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Plavi C-fikocijanin (C-PC), glavni protein mikoalge *Arthrospira platensis*, poseduje značajnu antioksidativnu, antikancersku, anti-inflamatornu i imunomodulatornu aktivnost, koje se pre svega pripisuju fikocijanobilinu (PCB), kovalentno (tioetarskom vezom) vezanoj tetrapirolnoj hromofori. Jedan PCB molekul je vezan za  $\alpha$ -subjedinicu preko Cys84, dok  $\beta$ -subjedinica vezuje dva molekula PCB-a preko Cys82 i Cys153. Oralno unet C-PC je podložan proteolizi, pri čemu se mogu dobiti biološki aktivni hromopeptidi (peptidi sa kovalentno vezanom hromoforom). Cilj ove studije je bio da se strukturno okarakterišu fiziološki relevantni hromopeptidi dobijeni nakon pepsinske digestije C-PC-a. SDS-PAGE je pokazala da se C-PC brzo digestuje pepsinom u simuliranoj želudačnoj tečnosti. Pet dominantnih frakcija je izolovano uz pomoć reverzno-fazne HPLC. Manuelni *de novo* pristup, u visoko rezolutivnoj tandemskoj masenoj spektrometriji, upotrebljen je u cilju određivanja strukture izolovanih hromopeptida. Sekvence hromopeptida su određene iz MS spektara, dok su za potvrđivanje sekvenci iskorišćeni MS2 i MS3 spektri roditeljskih jona, kao i MS i MS2 spektri čistog PCB-a. Šest hromopeptida je identifikovano, veličine 2-13 aminokiselinskih ostatka. Opisan pristup može biti od koristi za određivanje strukture hromopeptida i kovalentnih adukata proteina i tetrapirolnih hromofora.

## Structure determination of chromopeptides obtained by pepsin digestion of C-phycoyanin from microalga *Arthrospira platensis*

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Blue C-phycoyanin (C-PC), the major protein of microalga *Spirulina*, possesses significant antioxidant, anticancer, antiinflammatory and immunomodulatory effects, mostly ascribed to the covalently bonded (*via* tioether bond) linear tetrapyrrole chromophore phycoyanobilin (PCB). One PCB molecule is attached to  $\alpha$ -subunit *via* Cys84, while  $\beta$ -subunit binds two molecules of PCB *via* Cys82 and Cys153. Orally administrated C-PC is susceptible to proteolysis, wherein biologically active chromopeptides could be obtained. The aim of this study was the structural characterization of physiologically relevant chromopeptides obtained after the pepsin digestion of C-PC. SDS-PAGE revealed that C-phycoyanin is rapidly digested by pepsin in simulated gastric fluid. Five dominant chromopeptide fractions were isolated from pepsin digest by reversed phase HPLC. Manual *de novo* high resolution tandem mass spectrometry approach was applied to the determine structure of the isolated chromopeptides. Chromopeptide sequences were resolved from MS spectra. Confirmation of sequences was done by the analysis of MS2 and MS3 spectra of parent ions, and MS and MS2 spectra of the pure PCB. Six chromopeptides were identified, varying in size from 2 to 13 amino acid residues. The approach described here can be used for the identification of the structure of both chromopeptides and protein-tetrapyrrole covalent adducts.

## **Veživanje slobodnih masnih kiselina i bakar(II)-jona za HSA dovodi do promena u karbonilaciji i reaktivnosti Cys34 tiolne grupe sa metilglioksalom**

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Ljudski serumski albumin (Human serum albumin, HSA) predstavlja glavni antioksidant plazme zahvaljujući redukovanom Cys34. Veživanje masnih kiselina (FAs) za HSA može dovesti do promene u dostupnosti i reaktivnosti Cys34 tiolne grupe, njenog kapaciteta kao hvatača/antioksidanta. Cilj ovog rada je bio da se ispita efekat izabranih FAs (stearinska, miristinska, oleinska, ekstrakt ribljev ulja-FO i smeša-MixFAs) na veživanje Cu(II) jona za HSA, kao i sinergistički uticaj na reaktivnost HSA-SH i modifikaciju HSA metilglioksalom (MG). Veživanje FAs povećava reaktivnost HSA-Cys34-SH, k' vrednost (konstanta brzine pseudo prvog reda reakcije tiola sa Elmanovim reagensom) je bila povećana u nizu: MixFAs, oleinska, stearinska, FO i miristinska. Veživanje Cu(II) jona (0,1 mol/mol HSA) dovelo je do povećanja k' vrednosti ako je bio prisutan FO, ali je bila smanjena kada su ostale FAs bile prisutne. Sadržaj slobodne HSA Cys34-SH je bio smanjen za 10% posle veživanja Cu(II) jona, a dalje tokom inkubacije 24 h na 37 °C, bio je dodatno smanjen za 10% (stearinska, MixFAs) i 20% (miristinska, FO, oleinska). Karbonilovanje FA-HSA-Cu(II) kompleksa sa MG (20 mol/mol HSA) u toku 24 h, dovelo je do smanjenja sadržaja Cys34-SH 30-40% zavisno od prisutne FA. Karbonilovanje FA-HSA-Cu kompleksa može doprineti povećanju karbonilnog i oksidativnog stresa u dijabetesu i drugim bolestima.

## **Binding of FAs and Cu(II)-ions to HSA changes its carbonylation pattern and Cys34 thiol group reactivity with methylglyoxal**

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Human serum albumin (HSA) represents a major plasma antioxidant due to its Cys34 reduced/sulfhydryl form. FAs binding to HSA could lead to changes of Cys34 thiol group accessibility and reactivity, i.e. its scavenger capacity/antioxidant properties. The aim of this work was to investigate the effects of selected FAs (stearic, myristic, oleic, fish oil extract-FO, FAs mixture-MixFAs), on Cu(II) ion binding to HSA, and the synergistic influence on the reactivity of HSA-SH and HSA modified with methylglyoxal (MG). Binding of FAs increased HSACys34-SH reactivity, k' values (pseudo first order rate constant for thiol reaction with Ellman's reagent) increased in the order: MixFAs, oleic, stearic, FO and myristic. Binding of Cu(II) (0.1 mol/mol HSA) led to an increase of k' value if FO was present, but for other bound FAs k' value decreased. The content of free HSACys34-SH decreased 10% after Cu(II) ion binding, and during 24 h incubation at 37 °C, it further decreased for another 10% (stearic acid, MixFAs) or 20% (myristic, FO, oleic). Carbonylation of FA-HSA-Cu(II) complexes with MG (20 mol/mol HSA) for 24 h, lead to a decrease in Cys34-SH content depending on FA present: 30-40%. Carbonylation of FA-HSA-Cu complexes could contribute to a further enhancement of the oxidative and carbonyl stress in diabetes, as well as other diseases.

BH 05

## **Efekat odabranih 17-supstituisanih androstanskih derivata na ćelije kancera**

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Modifikovani steroidi najčešće ispoljavaju biološka i fiziološka svojstva različita u odnosu na prirodne, nemodifikovane steroide. Stoga se neka jedinjenja iz ove klase koriste za terapiju različitih steroidni hormon-zavisnih bolesti. U ovom radu je ispitivan antiproliferativni i pro-apoptotski potencijal  $17\alpha$ -pikolil i  $17(E)$ -pikolinilidenskih derivata androstana, kao i uticaj ovih jedinjenja na ćelijski ciklus najsenzitivnijih ćelijskih linija. Svi modifikovani steroidi su značajno smanjili proliferaciju MCF-7 i HT-29 ćelija. Rezultati protočno-citometrijske analize su pokazali da neka od jedinjenja menjaju ćelijski ciklus tretiranih ćelija kancera. Neka od jedinjenja su indukovala apoptozu u izvesnoj meri, što se moglo kvantifikovati na osnovu morfoloških promena tretiranih ćelija. Dobijeni rezultati bi mogli da ukažu na nove pravce u sintezi potencijalno bioaktivnih modifikovanih steroida za terapiju kancera.

## **The effect of selected 17-substituted androstane derivatives on cancer cells**

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Modified steroids usually exhibit biological and physiological properties different from the natural, unmodified steroids. Therefore, certain compounds of this class are used for the therapy of various steroid hormone-dependent diseases. In this study the antiproliferative and pro-apoptotic potential of  $17\alpha$ -picolyl and  $17(E)$ -picolinylidene androstane derivatives were studied, as well as the effect of these compounds on the cell cycle of the most sensitive cell lines. All modified steroids significantly reduced the proliferation of MCF-7 and HT-29 cells. The results of flow-cytometric analysis revealed that some of the compounds altered the cell cycle of the treated cancer cells. Some of the compounds induced apoptosis to some extent, quantifiable on the basis of the morphological changes of the treated cells. The results could indicate new directions in the synthesis of potentially bioactive modified steroids in the treatment of cancer.

BH P01

### **Efekti Majlardove reakcije na imunogenost $\beta$ -laktoglobulina**

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Majlardova reakcija se odvija tokom obrade hrane i dolazi do formiranja naprednih glikacionih krajnjih produkata (Advanced Glycation Endproducts - AGE) proteina hrane. AGE imaju značajan uticaj na alergene hrane. Mi smo izveli Majlardovu reakciju između model alergena hrane,  $\beta$ -laktoglobulina (BLG), i glukoze. Glikovanje BLG-a ne utiče na sekundarnu strukturu proteina, ali smanjuje njegov transport kroz jednoslojne Caco-2 ćelije. Nezrele dendritične ćelije (Dendritic Cells - DCs) preuzimaju glikovani BLG u značajno većoj meri nego nativni BLG. Unutar endolizozomalnih odeljaka DCs glikovani BLG podleže bržoj degradaciji.  $CD4^+$  T ćelije specifične na BLG pokazuju smanjenu produkciju citokina (IL-5, IL-13,  $INF\gamma$ ) kada se uzgajaju zajedno sa DCs koje su prethodno preuzele glikovani BLG, u odnosu na nativni BLG. Naši rezultati ukazuju da Majlardova reakcija ima značajan uticaj na imunogenost BLG-a, jer menja njegovu gastrointestinalnu biodostupnost, interakcije sa ključnim ćelijama imunskog sistema – DCs, i utiče na njegovu sposobnost da stimuliše  $CD4^+$  T ćelije.

*Ovo istraživanje je podržano od strane Ministarstva za prosvetu, nauku i tehnološki razvoj Republike Srbije, projekat br. 172024.*

### **Effects of Maillard reaction on immunogenicity of $\beta$ -lactoglobulin**

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Maillard reaction occurs during food processing and results in formation of Advanced Glycation Endproducts (AGE) of proteins. AGE of food allergens are of particular importance. We performed an extensive Maillard reaction with a model food allergen,  $\beta$ -lactoglobulin (BLG), and glucose. Glycation of BLG did not influence protein secondary structure but reduced its transport through Caco-2 monolayer. Uptake of glycated BLG by immature dendritic cells (DCs) significantly increased when compared to native BLG. Inside endolysosomal compartments of DCs, glycated BLG undergoes faster degradation. Compared to the native BLG, glycated BLG diminished cytokine production (IL-5, IL-13,  $INF\gamma$ ) by BLG-specific  $CD4^+$  T cells co-cultured with DCs. Our data indicate that the Maillard reaction plays a significant role in immunogenicity of BLG, influencing its gastrointestinal bioavailability, interactions with crucial cells of immune system, DCs, and its ability to stimulate  $CD4^+$  T cells.

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**Optimizacija visoko specifičnog fluorescentnog testa kod kvasca  
*Saccharomyces cerevisiae* za identifikaciju liganada androgenog receptora i  
kvantifikaciju njihovog afiniteta vezivanja**

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Poznato je da signalni put androgenih receptora (AR) ima važnu ulogu u razvoju i progresiji kancera prostate. Supresija njihove aktivnosti antagonistima AR može inhibirati rast kancera prostate. Stoga, AR predstavljaju obećavajuću metu u lečenju ove bolesti. Naš cilj je bio da razvijemo i optimizujemo neradioaktivni i visoko specifičan fluorescentni test kod kvasca za identifikaciju liganada androgenog receptora i kvantifikaciju njihovog afiniteta vezivanja. Ekspimirali smo ligand vezujući domen (LBD) AR spojen sa žutim fluorescentnim proteinom (YFP) kod *Saccharomyces cerevisiae*. Test se zasniva na fluorescentnom rezonantnom transferu energije (FRET) između dva molekula YFP nakon vezivanja liganda za AR i dimerizacije receptora. Testirano je vezivanje AR liganda, dihidrotestosterona, u različitim koncentracijama i kreirana je standardna kriva. Naš ćelijski fluorescentni test se može primeniti za skrining jedinjenja koja se vezuju za AR, kao što su potencijalni antikancerski lekovi.

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**Optimization of highly specific fluorescent assay in *Saccharomyces cerevisiae*  
for the identification of androgen receptor ligands and quantification of their  
binding affinity**

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It is known that the androgen receptor (AR) signaling pathway plays a major role in prostate cancer development and progression. Suppression of AR activity by antagonists could inhibit prostate cancer growth. Hence, ARs represent a promising target in the treatment of this disease. Our aim was to develop and optimize a nonradioactive and highly specific fluorescent assay in yeast for the identification of androgen receptor ligands and quantification of their binding affinity. We expressed the ligand binding domain (LBD) of AR fused with yellow fluorescent protein (YFP) in *Saccharomyces cerevisiae*. Our assay is based on the fluorescence resonance energy transfer (FRET) between two YFPs after ligand binding to the AR and receptor dimerization. Binding of the AR ligand, dihydrotestosterone, at various concentrations was tested and a standard curve was set up. Our cellular fluorescent assay could be applied for the screening of compounds that bind to ARs, such as potential anticancer drugs. This work was funded by the Ministry of Education, Science and Technological Development, Republic of Serbia (Project 172021).

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BH P03

**Imunoafinitetno profilisanje molekularnih vrsta specifičnog antigena prostate**Sanja R. Goč, Miroslava M. Janković*Institut za primenu nuklearne energije, Univerzitet u Beogradu, Banatska 31b, Beograd*

Molekulska vrsta predstavlja najmanju strukturnu i funkcionalnu jedinicu proteoma. Razvoj i primena tehnika masene spektrometrije (MS), otvorili su veliki broj mogućnosti za detekciju i definisanje diskretnih razlika u vrstama, koje su, u najvećoj meri, rezultat post-translacionih modifikacija. Cilj rada je bio imunoafinitetno profilisanje molekularnih vrsta specifičnog antigena prostate (PSA) u serumu. PSA je glikoprotein koji ispoljava izrazitu strukturnu heterogenost polipeptidnog i glikanskog lanca, a uvid u profil njegovih molekularnih vrsta u različitim fiziološkim stanjima, pored proširenja bazičnih znanja može biti od interesa i u laboratorijskoj dijagnostici. Identifikacija i detekcija molekularnih vrsta PSA u serumima osoba sa benignom hiperplazijom (BPH) i kancerom prostate (PCa) je vršena imunoafinitetnom hromatografijom na čipu i MS. Dobijeni rezultati su pokazali da se, bez obzira na fiziološko stanje, PSA-imunoreaktivne vrste u serumu mogu grupisati u četiri glikopeptidne grupe: gp28, gp22, gp18 i gp12 koje odgovaraju zrelom ili „nicked“ PSA. Pored toga, detektovan je i veliki broj vrsta PSA koje bi mogle predstavljati (auto) proteolitičke fragmente. Glavna razlika između BPH i PCa je uočena u broju i učestalosti vrsta u grupi gp18. Imunoafinitetno profilisanje PSA u serumu je ukazalo na moguć biomarkerski potencijal pojedinačnih molekularnih vrsta. Ovaj rad je finansiran od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije, br. projekta 173010.

**Immunoaffinity profiling of molecular species of prostate-specific antigen**Sanja R. Goč, Miroslava M. Jankovic*Institute for the Application of Nuclear Energy, University of Belgrade, Banatska 31b Belgrade*

Molecular species is the smallest structural and functional unit of the proteome. The development and application of mass spectrometry (MS) techniques have opened numerous possibilities for detecting and defining discrete differences in species which are mostly a result of post-translational modifications. The aim of this study was to evaluate immunoaffinity profile of molecular species of prostate-specific antigen (PSA) in sera. PSA is a glycoprotein with a pronounced structural heterogeneity of polypeptide and glycan chain. The insight into the profile of PSA species in different physiological conditions, apart from the improvement of basic knowledge, might be of interest for laboratory diagnostics. The identification and detection of PSA species in sera of subjects with benign prostatic hyperplasia (BPH) and prostate cancer (PCa) was performed using immunoaffinity chromatography and MS. Results show that, despite the physiological conditions, PSA-immunoreactive species in sera can be grouped into four glycopeptide groups: gp28, gp22, gp18 and gp12 corresponding to mature PSA or „nicked“ PSA. In addition, species which might represent (auto) proteolytic PSA fragments were detected. The main difference between BPH and PCa was the number and frequency of species in gp18 group. Immunoaffinity profiling of PSA in sera indicated a possible biomarker potential of individual PSA species. This study was supported by The Ministry of Education, Science and Technological Development of the Republic of Serbia, project No 173010.

