Ph.D. thesis

Investigation of the physicochemical properties of synthetic C5-curcuminoids containing a cyclanone ring

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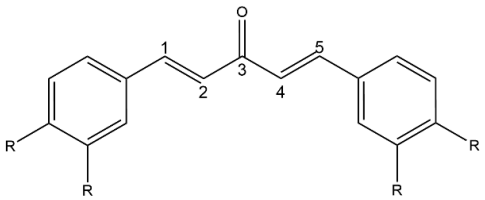
1. Introduction

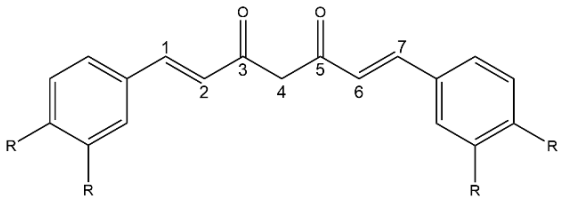
The significance of naturally derived bioactive compounds has steadily increased in pharmaceutical research over recent decades. Among these, curcumin—the principal polyphenolic compound extracted from *Curcuma longa L.* (turmeric)—has garnered particular attention. Although it is not currently included in routine clinical therapies, its broad spectrum of biological activities continues to make it the subject of extensive scientific investigation. Curcumin exhibits antioxidant, anti-inflammatory, antiproliferative, and neuroprotective effects, which suggest its potential utility as an adjuvant in the treatment of various diseases, including cancer, neurodegenerative disorders, and inflammatory conditions.

However, curcumin's therapeutic application is substantially limited by its unfavorable pharmacokinetic properties, such as poor aqueous solubility, chemical instability, and rapid metabolic degradation. Its bioavailability is exceptionally low; both preclinical and some clinical studies have demonstrated that following oral administration, curcumin primarily acts locally within the gastrointestinal tract, while its systemic concentrations are generally negligible.

In response to these limitations, numerous studies have focused on modifying the molecular structure of curcumin to improve its bioavailability. Synthetic analogues, such as C5- and C7-curcuminoids, have been developed, offering improved chemical stability and potentially more favorable solubility, lipophilicity, and permeability compared to the natural compound. These derivatives often incorporate additional ring systems—such as piperidone or benzosuberone moieties—which contribute to enhanced conformational rigidity and structural stability.



1. Figure Core scaffold of the C5 derivatives



2. Figure Core scaffold of the C7 derivatives

C5-curcuminoids bearing a cyclanone ring represent a particularly promising family of molecules. Their planar geometry, reduced conformational flexibility, and pronounced lipophilic character may provide new opportunities for improving both biological efficacy and bioavailability. Literature data indicate that these compounds are capable of inducing apoptosis,

exerting anti-inflammatory effects, and interacting with multiple biological targets, including inhibition of key signaling pathways such as STAT3, NF-κB, COX-2, and iNOS.

In contemporary drug research and development, increasing emphasis is placed on the early identification of compounds that meet the so-called “drug-like” criteria. This means not only exhibiting biological activity but also possessing suitable ADME (absorption, distribution, metabolism, excretion) characteristics. The likelihood of clinical applicability should ideally be assessed already during the preclinical screening phase, supported by both predictive *in silico* modeling and experimental determination of critical physicochemical parameters, such as solubility, lipophilicity, albumin binding, and membrane permeability.

The objective of the present doctoral research was to investigate the physicochemical properties of novel cyclic C5-curcuminoid derivatives. The study focused on determining solubility, lipophilicity, thiol reactivity, membrane permeability, and albumin-binding parameters, with the aim of elucidating structure–activity relationships. In parallel with these experiments, cytotoxicity data indicative of biological activity were also available, enabling a comparative analysis between physicochemical profiles and biological effects.

2. Objectives

Literature data suggest that C5-curcuminoid derivatives represent promising model compounds for the investigation of agents with anticancer, antiproliferative, apoptosis-inducing, cytotoxic, or cytoprotective properties.

