



Sveučilište u Zagrebu

FAKULTET KEMIJSKOG INŽENJERSTVA I TEHNOLOGIJE

Ivona Čipor

**FLUORESCENTNI SUPRAMOLEKULSKI SUSTAVI I
SENZORI ZA DOSTAVU LIJEKOVA I
PREPOZNAVANJE BIOMOLEKULA**

DOKTORSKI RAD

Zagreb, 2025.



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AND SENSORS FOR DRUG DELIVERY AND
BIOMOLECULE RECOGNITION**

DOCTORAL THESIS

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Mentori:
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SAŽETAK

Meki materijali poput supramolekulskih hidrogelova zauzimaju značajno mjesto u raznim područjima biomedicinskih istraživanja, posebice u dostavi lijekova, a porastom primjene fluorescencijskih tehnika u kemiji i biologiji sve su bitnija i istraživanja novih fluorescentnih senzora.

U okviru doktorskog rada istraženi su supramolekulski sustavi hidrogelova i senzori za biomakromolekule. Višestupnjevitom sintezom uspješno su razvijeni novi supramolekulski hidrogelatori (spojevi klase **A**) s obećavajućim potencijalom za dostavu lijekova i detekciju biomakromolekula. Kao najefikasniji hidrogelatori izdvojeni su spojevi **A6a** i **A6f**, koji su okarakterizirani spektroskopskim i mikroskopskim metodama. Također, priređeni su kompozitni hidrogelovi odabranih derivata s polivinilnim alkoholom (PVA). Pokazano je kako dodatak PVA u supramolekulske gelove uzrokuje povećanje termičke stabilnosti i stvaranje gušće gelske mreže, a spektroskopijom UV/Vis pokazano je da PVA utječe na otpuštanje lijeka iz gelova smanjivanjem količine otpuštenog doksorubicina. Pikolilamidni derivati fluorescentnih aminokiselina (**A6c**, **A9c** i **A6f**) istaknuli su se i kao probe za DNA/RNA, a interakcije fluorescentnih senzora s biomakromolekulama istražene su spektroskopijom UV/Vis i cirkularnog dikroizma te fluorescencijskom spektroskopijom. Derivat **A6f** pokazao je afinitet prema DNA/RNA, a sintetizirani triarilboranski derivati (**B4**, **B5**, **B6**) istaknuli su se kao probe za hidrofobne mete poput serumskog albumina iz goveda (BSA) i liposoma. Nadalje, pokazano je da stirilni derivati (**C**) djeluju kao efikasne selektivne probe za DNA/RNA, većinom ciljajući utore polinukleotida, kao agensi za vizualizaciju mitohondrija te pokazuju potencijal u razvoju teranostika. Osim toga, pokazano je da 1,3-benzotiazinska strukturna jedinica (**D**) može poslužiti u razvoju proba za DNA/RNA. Ispitan je i utjecaj metala na spektroskopska svojstva i interakcije s biomolekulama za fluorescentne ligande i njihove komplekse s renij(I) (**E**), a pokazano je kako ovakvi spojevi mogu, ovisno o metalu, davati suprotan fluorescencijski odgovor za iste mete poput humanog serumskog albumina (HSA), što ih čini potencijalnim senzorima za Re(I) u plazmi.

Ključne riječi: fluorescentni senzori, supramolekulski sustavi, DNA/RNA senzori, hidrogelovi, derivati aminokiselina, triarilborani, stirilni derivati, benzotiazini, organometalni kompleksi

SUMMARY

Soft materials such as supramolecular hydrogels occupy a significant place in various fields of biomedical research, particularly in drug delivery. With the increasing application of fluorescence techniques in chemistry and biology, the research of new fluorescent sensors is also becoming increasingly important.

In this dissertation, supramolecular hydrogel systems and sensors for biomacromolecules were investigated. Through multi-step synthesis, novel supramolecular hydrogelators (compounds **A**) with promising potential for drug delivery and biomacromolecule detection were successfully developed. Compounds **A6a** and **A6f** were identified as the most effective hydrogelators and characterized by spectroscopic and microscopic methods. Composite hydrogels of selected derivatives with polyvinyl alcohol (PVA) were also prepared. It was shown that the addition of PVA to supramolecular gels causes an increase in thermal stability and the formation of a denser gel network. UV/Vis spectroscopy showed that PVA affects drug release from the gels by generally reducing the amount of doxorubicin released. Picolylamide derivatives of fluorescent amino acids (**A6c**, **A9c**, and **A6f**) also stood out as probes for DNA/RNA, and the interactions of fluorescent sensors with biomacromolecules were investigated by UV/Vis, fluorescence and circular dichroism spectroscopy. Derivative **A6f** showed micromolar affinities for both DNA and RNA, and the synthesized triarylborane derivatives (**B4**, **B5**, **B6**) have potential as probes for hydrophobic targets such as bovine serum albumin (BSA) or liposomes. However, for practical applications in biomedicine and chemical biology, further optimization of structures and more detailed biological evaluation are needed. It was also found that styryl derivatives (**C**) act as efficient selective probes for DNA/RNA, mostly targeting polynucleotide grooves, as agents for visualizing mitochondria and have shown potential in theranostics development. In addition, it was shown that the 1,3-benzothiazine core (**D**) can find application in development of DNA/RNA probes. The influence of metals on the spectroscopic properties and interactions with biomolecules for fluorescent ligands and their rhenium(I) complexes (**E**) was also investigated, and it was shown that such compounds can, depending on the metal, give opposite fluorescence responses for the same targets such as the protein human serum albumin (HSA), making them potential sensors for Re(I) in plasma.

Keywords: fluorescent sensors, supramolecular systems, DNA/RNA sensors, hydrogels, amino acid derivatives, triarylboranes, styryl derivatives, benzothiazines, organometallic complexes