BH P04

## **Multivarijantno statističko poređenje hemijskog sastava biljnih ekstrakata: usrednjeni maseni sken ukupnog jonskog hromatograma, UMS-pristup**

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Nedavno je pokazano da se relativne zastupljenosti  $m/z$  vrednosti usrednjenih masenih skenova ukupnih jonskih hromatograma (UMS) mogu koristiti kao varijable pri multivarijantnoj statističkoj analizi (MVA) etarskih ulja. Ovaj tip varijabli se lakše primenjuje, daje pouzdanije i brže rezultate nego tradicionalne promenljive - procenti (površine ispod pikova) pojedinačnih sastojaka analiziranih ulja. U ovom radu smo ispitivali primenljivost UMS-varijabli za MVA poređenje hemijskog sastava odabranih biljnih ekstrakata. Da bi ovo postigli, usrednjeni maseni skenovi ukupnih jonskih hromatograma i hemijski sastavi (procentualna zastupljenost) 8 dietil-etarskih ekstrakata (6 različitih biljnih vrsta; ekstrakti su analizirani korišćenjem GC-FID i GC-MS) su zasebno upoređivani korišćenjem dve MVA metode: hijerarhijske klaster analize i analize glavne komponente. Dobijeni rezultati ukazuju na to da se MVA analiza složenih smeša isparljivih (pod uslovima GC-MS analize) jedinjenja, zasnovana na primeni UMS varijabli, može koristiti za njihovo lako, brzo i pouzdano poređenje. UMS pristup daje uporedive, ili čak bolje rezultate u odnosu na tradicionalni metod.

## **Multivariate statistical treatment of plant-extract compositional data: average mass scan of the total ion chromatogram (AMS) approach**

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It was recently confirmed that the relative abundances of  $m/z$  values of the average mass scan of the total GC chromatograms (AMS) are suitable variables for multivariate statistical comparison (MVA) of essential oils. These were shown to be even more applicable, reliable and faster than the traditionally used variables-percentages (peak areas) of individual oil constituents. Herein, we have explored whether AMS-derived variables are appropriate for MVA-comparison of plant solvent-extract compositional data. To achieve this, average mass scans of the total GC chromatograms and chemical compositions (relative percentages) of eight diethyl ether extracts (six different species; samples were analyzed using GC-FID and GC-MS) were separately compared using two MVA methods: agglomerative hierarchical clustering analysis and principal component analysis. The obtained results strongly suggest that MVA of complex volatile mixtures (GC-MS analyzable fractions of plant solvent extracts), using the corresponding AMS, could be considered as a promising time saving tool for easy and reliable comparison purposes. The AMS approach gives comparable or even better results than the traditional method.

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**Hemija i tehnologija hrane / Chemistry and Technology of Food**

HTH 01

**Šećerni profil kore i jezgra krompira kao indikator botaničkog porekla i sistema gajenja**Aleksandra M. Dramićanin, Filip Lj. Andrić\*, Nebojša M. Momirović\*\*, Sandra B. Šegan\*\*\*, Dušanka M. Milojković-Opsenica\**Hemijski fakultet, Univerzitet u Beogradu, P. fah 51, 11158, Beograd, Srbija;**\*Poljoprivredni fakultet, Univerzitet u Beogradu, Nemanjina 6, 11080 Zemun, Srbija;**\*\*IHTM-CH, P. fah 473, 11000 Beograd, Srbija;**\*\*\*ICHF u Beogradu d.o.o., Studentski trg 12-16, 11000 Beograd, Srbija*

Krompir (*Solanum tuberosum* L.) pripada redu vodećih kultura. Na osnovu produktivnosti, hranljive i biološke vrednosti krtola, krompir spada u red najprofitabilnijih ratarskih biljaka. Za ispitivanje ispoljavanja produktivnosti, hranljive i biološke vrednosti krtola krompira odabrane su četiri sorte: dve rane crvene sorte (Fantasy i Laura) i dve žute (Marabel, rana sorta i Jelly, kasna sorta). Sorte su uzgajane u tri različita sistema gajenja: organski, integralni i konvencionalni. Pokazano je da je šećerni profil jezgra i kore krompira dobar indikator botaničkog porekla i sistema gajenja. Kao najzastupljeniji šećeri u krtoli krompira identifikovani su: fruktoza (*Fru*), glukoza (*Glc*) i saharoza (*Sac*), dok se ostali - sorbitol (*Sor*), trehaloza (*Trh*), arabinoza (*Ara*) i turanoza (*Tur*) nalaze u tragovima. Multivarijantnom analizom sadržaja pomenutih šećera utvrđeno je da organski sistem gajenja rezultuje značajno smanjenim sadržajem *Tur* u odnosu na konvencionalne i integralne sisteme koje karakterišu značajno povišeni nivoi *Ara*, *Fru*, *Glc* i *Sor*.

**Sugar composition of potato peel and core as an indicator of its botanical origin and system of agriculture**Aleksandra M. Dramićanin, Filip Lj. Andrić\*, Nebojša M. Momirović\*\*, Sandra B. Šegan\*\*\*, Dušanka M. Milojković-Opsenica\**Faculty of Chemistry, University of Belgrade, P.O. Box 51, 11158 Belgrade, Serbia;**\*Faculty of Agriculture, University in Belgrade, Nemanjina 6, 11080 Zemun, Serbia;**\*\*ICTM-CC, P.O. Box 473, 11000 Belgrade, Serbia;**\*\*\*ICHF Ltd., Studentski trg 12-16, 11000 Belgrade, Serbia*

Potato (*Solanum tuberosum* L.) is one of the most widely produced crops. On the basis of productivity, nutritional and biological values of tubers, it can be considered as one of the most profitable cultivated plants. In order to test the manifestations of productivity, nutritional and biological values of potato tubers, four sorts of potato were selected: two red sorts (Fantasy and Laura), and two yellow sorts (Marabel and Jelly) which were produced using three different growing systems (organic, integrative, and conventional). Sugar profile of core and peel of studied crops have shown to be a good indicator of botanical origin and breeding system. The most abundant sugars in potato tubers are fructose (*Fru*), glucose (*Glc*) and sucrose (*Suc*), while other sugars: sorbitol (*Sor*), trehalose (*Trh*), arabinose (*Ara*), and turanose (*Tur*) can only be found in traces. Multivariate data analysis revealed that organic way of breeding results in significantly lower content of *Tur*, compared to conventional and integrative cultivation systems which yield in increased content of *Ara*, *Fru*, *Glc*, or *Sor*, *Thr* and *Sac*. The most promising chemical indicators of different botanical origin are: *Sah*, *Trh*, and *Glc*, which prominently distinguish yellow form red cultures, *i.e.*, Marabel from the rest of them.

HTH P01

## **Osobine V/U emulzija stabilizovanih sa polimernim emulgatorom Cithrol DPHS**

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Stabilnost emulzija zavisi od niza faktora kao što su osobine emulgatora, osobine vodene i uljne faze i uslova pripreme. Budući da su emulzije V/U vrlo nestabilni sistemi, a da imaju veliku primenu u prehrambenoj i farmaceutskoj industriji, ispitivane su karakteristike 30% (m/m) emulzija vode u parafinskom ulju i ulju koštica grožđa stabilizovanih dodatkom 1% (m/m) nejonskog, polimernog emulgatora Cithrol DPHS. Sprovedena ispitivanja obuhvatila su definisanje međufaznog ponašanja emulgatora primenom tenziometrije, kao i ispitivanje osobina 30% V/U emulzija. Na osnovu rezultata (veličine i raspodele veličina kapi, viskoziteta kontinualne faze i sedimentacione nestabilnosti u toku 30 dana) izvedeni su odgovarajući zaključci.

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## **Properties of W/O emulsions stabilized with polymeric emulsifier Cithrol DPHS**

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The stability of emulsions depends on many factors such as characteristics of emulsifier, properties of water and the oil phase and on preparation conditions. Since W/O emulsions are very unstable systems that have wide use in food and pharmaceutical industry, characteristics of 30% (w/w) emulsions of water in paraffin oil and grape seed oil, stabilized with 1% (w/w) non-ionic, polymeric emulsifier Cithrol DPHS, were investigated. The behavior of the emulsifier at W/O interface was determined by tensiometry. The characteristics of emulsions (droplet size and size distribution, viscosity of continuous phase and stability during 30 days of storage) were investigated too. On the basis of obtained results appropriate conclusions were made.

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**HTH P02**

**Jonske tečnosti - nove aktivne komponente dijetetskih suplemenata**

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U poslednjih nekoliko godina, jonske tečnosti (JT) nalaze se na samom vrhu primenljivosti u nauci i tehnologiji. Predstavljaju novu klasu rastvarača sa jedinstvenim osobinama kao što su zanemarljiv napon pare pri normalnim uslovima, visoka termička, hemijska i elektrohemijska stabilnost, kao i široka mogućnost "podešavanja" njihovih osobina poput polarnosti, hidrofobnosti i rastvorljivosti. Navedena svojstva su posledica mogućnosti neograničenog kombinovanja molekulskih karakteristika njihovih konstitutivnih jona. Ovo daje priliku za sintezu novih aktivnih komponenta dijetetskih suplemenata na bazi jonskih tečnosti sa biološki aktivnim katjonima i anjonima koji su bezbedni za ljudsku upotrebu i odobreni od strane FDA.

Zbog toga smo sintetisali novu jonsku tečnost, holinijum-aurat, i na osnovu rezultata toksikoloških, fizičko-hemijskih i termičkih analiza, razmotrili smo mogućnost njene upotrebe kao dijetetskog suplementa.

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**Ionic Liquids - New active ingredients in dietary supplements**

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In the past several years, ionic liquids (ILs) have been at the cutting edge of the most promising science and technology. This "neoteric" class of solvents generally presents interesting properties, namely, negligible vapor pressure at relatively ambient conditions; high thermal, chemical, and electrochemical stability; and widely tunable properties with regard to polarity, hydrophobicity, and solvent miscibility. These properties result from a matchless combination of molecular characteristics of their constitutive ions. This provides the ability to synthesize the new active components of dietary supplements based on ionic liquids with the biologically active cations and anions that are safe for human use and approved by FDA as SEDS (Substances Generally Recognized as Safe).

Given these traits, we synthesized a new ionic liquid, cholinium-aurate, and based on the results of toxicity, measurements of physico-chemicals and thermal properties, we considered its potential application as a food additive.

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## **Određivanje sastava masnih kiselina tokom fermentacije mleka kombuhom i konvencionalnim starter kulturama**

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Fermentisani mlečni proizvodi predstavljaju veoma važnu komponentu svakodnevne ishrane pre svega zbog svoje visoke nutritivne vrednosti i pogodnih zdravstvenih efekata. Zdravstveni aspekt fermentisanih mlečnih napitaka u velikoj meri zavisi od sastav masnih kiselina mlečne masti, kao jedne od veoma važnih komponenata ovih proizvoda. U cilju ispitivanja uticaja starter kulture na masno-kiselinski sastav fermentisanih mlečnih napitaka u ovom radu je praćen sastav masnih kiselina tokom fermentacije mleka primenom nekonvencionalne starter kulture, kombuhe, i konvencionalnih starter kultura, jogurtne odnosno probiotske. Za fermentaciju je korišćeno mleko sa 2,8% mlečne masti na temperaturi 42°C. Analiza masnih kiselina izvedena je primenom kapilarne gasne hromatografije u kombinaciji sa kvadrupolnom masenom spektrometrijom nakon prethodne ekstrakcije masti i derivatizacije. Dominantne masne kiseline u fermentisanim mlečnim proizvodima bile su: palmitinska, oleinska, stearinska i miristinska sa prosečnim sadržajem 32,62; 26,59; 11,12 i 10,78%, redom. Najpovoljniji sastav masnih kiselina, sa najnižim sadržajem zasićenih i najvišim sadržajem mononezasićenih i polinezasićenih masnih kiselina, dobijen je u napitcima fermentisanim primenom tradicionalne jogurtne kulture.

## **Determination of fatty acids during the fermentation of milk by kombucha and conventional starter cultures**

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Fermented milk products are a very important component of the daily diet primarily because of their high nutritional value and beneficial health effects. The health aspect of fermented milk beverages depends on the fatty acid composition of milk fat, as one of the most important components of those products. In order to investigate the influence of starter cultures on the fatty acid composition of fermented milk products, in this work the fatty acid composition during the fermentation of milk using non-conventional starter culture, kombucha, and conventional starter cultures or probiotic yoghurt was monitored. For fermentation a milk with 2.8% fat was used, at a temperature of 42 ° C. Fatty acid analysis was performed using capillary gas chromatography in combination with a quadrupole mass spectrometry after previous extraction and derivatization steps. The dominant fatty acids in fermented dairy products were: palmitic, oleic, stearic and myristic acids in content of 32.62; 26.59; 11.12 and 10.78%, respectively. The most favourable fatty acid composition, with the lowest content of saturated and the highest content of monounsaturated and polyunsaturated fatty acids, was derived from the fermented beverage using the traditional yoghurt cultures.

HTH P04

**Masno-kiselinski profil polena koji su medonosne pčele sakupile u Srbiji**

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Važan deo lipidne frakcije u polenu čine masne kiseline- bilo u obliku estara bilo u slobodnoj formi. Zastupljenost i raznovrsnost masnih kiselina u velikoj meri zavise od palinološkog porekla uzoraka.

U okviru ovog rada ispitano je dvadeset i šest uzoraka polena koji su medonosne pčele sakupile u različitim regionima Srbije. Analiza sadržaja masnih kiselina je izvršena GC metodom.

Ukupno je identifikovano dvadeset masnih kiselina. Od toga, šest kiselina (kaprilna, palmitinska, stearinska, oleinska, linolna i linolenska) je pronađeno u svim uzorcima, šest je bilo prisutno u većini uzoraka a osam masnih kiselina se mogu okarakterisati kao „retke“ jer su identifikovane u svega nekoliko uzoraka (ili u po jednom uzorku). Na pojavu masnih kiselina najveći uticaj je imalo palinološko poreklo uzorka. Po prisustvu „retkih“ masnih kiselina posebno se izdvojio uzorak br. 1 koji je predominantno sadržavao polen jasena. Najzastupljenija zasićena masna kiselina je bila palmitinska, a od nezasićenih oleinska kiselina.

**Fatty acids profile of bee pollen collected in Serbia**

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An important part of the bee pollen lipid fraction consists of fatty acids- either in the form of esters or as free form. Representation and diversity of fatty acids are largely dependent on palynological origin of samples.

In this work twenty six samples of bee pollen collected in different region of Serbia were examined. Analysis of fatty acids was carried out by GC method. In total, twenty fatty acids were identified. Six acids (caprylic, palmitic, stearic, oleic, linoleic and linolenic) were found in all samples, six acids were present in most of the samples and eight fatty acids can be characterized as "rare" because they were identified only in a few samples (or in one sample). Palynological origin of samples had the greatest impact on the occurrence of fatty acids. According to presence of the "rare" fatty acids sample no. 1 can be pointed as characteristic. It was predominantly consists of pollen of *Fraxinus* genus (ash). The most common saturated and unsaturated fatty acids were palmitic acid and oleic acid, respectively.

## **Karakterizacija flavan-3-ola u uzorcima šipurka primenom visoko efikasne tankoslojne hromatografije povezane sa masenom spektrometrijom**

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Plodovi šipurka se smatraju značajnim izvorom polifenolnih jedinjenja i vitamina. Istraživanja polifenolnog profila plodova šipurka su pokazala visok sadržaj fenolnih kiselina, flavonoid glikozida i proantocijanidina. Cilj ovog istraživanja bio je identifikacija jedinjenja iz grupe flavan-3-ola u četrnaest uzoraka šipurka upotrebom visoko efikasne tankoslojne hromatografije (HPTLC) povezane sa masenim spektrometrom sa elektronsprej jonizacijom (ESI-MS). Ukupno šest flavan-3-ola je identifikovano na osnovu  $[M-H]^-$  molekulskog jona i njegove MS/MS fragmentacije (katehin, proantocijanidin dimer, proantocijanidin dimer monoheksozid, proantocijanidin dimer diheksozid, proantocijanidin trimer diheksozid i proantocijanidin trimer triheksozid). Iako je sličan hromatografski profil dobijen za sve uzorke, mogu se uočiti razlike u zastupljenosti pojedinih flavan-3-ola u ispitivanih uzorcima šipurka.

## **Characterisation of flavan-3-ols from rose hips by high-performance thin-layer chromatography-mass spectrometry**

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The rose hip fruits are considered as important source of phenolic compounds and vitamins. Studies on the phenolic composition of rose hip have shown that its fruits are rich in phenolic acids, flavonoid glycosides and proanthocyanidin aglycones. The aim of this study was to investigate flavan-3-ols profile of fourteen rose hip samples using high-performance thin-layer chromatographic (HPTLC) coupled to electrospray ionisation mass spectrometer (ESI-MS). A total of six flavan-3-ols (catechin, proanthocyanidin dimer; proanthocyanidin dimer monohexoside, proanthocyanidin dimer dihexoside, proanthocyanidin trimer dihexoside, and proanthocyanidin trimer trihexoside) were identified based on the search for the  $[M-H]^-$  deprotonated molecule and its MS/MS fragmentation. Although similar chromatographic profiles were obtained for all samples, it was observed that there was a significant difference in the presence and zone intensity of some flavan-3-ols.

## **Detekcija egzogene vode u vinu pomoću masene spektrometrije odnosa izotopa**

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Jedna od najvažnijih primena masene spektrometrije odnosa izotopa je merenje odnosa  $^{18}\text{O}/^{16}\text{O}$ . Određivanje odnosa  $^{18}\text{O}/^{16}\text{O}$  iz vode iz vina se primenjuje u više zemalja da bi se definisalo geografsko poreklo vina, i predložena je metoda za detekciju egzogene vode. Cilj ovog rada je da se vidi da li su rezultati razblaženih uzoraka uporedivi i korisni za detekciju dodatka vode u vino. Dva uzorka vina (Rhine Riesling and Cabernet Sauvignon) su razblažena vodom mešanjem česmenske vode i vina u određenom odnosu. Uzorci su analizirani protočnom tehnikom u kojoj je uzorak nošen nosećim gasom. Sve analize su urađene na Finnigan GasBench II periferalu, sa autosemplerom, povezanim sa Delta V Advantage masenim spektrometrom. Dobijena je visoka korelacija između odnosa  $^{18}\text{O}/^{16}\text{O}$  i procenta dodate vode za svako vino. Iako eksperiment sa dodatkom vode nema veliku primenljivost zato što voda kojom je razblaženo vino i originalno vino često nisu dostupni, on ipak pokazuje da je ova metoda primenljiva za detekciju dodatka vode u vino.