The newly synthesized molecules may possess more favorable physicochemical and pharmacokinetic properties compared to curcumin, potentially improving their bioavailability and therapeutic applicability.

In the present doctoral work, the physicochemical parameters of these newly synthesized compounds were investigated to gain deeper insight into structure–activity relationships and molecular mechanisms. Over the course of the research, a total of 98 novel cyclic C5-curcuminoid derivatives were analyzed. Following structural verification, their physicochemical parameters were determined, and in parallel or subsequently, their biological activities were also assessed.

Our aims included the characterization of solubility, lipophilicity, and albumin binding, as well as the investigation of membrane permeability. In support of these objectives, appropriate

modern analytical techniques—available to our research group—were selected, developed, and optimized for experimental implementation. A further aim of the study was to establish an internal database, enabling the identification of correlations between biological results and physicochemical properties based on various chemical descriptors.

During our research, the following specific objectives were defined:

1. **Characterization of solubility:** Since solubility is an essential parameter for biological assays and further measurements, we aimed to characterize the aqueous solubility of selected derivatives.
2. **Assessment of thiol reactivity:** Based on literature data and our experimental observations, interactions between our compounds and macromolecular thiol groups in physiological media may influence pharmacokinetic behavior. Therefore, we aimed to study the kinetics of the Michael addition reaction between curcuminoids and low-molecular-weight thiol compounds.
3. **Evaluation of lipophilicity:** To obtain information about the apolar nature of the molecules, we planned to assess lipophilicity using multiple techniques (TLC, RP-HPLC, clogP calculations).
4. **Investigation of albumin interaction:** For selected compounds, we aimed to characterize the interaction with serum albumin in more detail using UV-Vis and fluorescence spectroscopy.
5. **Membrane permeability:** We sought to assess passive membrane diffusion of the compounds using the PAMPA (Parallel Artificial Membrane Permeability Assay) system.

3. Methods and Results

The derivatives examined in this study were selected from a previously synthesized library of cyclic C5-curcuminoids, primarily based on their cytotoxicity profiles. Cytotoxicity assays were performed on A549, PC-9, and NHLF cell lines using XTT and MTT assays. Compounds demonstrating significant biological activity were subjected to detailed physicochemical analysis.

3.1. Solubility

Stock solutions of the examined compounds were prepared using DMSO, followed by dilution to concentrations ranging from 0.5 to 10 mM. These solutions were further diluted with 0.01 M phosphate buffer at pH 7.40 to yield aqueous dilutions in the 5–100 μM range. Various methods were employed to assess kinetic solubility, including turbidimetry, direct UV spectrophotometry, and HPLC-DAD. In the turbidimetric analysis, optical density was measured at 335, 620, and 720 nm. For spectrophotometric determination, the solutions were homogenized, then centrifuged (Hettich Mikro 22, rotor diameter 87 mm, 4500 rpm, 2000g, 10 minutes), and the precipitated crystals were separated from the supernatant. The absorbance of the clear supernatant was measured at the compound's absorbance maximum using a Jasco V-750 UV-Vis spectrophotometer, in order of increasing concentration.

For chromatographic measurements, conditions were optimized for each derivative. Chromatography was carried out using an Agilent ZORBAX Eclipse XDB-C18 column (80 Å, 4.6 × 150 mm, 5 μm) and an Agilent 1100 Series system. Detection was performed using a UV-Vis detector at the specific absorbance maximum of each compound. All solvents used were of HPLC grade. Chromatograms were evaluated using ChemStation for LC 3D systems Rev. B.03.02-SR2 [341] August 2008.

Thermodynamic solubility was assessed after 72 hours of incubation at 37 °C and pH 7.4, based on equilibrium concentrations in aqueous media. It was found that kinetic solubility consistently yielded higher values than thermodynamic solubility. This discrepancy is due to the fact that in kinetic assessments, compounds are pre-dissolved in DMSO, effectively bypassing the energy barrier of lattice dissociation. Even at 1% concentration, DMSO significantly enhances solubility in aqueous media.

