Fmoc-α-amino acids were immobilized on Wang resin and transformed to the corresponding 2-nitrobenzenesulfonamides in two steps. After reduction of the nitro group, Fmoc-thioureas were synthesized followed by cyclization of the 1,2,4-benzothiadiazine-1,1-dioxide scaffold with diisopropylcarbodiimide (DIC). Cleavage of the Fmoc protecting group followed by spontaneous cyclative cleavage gave the target products in excellent crude purity.



Publikace v odborných časopisech

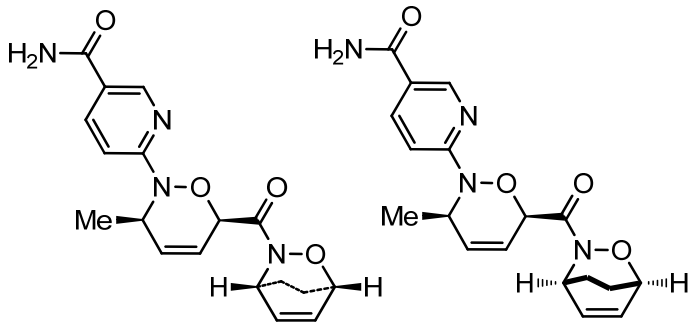
- Kadrić, J., Motyka, K., Dzubak, P., Hajduch, M., Soural, M. Tetrahedron Letters, (ID: TETL-D-14-00250R1)
  Synthesis, cytotoxic activity and fluorescence properties of a set of novel 3-hydroxyquinolin-4(1H)-ones
  - v tisku

  The targeted solid-phase synthesis of 3-hydroxyquinolin-4(1*H*)-one derivatives is described. The primary and secondary amines, 3-amino-4-(methoxycarbonyl)benzoic acid and 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone were used as starting materials. The structures of the final compounds were designed in accordance with previous information obtained from structure-activity relationship studies of similar cytotoxic derivatives. Representative prepared compounds were subjected to in vitro screening of cytotoxic activity against various cancer cell lines; the results obtained are discussed. Fluorescence properties of selected compounds were also studied to compare the data with those obtained in analogous derivatives.

- Smyslová, P.; Hlaváč, *J. Org. Biomol. Chem.*
  Copper catalysed and copper – free click reactions of 5-azidomethyl and 5´azido uridines
  v recenzním řízení

Publikace v odborných časopisech

- Harisson, A.; Melchionne, M.; Pilar, F.; Hlaváč, J. *J. Chromatography A.*
  Synthesis and chiral separation of 3,6-dihydro-2H-1,2-oxazine derivatives in their stereo/regioisomers mixture **- v tisku**



3,6-Dihydro-2*H*-1,2-oxazines are useful in the synthesis of many biologically active molecules due to the dihydro [1,2]-oxazine ring that is able to be subsequently derivatised. The Hetero-Diels-Alder (HDA) reaction from a nitroso-dienophile and diene that forms this scaffold results in the formation of two possible regioisomers, each subsequently forming two possible stereoisomers due to orientation of the precursors. Novel chiral stationary phases (CSPs) based on a chiral polysaccharide derivatives immobilised on silica support have been developed and are here used in the HPLC regio- and stereoisomeric separation of a diverse range of purified oxazines that were unable to be separated on traditional normal- or reverse-phase HPLC. It was found that those CSPs based on an amylose backbone were more efficient than those based on cellulose. Additionally, analytical samples without complete purification could be separated under the same conditions, for use in the optimisation of regio- and stereoselective synthesis of 3,6-dihydro-2H-1,2-oxazines.

- Funk, P.; Motyka, K.; Soural, M.; Klásková, J.; Maloň, M.; Koshino, H.; Hlaváč, J. *J. Org. Chem.*
  Unusual behavior of 2-amino-4(1H)-quinolinone under Mannich reaction conditions
  - v recenzním řízení

Výsledky aplikovaného výzkumu

Na poli aplikovaného výzkumu byly v rámci realizace projektu Kombichem řešeny:

- Užitné vzory
  - v oblasti výzkumu nových vlastností fluorescenčních sond
  - V oblasti vývoje nových metod pro přípravu cyklooktaselendiazolových derivátů tzv. click reakcí
- Patenty
  - pro nový typ linkeru na solid-phase syntézu
  - Vývoj nového přístupy pro přípravu a použití derivátů 2-fenyl-3-hydroxy-4(1*H*)-chinolonů

Seznam výsledků aplikovaného výzkumu

- Brulíková, L.; Motyka, K.; Hlaváč, J.
  Fluorescent probe based on rhodamine-pyrimidine skeleton for the pH determination
  užitný vzor, 24618, Univerzita Palackého, 2012 (MZ_4)

- Brulíková, L.; Hlaváč, J.; Motyka, K.
  The fluorescent probe of rhodamine-pyrimidine type for the determination of nitrite in water
  užitný vzor , 25893 , Úřad průmyslového vlastnictví, 2013

- Burglova, K.; Okorochenkov, S.; Hlaváč, J.:
  Nový typ hydrazinového linkeru
  Patent připravený k odeslání na patentový úřad

