Short theses for the degree of doctor of philosophy (Ph.D.)

Chiroptical, NMR and mechanistic studies of natural and synthetic heterocycles

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1. Background and Objectives of the Dissertation

In nature we can encounter numerous chiral molecules. Among the primary metabolites, both proteins and carbohydrates are chiral compounds, and with the exception of glycine all of the monomer units of proteins are also chiral. Besides the primary metabolites, there are also numerous chiral secondary metabolites a significant portion of which is formed in living organisms in enantiomerically pure form.

Similarly, an increasing number of chiral, optically active substances are being synthesized and utilized primarily in the pharmaceutical industry.

In addition to X-ray diffraction methods, spectroscopic techniques as well as the investigation of the mechanism of biosynthesis and synthetic reactions offer opportunities for the study of chiral compounds. As absolute methods, chiroptical spectroscopic techniques including ECD or VCD spectroscopy and methods based on optical rotation measurements are highlighted.

My dissertation is structured around four main topics. The first topic focuses on classical TDDFT-ECD and DFT-VCD calculations. The aim was to determine the absolute configuration of newly synthesized, potentially pharmacologically active isochroman-2*H*-chromene derivatives and to get an insight into the conformational distribution of these compounds. The results may provide efficient assistance in exploring structure-activity relationships in the future.

In the course of the second major topic the focus was on the test of the novel raw MD trajectories based sTDA-ECD method. The goal was to develop a method that, with relatively low computational cost, provides results comparable with classical approaches, allowing the study of molecules that would not be able to examine with classical methods. With the newly developed method, the aim was to determine the structure of a large teicoplanin-aglycon with special attention to the stereochemistry of the amide bond between the amino acids E and F.

In the third part of my dissertation I focused on the development of NMR correction parameters. The aim of the calculations was to determine the absolute configuration of lobatolide H. I approached the well-known exomethylene problem from three directions, based on literature and our previous experiences: a) testing three previously successful method pairs on the target molecules, b) testing 80 method pairs described in the literature on two model compounds, and then applying the best-performing ones on lobatolide H, c) developing parameters for two new method pairs on exomethylene-containing derivatives

with known structures, and then applying the new parameters on the target molecule.

In the final major topic, I planned to explore the mechanism of stereoselective reactions. Specifically, I intended to investigate two pathways of the Domino Knoevenagel-cyclization reactions: the mechanism leading to the formation of a cyclobutane-condensed derivative, and the mechanism leading to the formation of a hydroxyindole derivative.

2. Applied methods

In the course of my research I primarily applied *in silico* methods by using software packages including the Gaussian09 quantum chemistry package, the MacroModel module of the Schrödinger program package and the Amber16 molecular dynamics package.

In addition to *in silico* methods, chiroptical measurements were conducted on an ECD spectropolarimeter and a VCD spectrometer installed at the Department of Organic Chemistry.

3. New scientific results

3.1. Stereochemical Studies of Neuroprotective Isochroman-2*H*-chromene Conjugates

In our research group, four neuroprotective isochroman-2*H*-chromene conjugates were synthesized, out of which two (**1**-**2**) were produced in all possible stereoisomers, while for the other two (**3**-**4**) four and five stereoisomers were synthesized, respectively.

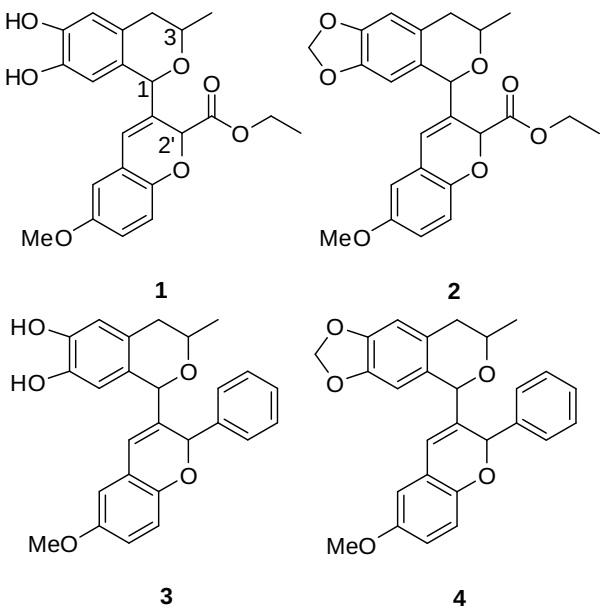


Figure 1: The structure of the hybrid isochroman-2*H*-chromene derivatives investigated in the thesis