Turbidimetric spectra showed that beyond the solubility limit, optical density continued to increase—albeit in a nonlinear fashion—indicating precipitation. Absorbance values measured at the wavelength of maximum absorption exhibited a saturation curve. Consequently, linear regression within this concentration range provided less accurate results. UV-Vis spectrophotometric and HPLC methods yielded comparable results, with good correlation and low standard deviation, confirming reproducibility. For two derivatives (**1, 2**), full solubility profiling, including thermodynamic solubility, was performed. In addition to experimental measurements, computational solubility predictions were generated using open-access models

available at swissadme.ch and aqsolpred.streamlit.app. The SILICOS-IT algorithm predicted very low solubility values, which are likely close to the true thermodynamic solubility. Overall, the results indicate that, with a few exceptions, the examined derivatives exhibit poor aqueous solubility, and some are practically insoluble in water. Compounds possessing ionizable groups, such as carboxylic acids (e.g., derivatives **3**, **4**, and **5**), showed significantly increased solubility compared to others in the series. Nevertheless, with respect to solubility as a key physicochemical parameter, the newly synthesized derivatives did not outperform natural curcumin.

3.2. Lipophilicity

Lipophilicity is a key factor in drug discovery, as it directly influences membrane permeability, absorption, and distribution of molecules. In this study, three distinct methods were applied to characterize the lipophilicity of the C5-curcuminoid derivatives: computational predictions, thin-layer chromatography (TLC), and logP determination by HPLC.

For TLC-based logP estimation, we used silanized silica gel 60 F_{254} plates (20 × 20 cm, Merck, Germany). Prior to use, the plates were washed with methanol, dried, and activated at 160 °C for 1 hour. The compounds of interest, as well as validation and calibration standards, were dissolved in a methanol–chloroform mixture (1:1, v/v) at a concentration of 2 mg/mL. A volume of 2 μL (4 μg) was applied to the plate. The mobile phase consisted of methanol–water (60:40, v/v). The chromatography chamber, lined with filter paper, was pre-saturated with the mobile phase for 30 minutes prior to development. After development (~150 mm), the plates were dried and visualized under UV light (λ = 254 nm). The system was partially validated using diazepam and progesterone as reference drugs.

For the HPLC method, test compounds and standard substances were dissolved in acetonitrile at 0.02 mg/mL and injected onto a Kinetex-C18 column using an acetonitrile–water mobile phase at a flow rate of 2 mL/min. Detection was carried out using a UV-Vis detector (Agilent 1100 series). Retention times were dependent on compound lipophilicity and varied with the proportion of the organic solvent in the mobile phase. Dead time was determined using KNO_3 solution. Chromatograms were evaluated using ChemStation software. The retention parameters were compared with data from standard compounds of known lipophilicity. Plotting the retention time against the organic solvent ratio yielded regression lines, where the y-intercept was proportional to the standardized logP value. The slope reflected the influence of

mobile phase polarity, while the intercept indicated the degree of interaction between the compound and the hydrophobic stationary phase.

Calculated clogP values were obtained using ChemAxon software (Calculator Plugins for structure–property prediction, Marvin Suite version 15.2.23, ChemAxon, 2022), applying the consensus method, which accounts for tautomerism and resonance structures. Electrolyte concentrations (Na^+, K^+, Cl^-) were set to 0.1 M. Theoretical predictions placed the logP values in the range of 3 to 5, indicating considerable lipophilicity. However, in some cases, these values exceeded the optimal range for biological availability (commonly considered to be 0.5–3.5). Experimental logP values obtained via HPLC showed a similar trend and correlated well with Rf values from the TLC method. From the distribution of logP values, we identified a "quasi-optimal logP range" between 0.7–2 and 3.22–4.11, which corresponded to derivatives exhibiting the highest cytotoxic activity.