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## **Detection of exogenous water in wine using isotope ratio mass spectrometry**

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One of the most important applications of isotope ratio mass spectrometry (IRMS) is the measurement of the  $^{18}\text{O}/^{16}\text{O}$  ratio of water. The determination of oxygen ratio ( $^{18}\text{O}/^{16}\text{O}$ ) from the water content of the wine (wine water), have been used in several countries to define the geographical origin of wine, and it is proposed as a method to detect the addition of exogenous water to wine. The aim of this work was to check the usefulness and the comparability of the results for spiked samples for detection of wine adulteration. To achieve this, two wine samples (Rhine Riesling and Cabernet Sauvignon) were watered-down after mixing specific quantities of tap water with original, unadulterated wine. All samples were analyzed by continuous flow technique in which the sample is entrained in a carrier gas. All analyses were done on Finnigan GasBench II with autosampler-assisted loop injection coupled with Delta V Advantage mass spectrometer. Results show high correlation between  $^{18}\text{O}/^{16}\text{O}$  ratio of water and percentage of added water for each wine. Even though this experiment using spiked samples has no great applicability, as the water used to dilute a wine and the original, unadulterated wine are not usually available in the case of suspicious wines, the results prove the workability of the method.

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**Плодови трњине (*Prunus spinosa*) и глога (*Crataegus laevigata*) као  
потенцијални антиоксиданти и њихова стабилност у условима  
*in vitro* дигестије**

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У циљу испитивања метанолских екстраката плода биљака *Prunus spinosa* (трњина) и *Crataegus laevigata* (глог) одређена је укупна количина фенолних једињења, флавоноида и антоцијана, као и ниво антиоксидативне активности екстраката. Екстракт плода глога садржи већу количину укупних фенола (541,09  $\mu\text{mol}$  галне киселине/g екстракта) и флавоноида (150,53  $\mu\text{mol}$  кверцетина/g) у односу на екстракт плода трњине (97,52  $\mu\text{mol}$  галне киселине/g, односно 54,89  $\mu\text{mol}$  кверцетина/g), док су количине антоцијана у екстрактима биле приближно исте. Екстракт плода глога показао је знатно бољу антиоксидативну активност у односу на екстракт плода трњине на нивоу DPPH<sup>•</sup> и ABTS<sup>+</sup> радикала. Такође, испитане су и промене у количини укупних фенолних једињења у екстрактима и нивоу антиоксидативне активности у току процеса симулиране *in vitro* дигестије. Добијени резултати су показали да се количина фенолних једињења у екстрактима и њихов антиоксидативни потенцијал мењају у зависности од времена дигестије.

**Fruits of blackthorn (*Prunus spinosa*) and hawthorn (*Crataegus laevigata*) as  
potential antioxidants and their stability during *in vitro* digestion**

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The aim of this study was to determine concentration of total phenolic, flavonoids and anthocyanins in methanol extracts of *Prunus spinosa* (blackthorn) and *Crataegus laevigata* (hawthorn) fruits, as well as the level of antioxidant activity of these extracts. The extract of hawthorn fruit contained higher amounts of total phenolics (541.09  $\mu\text{mol}$  gallic acid/g dry extract) and flavonoids (150.53  $\mu\text{mol}$  quercetin/g) with respect to blackthorn fruit extract (97.52  $\mu\text{mol}$  gallic acid/g and 54.89  $\mu\text{mol}$  quercetin/g, respectively), while the amounts of anthocyanins in the extract were quite similar. The hawthorn fruit extract showed significantly higher antioxidant activity in comparison to blackthorn fruit extract measured by DPPH<sup>•</sup> and ABTS<sup>+</sup> radical scavenging activity methods. Also, the changes in the amount of the total phenolic compounds in the extracts and the level of antioxidant activity in the process of simulated *in vitro* digestion have been evaluated. The results showed that the amounts of phenolic compounds in the extracts and their antioxidant activity changed depending on the time of digestion.

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## **Sadržaj sekundarnih metabolita i njihov uticaj na antioksidativnu aktivnost u različitim sortama jagoda**

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Određeni su sadržaji sekundarnih metabolita u četiri različite sorte gajenih jagoda (*Fragaria ananassa*): Albion, Senga Sengana, Elsanta i Cleary, u jednoj divljoj jagodi (*Fragaria vesca* L.) i antioksidativne aktivnosti prema stabilnim slobodnim radikalima DPPH i ABTS. Rezultati su pokazali da postoji statistički značajna razlika kako u sadržaju sekundarnih metabolita, tako i u antioksidativnoj aktivnosti među različitim sortama jagoda, te da na ovu aktivnost najviše utiče sadržaj ukupnih fenola i ukupnih flavonola.

## **The content of secondary metabolites and their impact on the antioxidant activity in different varieties of strawberries**

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Contents of secondary metabolites in four different varieties of cultivated strawberries (*Fragaria ananassa*): Albion, Senga Sengana, Elsanta and Cleary, and in a wild strawberry (*Fragaria vesca* L.) were determined. At the same time the antioxidant activities according to the stable free radical DPPH and ABTS were determined. The results showed a statistically significant difference in the content of secondary metabolites and the antioxidant activity among different varieties of strawberries and that this activity is mostly influenced by the content of total phenols and total flavonols.

## Hemija i tehnologija makromolekula Chemistry and Technology of Macromolecules

HTM PO1



### Poređenje hidrolitičke, enzimске i degradacije u kompostu PCL/PEO diblok kopolimera

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U ovom radu je prikazana hidrolitička i enzimska degradacija poli( $\epsilon$ -kaprolaktona) (PCL) i serije diblok kopolimera (PCL/PEO) sa malim sadržajem hidrofilnog poli(etilen-oksidnog) (PEO) segmenta. Ispitivan je uticaj uvođenja lateralnog PEO segmenta u PCL lanac na degradativna svojstva kopolimera. Hidrolitička degradacija je izvođena u fosfatnom puferu tokom 8 nedelja. FTIR analizom je utvrđena bolja degradativna sposobnost diblok kopolimera usled veće hidrofilnosti u poređenju sa PCL-om. Enzimska degradacija, testirana u "cell-free" ekstraktu *Pseudomonas aeruginosa* PAO1, tokom dve nedelje, je praćena na osnovu promena mase, hrapavosti površine polimernih filmova kao i FTIR analizom. Rezultati su potvrdili da svi uzorci podležu enzimskoj degradaciji, koja se odigrava po mehanizmu površinske erozije i uz smanjenje molarne mase. Diblok kopolimeri su pokazali značajno veći gubitak mase i smanjenje molarne mase u odnosu na PCL. AFM analiza je potvrdila intenzivnu površinsku eroziju i povećanje RMS vrednosti. Testirana je i biodegradacija polimernih filmova u kompostu na 37 °C gde je utvrđena izražena degradacija ispitivanih blok kopolimera.

### Comparative analysis of hydrolytic, enzymatic and degradation in compost of PCL/PEO diblock copolymers

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In this paper, hydrolytic and enzymatic degradation of poly( $\epsilon$ -caprolactone) (PCL) and series of diblock (PCL/PEO) copolymers, with a low content of hydrophilic PEO segments is presented. The effect of the introduction of PEO as lateral segment in the PCL chain on copolymer biodegradation properties was investigated. The hydrolytic degradation was performed in phosphate buffer for up to 8 weeks. FTIR results revealed higher degradation ability of diblock copolymers due to a higher hydrophilicity compared to PCL. Enzymatic degradation was tested using cell-free extracts of *Pseudomonas aeruginosa* PAO1, for two weeks by following the weight loss, changes in surface roughness, and changes in carbonyl and crystallinity index. The results confirmed that all samples underwent enzymatic degradation through surface erosion accompanied with a decrease in molecular weights. Diblock copolymers showed significantly higher weight loss and decrease in molecular weight compared to PCL. AFM analysis confirmed significant surface erosion and increase in RMS values. Biodegradation of polymer films was also tested in compost model system at 37°C, where an effective degradation of block copolymers was observed.

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## HTM P01

**Sinteza graftovanog kopolimera upotrebom mikrobnog levana i polistirena**

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Poslednjih godina se javlja veliki interes za modifikaciju polistirena, kao jednog od najdominantnijih materijala za proizvodnju plastičnih materijala, sa različitim polisaharidima. Publikovane su modifikacije polistirena sa polisaharidima kao što su hitin, celuloza i skrob. Zahvaljujući svojoj antitumornoj, prebiotskoj i imunostimulirajućoj aktivnosti, mikrobn levan privlači mnogo pažnje, kao potencijalni supstrat za primenu u farmaciji, medicini i industriji hrane. Cilj ovog rada je bio izolovanje levana iz soja *Bacillus licheniformis* i sinteza novog levan-polistiren graftovanog kopolimera. Sinteze su rađene slobodnoradikalskom reakcijom i upotrebljavan je kalijum-persulfat kao inicijator reakcije. Ispitivan je uticaj reakcije temperature i atmosfere, a dobijeni kopolimer je karakterisan pomoću skenirajuće elektronske mikroskopije (SEM). Rezultati su pokazali da se najviši procenat graftovanja ( $G (\%) = 24,1 (\%)$ ) postiže na temperaturi od  $60\text{ }^{\circ}\text{C}$  i u prisustvu kiseonika. U slučaju atmosfere azota, najpogodnija temperatura bila je  $55\text{ }^{\circ}\text{C}$  sa  $G (\%) = 50,9 (\%)$ . SEM mikrografi levan-polistiren graftovanog kopolimera su pokazali da su u njemu prisutne obe komponente. Zahvalnica: Ovaj rad je podržan od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije kroz stipendije za studente doktorskih studija i projekte III 43004 and OI 172001.

**Synthesis of graft copolymer using microbial levan and polystyrene**

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In recent years, there has been a great interest in modifications of polystyrene, as one of the most dominant materials for plastic production, with different polysaccharides. Modifications of polystyrene with polysaccharides such as chitin, cellulose and starch have been reported. Due to its antitumor, prebiotic and immune-stimulating activity, microbial levan attracted much attention for potential use in pharmacy, medicine and food industry. The aim of this work was isolation of levan from *Bacillus licheniformis* strain and synthesis novel levan-polystyrene graft copolymer. Syntheses were performed by the free radical reaction using potassium persulfate as initiator. The influence of reaction temperature and atmosphere was investigated and obtained copolymer was characterized by Scanning Electron Microscopy (SEM). Results showed that the highest percent of grafting ( $G (\%) = 24.1 (\%)$ ) was achieved at  $60\text{ }^{\circ}\text{C}$  oxygen atmosphere. In case of nitrogen atmosphere,  $55\text{ }^{\circ}\text{C}$  was the most suitable temperature for synthesis of levan-polystyrene graft copolymer with  $G (\%) = 50.9 (\%)$ . SEM micrographs of obtained levan-polystyrene graft copolymer showed presence of both components. Acknowledgement: This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia through scholarships for PhD students and funding for Projects III 43004 and OI 172001.

## **Priprema i svojstva nanokompozita biodegradabilnog poli( $\epsilon$ -kapolaktona) i organomodifikovanih sepiolita**

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Biodegradabilni alifatski poliestri su aktuelno polje istraživanja, jer predstavljaju jedno od rešenja za rastuće ekološke probleme. Mehanička, barijerna i termička svojstva alifatskih poliestara mogu se poboljšati dodavanjem punioca nano-dimenzija, kao što su sepioliti. Tri serije nanokompozita poli( $\epsilon$ -kapolaktona) (PCL) i tri vrste sepiolita: nemodifikovani, modifikovani kovalentnim vezivanjem (3-merkaptopropil)trimetoksisilana i modifikovani jonskom izmenom sa heksadecilaminom, su pripremljene iz rastvora u hloroformu. Sadržaj sepiolita u nanokompozitima je iznosio 1, 3 i 5 mas.%, a uzorci su dobijeni u obliku filmova debljine 100 - 220  $\mu\text{m}$ . Morfologija nanokompozita je ispitana optičkom mikroskopijom i uočena je promena sferulitne strukture PCL pri dodatku sepiolita. Ispitivan je efekat dodatka modifikovanog i nemodifikovanog sepiolita na termička, mehanička i reološka svojstva nanokompozita. Temperature topljenja i stepeni kristaliničnosti su određeni DSC analizom, a termička stabilnost nanokompozita je ispitana TG analizom u neizotermnim ogledima. Stepem dispergovanosti nanopunioca je procenjen ispitivanjem reoloških svojstva rastopa u dinamičkim ogledima u temperaturnom opsegu 70 - 140  $^{\circ}\text{C}$ . Mehanička svojstva i termički prelazi u nanokompozitima su ispitani dinamičko-mehaničkom analizom u temperaturnom intervalu od - 120 - 60  $^{\circ}\text{C}$ .

## **Preparation and properties of nanocomposites of biodegradable poly( $\epsilon$ -caprolactone) and organomodified sepiolites**

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Biodegradable aliphatic polyesters have become attractive field of research and represent one of the solutions to the growing environmental problems. Mechanical, barrier and thermal properties of aliphatic polyesters can be improved by adding nano-sized fillers, such as sepiolite. Three series of nanocomposites based on poly( $\epsilon$ -caprolactone) (PCL), and three types of sepiolite: unmodified, modified by covalent attachment of (3-mercaptopropyl)trimetoxysilane, and modified by ionic exchange with hexadecylamine, were prepared by solution casting from chloroform. The content of sepiolite in the nanocomposites was 1, 3 and 5 wt.%, and the samples were obtained in the form of a film with a thickness of 100 - 220  $\mu\text{m}$ . The morphology of nanocomposites was examined using an optical microscope, and the change in spherulitic structure of the PCL with the addition of sepiolites was observed. The effect of the addition of unmodified and modified sepiolite on thermal, mechanical and rheological properties of nanocomposites was examined. Melting temperatures and degree of crystallinity were determined by DSC analysis, while thermal stability of the nanocomposites was investigated by TG analysis in non-isothermal experiments. The degree of dispersion was estimated by examining rheological properties of the melt in dynamic experiments in a temperature range 70 - 140  $^{\circ}\text{C}$ . Mechanical properties and thermal transitions were investigated by dynamic mechanical analysis in a temperature range from - 120 - 60  $^{\circ}\text{C}$ .

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HTM P03

### **Uklanjanje tekstilnih boja iz otpadne vode pomoću hidrogelova hitozana**

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Porast upotrebe boja u tekstilnoj industriji za posledicu ima povećanje zagađenja otpadnih voda i veliki ekološki problem. Među mnogobrojnim postupcima kojima se obezbeđuje zadovoljavajući stepen obezbojavanja otpadnih voda, sorpcija se izdvojila kao jednostavan i efikasan način. Kao sorbenti su do sada korišćeni različiti materijali: razne vrste otpada (bademova ljuska, piljevina i dr.), aktivni ugalj, zeoliti, umreženi polimeri, a naročito oni koji se dobijaju iz obnovljivih izvora.

Cilj ovog rada je da se ispita mogućnost primene hidrogelova hitozana, itakonske i metakrilne kiseline za prečišćavanje otpadnih voda iz tekstilne industrije. Uklanjanje boja je praćeno u rastvoru koji simulira standardnu otpadnu vodu, a kao model korišćene su boje za bojenje vune, pamuka, najlona (*C.I. Acid Orange 7* i *C.I. Basic Red 1*), kao i bazna boja metilensko plavo (*Methylene Blue*). Praćen je uticaj temperature, pH vrednosti i sadržaja saharoze u simuliranoj otpadnoj vodi na efikasnost uklanjanja boja. Utvrđeno je da na efikasnost uklanjanja boja značajno utiče pH i prisustvo saharoze, dok promena temperature u intervalu od 25 °C do 50 °C nema značajan uticaj.

### **Removal of textile dyes from wastewater by chitosan hydrogels**

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Increased use of dyes in the textile industry has lead to water pollution on a large scale and represents an ecological problem. Among many treatments taken to remove colors from wastewater to a satisfactory level, sorption stands out as simple and efficient process. Up to now, many materials have been used as sorbents: wastes (almond shells, sawdust etc), zeolites, activated carbon, crosslinked polymers, especially those obtained from renewable sources, etc.

The goal of this paper is to investigate possible application of chitosan, methacrylic and itaconic acid based hydrogels for textile wastewater purification. Dye removal was observed in a solution that simulates standard wastewater. Two dyes, which have industrial application in dyeing wool, cotton and nylon (*C.I. Basic Red 1* and *C.I. Acid Orange 7*) were used as model dye, as well as basic dye *Methylene Blue*. The effect of temperature, pH value and sucrose content in wastewater on the removal efficiency was studied. It was found that pH and sucrose affected dye removal, while the removal efficiency was not significantly altered in temperature range from 25 °C to 50 °C.

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## Uticaj specifičnih anjona na afinitet sorpcije pektina prema $\text{Cu}^{2+}$ jonima

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Cilj ovog rada bilo je ispitivanje specifičnog uticaja anjona Hofmeister-ovog niza ( $\text{Cl}^-$ ,  $\text{NO}_3^-$ ,  $\text{CH}_3\text{COO}^-$ ,  $\text{SO}_4^{2-}$ ) na proces umrežavanja pektina jonima bakra, primenom sorpcije kao indirektno metode kvantifikacije. Pektinske čestice dobijene su umrežavanjem u rastvorima četiri bakarne soli ( $\text{CuSO}_4$ ;  $\text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_2$ ;  $\text{CuCl}_2$ ;  $\text{Cu}(\text{NO}_3)_2$ ) različite koncentracije ( $0,5\text{-}10 \text{ g/dm}^3$ ). Nađeno je da je uticaj anjona na kapacitet sorpcije pektina u skladu sa specifičnim uticajem jona na makromolekule u vodenim rastvorima koje je predložio Hofmeister: najveći kapacitet sorpcije  $\text{Cu}^{2+}$  jona postignut je iz rastvora sulfata, dok opada u prisustvu  $\text{CH}_3\text{COO}^-$ ,  $\text{Cl}^-$  i  $\text{NO}_3^-$  jona, redom. Rezultati sorpcije dobijeni primenom atomske apsorpcione spektroskopije (AAS) opisani su modelima Lengmuir-ove i Freundlich-ove sorpcione izoterme, pri čemu su izračunati parametri potvrdili podsticajnu prirodu sulfatnog jona u procesu vezivanja metala.