I recorded the ECD and VCD spectra of all synthesized stereoisomers and assigned the absolute configuration of the isomers by means of TDDFT-ECD and DFT-VCD calculations. The calculations also helped clarify that the spectra of the non-synthesized stereoisomers significantly differed from the measured ones, confirming that 4 and 3 stereoisomers (**3-4**) were indeed not synthesized (it was not always obvious which streoisomers were formed in the reactions). The measured spectra with the assigned absolute configurations can be seen in Figures 2-5.

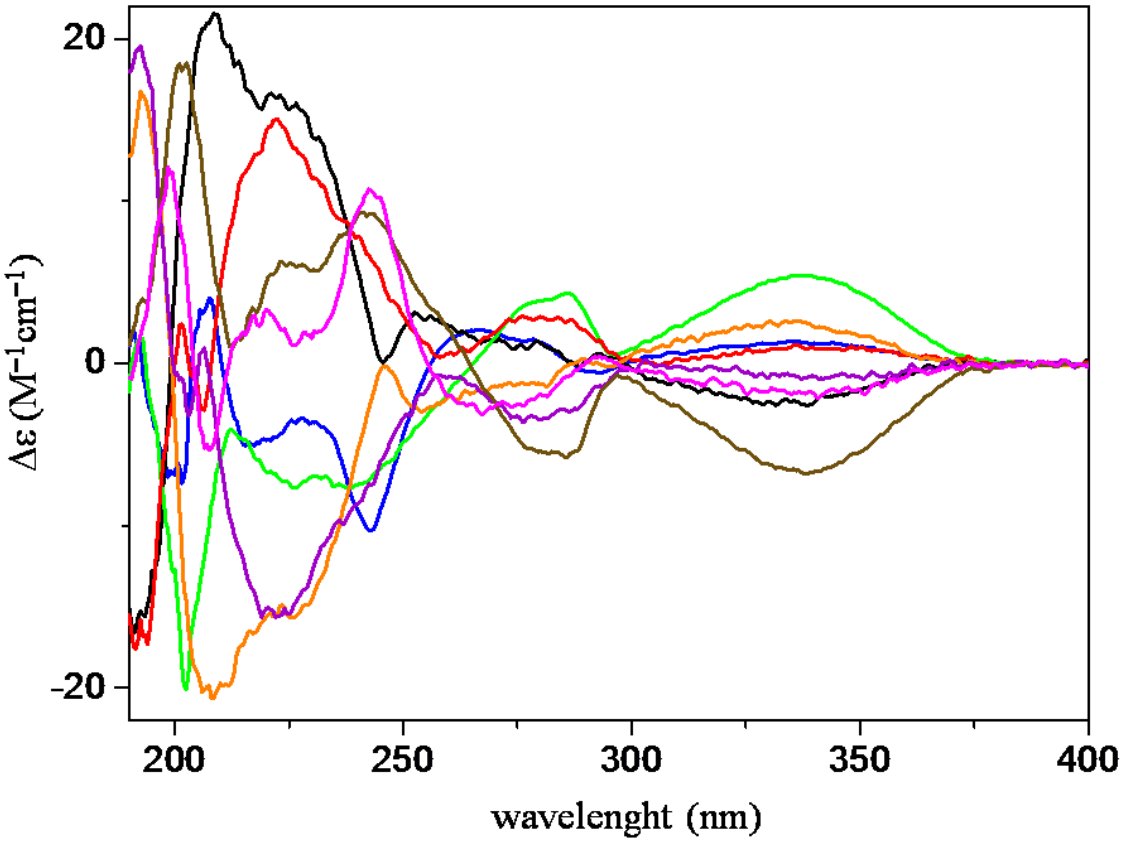


Figure 2: ECD spectra measured in acetonitrile for the stereoisomers of **1**: (black - (1*R*,3*R*,2'*R*), orange - (1*S*,3*S*,2'*S*), red - (1*S*,3*R*,2'*R*), dark purple - (1*R*,3*S*,2'*S*), light purple - (1*R*,3*R*,2'*S*), blue - (1*S*,3*S*,2'*R*), brown - (1*S*,3*R*,2'*S*), green - (1*R*,3*S*,2'*R*))