Nonetheless, no strong correlation could be established between lipophilicity (logP) and cytotoxicity (IC_{50}), suggesting that biological activity is not governed solely by lipophilicity. Other structural factors—such as the presence of electron-withdrawing or electron-donating substituents and the inherent reactivity of the compounds—also appear to play critical roles. While the lipophilicity of the derivatives was generally suitable for membrane penetration, excessive lipophilicity in some cases may have reduced aqueous solubility and increased non-specific binding.

3.3. Thiol Reactivity

The analysis of thiol reactivity provides insight into the potential biological interactions of the compounds under investigation. In the case of C5-curcuminoid derivatives, this parameter is particularly relevant due to the presence of α,β-unsaturated carbonyl systems in their structure, which may act as Michael acceptors. To assess their reactivity, the nucleophiles glutathione (GSH) and cysteine (CYS) were employed.

Preliminary experiments utilized spectrophotometric methods to evaluate the reactivity of the selected compounds with GSH. Five derivatives with varying biological activity (compounds **1**, **2**, **10**, **11**, and **12**) were tested. Aqueous solutions of the curcuminoids were prepared similarly to the method used in the kinetic solubility studies, with the exception that the phosphate buffer also contained glutathione. Final concentrations in the incubation mixtures were set at 50 μM

for the curcuminoid and 5 mM for GSH (1:100 molar ratio), reflecting physiological concentrations found in hepatocytes. Incubations were performed in a 25 °C water bath, and aliquots were taken at regular intervals for measurement of absorbance at each compound's λ_{max}.

Quantitative determination of glutathione was conducted using the Ellman assay, applying DTNB as the chromogenic reagent. After vortexing the samples and allowing a 5-minute reaction period, absorbance was measured at 412 nm. Curcuminoid solutions were prepared in DMSO and mixed with analytically pure L-glutathione, L-cysteine, glycine, or cystamine dihydrochloride in phosphate buffer (pH 7.4, 0.01 M), using different molar ratios (1:0, 1:1, 1:10, 1:100). After homogenization, the mixtures were incubated at 25 °C for 30 minutes, and UV spectra were recorded in the 250–450 nm range. For spectral acquisition and analysis, Spectra Manager 2.00.01 and OriginPro 2018 software were used.

The results revealed clear differences in reactivity depending on structural variations. The linear absorbance decay observed for several compounds indicated pseudo-zero-order kinetics, suggesting that the reaction rate was influenced not only by the initial concentration but also by the diffusion capacity of the compounds. The highest reactivity was observed for derivatives containing electron-withdrawing substituents, such as chloro or carbonyl groups. Faster reaction kinetics were observed at higher GSH concentrations, consistent with behavior expected under physiological conditions. UV spectral shifts, intensity changes, and a decrease in glutathione concentration all pointed to significant interactions, likely involving changes in the chromophore environment. Mass spectrometric analysis confirmed the formation of mono-conjugates. In the case of glutathione, bis-adducts could also be detected, albeit at low intensity. In contrast, no significant conjugate formation was observed with glycine or cystamine, reinforcing the conclusion that thiol reactivity is primarily associated with sulfur-containing nucleophilic species.

3.4. Permeability

The passive membrane permeability of C5-curcuminoid derivatives was evaluated using the PAMPA (Parallel Artificial Membrane Permeability Assay) model. The objective was to determine the extent to which the compounds are capable of diffusing across an artificial lipid membrane—an essential parameter influencing oral bioavailability. In the PAMPA system, 300 μL of concentrated curcuminoid solution (10 or 20 μM) prepared in 1% (v/v) DMSO and

phosphate-buffered saline (PBS; pH 7.4, 0.01 M) was pipetted into the donor chamber. The acceptor chamber contained 200 µL of PBS buffer. The donor and acceptor plates were then assembled and incubated at room temperature (approximately 22–25 °C) in the dark for five hours. The membrane surface area was 0.3 cm², while the donor and acceptor volumes were 0.3 mL and 0.2 mL, respectively. After incubation, the concentrations in the donor (c_D), acceptor (c_A), and initial (c_0) solutions were measured using UHPLC-MS. Calibration curves for concentration–AUC (area under the curve) were established using a dilution series ranging from 10 nM to 20 µM.