## The specific anion influence on the sorption affinity of pectin toward $\text{Cu}^{2+}$ ions

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The objective of this study was to investigate if there was any (specific) influence of anions from Hofmeister series ( $\text{Cl}^-$ ,  $\text{NO}_3^-$ ,  $\text{CH}_3\text{COO}^-$ ,  $\text{SO}_4^{2-}$ ) on the cross-linking process of pectin via  $\text{Cu}^{2+}$  ions, wherein sorption was implemented as the indirect quantification method. The pectin beads were obtained via cross-linking in four copper salt solutions ( $\text{CuSO}_4$ ;  $\text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_2$ ;  $\text{CuCl}_2$ ;  $\text{Cu}(\text{NO}_3)_2$ ) of different initial concentration ( $0.5\text{-}10 \text{ g/dm}^3$ ). It was found that the anions affected the sorption capacity of pectin according to ion-specific influence on macromolecules in aqueous systems proposed by Hofmeister:  $\text{Cu}^{2+}$  sorption capacity from the sulfate solution was the highest, while it decreased in the presence of  $\text{CH}_3\text{COO}^-$ ,  $\text{Cl}^-$  and  $\text{NO}_3^-$  ions, respectively. The sorption data obtained from atomic absorption spectroscopy (AAS) were applied to the Langmuir and Freundlich isotherm models and various calculated parameters confirmed the supportive nature of sulfate anion in metal ion binding.

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## **Termički osetljivi hidrogelovi na bazi poli(*N*-izopropilakrilamida) i hijalorunske kiseline umreženi nanoglinama**

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Predmet ovog rada je sinteza semi-interpenetrirajućih polimernih mreža na bazi poli(*N*-izopropilakrilamida) (PNIPA) i vodorastvorne soli hijaluronske kiseline (Na-HI), fizički umreženih sintetskim nanoglinama (Laponit XLG). PNIPA hidrogelovi umreženi glinama pored odličnih mehaničkih svojstva poseduju transparentnost i veliku brzinu absorpcije/otpuštanja vode. Hidrogelovi su sintetisani radikalnom polimerizacijom *N*-izopropilakrilamida u suspenziji nanoglina, čije čestice predstavljaju multifunkcionalna mesta umreženja. Hidrogelovi različite gustine umreženosti su sintetisani variranjem sadržaja gline (1, 3 i 5 mas.%), kao i tri serije semi-IPN sa 0,1; 0,15 i 0,25 mas.% linearnog polimera Na-HI. Izučavan je uticaj sadržaja gline i hijaluronske kiseline na brzinu procesa bubrenja/dehidratacije. Struktura i heterogenost hidrogelova su analizirani pomoću elektronske skenirajuće mikroskopije (SEM) i širokougaone rentgenske difrakcije (WAXS), dok je sadržaj inkorporirane gline određivan pomoću termogravimetrijske analize. Reološka svojstva sintetisanih hidrogelova su analizirana DMA analizom u osnovnom i nabubreloom stanju. Ovi hidrogelovi sa poboljšanim mehaničkim svojstvima su novi nanomaterijali, koji u kombinaciji sa prirodnim polimerom kao što je hijaluronska kiselina mogu da nađu primenu u biomedicini za izradu flastera za brzo zaceljivanje rana i regeneraciju tkiva, kao i u kontrolisanom otpuštanju lekova.

## **Thermo-sensitive hydrogels based on poly(*N*-isopropylacrylamide) and hyaluronic acid crosslinked with nanoclays**

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The subject of this paper is the synthesis of the semi-interpenetrating polymer networks based on poly(*N*-isopropylacrylamide) (PNIPA) and water-soluble sodium salts of hyaluronic acid (Na-HI), physically crosslinked with synthetic nanoclay (Laponite XLG). PNIPA hydrogels crosslinked with nanoclays exhibited excellent mechanical properties, high transparency and fast adsorption/release of water. Hydrogels are synthesized by free radical polymerization of *N*-isopropylacrylamide in nanoclay suspension, whose particles act as multifunctional crosslinker. Hydrogels with different crosslinking densities were prepared by varying the content of clay (1, 3 and 5 wt.%) and three series of semi-IPN with 0.1; 0.15 and 0.25 wt.% of Na-HI. The influence of clay and hyaluronic acid content on the rate of swelling/deswelling was analyzed. The structure and heterogeneity of the semi-IPN hydrogels was examined by SEM and WAXS. The content of clay incorporated in the gel was determined by TGA. Rheological properties of synthesized hydrogels are analyzed by dynamic-mechanical spectroscopy in as-prepared and swollen state. These hydrogels with improved mechanical properties are new nanomaterials, which in combination with a natural polymer, such as hyaluronic acid, may find use in biomedical applications to create patches for fast wound healing and tissue regeneration as well as drug release systems.

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## **Sinteza i karakterizacija biodegradabilnih triblok kopoliestara na bazi poli( $\epsilon$ -kapolaktona), poli(butilen-sukcinata) i poli(butilen-adipata)**

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Alifatski poliestri su najznačajnija grupa biodegradabilnih sintetskih polimera, aktuelnih kako za zaštitu životne sredine tako i u biomedicini i farmaciji. Svojstva alifatskih biodegradabilnih poliestara, kao što su termička, mehanička i reološka, kao i podložnost biodegradaciji mogu se podešavati kopolimerizacijom i strukturom kopolimernog lanca. U ovom radu, sintetisane su dve serije biodegradabilnih triblok kopoliestara: poli( $\epsilon$ -kapolakton)-poli(butilen-sukcinat)-poli( $\epsilon$ -kapolakton), PCL/PBS/PCL, i poli( $\epsilon$ -kapolakton)-poli(butilen-adipat)-poli( $\epsilon$ -kapolakton), PCL/PBA/PCL, kod kojih je dužina PCL blokova varirana od 10000 do 20000 g/mol. Kopoliestri su sintetisani polimerizacijom otvaranja prstena  $\epsilon$ -kapolaktona, iniciranom završnim hidroksilnim grupama prepolimera PBS (2810 g/mol) i PBA (2523 g/mol) uz katalizator kalaj(II)-oktoat. Molekulska struktura triblok kopoliestara je potvrđena  $^{13}\text{C}$  i  $^1\text{H}$  NMR spektroskopijom, dok su vrednosti molarnih masa i polidisperznost određeni GPC analizom, gde je zabeležen očekivani trend. Temperature topljenja i stepeni kristaliničnosti određeni su diferencijalnom skenirajućom kalorimetrijom, a termička stabilnost kopoliestara ispitana je termogravimetrijskom analizom. Uticaj strukture polimernog lanca blok kopoliestara na reološka svojstva njihovih rastopa ispitan je u dinamičkim oscilatornim ogledima na različitim temperaturama.

## **Synthesis and characterisation of biodegradable triblock copolyesters based on poly( $\epsilon$ -caprolactone), poly(butylene succinate) and poly(butylene adipate)**

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Aliphatic polyesters are the most important group of synthetic biodegradable polymers, which are relevant materials in environmental protection as well as in biomedicine and pharmacy. Properties of aliphatic polyesters such as thermal, mechanical and rheological as well as susceptibility to biodegradation can be tuned through copolymerization and structure of polymer chain. In this study, two series of block copolyesters are synthesized: poly( $\epsilon$ -caprolactone)-poly(butylene succinate)-poly( $\epsilon$ -caprolactone), PCL/PBS/PCL, and poly( $\epsilon$ -caprolactone)-poly(butylene adipate)-poly( $\epsilon$ -caprolactone), PCL/PBA/PCL, where the length of PCL blocks was varied from 10000 to 20000 g/mol. Block copolyesters were synthesized by ring-opening polymerization of  $\epsilon$ -caprolactone, initiated by the terminal hydroxyl groups of prepolymers PBS (2810 g/mol) and PBA (2523 g/mol) in the presence of catalyst tin(II)-octoate. Molecular structure was confirmed by  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectroscopy, while the molecular weights and polydispersity indices were determined by GPC analysis, where an expected trend was observed. The melting temperatures and the degrees of crystallinity were determined by differential scanning calorimetry, and thermal stability of copolyesters was investigated by thermogravimetric analysis. The influence of the polymer chain structure of block copolyesters on the rheological properties of their melt was tested in dynamic oscillatory experiments at different temperatures.

*Rad je finansiran od strane Ministarstva prosvete i nauke Republike Srbije: Projekat 172062*

**Organska hemija / Organic Chemistry**

OH S

**Potruga za mehanizmom dejstva inhibitora botulinum neurotoksina ili  
Kako pokvariti molekulsku mašinu**

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Botulinum neurotoksini (BoNT) su najjači poznati biotoksini, i produkt su anaerobne gram-pozitivne bakterija *Clostridium botulinum*. Postoji sedam serotipova BoNT, koji su sačinjeni od teškog (HC) i lakog lanca (LC). BoNT LC je cink-zavisna metaloproteaza koja fragmetiše specifične proteine u neuronskom citosolu i tako sprečava otpuštanje neurotransmitera u sinaptički prostor i prenos signala. Najjači i najdugotrajniji od svih serotipova BoNT je serotip A. Veliki interes za istraživanja malih molekula koji deluju kao inhibitori njihove protolitičke aktivnosti ne potiče od njihove upotrebe u kozmetici i medicini, već zbog osobina koje ih čine potencijalnim biološkim oružjem i svrstavaju ih u kategoriju A bioloških agenasa.

Da bi razjasnili i istražili inhibitornu aktivnost koje je prema BoNT/A LC u *in vitro* uslovima pokazala serija jedinjenja bazirana na zajedničkom skeletu koristili smo simulirana vezivanja (*molekulski docking*). Male razlike u načinu vezivanja i formiranje različitih interakcija između liganada i aminokiselinskih ostataka u aktivnom centru proteaze su nam dale uvid u različite inhibitorne mogućnosti i podatke za dizajniranje novih struktura, sa potencijalno većim aktivnostima.

**In a search of a mechanism of action of botulinum neurotoxin inhibitors or  
How to sabotage the molecular machine**

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Botulinum neurotoxins (BoNT) are the most potent of all biological toxins, and are produced by anaerobic, spore-forming gram-positive bacteria *Clostridium botulinum*. There are seven serotypes of BoNT, consisting of heavy (HC) and light chain (LC). BoNT LC is zinc dependent metalloprotease that fragments specific proteins in neuronal cytosol, eliminating neurotransmitter release in to the synaptic cleft and signal transfer. The most potent and longest acting of the BoNT serotypes is serotype A. The large interest in research of small molecules acting as inhibitors of their proteolytic activity emerged not from their use in cosmetics and medicine, but from the properties that makes them potential biological weapon, classified as category A biothreat agents.

We used docking simulations to rationalize and clarify observed *in vitro* BoNT/A LC inhibitory activities of a series of compounds based on similar scaffold. The small differences in their binding schemes and the formation of different interactions between the ligands and amino acid residues in the protease's catalytic cleft provide the insights into variable inhibitory potencies and data for designing new structures with potentially higher activities.

OH 01

**Sinteza i biološko ispitivanje novih triazolских Mannich-ovih baza**

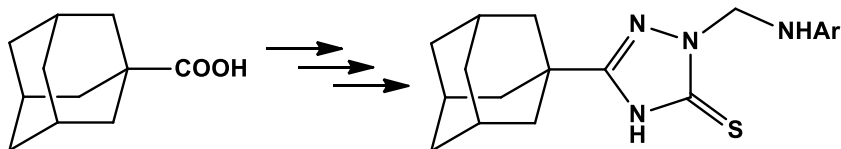
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Sintetizovana je serija od 18 novih *N*-Mannich-ovih baza izvedenih iz 5-adamantil-1,2,4-triazol-3-tiona. Dobijanje finalnih jedinjenja ostvareno je polazeći od 1-adamantanske kiseline koja je prevedena u kiselinski hlorid da bi on dalje bio derivatizovan reakcijom sa tiosemikarbazidom. Nastali 1-adamantoyl tiosemikarbazon u prisustvu baze podleže intramolekularskoj ciklizaciji i daje željeni prekursor, 5-adamantil-1,2,4-triazol-3-tion. U Mannich-ovoj reakciji triazolски prekursor reaguje sa ekvimolarnom količinom formalina i odgovarajućeg primarnog amina u THF-u i nakon 48 h mešanja na sobnoj temperaturi, dobijene su finalne Mannich-ove baze. Tačna struktura dobijenih jedinjenja određena je pomoću rendgenske strukturne analize i NMR spektroskopije. Održana je i citotoksična aktivnost novosintetizovanih jedinjenja, kao i njihov mehanizam delovanja pomoću "western blot" analize ključnih proteina uključenih u apoptozu i ispitivanjem njihove antiangiogene aktivnosti.



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**Synthesis and biological screening of novel triazole Mannich bases**

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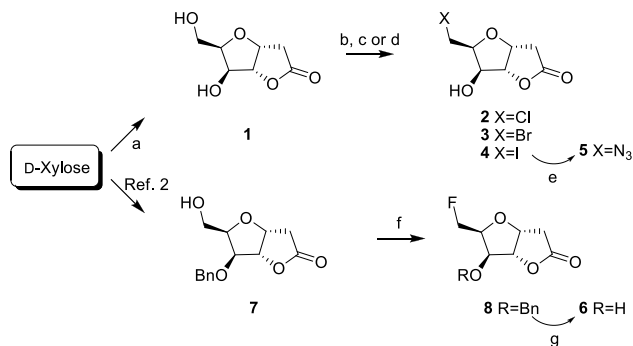
The synthesis of 18 novel 5-adamantyl-1,2,4-triazol-3-thion *N*-Mannich bases was performed. The targeted compounds were obtained starting from 1-adamantanecarboxylic acid, its transformation into corresponding acid chloride and derivatization with thiosemicarbazide. The formed 1-adamantoyl thiosemicarbazone in the presence of a base undergoes intramolecular cyclization giving the desired precursor, 5-adamantyl-1,2,4-triazol-3-thion. Further, in a Mannich reaction, the triazole precursor reacts with equimolar amount of formaline and corresponding primary aromatic amine in THF, giving final Mannich bases after 48 h of stirring at room temperature. The exact structure of newly synthesized compounds was determined by means of X-ray diffraction and NMR spectroscopy. The cytotoxic activity of these compounds was evaluated, as well as their molecular action through western blot analysis of key proteins involved in apoptosis and determination of anti-angiogenic activity.

This work has been funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project No. 172016 and 175011).

## Sinteza i antitumorska aktivnost defenilovanih analoga goniofufurona

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Goniofufuron, prirodni steryl-lakton izolovan iz kore drveta *Goniothalamus giganteus*, je potentan antitumorski agens.<sup>1</sup> Ovde želimo da saopštimo sintezu defenilovanog analoga goniofufurona (**1**), kao i niza defenilovanih analoga koji na C-7 imaju halogenidnu funkciju (**2–6**). Rezultati ispitivanja *in vitro* antitumorske aktivnosti sintetizovanih jedinjenja prema odabranim tumorskim ćelijskim linijama biće takođe prikazani i detaljno diskutovani.



Scheme 1. (a) Meldum's acid, Et<sub>3</sub>N, DMF, 46 °C; (b) CCl<sub>4</sub>, Ph<sub>3</sub>P, Py, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 38%; (c) CBr<sub>4</sub>, Ph<sub>3</sub>P, Py, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 28%; (d) I<sub>2</sub>, Ph<sub>3</sub>P, Im, THF, reflux, 63%; (e) NaN<sub>3</sub>, NH<sub>4</sub>Cl, DMF, 50 °C, 66%; (f) DAST, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 42% (calc. on reacted **7**); (g) H<sub>2</sub>, Pd/C, conc. HCl, EtOAc, rt, 73% (calc. on reacted **8**).

## Synthesis and antitumour activity of dephenylated goniofufurone analogues

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Goniofufurone, natural styryl lactone isolated from the stem bark of *Goniothalamus giganteus*, is potent antitumour agent.<sup>1</sup> Herein, we disclose synthesis of dephenylated goniofufurone analogue (**1**) and a series of dephenylated analogues bearing halogen atoms at C-7 (**2–6**). The results of *in vitro* antitumor activities of synthesized compounds against a number of human tumour cell lines were recorded. These results will be presented and discussed in details.

**Acknowledgement:** The work was supported by a grant from the Ministry of Education, Science and Technological Development (Project 172006).

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## Nova farmakofora aktivna na Ebola virus

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Ebola virus je veoma virulentan patogen koji uzrokuje smrtonosnu hemoragijsku groznicu kod ljudi i primata. Pokazalo se da imuno terapeutici, kao i druge složene makromolekulske formulacije, predstavljaju obećavajuće kandidate za lek. Ipak, nijedan od njih ne poseduje važne kvalitete malih molekula, kao što su niska cena, relativna jednostavnost pripreme, dug rok trajanja, lakoća skladištenja i mogućnost mehanizma dejstva na koji ne utiču brze mutacije virusa. Raniji rezultati dobijeni sa diazahrizenima<sup>1</sup>, naveli su nas da razvijemo novo, manje hidrofobno i rastvorljivije 1,5-naftiridinsko jezgro. Sintetisali smo nekolicinu mono- i di-alkilamino supstituisanih derivata, i ustanovili da najaktivniji (struktura 1) poseduju IC<sub>50</sub> vrednosti do 780 nM u *in vitro* testovima baziranim na HeLa ćelijama. Takođe, oni poseduju vreme poluživota duže od 60 minuta u ljudskim mikrozomima, nizak „klirens“ (<23 µL/min/mg) i generalno nisku hepatotoksičnost u *in vitro* testovima na 24 sata sa HepG2 ćelijama (broj ćelija, veličina i intenzitet jedara, zaustavljanje ćelijskog ciklusa, mitohondrijski potencijal i masa, steatoza i aktivnost p53).