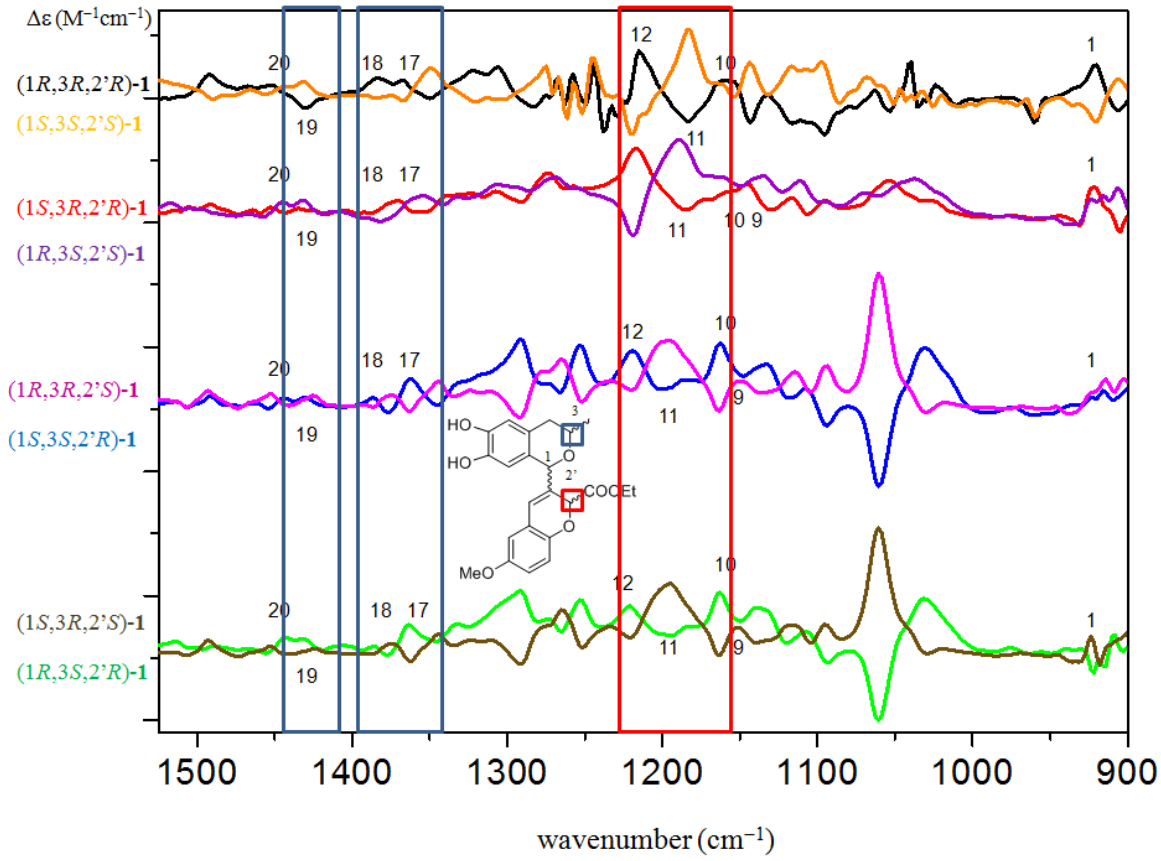


Figure 3: VCD spectra of the stereoisomers of **1** measured in $CDCl_3$, and in acetone-d6 for (1*R*,3*R*,2'*R*)-**1** and (1*S*,3*S*,2'*S*)-**1**. (Differently colored squares indicate regions characteristic of the corresponding chirality centers.)

