## Project summary

Development of molecules with anti-inflammatory and cardioprotective activity within the Project 172041 is planned. That includes structural modifications, modeling, physicochemical characterization and formulation investigation. Biopharmaceutical investigations of radiodiagnostic, radioprotective agents and selected compounds with antiproliferative activity are also planned. Development and validation of certain analytical methods are necessary for successful realization of planned investigations.

Main individual planned goals (G1-G8) of the Project are:

G1. Design, synthesis and biopharmaceutical characterization of steroidal and nonsteroidal compounds with antiinflammatory activity:

a. C21 esters of glucocorticoids with α-alkoxyalkanoic and α-aryloxyalkanoic acids as potential prodrugs for local application.

b. Derivatives of cortienic acids (metabolites of glucocorticoids) as potential soft drugs for local application.

c. Derivatives of β-hydroxy-β-arylalkanoic acids with potential systemic antiinlammatory activity.

G2. Design, synthesis, physicochemical and biopharmaceutical characterization of

phenylpropiofenone analogs and intermediers named chalcones with potential cardioprotective, antiproliferative and antimicrobial activity.

G3. For selected cardioprotective drugs from the group of statins, antihypertensive drugs and bioflavonoids, metabolic profile testing is planned including drug-drug and drug-nutriment in vivo interactions in combination therapy. QSAR and docking studies for compounds from the group of AT1-receptor antagonists are also planned, as well as development and validation of HPLC method for detrmination of losartan and irbesartan in dosage forms which contain hydrochlorothiazide.

G4. Development and validation of analytical method for determination of ester derivatives of ethanediamine-N,N'-di-(3-cyclohexyl)propanoic acid and 1,3-propanediamine-N,N'-di-2-(3-cyclohexyl)propanoic acid with potential antiproliferative activity and use of proposed analytical method in preclinical trials.

G5. Use of various chromatographic techniques and in silico molecular descriptors in order to select appropriate hydrophobic parameters for prodrugs from ACE inhibitor class. Those parameters are required to build the absorption models using multilinear regression analysis.

G6. Investigation of radiodiagnostic and radioprotective agents:

a. Experimental determination of lipophilicity, biodistribution, plazma protein binding and influence of bilirubin on biokinetics of 99mTc-complexes of synthesized ligands with high values of logP (DIETHYLIODIDA and DIISOPROPYLIODIDA)

b. In vitro investigations of effects on blood coagulation of compounds with potential cardioprotective and radioprotective activity such as bioflavonoids hesperidin, rutin, morin, quercetin and their complexes with selected metal ions. For determination of those compounds in different samples, development and validation of spectroscopic and chromatographic methods are planned.

G7. Development, validation and verification of chromatographic and spectroscopic methods for quantification of drugs with antiinflammatory, cardioprotective and antiproliferative activity, as well as quantification of their impurities. Validation of methods for analysis of surfactants in vaccines and metals in tea products are also planned.

G8. Formulation studies of antiinflammatory drugs with standard excipiens and development of novel carriers in order to achieve satisfactory liberation profiles and overall efficiency of investigated drugs in therapy.

Keywords: synthesis, prodrug, soft drugs, anti-inflammatory drugs, cardioprotective drugs, antiroliferative drugs, interactions, drug design, physicochemical characterization, formulations

## Sažetak projekta

U okviru projekta 172041 planiran je razvoj molekula sa antiinflamatornim i kardioprotektivnim dejstvom: strukturne modifikacije, modelovanje, fizičkohemijska karakterizacija i formulaciona ispitivanja. Uz navedena ispitivanja planirana su i biofarmaceutska ispitivanja radiodijagnostičkih i radioprotektivnih sredstava i odabranih supstanci sa antiproliferativnim dejstvom. Za uspešnu realizaciju planiranih ispitivanja neophodan je razvoj i validacija pogodnih analitičkih metoda.

Glavni pojedinačni ciljevi projekta su:

C1. Planirani su dizajn, sinteza i biofarmaceutska karakterizacija steroidnih i nesteroidnih molekula sa antiinflamatornim dejstvom:

a) C-21 estri glukokortikoidnih supstanci sa α-alkoksialkanskim i α-ariloksialkanskim kiselinama kao potencijalnih prolek molekula za lokalnu primenu;

b) derivati kortienskih kiselina (metabolita glukokortikoida) kao potencijalnih soft kortikosteroida namenjenih za lokalnu primenu;

c) derivati β-hidroksi-β-arilalkanskih kiselina sa potencijalnom sistemskom antiinflamatornom aktivnošću;

C2. Planiran je dizajn, sinteza, fizičkohemijska i biofarmaceutska karaterizacija analoga fenilpropiofenona, kao i halkona kao intermedijera u sintezi, sa potencijalnim kardioprotektivnim, antiproliferativnim i antimikrobnim dejstvom;

C3. Za odabrane kardioprotektivne lekove iz grupe statina, antihipertenziva i bioflavonoida planirana je određivanje metaboličkog profila kao i ispitivanja in vivo interakcija tipa lek-lek i lek-nutriment u kombinovanoj terapiji; planirani su QSAR studije i docking testovi za jedinjenja iz grupe antagonista AT1 receptora, kao i razvoj i validacija HPLC metode za određivanje losartana i irbesartana u doziranim oblicima sa hidrohlorotiazidom;

C4. Za estarske derivate etandiamin-N,N’-di-2-(3-cikloheksil)propanske kiseline, 1,3-propandiamin-N,N’-di-2-(3-cikloheksil)propanske kiseline sa potencijalnim antiproliferativnim delovanjem planiran je razvoj i validacija analitičke metode i njena primena u pretkliničkim ispitivanjima;