### A novel anti-Ebola pharmacophore

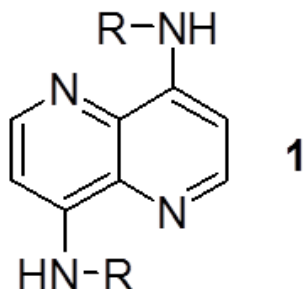
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The Ebola virus is a highly virulent pathogen that causes a deadly hemorrhagic fever in humans and non-human primates. Immuno-based therapeutics, as well as other

intricate macromolecular formulations, have proven to be promising drug candidates. Nevertheless, non of these possess the important attributes associated with small molecules, such as inexpensiveness, ease of preparation, long shelf life, facile storage, and the possibility of mechanisms of action circumventing rapid viral mutations. Earlier results of diazachrysene<sup>1</sup> derivatives led us to develop a novel, less hydrophobic and more water soluble 1,5-naphthyridine core. We synthesized several mono- and di-alkylamino substituted derivatives, and found that the most potent ones (structure 1), poses IC<sub>50</sub> values as low as 780 nM in HeLa cell based *in vitro* studies, show a higher than 60 minute half-life in human microsomes, low clearance rates (<23 µL/min/mg) and overall low hepatotoxicity in 24h *in vitro* HepG2 based tests (measuring total cell count, nuclear size and intensity, cell cycle arrest, mitochondrial potential and mass, steatosis and p53 activity).

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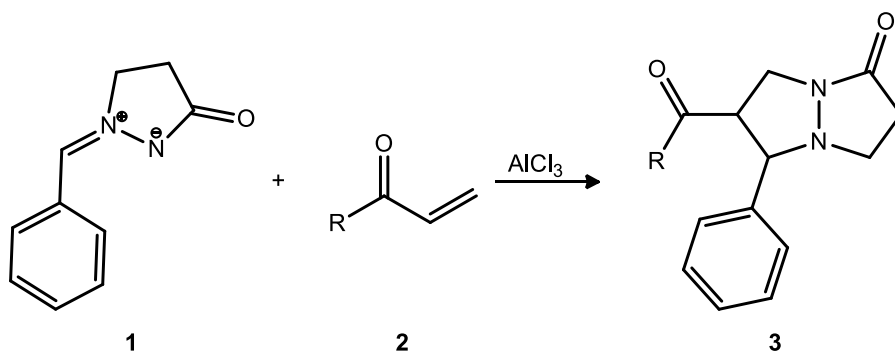
## OH O4

**Sinteza 6-acil-5-feniltetrahidropirazolo[1,2-*a*]pirazol-1(5H)-ona**

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[3+2] Cikloadicije *N,N'*-cikličnih azometin imina su se ustalile kao pogodan metod za sintezu *N,N'*-bicikličnih heterocikala.<sup>1</sup> Ovaj strukturni fragment predstavlja čest konstituent brojnih farmaceutskih preparata, agrohemijskih proizvoda i drugih biološki aktivnih jedinjenja. U ovom radu će biti prikazana sinteza serije 6-acil-5-feniltetrahidropirazolo[1,2-*a*]pirazol-1(5H)-ona (**3**) ostvarena reakcijom između odgovarajućih enona (**2**) i azometin imina **1** u prisustvu AlCl<sub>3</sub> kao katalizatora. Dobijena jedinjenja će biti spektroskopski okarakterisana.



R = Me, Et, Ph, 4-Tol, thienyl, 2-Me-thienyl

**Synthesis of 6-acyl-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5H)-ones**

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[3+2] Cycloadditions of *N,N'*-cyclic azomethine imines are established as convenient method for the synthesis of *N,N'*-bicyclic heterocycles.<sup>1</sup> This structural fragment is the frequent constituent of numerous pharmaceuticals, agrochemicals, and other biologically active compounds. In this report we will describe the synthesis of the series of 6-acyl-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5H)-ones (**3**) achieved by the reaction of corresponding enones (**2**) and *N,N'*-cyclic azomethine imine **1** in the presence of AlCl<sub>3</sub> as the catalyst. The obtained compounds will be characterized by spectroscopic techniques.

**Acknowledgement:** This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project 172034).

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## Ispitivanje antiproliferativne aktivnosti novih derivata benzotiazolamina prema MCF-7 ćelijskoj liniji humanog kancera dojke

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Poznato je da se mnogi lekovi, derivati benzotiazola, vrlo uspešno koriste u tretmanu različitih kliničkih stanja.<sup>1</sup> Takođe, značajno mesto zauzimaju u istraživanjima antitumorskih agenasa i veliki broj strukturnih modifikacija jezgra benzotiazola načinjen je s ciljem poboljšanja njihove antitumorske aktivnosti. U okviru naših istraživanja u ovoj oblasti sintetisana je serija novih karbamata i amida 6-alkiltio-supstituisanih benzotiazolamina i ispitana je njihova antiproliferativna aktivnost prema MCF-7 ćelijskoj liniji humanog karcinoma dojke. Pokazano je da derivati benzotiazolamina izazivaju visoko specifičnu programiranu ćelijsku smrt apoptozu u značajnom procentu tretiranih MCF-7 ćelija. Ispitan je i uticaj novih jedinjenja na ćelijski ciklus, mitohondrijski membranski potencijal i nivo unutarćelijskih reaktivnih kiseoničnih vrsta.

## Investigation of antiproliferative activity of new benzothiazolamine derivatives against MCF-7 human breast cancer cell line

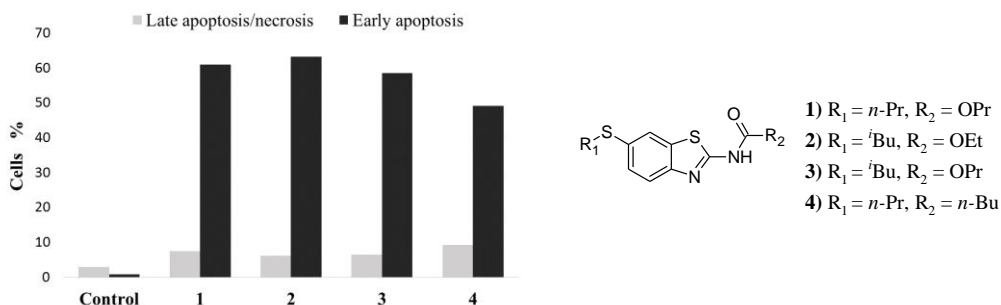
Milica Videnović, Tatjana Srdić-Rajić,\* Igor Opsenica,\*\* Siniša Radulović,\* Bogdan Šolaja\*\*

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Numerous benzothiazole-based clinical drugs have been extensively used in practice to treat various type of diseases with high therapeutic efficacy.<sup>1</sup> In addition, benzothiazole derivatives are compounds of an undoubted interest in anticancer research and a lot of structural modifications on their core nuclei have been made to improve their antitumor activity. Therefore, we have synthesized a series of novel 6-alkylthio-substituted benzothiazolamine carbamates and amides. To investigate their anticancer potency, we have used MCF-7 human breast cancer cell line. Benzothiazolamine derivatives show great potency for promoting highly specific programmed cell death apoptosis in MCF-7 cancer cell line. Our research continued towards examination of our compounds influence on cell cycle phase distribution, reactive oxygen species level and mitochondrial membrane potential.



**Acknowledgment:** This research was supported by the Ministry of Education, Science and Technological Development of Serbia (grant no. 172008)

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## OHP 01

### Antibakterijska aktivnost arildiketo kiseline prema rezistentnim sojevima bakterija

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Sojevi bakterija otporni na dejstvo poznatih antibiotika predstavljaju veliki zdravstveni problem za ljudsku zajednicu. Arildiketo kiseline (ADK) su aktivne prema nekoliko rezistentnih sojeva Gram-pozitivnih *S. aureus* bakterija [1]. Jedinjenja sa voluminoznim supstituentima u *ortho*-položaju fenilnog jezgra su najaktivnija. Strukturnim modifikacijama ove klase molekula pokazano je da je diketo deo molekula esencijalan za antibakterijsku aktivnost ADK. Ovi rezultati, zajedno sa podacima iz literature [2], ukazuju na to da su prenil-transferaze (enzimi uključeni u biosintezu ćelijskog zida bakterije) moguće biološke mete dejstva ADK u bakterijskoj ćeliji. 3D QSAR modelom zasnovanim na poljima molekulskih interakcija izdvojene su važne strukturne karakteristike za antibakterijsku aktivnost ADK. Dobijeni model može se iskoristiti za dizajn aktivnijih derivata ADK kao i za virtuelni skrining.

### Antibacterial activity of aryldiketo acids toward multidrug resistant bacterial strains

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Multidrug resistant (MDR) bacterial strains represent major health problem for the community, because of their rapidly growing resistance and pandemic potential. Aryldiketo acids (ADK) exerted antimicrobial activity against several resistant strains of Gram-positive *S. aureus* bacteria. Compounds having bulky alkyl group in *ortho*-position of phenyl ring were the most potent. Structural modifications of this class of molecules confirmed the importance of diketo moiety for antibacterial activity. These results, in combination with literature data, suggest that the enzymes prenyl-transferases (involved in cell wall biosynthesis) could be a possible biological target for ADK in bacterial cells. Using alignment independent 3D QSAR model based on molecular interaction fields, structural features important for antibacterial activity of ADK were found. Obtained model was statistically significant and could be used to guide the design of more potent derivatives as well as in virtual screening of novel antibacterial agents.

**Acknowledgement:** Ministry of Education, Science, and Technological Development of Serbia (Grant No. 172035) supported this work.

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OH P02

**Kvantitativni odnos strukture i retencionih vremena arilamida  
4-aril-4-okso-2-butenskih kiselina zasnovanih na GRIND-2 deskriptorima**

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Arilamidi 4-aril-4-okso-2-butenskih kiselina ispoljavaju antiproliferativnu aktivnost *in vitro* prema ćelijskim linijama humanih tumora u mikromolarnim i submikromolarnim koncentracijama [1]. Tokom rutinske karakterizacije jedinjenja, zapažen je kvalitativan odnos između retencionih vremena određenih HPLC metodom i strukture jedinjenja. Retenciona vremena određena su na RP-C18 koloni i korelisana sa 3D strukturom jedinjenja, optimizovanom na MP2 nivou. Upotrebom GRIND-2 deskriptora, izvedenih iz polja molekulskih interakcija, dobijeni su jasni kvantitativni odnosi između 3D strukture jedinjenja i retencionih vremena. Strukturna svojstva 30 kongenera koja utiču na retenciona vremena su detaljno opisana.

**Quantitative structure-retention relationships of 4-aryl-4-oxo-2-butenic acid  
arylamides based on GRIND-2 descriptors**

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*\*Center for Chemistry, IChTM, University of Belgrade*

4-Aryl-4-oxo-2-butenic acid arylamides exert antiproliferative activity toward human tumor cells *in vitro* in low micromolar to submicromolar concentrations [1]. During routine characterization of compounds, we observed qualitative relationship between HPLC retention times and structure of the compounds. Liquid chromatography (LC) was performed using RP-C18 column, and in this way obtained retention times correlated with the 3D structure of the compounds, optimized on MP2 level of theory. Using GRIND-2 descriptors, derived from molecular interaction fields, robust 3D quantitative structure-retention relationships were obtained. Structural features that differentiate 30 studied congeners in relation to LC retention times are described in details.

**Acknowledgements:** *This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Grant OI172035.*

**References:**

1. M. D. Vitorović-Todorović *et al.*, *Eur. J. Med. Chem.* 62 (2013) 40-50.

## Ekperimentalno i kvantno-hemijsko proučavanja azo-hidrazon tautomerije kod hinolonskih azo boja

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Veliki broj heterocikličnih jedinjenja koristi se pri sintezi različitih boja i pigmentata. Među njima, najveću pažnju privukli su 2-piridoni i 2-hinoloni. U ovom radu, ispitivana su spektralna svojstva i tautomerija sintetisanih 4-supstituisanih fenilazo-4-hidroksi-2-hinolona (Slika 1), kao i kvantno-hemijski podaci mogućih tautomera. Eksperimentalni podaci su korelisani DFT teorijskim podacima i na osnovu dobijenih rezultata izvedeni su novi zaključci u vezi tautomerije kod ispitivanih hinolonskih azo boja.

## Experimental and quantum-chemical study of azo-hydrazone tautomerism in certain quinolone azo dyes

Violeta M. Arsovski, Bojan Đ. Božić\*, Jelena M. Mirković\*, Vesna D. Vitnik\*\*,

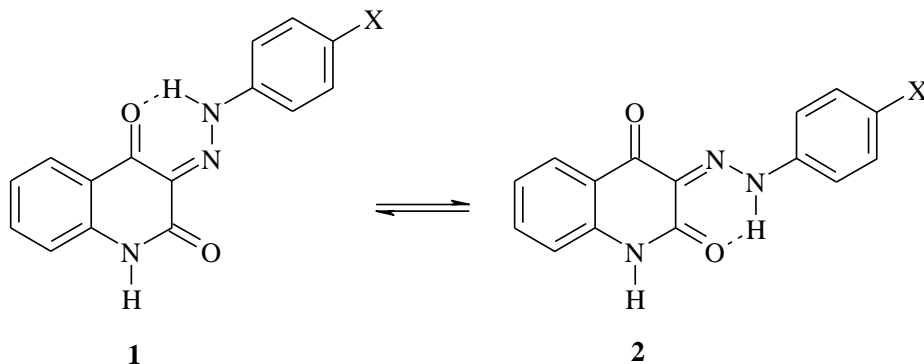
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A number of heterocyclic compounds have been used in the preparation of dyes and pigments. Among them 2-pyridones and 2-quinolones have gained considerable attention. In this work, the tautomerism of 4-substituted phenylazo-4-hydroxyl-2-quinolones (Figure 1), their spectral characterization and quantum-chemical results of possible tautomers are studied. Experimental and calculated data were correlated and new facts on tautomerism in quinolone azo dyes are presented.



Slika 1. Najdominantniji tautomerni oblici kod ispitivanih hinolonskih azo boja  
Figure 1. The most dominant tautomeric forms of the investigated quinolone azo dyes  
(X = OH, MeO, Me, H, F, Cl, Br, CN, COCH<sub>3</sub>, NO<sub>2</sub>).

**Acknowledgment.** Authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project 172013) for the financial support of this work.

### Solvatohromna svojstva azo boja na bazi 4-hidroksi-2-hinolona: Eksperimentalno i kvantno-hemijsko proučavanje

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UV-Vis apsorpcioni spektri, solvatochromizam i tautomerija serije 4-supstituisanih fenilazo-4-hidroksi-2-hinolona (Slika 1) analizirani su u dvadeset različitih rastvarača. Efekat polarnosti rastvarača, kao i proton-donorskih i proton-akceptorskih interakcija rastvarača sa molekulima azo boja proučavan je metodom linearne korelacije energije solvatacije (LSER analiza) korišćenjem Kamlet-Taftove i Katalanove jednačine. Takođe, analiza uticaja supstituenata na apsorpcione maksimume urađena je pomoću metode linearne korelacije slobodnih energija (LFER model) i to primenom Hametove jednačine.

### Solvatochromic properties of azo dyes derived from 4-hydroxyl-2-quinolone: Experimental and quantum-chemical study

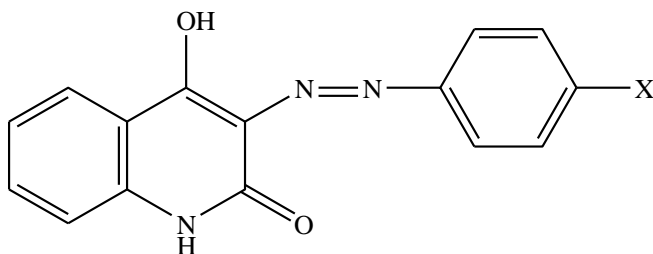
Violeta M. Arsovski, Jelena M. Mirković\*, Julijana Tadić\*, Bojan Đ. Božić\*, Vesna D. Vitnik\*\*, Željko J. Vitnik\*\*, Gordana S. Ušćumlić\*, Dušan Ž. Mijin\*

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UV-Vis absorption spectra, solvatochromism and tautomerism of 4-substituted phenylazo-4-hydroxyl-2-quinolones (Figure 1) in twenty solvents have been analyzed. Effect of solvent polarity as well as proton-donating and proton-accepting interaction of solvent with azo dyes molecules have been investigated by means of linear solvation energy relationship (LSER) using the Kamlet-Taft and Catalán solvatochromic equations. Moreover, insight into substituent effects determining the absorption maxima shifts have been studied by the linear free energy relationship (LFER) concept proposed by Hammett.



X = -N(CH<sub>3</sub>)<sub>2</sub>, -OH, -OCH<sub>3</sub>, -CH<sub>3</sub>, -H, -F, -Cl, -Br, -COCH<sub>3</sub>, -COOH, -CN, -NO<sub>2</sub>

Slika 1. Struktura arilazo hinolonskih boja.

Figure 1. Structure of investigated arylazo quinolone dyes.

**Acknowledgment:** Authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project 172013) for the financial support of this work.