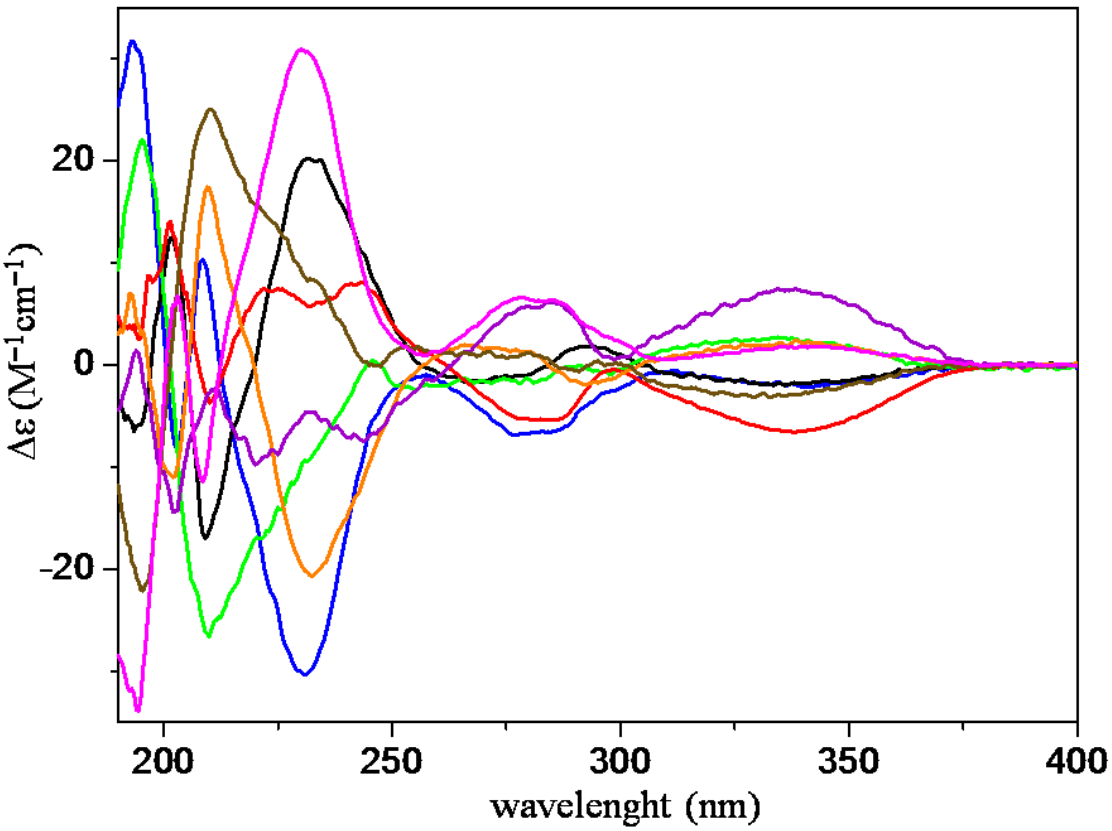


Figure 4: ECD spectra measured in acetonitrile for the stereoisomers of **2**: (black - (1*S*,3*R*,2'*S*), orange - (1*R*,3*S*,2'*R*), red - (1*R*,3*R*,2'*S*), dark purple - (1*S*,3*S*,2'*R*), light purple - (1*S*,3*R*,2'*R*), blue - (1*R*,3*S*,2'*S*), brown - (1*R*,3*R*,2'*R*), green - (1*S*,3*S*,2'*S*))