C5. Za prolekove iz grupe ACE inhibitora planirana je primena različitih hromatografskih tehnika i in silico molekulskih deskriptora za odabir odgovarajućih hidrofobnih parametara za postavku in vitro modela za apsorpciju primenom višestruke linearne regresione analize;

C6. Planirana su ispitivanja radiodijagnostičkih i radioprotektivnih sredstava:

a) Za komplekse tehnecijuma-99m sa novosintetisanim ligandima sa najvećim izračunatim vrednostima log P (dietiljodida i diizopropiljodida) planirano je eksperimentalno određivanje lipofilnosti, ispitivanje biodistribucije i vezivanje za proteine plazme, kao i uticaj bilirubina na njihovu biokinetiku;

b) Za bioflavonoide hesperidin, rutin, morin, kvercetin i njihove komplekse sa odabranim jonima metala, kao supstancama sa potencijalnim kardioprotektivnim i radioprotektivnim dejstvom, planirano je in vitro ispitivanje efekata na koagulaciju krvi. Za određivanje navedenih jedinjenja u različitim uzorcima planiran je razvoj i validacija spektroskopskih i hromatografskih metoda;

C7. Planiran je razvoj, validacija i verifikacija hromatografskih i spektroskopskih metoda za kvantifikaciju lekova sa antiinflamatornim, kardioprotektivnim i antiproliferativnim dejstvom u farmaceutskim doziranim oblicima uz analizu nečistoća. Planiran je i validacija metode za analizu surfaktanata u vakcinama, kao i metala u čajevima.

C8. Planirana su formulaciona ispitivanja antiinflamatornih lekova sa standardnim ekscipijensima i razvoja novih nosača u cilju postizanja zadovoljavajućih profila oslobađanja i efikasnosti ispitivanih lekovitih supstanci u terapiji.

Ključne reči: sinteza, prolekovi, *soft* lekovi, antiinflamatorni lekovi, kardioprotektivni lekovi, antiproliferativni lekovi, molekulsko dizajniranje, fizičko-hemijska karakterizacija, interakcije, formulacije

## Selected results/Odabrani rezultati

1. Tubic BK, Vladimirov SS, Markovic BD, Sabo TJ (2018) Prediction of in vivo Bioavailibility by in vitro Characterization of Ethylenediamine Dipropanoic Acid Derivatives with Cytotoxic Activity, ACTA CHIMICA SLOVENICA, vol. 65, br. 1, str. 59-64
2. Dobricic VD, Savic JS, Nikolic KM, Vladimirov SM, Vujic ZB, Brboric JS (2017) Application of biopartitioning micellar chromatography and QSRR modeling for prediction of gastrointestinal absorption and design of novel beta-hydroxy-beta-arylalkanoic acids, EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 100, br. , str. 280-284
3. Savic JS, Dobricic VD, Nikolic KM, Vladimirov SM, Dilber SP, Brboric JS (2017) In vitro prediction of gastrointestinal absorption of novel beta-hydroxy-beta-arylalkanoic acids using PAMPA technique, EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 100, br. , str. 36-41
4. Dobricic VD, Markovic BD, Milenkovic N, Savic VM, Jacevic VM, Rancic N, Vladimirov SM, Cudina OA (2014) Design, Synthesis, and Local Anti-Inflammatory Activity of 17 beta-Carboxamide Derivatives of Glucocorticoids, ARCHIV DER PHARMAZIE, vol. 347, br. 11, str. 786-797
5. Dobricic VD, Markovic BD, Nikolic KM, Savic VM, Vladimirov SM, Cudina OA (2014) 17 beta-carboxamide steroids - in vitro prediction of human skin permeability and retention using PAMPA technique, EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 52, br. , str. 95-108
6. Ivkovic BM, Nikolic KM, Ilic BB, Zizak ZS, Novakovic RB, Cudina OA, Vladimirov SM (2013) Phenylpropiophenone derivatives as potential anticancer agents: Synthesis, biological evaluation and quantitative structure-activity relationship study, EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 63, br. , str. 239-255
7. Brboric JS, Jovanovic MS, Vranjes-Djuric SD, Cudina OA, Markovic BD, Vladimirov SM (2013) The effect of lipophilicity on the hepatobiliary properties of iminodiacetic acid derivatives in the conditions of hyperbilirubinemia, APPLIED RADIATION AND ISOTOPES, vol. 74, br. , str. 31-35
8. Crevar-Sakac M, Vujic ZB, Brboric JS, Kuntic VS, Uskokovic-Markovic SM (2013) An Improved HPLC Method with the Aid of a Chemometric Protocol: Simultaneous Determination of Atorvastatin and Its Metabolites in Plasma, MOLECULES, vol. 18, br. 3, str. 2469-2482
9. Odovic JV, Markovic BD, Injac RM, Vladimirov SM, Karljikovic-Rajic KD (2012) Correlation between ultra-high performance liquid chromatography-tandem mass spectrometry and reversed-phase thin-layer chromatography hydrophobicity data for evaluation of angiotensin-converting enzyme inhibitors absorption, JOURNAL OF CHROMATOGRAPHY A, vol. 1258, br. , str. 94-100
10. Cudina Olivera A,Markovic Bojan D,Karljikovic-Rajic Katarina D,Vladimirov Sote M (2012) Biopartitioning Micellar Chromatography-Partition Coefficient Micelle/Water as a Potential Descriptor for Hydrophobicity in Prediction of Oral Drug Absorption, ANALYTICAL LETTERS, vol. 45, br. 7, str. 677-688