## Project summary

Genetic studies have fostered the development of new ligands acting through benzodiazepine binding site of GABAA receptors: those selectively acting through alpha2/3 subunit-containing receptors as positive allosteric modulators (PAMs), with potential use in anxiety disorders and cognitive symptoms of schizophrenia, and those selective for alpha5 receptors as negative allosteric modulators (NAMs), targeted for different cognitive impairments. On the grounds of our previous results, this project will assess the behavioral profiles of three selective PAMs (SH-053-2’N, ZJW-II-40 and YT-III-38) and three selective NAMs (PWZ-029, SR-II-97 and YT-II-76) following acute and repeated administration (10 or 28 days) in rats. The two types of selective modulators will be tested in two separate blocks of experiments, in comparison with standard psychopharmacologic drugs risperidone and escitalopram, as well as diazepam or DMCM as positive controls. The ligands will be applied orally as suspensions of purposefully prepared and in vitro/in vivo characterized microparticles. The behavioral tests will include spontaneous locomotor test, elevated plus maze, rotarod test, grip strength, novel object recognition test, water maze, forced swim test and three paradigms of acoustic startle response. The results obtained in healthy rats would elucidate the differences in behavioral profiles depending on receptor selectivity of tested ligands and be a good basis for further disease-centered studies.

Keywords: selective allosteric modulator of GABAA receptor; oral delivery; repeated administration; behavior

## Sažetak projekta

Genetska istraživanja podstakla su razvoj novih supstanci koje deluju preko benzodiazepinskog mesta vezivanja GABAA receptora: supstanci selektivnih za alfa2/3 podtip receptora - pozitivni alosterni modulatori (PAM), sa mogućom primenom kod anksioznih poremećaja i kognitivnih simptoma shizofrenije, i onih selektivnih za alfa5 podtip receptora - negativni alosterni modulatori (NAM), sa mogućom primenom kod različitih kognitivnih poremećaja. Na temelju ranijih studija, u ovom projektu ispitivaće se bihejvioralni profili tri selektivna PAM-a (SH-053-2’N, ZJW-II-40 i YT-III-38) i tri selektivna NAM-a (PWZ-029, SR-II-97 i YT-II-76) nakon akutne i ponavljane primene (10 ili 28 dana) na pacovima. Dva tipa selektivnih modulatora biće testirana u dva odvojena eksperimentalna bloka, i poređena sa standardnim psihofarmakološkim lekovima risperidonom i escitalopramom, kao i sa pozitivnim kontrolama diazepamom ili DMCM-om. Supstance će se primenjivati u obliku oralnih suspenzija posebno pripremljenih i in vitro/in vivo okarakterisanih mikročestica. Bihejvioralna ispitivanja obuhvataju sledeće testove: spontana lokomotorna aktivnost, uzdignuti plus lavirint, rotarod, jačina stiska, prepoznavanje novog objekta, vodeni lavirint, forsirano plivanje i tri paradigme odgovora preneraženjem. Rezultati dobijeni na zdravim pacovima ukazaće na razlike u bihejvioralnim profilima ovih jedinjenja u zavisnosti od njihove receptorske selektivnosti i biti dobra osnova za dalja istraživanja zasnovana na modelima bolesti.

Ključne reči: selektivni alosterni modulatori GABAA receptora; oralna primena; ponavljana primena; ponašanje

## Selected results/Odabrani rezultati

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