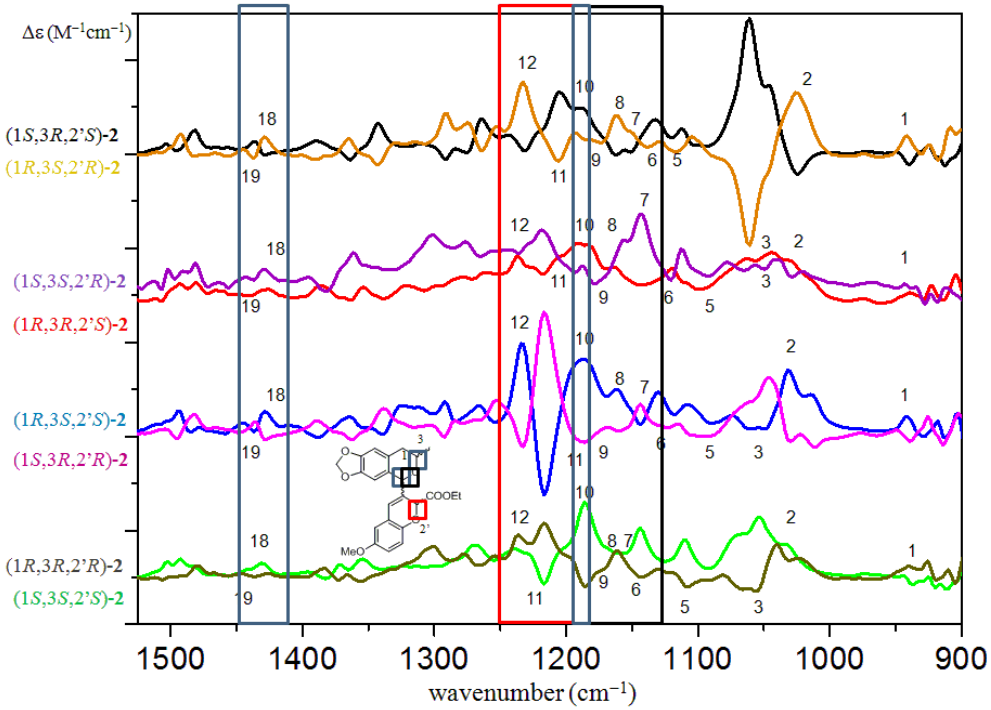


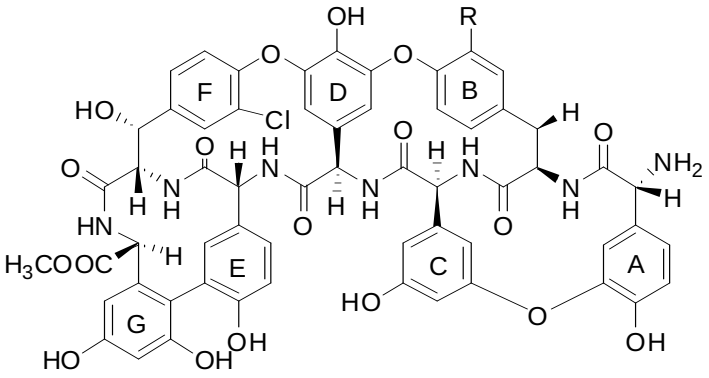
Figure 5: VCD spectra of the stereoisomers of **2** measured in $CDCl_3$. (Differently colored squares indicate regions characteristic of the corresponding chirality centers.)

Based on the measurements and calculations characteristic regions were identified in the spectra of **1** and **2** that could potentially be used in the future to determine the absolute configuration of similar compounds without further calculations. These bands labeled with numbers in Figures 3 and 5 were much more prominent in the VCD spectra. In addition to searching for characteristic bands, I examined the conformational relationships of the stereoisomers of the investigated compounds which could assist in uncovering structure-activity relationships in the future.

3.2. Molecular Dynamics and sTDA Investigation of Glycopeptide Antibiotics Aglycons

In previous studies of glycopeptide antibiotics conducted at the Department of Pharmaceutical Chemistry it was shown that the distinct biological and chiroptical behavior of the ristocetin-aglycon and teicoplanin-aglycon (**8**, Figure 6) is not directly attributed to the presence or absence of halogen atoms, but rather to their different conformational behavior. Based on previous calculations questions arose regarding the place of this difference and also

the relative configuration of the amide bond between the amino acids E and F. Due to the size and flexibility of the system, instead of classical methods, a novel approach utilizing molecular dynamics-based sTDA-ECD calculations was applied.



8

Figure 6: The structure of the investigated teicoplanin-aglycon

To determine the stereochemistry 100 ns long molecular dynamics simulations were carried out at 310 K with a 2 fs time step starting from the lowest energy EF *cis* and EF *trans* conformers of the teicoplanin-aglycon. From the molecular dynamics trajectories 100 structures were extracted without solvent molecules at intervals of 1 ns. Subsequently, sTDA calculations were performed on these structures at various levels.