The experiments were extended to include the presence of glutathione, cysteine, and bovine serum albumin (BSA) at molar ratios of 1:1, 1:10, and 1:100. The results showed that GSH and CYS significantly reduced permeability, especially at the 1:100 ratio. In contrast, the presence of BSA led to detectable reductions in permeability even at lower ratios. These observations suggest that thiol reactivity and non-covalent interactions contribute to permeability modulation, consistent with findings from the thiol reactivity studies. For the **10** compounds tested, variations in the initial donor concentration had no substantial effect on permeability, indicating that relative concentration ratios, rather than absolute concentrations, play a dominant role in determining transmembrane flux. Permeability values obtained in a previous blood–brain barrier (BBB) model were notably lower than those measured with the PAMPA system, particularly for compound **10**, which showed a two-order-of-magnitude difference. This discrepancy underscores the greater complexity and restrictive nature of the BBB model compared to the PAMPA system.

In addition to permeability data, IC_{50} values were also determined for various central nervous system tumor cell lines, supporting the biological relevance of the investigated compounds. However, for compounds exhibiting high mass retention values, the interpretation of the PAMPA results becomes limited or potentially misleading. Low permeability values observed in these cases are characteristic of compounds belonging to BCS Class IV and highlight the need for structural optimization to enhance drug-likeness.

3.5. Albumin Binding

The binding affinity of the cyclic C5-curcuminoid derivatives to human serum albumin (HSA) and bovine serum albumin (BSA) was investigated using UV-Vis spectrophotometry, fluorescence quenching, and temperature-dependent spectroscopic methods, supported by in

silico molecular docking simulations. The aim was to characterize plasma protein binding affinity, elucidate the binding mechanism, and determine thermodynamic parameters, all of which are essential for assessing pharmacokinetic behavior—particularly the free drug fraction and volume of distribution.

For UV-Vis measurements, compounds **10**, **11**, and **12** were analyzed in phosphate buffer (pH 7.4) at final concentrations ranging from 5 to 20 μM in the presence of a constant 10 μM HSA. Spectrophotometric measurements were performed at 25 °C using a Jasco V-750 UV-Vis spectrophotometer and 1 cm quartz cuvettes. In the UV spectra of the curcuminoid–albumin mixtures, a hypsochromic shift and hypochromic effect were observed in the curcuminoid absorption region, along with a slight hyperchromic shift in the albumin absorption region. These findings indicate complex formation and conformational changes within the protein structure.

Binding constants were calculated using the Benesi–Hildebrand method, which showed that the compounds possess moderate binding affinity. Fluorescence quenching experiments were also performed, using HSA at a concentration of 1 μM and curcuminoids at concentrations ranging from 0.25 to 16 μM. Excitation was set at 295 nm to selectively excite tryptophan residues while minimizing contributions from tyrosine and phenylalanine. The concentration-dependent decrease in fluorescence intensity was attributed to microenvironmental changes surrounding Trp-214, suggesting interaction with hydrophobic binding pockets.

The quenching mechanism was determined to be static, based on its temperature dependence, indicating the formation of stable, non-covalent complexes. Binding constants were calculated using the Stern–Volmer equation and nonlinear fitting models. The resulting logK values ranged between 10^5 and 10^6 M^{-1}, consistent with relatively strong protein binding. Corrections for the inner filter effect were applied to ensure quantitative accuracy.

Thermodynamic analyses were carried out at 25, 30, 35, 40, and 45 °C using temperature-controlled cuvettes. From the temperature-dependent binding constants, the changes in enthalpy (ΔH) and entropy (ΔS) were calculated using the van't Hoff equation. Negative Gibbs free energy values (ΔG) in all cases indicated spontaneous complex formation. The results suggest that hydrophobic interactions and hydrogen bonding were the dominant forces driving the binding. For compound **10**, a positive entropy change also pointed to the presence of electrostatic interactions.