## OH P05

**Identifikacija proizvoda termolize metil-*N*-metil-*N*-nitrozoantranilata**

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Poznato je da su *N*-nitrozo jedinjenja termalno nestabilna, ali se malo toga zna o reakcijama koje se odvijaju prilikom njihovog zagrevanja. Utvrđeno je da metil-*N*-metil-*N*-nitrozoantranilat (**1**), pri uslovima gasne hromatografije (GC-MS), podleže potpunoj termalnoj degradaciji dajući kao glavne proizvode metil-*N*-metilantranilat (**2**) i proizvod kuplovanja identifikovan kao 2,2'-(1,2-dimetilhidrazin-1,2-diil)dibenzoat (**3**). U cilju potvrde strukture proizvoda **3**, izvedena je preparativna termoliza jedinjenja **1**. Među 46 različitih sastojaka identifikovan je i potpuno spektralno okarakterisan novi proizvod kuplovanja metil-5-metil-6-okso-(5*H*)-fenantridin-4-karboksilat, dok proizvod **3** nije detektovan u termolizatu. Pažljivim razmatranjem struktura identifikovanih sastojaka termolizata predloženi su glavni putevi termolize jedinjenja **1** u parnoj i kondenzovanoj fazi. Generalno, identifikovani proizvodi bi mogli da se svrstaju u dve grupe, na one koji nastaju inicijalnim raskidanjem N–NO veze ili, neočekivano, Ar–NNO veze, tj. na proizvode koji su derivati antranilne i benzojeve kiseline. Strukturna raznolikost identifikovanih proizvoda i značajne razlike između termolize koja se odvija u parnoj i kondenzovanoj fazi ukazuju na mogući sintetski značaj termolize *N*-nitrozo jedinjenja.

**Structural elucidation of thermolysis products of methyl *N*-methyl-*N*-nitrosoanthranilate**

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Although it is common knowledge that *N*-nitroso compounds are thermally (and otherwise chemically) labile, little is known about the specific reactions that occur upon their heating. Methyl *N*-methyl-*N*-nitrosoanthranilate (**1**) was found to undergo complete thermal degradation under gas chromatographic (GC-MS) conditions yielding methyl *N*-methylantranilate (**2**) and a coupling product tentatively identified as dimethyl 2,2'-(1,2-dimethylhydrazine-1,2-diyl)dibenzoate (**3**), as the major ones. In an attempt to corroborate this find, a preparative scale thermolysis of compound **1** was carried out. Among 46 different products, a novel coupling product, methyl 5-methyl-6-oxo-(5*H*)-phenanthridine-4-carboxylate (**4**), was identified and fully spectrally characterized, while **3** was not detected in the thermolysate. A careful consideration of the structures of the identified thermolysate constituents led us to propose the major thermolysis pathways of **1** both in condensed and vapor phases. Generally, the identified products could be classified as those arising from fission of the N–NO bond or rather unexpectedly, the Ar–NNO bond, *i.e.* products related to anthranilic and benzoic acids, respectively. The structural diversity of the identified products and the noted marked differences between vapor and condensed phases point to the possible synthetic utility of thermolysis of *N*-nitroso compounds.

**Acknowledgement:** Ministry of Education, Science and Technological Development of Serbia (Grant No. 172061).

## OH P06

**Novi pirazolski pseudo-C-nukleozidi kao inhibitori rasta tumorskih ćelija**

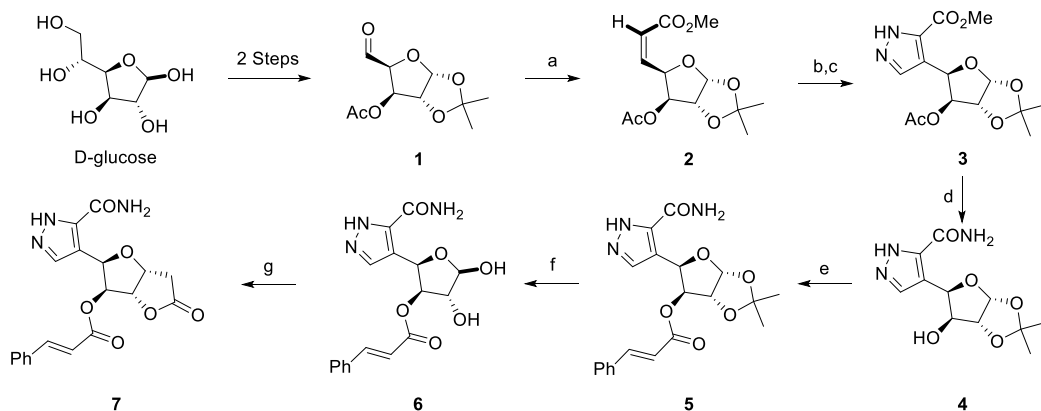
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U radu je ostvarena višefazna sinteza novih pseudo-C-nukleozida sa pirazolskim prstenom iz D-glukoze. Aldehyd **1** je uspešno preveden u ciljani molekul **7** nizom selektivnih hemijskih transformacija koje su prikazane na Shemi 1. Rezultati ispitivanja *in vitro* antiproliferativne aktivnosti jedinjenja **5** i **7** prema ćelijskim linijama odabranih humanih tumora biće takođe saopšteni i diskutovani.



**Scheme 1.** Reagents and conditions: (a) MCMP/MeOH, 0 °C → rt, 1.5 h; (b) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 0 °C, 3 h; (c) Cl<sub>2</sub>, CCl<sub>4</sub>, 3 h; (d) NH<sub>3</sub>, MeOH, 5 days; (e) cinnamic acid, DCC, DMAP, MeCN, rt, 45 h; (f) 90% aq TFA, rt, 1 h; (g) Meldrum's acid, DMF, Et<sub>3</sub>N, 46 °C, 80 h.

**Novel pyrazole pseudo-C-nucleosides as inhibitors of tumour cells growth**

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Multi-step synthesis of novel pseudo-C-nucleosides containing pyrazole ring (compounds **5** and **7**) has been achieved starting from D-glucose. The aldehyde **1** was converted to the target **7** through a seven-step sequence outlined in Scheme 1. Results related to *in vitro* antiproliferative activity of **5** and **7** against a number of tumor cell lines will be presented and discussed.

**Acknowledgement:** The work was supported by a grant from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project 172006).

OH P07

**Azo-hidrazon tautomerija novih 5-arilazo-6(2)-hidroksi-4-metil-3-ciano-N(1)-fenil-2(6)-okso-piridin-3-karbonitrilnih boja**

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Fizičko-hemijska svojstva arilazopiridonskih boja su usko povezana sa njihovim azo-hidrazo tautomerizmom. Pošto tautomeri imaju različita tehnička svojstva i performanse bojenja, proučavanje njihovog tautomerizma je važno kako sa teorijske, tako i sa praktične tačke gledišta. Mala razlika u energiji tautomera ih čini veoma osetljivim na uticaj sredine i efekata supstituenata. Tautomerna ravnoteža jedanaest arilazo piridonskih boja je proučavana na osnovu UV-Vis apsorpcionih spektara uz pomoć kvantno-mehaničkog modelovanja. NMR i teorijska izračunavanja korišćenjem PCM/xB97X-D/6-311G(d,p) metoda, potvrdili su da pripremljena jedinjenja postoje uglavnom u Hidrazo obliku. AIM topološka analiza i ukupna elektronska gustina na kritičnoj tački veze (BCP) potvrđuju su prisustvo jake intramolekulske vodonične veze koja doprinosi većoj stabilnosti Hidrazo oblika.

**Azo-hidrazo tautomerism of novel 5-arylazo-6(2)-hydroxy-4-methyl-3-cyano-N(1)-phenyl-2(6)-oxo-pyridine-3-carbonitrile dyes**

Milica Rančić, Ivana Stojiljković, Hana Elshaflu\*, Miloš Milčić\*\*, Aleksandar Marinković\*  
*Faculty of Forestry, University of Belgrade, Serbia*

\**Faculty of Technology and Metallurgy, University of Belgrade, Serbia*

\*\**Faculty of Chemistry, University of Belgrade, Serbia*

The physico-chemical properties of arylazo pyridone dyes are closely related to their azo-hidrazo tautomerism. Since the tautomers have different technical properties and dyeing performances, studying the state of tautomeric equilibria is important from both theoretical and practical point of view. The small free energy difference between tautomers makes them sensitive to the influence of environment and substituent effects. The state of the tautomeric equilibria of eleven arylazo pyridone dyes was evaluated from UV-Vis absorption spectra with the aid of the quantum mechanical modeling. NMR analysis and theoretical calculations, by PCM/xB97X-D/6-311G(d,p) method, confirmed that prepared compounds exist mainly in Hydrazo form. AIM topological analysis and total electron density at the bond critical point (BCP) confirmed a presence of strong hydrogen bond which contributes to higher stability of Hydrazo form.

## Ispitivanje kinetike i mehanizma fenilselenolaktonizacije 4-pentenske kiseline katalizovane trietilaminom

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U radu su predstavljeni rezultati ispitivanja kinetike i mehanizma fenilselenolaktonizacije 4-pentenske kiseline pomoću PhSeCl i PhSeBr, katalizovane trietilaminom. Glavni proizvod ove reakcije je  $\gamma$ -lakton koji u bočnom nizu sadrži PhSe-grupu koja posredstvom veoma jednostavnih hemijskih transformacija može lako biti prevedena u veliki broj korisnih funkcionalnih grupa. Takođe, značaj  $\gamma$ -laktona se ogleda i u tome što veliki broj molekula iz ove grupe predstavlja česte strukturne elemente mnogih biološki aktivnih jedinjenja.<sup>1</sup> Kinetika i mehanizam ovih reakcija ispitivani su UV-Vis spektrofotometrijski. Konstante brzine, kao i termodinamički parametri ( $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$ ) su određeni koristeći UV-Vis metodu na tri različite temperature (288, 298 i 308K), u tetrahidrofuranu kao rastvaraču. Dobijeni rezultati ukazuju na veću efikasnost PhSeCl kao ciklizacionog reagensa u odnosu na PhSeBr. Takođe, visoke negativne vrednosti za entropiju aktiviranja i niske vrednosti entalpije aktiviranja sugerišu  $S_N2$  mehanizam nukleofilne supstitucije.

## Kinetic and mechanistic studies of triethylamine-catalyzed phenylselenolactonization of 4-pentenoic acid

Marina D. Kostić, Vera M. Divac, Nenad Ž. Janković, Jelena M. Petronijević  
*Faculty of Science Kragujevac, Radoja Domanovića 12, 34000 Kragujevac*

The aim of this work is exploration of kinetic and mechanistic aspects of triethylamine-catalyzed phenylselenolactonization of 4-pentenoic acid by means of phenylselenenyl halides (PhSeCl and PhSeBr). The major product of these reactions is  $\gamma$ -lactone with PhSe-functionalized side chain, which can be easily transformed in numerous useful functional groups by very simple chemical reactions. In addition, the importance of  $\gamma$ -lactones is reflected in the fact that a large number of these molecules present structural units of biologically active compounds.<sup>1</sup> The kinetic and mechanism for these reactions have been investigated by the UV-Vis spectrophotometry. The rate constants, as well as thermodynamic parameters ( $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$ ) have been determined using UV-Vis method at three different temperatures (288, 298 and 308K) in THF as solvent. The large negative values for the entropy of activation and low enthalpy of activation with both reagents support the  $S_N2$  mechanism, and obtained values for the rate constants have indicated higher reactivity of PhSeCl as reagent for cyclization.

*Ovaj rad je finansijski potpomognut od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije, projekat br. 172011.*

1. T. Janecki, Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity, Wiley VCH, Verlag, 2013.

OH P09

## Regioselektivnost i kinetika Co(II)hlorid katalizovane fenilselenociklizacije 6-metil-hept-5-en-2-ola

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Selenociklizacione reakcije verovatno predstavljaju najkorisniju primenu elektrofilnih seleno(II) reagenasa. Adicija ovih reagenasa na dvostruku vezu inicira nukleofilni napad pogodno orjentisane grupe, koja je sastavni deo supstrata, što rezultira stvaranjem cikličnog proizvoda. Zahvaljujući velikoj raznovrsnosti nukleofila koji se mogu upotrebiti, ove reakcije su našle rasprostranjenu primenu u sintezi prirodnih proizvoda, gde selenociklizacija predstavlja ključni korak u sintezi.<sup>1</sup> Iako ove reakcije imaju dobro utvrđenu sintetičku primenu, vrlo malo je učinjeno po pitanju boljeg razumevanja mehanizma i kinetike ovih reakcija. U ovom radu, mi smo pokušali da postignemo bolji uvid u mehanizam fenilselenoeterifikacije 6-metil-hept-5-en-2-ola kroz sintetičku i kinetičku studiju Co(II)hlorid-katalizovane ciklizacije pod uslovima reakcije *pseudo*-prvog reda uz pomoć UV-Vis spektrofotometrije. Poredeći sa rezultatima bazno katalizovanih reakcija, primećeno je da reakcije katalizovane sa CoCl<sub>2</sub> ispoljavaju mnogo bolju regioselektivnost. Dobijene vrednosti konstanti brzina reakcija potvrdile su katalitičku ulogu CoCl<sub>2</sub>.

## Regioselectivity and kinetics of Cobalt(II) chloride catalyzed phenylselenocyclization of 6-methyl-hept-5-en-2-ol

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Selenocyclization reactions are probably the most useful utilization of the electrophilic selenium(II) reagents. Addition of the reagents to the double bond triggers the nucleophilic attack of the suitably positioned pendant group resulting in the generation of a cyclic product. Due to the great diversity and versatility of pendant nucleophiles that can be used, these reactions have found widespread usage in some natural product synthesis, where the selenocyclization reaction represents the key step in their synthesis.<sup>1</sup> Although, these reactions have established synthetic utility, very little has been done in improvement of understanding the mechanism and kinetics of these reactions. In this work we tried to achieve better insight in the mechanism of phenylselenoetherification of 6-methyl-hept-5-en-2-ol through the synthetic and kinetic study of the Co(II) chloride catalyzed cyclization under *pseudo*-first order conditions by UV-Vis spectrophotometry. Compared to the Lewis base catalyzed reactions, of this alkenol, much better regioselectivity was expressed with CoCl<sub>2</sub>. The obtained values for the rate constants have confirmed catalytic role of the CoCl<sub>2</sub>.

Ovaj rad je finansijski potpomognut od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije, projekat br. 172011.

1. X. Jiang, H. Lui, in *Comprehensive organic synthesis*, P. Knochel, G. A. Molander, Ed(s)., Elsevier, 2014, p. 466.

## OH P10

**Sinteza, karakterizacija i citotoksičnost novih antrahinonskih amida**

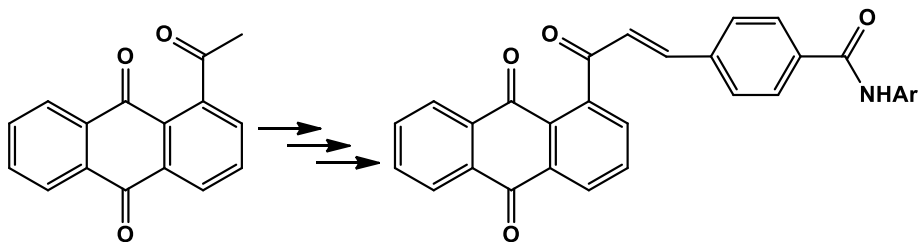
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Hibridni organski molekuli, koji u svojoj strukturi sadrže halkonsku i antrahinonsku farmakoforu, pokazali su izraženu citotoksičnost prema HeLa ćelijama uz relativno visoku selektivnost u odnosu na normalnu MRC-5 ćelijsku liniju.<sup>1</sup> Ovi rezultati podstakli su nas da sintetizujemo nove antrahinonske hibridne derivate koji sadrže  $\alpha,\beta$ -nezasićeni konjugovani sistem u cilju poboljšanja citotoksične aktivnosti i selektivnosti dobijenih molekula. Dobijanje takvih jedinjenja ostvareno je polazeći od 1-acetil-antrahinona, koji u reakciji sa 4-formilbenzoeskom kiselinom daje odgovarajući halkonski prekursor koji se može dalje derivatizovati zahvaljujući prisustvu karboksilne grupe koja preko kiselinskog hlorida sa aromatičnim aminima daje finalne amidne derivate. Preliminarni rezultati citotoksične aktivnosti ukazuju na značajan antiproliferativni potencijal koji nameće potrebu daljeg ispitivanja mehanizma njihovog delovanja prema HeLa ćelijama.



Rad je finansiran sredstvima Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije u okviru projekata OI 172016 i 175011.

**Synthesis, characterization and cytotoxicity of novel anthraquinone amides**

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Hybrid organic molecules with chalcone and anthraquinone pharmacophores showed a pronounced cytotoxicity against HeLa cell line with good selectivity against normal MRC-5 cells.<sup>1</sup> These results encouraged us to prepare novel hybrid anthraquinone derivatives which contain  $\alpha,\beta$ -unsaturated conjugated system, with intention to increase cytotoxicity and selectivity of obtained molecules. The synthesis of these compounds starts with the reaction of 1-acetyl-anthraquinone with 4-formylbenzoic acid giving the corresponding chalcone precursor, which can be subjected to further derivatization due to the presence of carboxylic group which can be transformed into corresponding chloride and react with aromatic amines to give final amid derivatives. Preliminary results of cytotoxic activity show considerable antiproliferative potential which impose the necessity to further examine their mechanism of action against HeLa cell line.