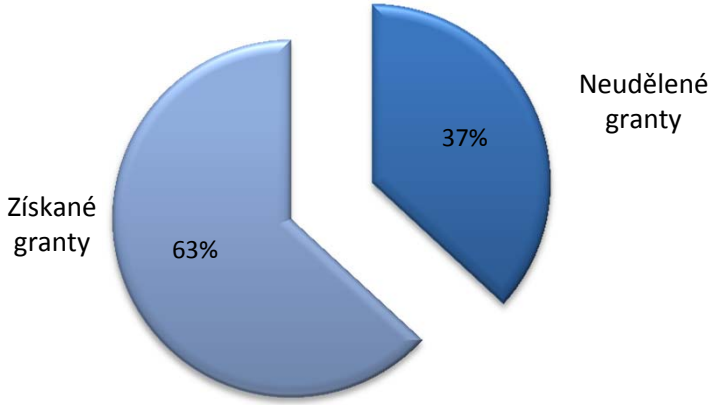
- Smyslova, P.; Hlaváč, J.:
  Cyklooktaselenadiazolový systém pro nekatalyzované click reakce
  Užitný vzor připravený k odeslání na patentový úřad

- Krejčí, P.; Hradil, P.; Hlaváč, J.; Hajdúch, M.
  Derivatives 2-phenyl-3-hydroxyquinoline-4(1H)-ones and methods of their preparation and utilization
  udělený patent, EP 2064200

- Krejčí, P.; Hradil, P.; Hlaváč, J.; Hajdúch, M.
  Derivatives 2-phenyl-3-hydroxyquinoline-4(1H)-ones and methods of their preparation and utilization
  udělený patent, US 8, 299, 092, B2

Grantová činnost

- V průběhu realizace projektu Kombichem bylo podáno celkem 19 grantových přihlášek u grantových agentur:
  - GAČR
  - TAČR
  - MŠMT (OP VK)
  - IGA
  - MOBILITY
  - EHP Norska
  - Klastr Medchembio II
- Celkem bylo v průběhu realizace projektu Kombichem uděleno 12 grantů



Grantová činnost – získané granty

- GAČR Syntéza diverzních peptidomimetik s rigidní strukturou na pevné fázi;
- TAČR Centrum vývoje originálních léčiv;
- OP VK 2.4 Rozvoj a posílení vzájemné spolupráce mezi akademickými i soukromými subjekty se zaměřením na chemický a farmaceutický výzkum.
- OP VK 2.3. Propojení výzkumu a vzdělávání v oblasti mediciální chemie;
- Klastr Medchembio II – Operační program podnikání a inovace
- IGA – Studium vybraných přeměn 2-substituovaných 3-hydroxychinolin-4(1*H*)-onů a jejich fluorescenčních vlastností (PrF_2013_034)
- IGA - Příprava derivátů 2,3-dihydro-1*H*-chinazolin-4-onu s pomocí syntézy na pevné fázi (PrF_2013_027)
- IGA - Využití Mitsunobu reakce v syntéze N-substituovaného 2-fenyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-karbonitrilu (PrF_2013_029)
- IGA - Syntéza pyrazolopyrimidinů a testování jejich CKD inhibiční a protinádorové aktivity (PrF_2013_036)
- IGA - Syntéza derivátů 3*H*-[1,2,3]triazolo[4,5-b]chinolinu substituovaných v poloze 9 (PrF_2013_025)
- TAČR: Centrum kompetence pro molekulární diagnostiku a personalizovanou medicínu (TE02000058)
- Aktivita mezinárodní spolupráce ve výzkumu a vývoji na podporu mobility výzkumných pracovníků a pracovnic MOBILITY (3. vlna – Argentina) - Syntéza biologicky aktivních látek v pevné fázi (7AMB14 AR031)

Vzdělávací činnost

- V rámci realizace projektu Kombichem byly realizovány vzdělávací akce:
  - Interní semináře
  - Odborné semináře
  - Konference
  - Letní školy
  - Semináře MedChemBio
  - Kurz „Syntézy na pevné fázi“ pro studenty bakalářských a magisterských oborů

Podpora výzkumných pozic

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- Mgr. Barbora (Vaňková) Lemrová, Ph.D.
- Mgr. Cleopatra Neagoie, Ph.D.
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- Mgr. Marc Verhille, Ph.D.
- Mgr. Niall John Dickinson, Ph.D.
- Mgr. Maitia Labora, Ph.D.
- Mgr. Michele Melchiona, Ph.D.
- Mgr. Ivano Messina, Ph.D.
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- Ing. Jiří Verner, Ph.D.
- Ing. Robert Kaplánek, Ph.D.
- Bc. Agustina La Venia, Ph.D.
- Mgr. Padraic Nagle, Ph.D.
- prof. Mgr. Ameneh Tatar, Ph.D.
- Thomas Ruhl, Ph.D.

Ph.D. studenti

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- Mgr. Veronika Fülöpová
- Mgr. Tomáš Ručil
- Mgr. Marek Petráček
- Mgr. Adam Šimáček
- Mgr. Wim Dehaen
- Mgr. Yu Tian