Molecular docking studies corroborated the experimental findings: all three compounds bound stably to multiple sites on HSA, particularly at the heme and fatty acid binding site 6. Compound **12** demonstrated the highest binding affinity, as evidenced by the lowest predicted binding free energies across multiple binding pockets. The stability of the binding interactions was influenced not only by hydrogen bonding and hydrophobic interactions but also by the structural features of the molecules, including the polarity of side chains and the substitution patterns on the aromatic rings. In summary, the C5-curcuminoid derivatives exhibited strong non-covalent binding to serum albumins. Their albumin-binding capabilities were characterized by distinct structural and thermodynamic features, which may influence their pharmacokinetic behavior, particularly the free drug concentration and tissue distribution.

4. Summary

A primary objective of this doctoral research was to map the physicochemical properties of newly synthesized cyclic C5-curcuminoid derivatives and subsequently compare them with biological activity data—such as IC_{50} values obtained on cell lines—to facilitate the exploration of potential structure–activity relationships. In the course of the study, the lipophilicity of 98 novel molecules was characterized, and key physicochemical parameters relevant to biological activity—including solubility, thiol reactivity, membrane permeability, and albumin binding—were examined for a selected subset of compounds.

Structurally, the newly synthesized derivatives differ from natural curcumin in that the continuously conjugated C7 bridge between aromatic rings is replaced with a cross-conjugated C5 linker. All compounds contain a dienone moiety, most exhibit molecular symmetry, and the central scaffold in the majority of cases is a 4-piperidone ring. These structural modifications were intended to enhance cytotoxic potency. In drug development, α,β-unsaturated ketone moieties are often classified as potential toxicophores due to their electrophilic nature and ability to form covalent adducts with proteins or DNA, potentially leading to undesirable side effects. However, in this context, the compounds' poor bioavailability may be advantageous, as it likely prevents their accumulation in healthy tissues, while allowing accumulation in highly vascularized and metabolically active tumor environments—where they may exert selective toxicity.

From a chemical perspective, the dienone or α,β-unsaturated ketone functionality can act as a Michael acceptor, and this type of conjugate addition likely contributes to biological activity. For example, in the case of the synthetic curcuminoid CLEFMA, the addition of N-acetylcysteine during in vitro assays protected cancer cells from CLEFMA-induced cell death. Thus, Michael addition and interactions with nucleophilic biomolecules are likely involved in the pharmacological mechanism of action.

Spectroscopic analysis confirmed that five selected derivatives formed adducts with glutathione and cysteine but not with glycine or cystamine. Mass spectrometry confirmed the formation of mono-adducts based on m/z values.

Overall, the examined derivatives showed very poor solubility in aqueous media. Notable improvements compared to curcumin and other derivatives in the series were observed for compounds **3**, **4**, and **5**, all of which contain a carboxylic acid group. These solubility enhancements could not be predicted by computational tools. The experimentally determined kinetic solubilities ranged from 18.21 μM to >1000 μM. Since improved aqueous solubility is a fundamental prerequisite for enhanced bioavailability, optimization of solubility is a key priority. Various drug delivery systems may increase efficacy while avoiding toxic concentrations. For example, complexation with cyclodextrins may enhance solubility, and such studies are planned for future investigation. Other formulation strategies are also under consideration, including encapsulation into liposomes, development of cyclodextrin complexes, and nanosizing approaches. These efforts are justified by the fact that several derivatives in the studied series demonstrated high efficacy against tumor cell lines, indicating that these compounds represent highly promising leads.

Permeability studies using the PAMPA model demonstrated that compound **10** had significantly higher permeability—by an order of magnitude—compared to compounds **1** and **11**. The initial concentration in the donor phase had no significant effect on permeability. The addition of Michael donor molecules or albumin reduced permeability, likely due to the formation of adducts or non-covalent interactions.