*This work has been funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project No. 172016 and 175011).*

1. V. Marković et al. *Eur. J. Med. Chem.* **89** (2015) 401.

OH P11

**Sinteza i karakterizacija 1,3,5-trisupstituisanog-1,2-azaboracikloheksana**

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Visoko regioselektivnom reakcijom benzilamina i etil-propiolata moguće je dobiti  $\delta$ -dienamino estar u neutralnim uslovima, ili  $\beta$ -*N,N*-dienamino estar u baznim uslovima.  $\delta$ -Dienamino estar upotrebljen je kao supstrat za stereoselektivnu sintezu 1,3,5-trisupstituisanog-1,2-azaboracikloheksana. Dobijeno jedinjenje okarakterisano je na osnovu IC, HRMS, 1D i 2D NMR spektroskopije. NOE eksperiment ukazao je na *trans* konfiguraciju dve estarske grupe, pri čemu je grupa vezana za C-3 atom u ekvatorijalnom položaju, a grupa vezana za C-5 atom u aksijalnom položaju. Benzil-grupa vezana za atom azota je ekvatorijalno orijentisana.

**Zahvalnica:** *Autori se zahvaljuju Ministarstvu prosvete, nauke i tehnološkog razvoja Republike Srbije za finansijsku podršku (Projekat br. 172020).*

**Synthesis and Characterization of  
1,3,5-Trisubstituted-1,2-azaboracyclohexane**

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The highly regioselective reaction of benzylamine and ethyl propiolate affords  $\delta$ -dienamino ester under neutral conditions, or  $\beta$ -*N,N*-dienamino ester under basic conditions. The former was employed as a substrate for the stereoselective synthesis of 1,3,5-trisubstituted-1,2-azaboracyclohexane. It was characterized on the basis of IR, HRMS, 1D and 2D NMR techniques. The NOE experiment revealed *trans* relationship between the two ester groups, the one attached at the C-3 being in equatorial position and the one attached at the C-5 in the axial position. The *N*-Bn substituent is equatorially oriented.

**Acknowledgement:** *Financial support from the Ministry of education, science and technological development of the Republic of Serbia is acknowledged (Project No. 172020).*

## Sinteza i antitumorska aktivnost (–)-kleistenolida

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(–)-Kleistenolid (**1**) je prirodni proizvod izolovan iz biljke *Cleistochlamys kirkii* poreklom iz Tanzanije i Mozambika. Jedinjenje **1** pokazuje antibakterijsku (*Staphylococcus aureus* i *Bacillus anthracis*) i antigljivičnu aktivnost (*Candida albicans*). Ovom prilikom želimo da saopštimo novu totalnu sintezu jedinjenje **1** polazeći iz diacetonida D-glukoze (**2**). Molekul **2** je preveden u finalni proizvod **1** primenom višefazne sintetičke sekvence prikazane na reakcionoj shemi. Kolorimetrijskim MTT testom je po prvi put utvrđeno da molekul **1** pokazuje *in vitro* antitumorsku aktivnost prema panelu malignih ćelijskih linija.

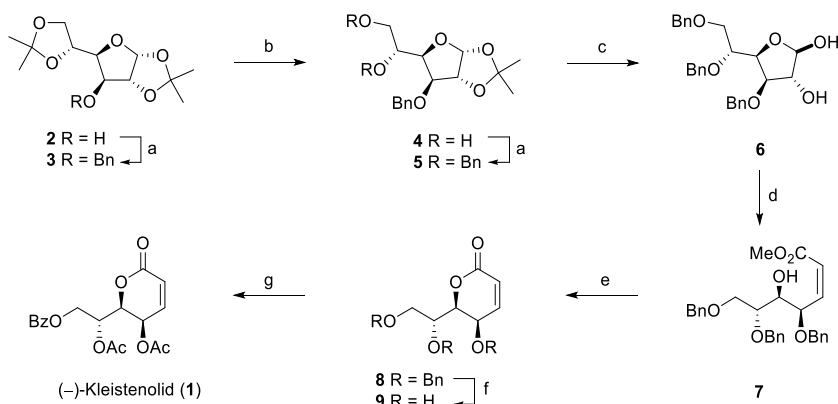
## Synthesis and antitumour activity of (–)-cleistenolide

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Vesna Kojić\*, Velimir Popsavin

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(–)-Cleistenolide (**1**) is a natural product isolated from the plant *Cleistochlamys kirkii* originating from Tanzania and Mozambique. Compound **1** shows antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, as well as antifungal activity against *Candida albicans*. Herein we wish to report a new total synthesis of natural product **1** starting from diacetonide D-glucose (**2**). Molecule **2** was converted to the final product **1** through a multi-step sequence outlined in the reaction scheme. Using the MTT colorimetric assay it was found, for the first time, that molecule **1** shows *in vitro* antitumour activity against a panel of malignant cell lines.



Reagents and conditions: (a) *BnBr*, *NaH*, *DMF*, 0°C, rt; (b) aq 60% *AcOH*, rt; (c) aq 50% *TFA*, rt; (d) (i) *H<sub>5</sub>IO<sub>6</sub>*, *EtOAc/H<sub>2</sub>O*; (ii) *MeOH*, *MCMP*, rt; (e) *TsOH*, *CH<sub>2</sub>Cl<sub>2</sub>*, rt; (f) *FeCl<sub>3</sub>*, *CH<sub>2</sub>Cl<sub>2</sub>*, rt; (g) *BzCl*, *Ac<sub>2</sub>O*, *CH<sub>2</sub>Cl<sub>2</sub>/Py*, rt.

**Acknowledgement:** The work was supported by a grant from the Ministry of Education, Science and Technological Development (Project 172006).

## OH P13

**Sinteza novih anilidopiperidina kao potencijalnih opioidnih agonista**

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U okviru našeg istraživanja o farmakološki aktivnim anilidopiperidinima sintetisali smo četiri nova analoga, *trans*-1-fenetil-4-(*N*-fenilpropionamido)piperidin-3-karboksamid (**3**), *trans*-metil (1-fenetil-4-(*N*-fenilpropionamido)piperidin-3-il)karbamat (**4**) i *cis* i *trans*-5-fenetil-1-fenilheksahidro-1H-imidazo[4,5-*c*]piridin-2(3H)-on (**5** i **6**). Ovde je predstavljena njihova parcijalna sinteza polazeći od *cis/trans* izomera 1-fenetil-4-(fenilamino)piperidin-3-karboksamida (**1** i **2**). Jedinjenja **4**, **5** i **6** dobijena su modifikovanom metodom Hofmann-ovog premeštanja, koju smo nedavno objavili, (put A odnosno put B). **Put A:** *N*-ptopionilovanjem karboksamida **1** propionil hloridom u prisustvu trietilamina, dobijen je karboksamid **3**, u skromnom prinosu (40%). U reakciji Hofmann-ovog premeštanja, pod sledećim reakcionim uslovima: *N*-bromoacetamid, litijum hidroksid, metanol, karbamat **4** dobijen je stereoselektivno u visokom prinosu (80%) iz karboksamida **3**. **Put B:** direktnim Hofmann-ovim premeštanjem karboksamida **1** i **2** pod već pomenutim uslovima, dobijene su ciklične uree, **5** i **6** stereoselektivno u visokom prinosu (~85%).

Reakcije su stereoselektivne (u oba reakciona puta), jednostavne za izvođenje, podrazumevaju laku obradu i izolovanje proizvoda reakcije i upotrebu jeftinih reagenasa.

**Synthesis of novel anilidopiperidines as potencial opioid agonists**

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As a part of our ongoing research on pharmacologically active anilidopiperidines, four new analogs namely *trans*-1-phenethyl-4-(*N*-phenylpropionamido)piperidine-3-carboxamide(**3**), *trans*-methyl (1-phenethyl-4-(*N*-phenylpropionamido)piperidin-3-yl)carbamate (**4**), and *cis* and *trans*-5-phenethyl-1-phenylhexahydro-1H-imidazo[4,5-*c*]pyridin-2(3H)-one (**5** and **6**) were synthesized. Herein we present their partial synthesis from *cis* and *trans* isomers of 1-phenethyl-4-(phenylamino) piperidine-3-carboxamide (**1** and **2**). Compounds **4**, **5** and **6**, were obtained by Hofmann rearrangement, a novel method that we published recently, pathway A and B, respectively. **Pathway A:** *N*-propionylation of carboxamide **1** with propionyl chloride in the presence of triethyl amine provided carboxamide **3** in moderate yields (~40%). In the reaction of Hofmann rearrangement under following reaction conditions: *N*-bromoacetamide, lithium hydroxide, methanol/, carbamate **4** was obtained from carboxamide **3**, in high yields (~80%). **Pathway B:** a direct Hofmann rearrangement of carboxamides **1** and **2**, under the aforementioned reaction conditions, afforded *cis* and *trans* cyclic ureas **5** and **6** (yield ~85%).

Reactions are stereoselective (in both pathways), and easy to perform. The products could be isolated by simple procedure and reagents are cheap.

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## OH P14

### Sinteza, antimikrobna i antioksidativna aktivnost novih benzociklobutan-2,5-diona

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ICTM – Center for Chemistry, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia

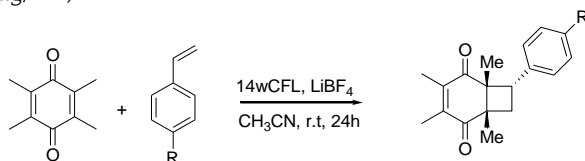
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Nekoliko novih benzociklobutan-2,5-diona je sintetisano reakcijom fotocikloadicije durohinona sa nekoliko razlicito supstituisanih etilena. Reakcija je izvedena u prisustvu 14W CFL lampe kao izvora svetlosti. Dobijena jedinjenja su testirana na antimikrobno i antioksidativno dejstvo. Antimikrobna aktivnost je testirana na Gram –pozitivnim bakterijama (*Bacillus spizizenii* ATCC 6633 and *Staphylococcus aureus* ATCC 6538) i tri Gram-negativne bakterije (*Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027 and *Salmonella abony* NCTC 6017). Minimalne inhibitorne koncentracije (MIK) su varirale izmedju 0.25 i 1 mg/ml. Svi testirani uzorci su bili aktivni na *B. spizizenii*, *S. aureus* i *P. aeruginosa* a neaktivni protiv *E. coli* i *S. abony*.

Lipidno peroksidativna aktivnost sintetisanih jedinjenja merena je TBA-MDA testom (tiobarbiturna kiselina-malondialdehid). Testirana jedinjenja su pokazala veoma dobra antioksidativna svojstva (sa IC<sub>50</sub> vrednostima izmedju 53.88 i 81.51 µg/ml). Njihova antioksidativna svojstva su uporediva sa kvercetinom (IC<sub>50</sub> = 10.47 µg/mL).



Scheme 1. Synthesis of benzocyclobutane-2,5-diones

### Synthesis, antibacterial and antioxidant activity of new benzocyclobutane-2,5-diones

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Several new benzocyclobutane-2,5-diones were synthesized using photocycloaddition reaction of duroquinone with various phenylsubstituted ethylenes. Reaction is performed in the presence of 14W CFL lamp i.e. reaction is catalyzed by visible light. Upon synthesis their antibacterial and antioxidant properties were examined.

Antimicrobial activity was evaluated against two Gram-positive bacteria (*Bacillus spizizenii* ATCC 6633 and *Staphylococcus aureus* ATCC 6538) and three Gram-negative bacteria (*Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027 and *Salmonella abony* NCTC 6017). The minimal inhibitory concentrations (MICs) varied between 0.25 and 1.0 mg/mL. All tested samples were effective against *B. spizizenii*, *S. aureus* and *P. aeruginosa* but also inactive against *E. coli* and *S. abony*. Lipid peroxidation (LP) inhibition level in the presence of the synthesized compounds, was measured by thiobarbituric acid-malondialdehyde (TBA-MDA) test. Tested compounds possessed very good antioxidant properties (with IC<sub>50</sub> values between 53.88 and 81.51 µg/mL). Their antioxidant effects are comparable to that of quercetin (IC<sub>50</sub> = 10.47 µg/mL).

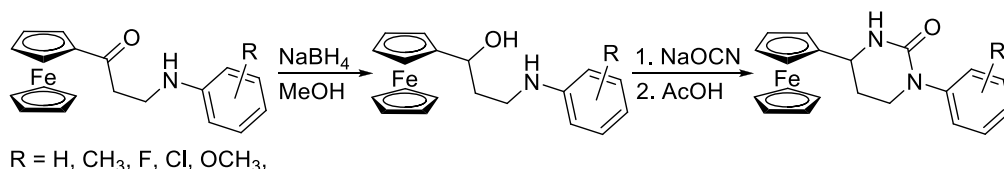
This work was supported by the Ministry of Education and Science of the Republic of Serbia (project No. 172020)

## OH P15

**Sinteza 1-aryl-4-feroceniltetrahidropirimidin-2(1H)-ona**Aleksandra Minić, Dragana Stevanović, Anka Pejović, Niko Radulović\*, Rastko D. Vukićević  
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Jedinjenja čije strukture obuhvataju tetrahidropirimidinonski prsten pokazuju različite oblike biološke aktivnosti,<sup>1</sup> pa postoji stalno interesovanje za njihovu sintezu. U ovom radu biće opisana sinteza serije derivata ovog heterocikla koji sadrže i ferocensko jezgro - 1-aryl-4-feroceniltetrahidropirimidin-2(1H)-ona, polazeći od ranije opisanih 3-amino-aryl-1-ferocenilpropan-1-ona.<sup>2</sup> Redukcija ovih pomoću NaBH<sub>4</sub> daje odgovarajuće 1,3-amino-alkohole, koji pod dejstvom ultrazvučnih talasa reaguju sa natrijum-cijanatom dajući hidroksiuree. Tetiranjem hidroksiurea sirćetnom kiselinom (preko stabilnog α-ferocenil-karbokatjona) nastaju ciljna jedinjenja.<sup>3</sup>

**Synthesis of 1-aryl-4-ferocenyltetrahydropyrimidin-2(1H)-ones**Aleksandra Minić, Dragana Stevanović, Anka Pejović, Niko Radulović\*, Rastko D. Vukićević  
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Compounds containing a tetrahydropyrimidinone ring exhibit different kinds of biological activity,<sup>1</sup> therefore, there is a permanent interest in their synthesis. In this work we wish to report on a protocol for the synthesis of a series of derivatives of this heterocycle containing also a ferrocene nucleus - 1-aryl-4-ferocenyltetrahydropyrimidin-2-(1H)-ones – starting from 3-aminoaryl-1-ferocenylpropan-1-ones, recently described by us.<sup>2</sup> The NaBH<sub>4</sub> reduction of these compounds gave the corresponding 1,3-aminoalcohols which were, then, submitted to the reaction with sodium cyanate under an ultrasound irradiation. This gave the corresponding hydroxyureas, which in a subsequent treatment with acetic acid gave (*via* a stable α-ferrocenyl carbocation) the target molecules.<sup>3</sup>

**Acknowledgement:** This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project 172034).

1. P. Babczinski *et al.*, *Pestic. Biochem. Phyziol.*, **52** (1995) 33.
2. a) I. Damljanović *et al.*, *J. Organomet. Chem.* **696** (2011) 3703; b) A. Pejović *et al.*, *Helv. Chim. Acta*, **95** (2012) 1425.
3. A. Minić *et al.*, *RSC Adv.*, **5** (2015) 24915.

## Primena acil-piruvata u sintetičkoj hemiji

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Crnotravska 17, Beograd

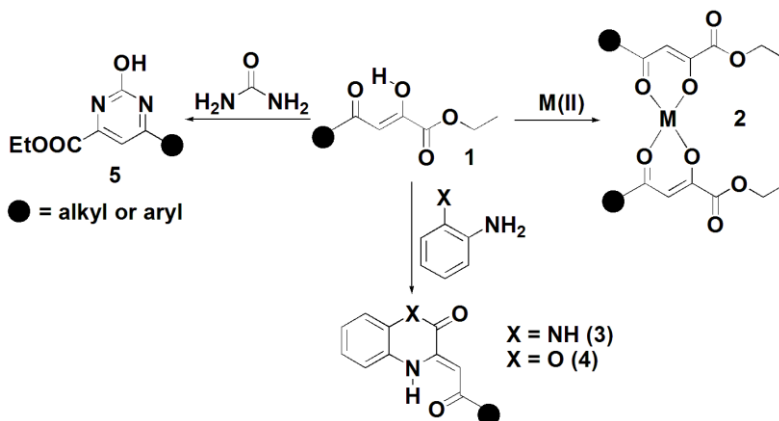
Acil-piruvati (1) predstavljaju klasu molekula koji imaju značajnu primenu u sintetičkoj hemiji.<sup>1</sup> Korišćeni su kao polazna jedinjenja u sintezi malih biblioteka novih M(II) kompleksa (2), hinoksalin-2(1H)-ona (3), benzo[b][1,4]oksazin-2-ona (4) i 2-hidroksi-pirimidina (5). Sva jedinjenja su dobijena u dobrim do odličnim prinosima.

## Application of acyl pyruvates in sintethic chemistry

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Acyl pyruvates (1) represent a class of molecules that have attracted a considerable interest in synthetic chemistry.<sup>1</sup> These molecules were used as a starting compounds in synthesis small libraries of novel M(II) complexes (2), quinoxalin-2(1H)-ones (3), benzo[b][1,4]oxazin-2-ones (4) and 2-hydroxy-pyrimidines (5). Yields were good-to-excellent for all compounds.



**Acknowledgements:** The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia for financial support (Grant 172011)

1. S. V. Ryabukhina et. al. *Tetrahedron Lett.* **51**(2010) 4229.



### **Biološki aktivno vlakno sa ceftriaksonom**

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Univerzitet u Banjoj Luci, Tehnološki fakultet, Banja Luka, Republika Srpska, BiH

Osobine biološki aktivnih vlakna zavise od vrste nosača i od strukture samog lijeka. U ovom radu selektivnom oksidacijom celuloznog zavoja dobijena je oksidovana celuloza (OC) sa različitim sadržajem karboksilnih grupa koja je iskorištena za hemijsko vezivanje antibiotika ceftriaksona.

Vezivanje lijeka vršeno je iz vodenog rastvora antibiotika koncentracije  $c=3,4 \cdot 10^{-3}$  mol/L na sobnoj temperaturi ( $22 \pm 1$  °C), a desorpcija lijeka u fiziološkom rastvoru. Količine vezanog i otpuštenog lijeka određene su spektrofotometrijski u UV području. Maksimalna količina vezanog lijeka (0,1032 mmol/g) dobijena je sorpcijom na modifikovani zavoj sa 2,276 mmol/g COOH, a maksimalna količina desorbovanog ceftriaksona iznosila je 0,0060 mmol/g. Antimikrobno djelovanje uzoraka zavoja sa vezanim ceftriaksonom testirano je *in vitro* na kulture *Staphylococcus aureus*, *Bacillus subtilis* i *Escherichia coli* metodom difuzije na agarnoj ploči. Najveća zona inhibicije dobijena je u odnosu na *Staphylococcus aureus*.

U radu se proučava uticaj hemijske strukture ceftriaksona, pH vrijednosti rastvora iz koga se vrši sorpcija kao i sadržaja karboksilnih grupa OC na količinu vezanog lijeka. Ustanovljeno je da se vezivanje ostvaruje jonskim i vodoničnim vezama lijeka sa oksidovanim celuloznim zavojem.

### **Biologically active fiber containing ceftriaxone**

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Properties of biologically active fiber depend on the type of carrier and the structure of the drug. In this paper oxidized cellulose (OC) with different carboxylic group content is obtained by selective oxidation and used for chemical bonding of antibiotic ceftriaxone.

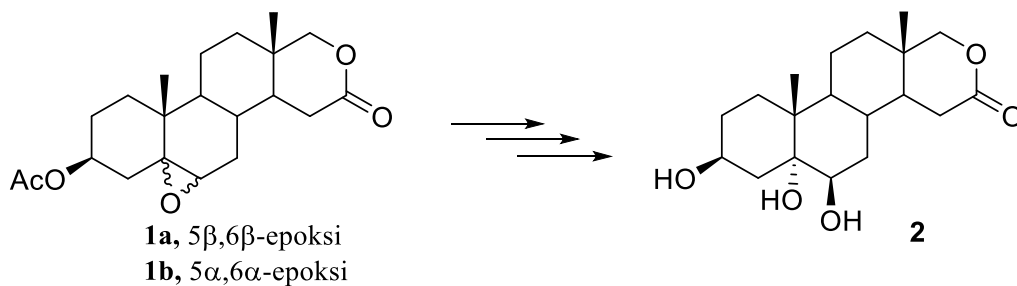
The bonding was performed in antibiotic water solution concentration of  $c=3,4 \cdot 10^{-3}$  mol/L at room temperature ( $22 \pm 1$  °C), while desorption was performed in physiological solution. The amounts of bonded and released antibiotic were determined spectrophotometrically in UV range. Maximum amount of bound drug (0,1032 mmol/g) was obtained during the sorption on the oxidized bandage with 2,276 mmol/g COOH and the maximum amount of released ceftriaxone was 0,0060 mmol/g. Antimicrobial activity of the samples with bonded ceftriaxone was tested *in vitro* against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* by agar diffusion test. The biggest zone of inhibition was obtained for *Staphylococcus aureus*.

The paper studies the influence of ceftriaxone chemical structure, solution pH in which sorption is performed and content of carboxyl group OC, on the amount of bonded drug. It was established that the drug bonding was achieved by ionic bonds and the hydrogen bonds of the drug functional groups with oxidised cellulose bandage.

## Hemijske modifikacije 5 $\alpha$ ,6 $\alpha$ - i 5 $\beta$ ,6 $\beta$ -epoksida u cilju dobijanja 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -trihidroksi derivata steroidnog D-homo laktona

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Budući da su se steroidni derivati sa hidroksilnim funkcijama u A- i B-prstenovima pokazali kao potentni citotoksični agensi, 3 $\beta$ -acetoksi-5 $\beta$ ,6 $\beta$ -epoksi-17-oxa-17a-homoandrost-16-on (**1a**) i njegov 5 $\alpha$ ,6 $\alpha$ -epoksi derivat (**1b**)<sup>1</sup>, podvrgnuti su nizu hemijskih modifikacija u cilju dobijanja 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -trihidroksi-17-oxa-17a-homoandrost-16-ona (**2**). Nakon oksidativnog otvaranja epoksida **1a** i **1b**, usledile su redukcija dobijene karbonilne grupe u položaju C6 i deacetilovanje u položaju C3 steroidnog skeleta. Redosled poslednje dve faze u sintezi je menjan radi utvrđivanja najefikasnijeg reakcionog puta, a u cilju povećanja prinosa željenog trihidroksilnog proizvoda **2**.



## Chemical modifications of the 5 $\alpha$ ,6 $\alpha$ - and the 5 $\beta$ ,6 $\beta$ -epoxide in the purpose of obtaining 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -trihydroxy steroidal D-homo lactone

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Considering that steroidal derivatives with the hydroxyl functions in the A and B-rings have shown themselves as potent cytotoxic agents, 3 $\beta$ -acetoxy-5 $\beta$ ,6 $\beta$ -epoxy-17-oxa-17a-homoandrost-16-one (**1a**), as well as its 5 $\alpha$ ,6 $\alpha$ -epoxy derivative (**1b**)<sup>1</sup>, were subjected to a series of chemical modifications in the purpose of obtaining 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -trihydroxy-17-oxa-17a-homoandrost-16-one (**2**). Oxidative opening of the epoxide **1a** i **1b** was followed by the reduction of the resulting carbonyl group in the position C6 and the deacetylation in position C3 of the steroid skeleton. The order of the last two phases of the synthesis was changed in order to determine the most efficient reaction pathway and to increase the yield of the desired product **2**.

1. E. A. Đurendić, M. P. Savić, O. R. Klisurić, M. N. Sakač, G. M. Bogdanović, D.S. Jakimov, K. M. Penov Gaši, Struct. Chem. **23** (2012) 1761–1767

## OH P19

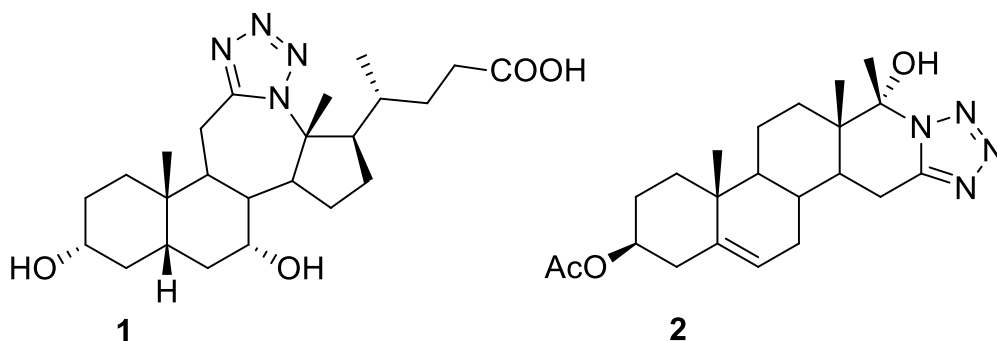
**Sinteza novih C i D kondenzovanih steroidnih tetrazola**

Aleksandar M. Oklješa, Dušan Đ. Škorić, Andrea R. Nikolić, Katarina M. Penov-Gaši,  
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Tetrazoli poseduju različite biološke, kao i jedinstvene fizičko-hemijske i farmakološke osobine. Imajući ovo u vidu, cilj ovog rada bio je sinteza steroidnih tetrazola.

Holna kiselina, odnosno dehidroepiandrosteron su poslužili kao polazna jedinjenja u sintezi željenih tetrazola. Ključni korak u sintezi tetrazola **1** je reakcija odgovarajućeg 12-okso intermedijera sa hidrazoinском kiselinom ( $\text{HN}_3$ ), u prisustvu bortrifluorid-eterata kao katalizatora, a u slučaju sinteze tetrazola **2** je reakcija 16,17-seko-16-nitrila sa natrijum-azidom.

Struktura novosintetisanih jedinjenja potvrđena je NMR spektroskopskom analizom.

**Synthesis of new C and D fused steroidal tetrazoles**

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Tetrazoles possess various biological, and unique physicochemical and pharmacological properties. Having that in mind the aim of our work was to synthesise steroidal tetrazoles. Holic acid and dehydroepiandrosterone were used as starting compounds for synthesis of desired tetrazoles. The key step in synthesis of tetrazole **1** is the reaction between 12-oxo intermediate and hydrazoic acid ( $\text{HN}_3$ ) in the presence of borontrifluoride-etherate as a catalyst, while in synthesis of tetrazole **2** is reaction between 16,17-seco-16-nitrile and sodium azide.

Structures of newly synthesized compounds were confirmed by NMR analysis.

*Realizacija ovog rada finansirana je od strane Ministarstva prosvete, nauke i tehnološkog razvoja (Projekat ON172021).*



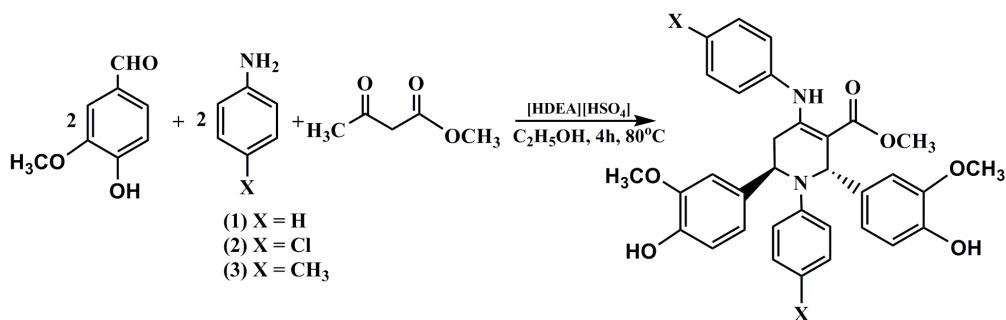
## OHP 21

## Diastereoselektivna one-pot sinteza vanilin-piperidinskih derivata i ispitivanje njihove antioksidativne aktivnosti

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U efikasnoj dvostrukoj one-pot Manihovoj reakciji između vanilina, metil-acetoacetata i različitih supstisuanih anilina dobijeni su visoko funkcionalizovani piperidinski derivati u dobrom prinosu (Shema 1). Kao reciklabilan katalizator ove reakcije upotrebljena je jonska tečnost dietanolamonijumhidrogensulfat. Važno je istaći da je ova ekonomična reakcija *anti*-diastereoselektivna, odnosno da je u njoj nastao samo *anti*-diastereoisomer.

Sintetizovana jedinjenja reaguju dobro sa DPPH radikalom i ispoljavaju visoku aktivnost, malo nižu u odnosu na referentno jedinjenje NDGA. Jedinjenja **1-3** imaju slične IC<sub>50</sub> vrednosti i one iznose 10.9, 12.5 i 11.1 μM.



## Diastereoselective one-pot synthesis of vanillin-piperidine derivatives and investigation of their atioxidative activity

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In the efficient one-pot double Mannich reaction of vanillin, methyl acetoacetate and different substituted anilines were obtained highly functionalized piperidine derivatives in good yield (Scheme 1). The ionic liquid diethanolammonium hydrogensulfate was used as recyclable catalyst. It is worth pointing out that this economical reaction is *anti*-diastereoselektivna, namely in this reaction was formed only *anti*-diastereomer.

The synthesized compounds interact well with DPPH radical, and exhibit high activity, slightly lower than the reference compound NDGA. Compounds **1-3** have similar IC<sub>50</sub> values 10.9, 12.5 i 11.1 μM, respectively.

*This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Project No. 172016.*

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1. Hamid Reza Shaterian, Kobra Azizi, *Journal of Molecular Liquids* **180** (2013) 187-191

OH P22

## Sinteza i antifungalna aktivnost novih izokumarinskih i tioizokumarinskih derivata

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Izokumarini su sekundarni metaboliti biljaka, gljiva i nekih bakterija. Ovi prirodni proizvodi pokazuju širok spektar farmakološkog dejstva, uključujući antimikrobno, citotoksično, antimalarijsko i antiinflamatorno dejstvo. Naša prethodna istraživanja su pokazala da sintetski izokumarini supstituisani azolima u položaju 3 pokazuju značajnu antifungalnu aktivnost. Cilj ovog rada je sinteza novih izokumarinskih i tioizokumarinskih derivata i evaluacija njihove *in vitro* antifungalne aktivnosti prema gljivici *Candida albicans*. Rezultati su pokazali da dobijeni tioizokumarinski derivati pokazuju antifungalnu aktivnost uporedivu sa vorikonazolom, dok se aktivnost nitro-izokumarina nije pokazala značajnom.

**Zahvalnica:** Ovo istraživanje je podržano od strane Ministarstva prosvete, nauke i tehnološkog razvoja Srbije (projekti br. 172009 i 173048).

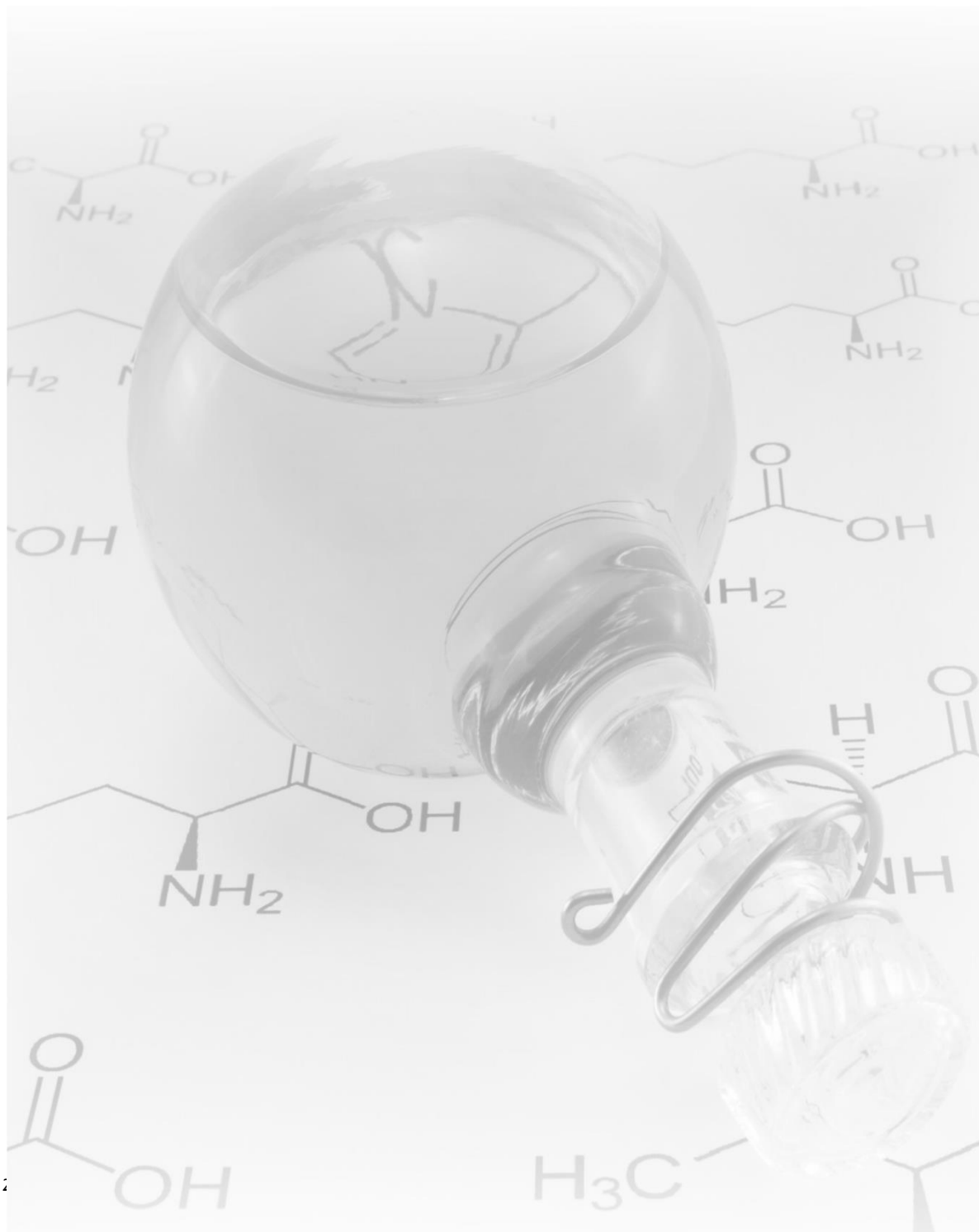
## Synthesis and antifungal activity of novel isocoumarin and thioisocoumarin derivatives

Milena Simic, Ivan Boric, Sandra Vojnovic\*, Jasmina Nikodinovic-Runic\*, Gordana Tasic, Milos Petkovic, Predrag Jovanovic, Vladimir Savic  
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Isocoumarins are secondary metabolites of the plants, fungi, and some bacteria. These natural products exhibit a broad range of pharmacological activities, including antimicrobial, cytotoxic, antimalaric and antiinflammatory activity. Our previous work showed that azol-substituted isocoumarins have significant antifungal activity. The aim of his study was the synthesis of new isocoumarins and thioisocoumarins (1*H*-isochromen-1-thion) substituted in position 3 and evaluation of their *in vitro* antifungal activity against *Candida albicans*. Synthesised thio derivatives showed antifungal activity comparable with voriconazole.

**Acknowledgements:** This research was supported by the Ministry of Education, Science and Technological development of Serbia (Grants No. 172009 and 173048).



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