Albumin binding was assessed using fluorescence quenching, which revealed relatively strong interactions between the three examined derivatives and HSA. These findings were supported by docking simulations. Compound **12** exhibited the most favorable calculated binding free energy at both binding sites, in line with experimental data (nonlinear fit). This same compound

also displayed the least favorable IC_{50} values against astrocytoma and neuroblastoma cell lines. Based on nonlinear fit models and docking data, compound **10** showed the weakest binding to HSA. However, in cell line experiments, this compound demonstrated the most favorable IC_{50} values, suggesting that it may exist in a larger free fraction and therefore in a more biologically active form in cell cultures.

In recent years, predictive tools have advanced significantly, and many open-source platforms are now available on GitHub. For molecular docking, AutoDock Vina is widely used; for ADMET prediction, pkCSM; and for machine learning-based modeling, RDKit and DeepChem are prominent resources. These tools can dramatically reduce the time and cost associated with early-phase drug development and offer valuable insights for informed decision-making. While modern algorithms trained on increasingly large datasets provide ever more accurate predictions, discrepancies between predicted and experimental values persist. At present, regulatory authorities do not accept model-derived predictions alone at any stage of drug development. Therefore, experimental validation remains essential. In many cases, empirical data support computational estimates, but deviations can and do occur.

In summary, this study successfully characterized key physicochemical parameters—solubility, lipophilicity, permeability, and albumin binding—that fundamentally influence the pharmacokinetics of synthetic cyclic C5-curcuminoid derivatives. Our group's earlier and ongoing results suggest that the presence of electron-withdrawing substituents on benzylidene groups, as well as nitrogen-containing heterocycles in the central scaffold, substantially enhance biological performance and antiproliferative activity. Therefore, for any future drug development, it will be essential to elucidate structure–activity relationships, understand physicochemical profiles, and develop strategies for their optimization.

5. Summary of novel findings

- The kinetic solubility of newly synthesized, biologically active cyclic C5-curcuminoid derivatives was determined using UV-Vis and HPLC-based methods. In addition, thermodynamic solubility was measured for two compounds.
- The permeability of compounds **1**, **2**, and **10** was evaluated using the PAMPA model.
- The examined curcuminoids selectively participated in Michael-type additions with thiol groups. The presence of thiol adducts was confirmed by mass spectrometric

analysis. Using a modified PAMPA assay, the influence of thia-Michael addition on pharmacokinetic parameters was substantiated.

- The lipophilicity of numerous cyclic C5-curcuminoids was characterized using TLC, HPLC, and *in silico* methods.
- For three selected derivatives (**10**, **11**, **12**), interactions with human serum albumin were studied using UV-Vis spectroscopy and fluorescence quenching. The interactions were determined to be of static nature, with binding affinity values depending on the applied computational model ($K = 10^4–10^6$). The binding induced conformational changes in the albumin, which may affect its transport function and interactions with other ligands.

6. List of publications

Journal articles forming the basis of the dissertation:

Huber, I., Pandur, E., Sipos, K., Barna, L., Harazin, A., Deli, M. A., **Tyukodi, L.**, Gulyás-Fekete, G., Kulcsár, G., & Rozmer, Z. (2022). Novel cyclic C5-curcuminoids penetrating the blood-brain barrier: Design, synthesis and antiproliferative activity against astrocytoma and neuroblastoma cells. European Journal of Pharmaceutical Sciences, 173. https://doi.org/10.1016/j.ejps.2022.106184 **[IF: 4,2; Q1]** 2023-as érték

Tyukodi, L., Zsidó, B. Z., Hetényi, C., Kőszegi, T., Huber, I., & Rozmer, Z. (2023). Serum albumin binding studies on antiproliferative cyclic C5-curcuminoid derivatives using spectroscopic methods and molecular modelling. Journal of Molecular Structure, 1287, 135761. https://doi.org/10.1016/j.molstruc.2023.135761 **[IF: 3,2; Q2]** 2023-as érték

Leib D., **Tyukodi L.**, Rozmer Zs.: Ciklikus C5-kurkuminoid-származékok oldhatóságának vizsgálata különféle módsz. Gyógyszerészet 68. évfolyam, 8. szám, 409-412, (2024) **[IF: -]**

Abedalqader S. M., **Tyukodi L**., Harmath L., Kiss E., Huber I., Rozmer Zs.: Physicochemical properties and anticancer activity of cyclic C5-curcuminoid derivatives: A structure-activity relationship study. *közlésre előkészítve*

Tyukodi L., Kulcsár Gy., Huber I., Rozmer Zs.: Impact of thiol reactivity on passive membrane permeability: A PAMPA-based study *közlésre előkészítve*

Other publications serving as the basis of the thesis:

Levente Tyukodi, Imre Huber, Zsuzsanna Rozmer Investigation of novel cyclic C5-curcuminoid analogs in spectral aspects *Medical Conference for PhD Students and Experts of Clinical Sciences (MedPECS2021)*, online, 2021. május 15. (poszter)

Levente Tyukodi, Imre Huber, Zsuzsanna Rozmer Investigation of novel cyclic C5-curcuminoid analogs in spectral aspects, *PhD Scientific Days* online, 2021 július 7. (poszter)

Új C5 kurkuminoid analógok albumin-kötődésének vizsgálata spektroszkópiai módszerekkel *MGYT Gyógyszeripari Szervezete és Gyógyszertechnológiai Szakosztálya által szervezett XIV. Clauder Ottó emlékverseny*, Budapest, 2021 november 11. (előadás)

Levente Tyukodi, Imre Huber, Zsuzsanna Rozmer Ciklikus C5-kurkuminoid analógok albuminkötődésének és permeábilitásának vizsgálata, *MGYT Gyógyszeranalitikai Szakosztálya által szervezett XLV. Gyógyszeranalitikai Továbbképző Kollokvium*, Kecskemét, 2022. április 28. (poszter)

Szintetikus C5 kurkuminoidok albumin kötődésének vizsgálata, *MGYT Gyógyszerkutatási Szakosztály által szervezett Fiatal Kutatók Fóruma*, Budapest, 2022. november. 25. (előadás)

Levente Tyukodi, Imre Huber, Zsuzsanna Rozmer Ciklikus C5-kurkuminoidok vizsgálata: permeábilitás vizsgálatok, *MGYT Gyógyszeranalitikai Szakosztálya által szervezett XLVI. Gyógyszeranalitikai Továbbképző Kollokvium*, Nyíregyháza, 2023. április 20-22, (poszter)

Physicochemical analysis of cyclic C5-curcuminoids, *Zechmeister Lecture Day (in the organisation of the Chemical Biology Work Group of the Hungarian Academy of Sciences)*, Pécs, 2023. november 17. (előadás)

Levente Tyukodi, Imre Huber, Zsuzsanna Rozmer Role of Michael Addition in the Reactivity of Cyclic C5-Curcuminoids *Congressus Pharmaceuticus Hungaricus (CPH) XVII. and EUFEPS Annual Meeting* Debrecen, 2024. május 23-25 (poszter)

Other journal articles and communications:

Rozmer, Zs., Kenari, F., **Tyukodi, L.,** Kulcsár, Gy., & Perjési, P. (n.d.). A PTE GYTK Gyógyszerészi Kémiai Intézetben folyó kutatásokról I. Szerkezet-reaktivitás és szerkezet-hatás vizsgálatok. Magyar Kémiai Folyóirat 53 128. évfolyam, 2. szám, 53-59, 2022. https://doi.org/10.24100/MKF.2022.02.53 **[IF: -]**

Dombi, G., Tyukodi, L., Dobó, M., Molnár, G., Rozmer, Z., Szabó, Z. I., Fiser, B., & Tóth, G. (2024). Enantioselective Binding of Proton Pump Inhibitors to Alpha1-Acid Glycoprotein and Human Serum Albumin—A Chromatographic, Spectroscopic, and In Silico Study. International Journal of Molecular Sciences, 25(19), 10575. https://doi.org/10.3390/IJMS251910575/S1 **[IF: 5,6; Q1]** 2022-es metrics

Cumulative impact factor: 13

Number of independent citations: 13

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