Single point calculations were performed on the raw structures obtained from the molecular dynamics simulations using the CAM-B3LYP/TZVP, LC-BLYP/TZVP and ωB97X/TZVP levels of theory. Subsequently, the sTDA program was used to compute the ECD spectra at LC-BLYP and ωB97X levels with an energy window of 10 eV and 15 eV for CAM-B3LYP. The calculated average spectra can be seen in Figures 7 and 8.

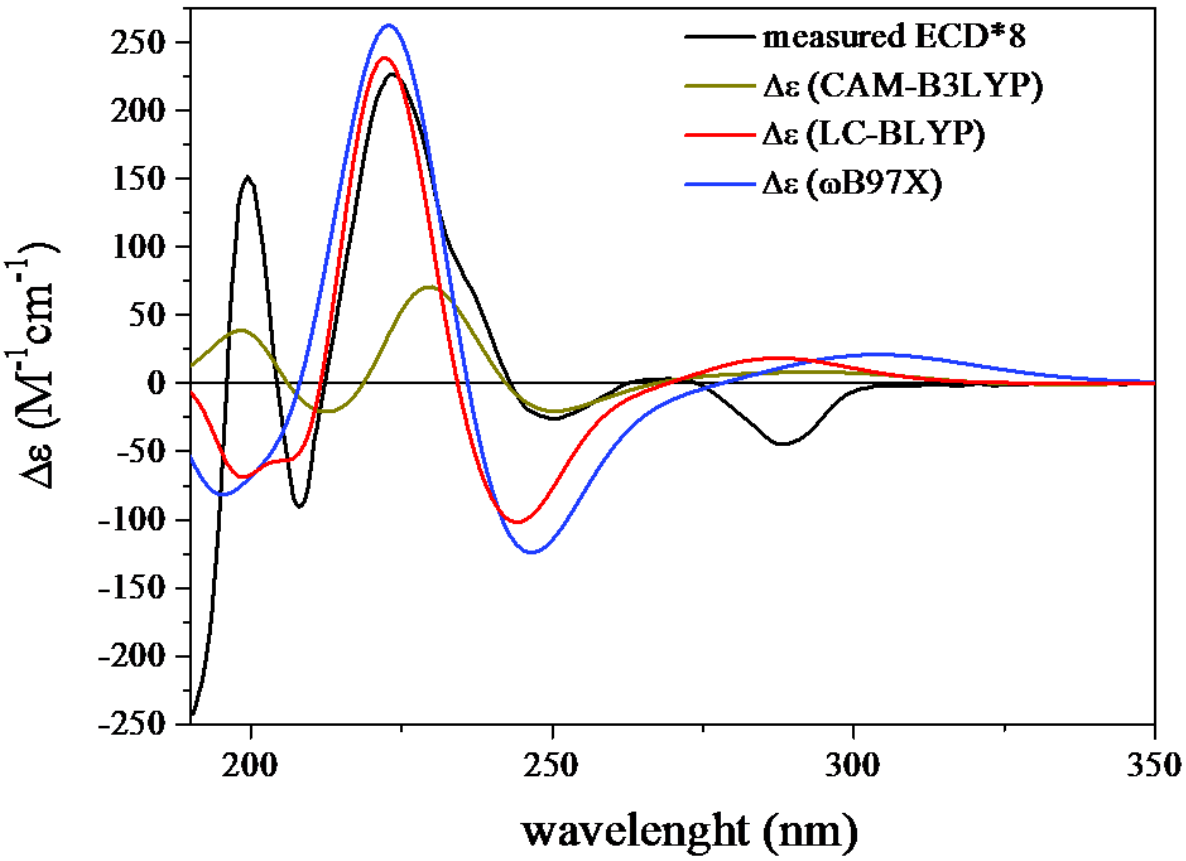


Figure 7: ECD spectra calculated with the sTDA method for 100 raw structures obtained from the aqueous molecular dynamics simulation of the low-energy EF *cis* conformer of teicoplanin-aglycon (**8**) compared to the experimental ECD spectrum measured in water

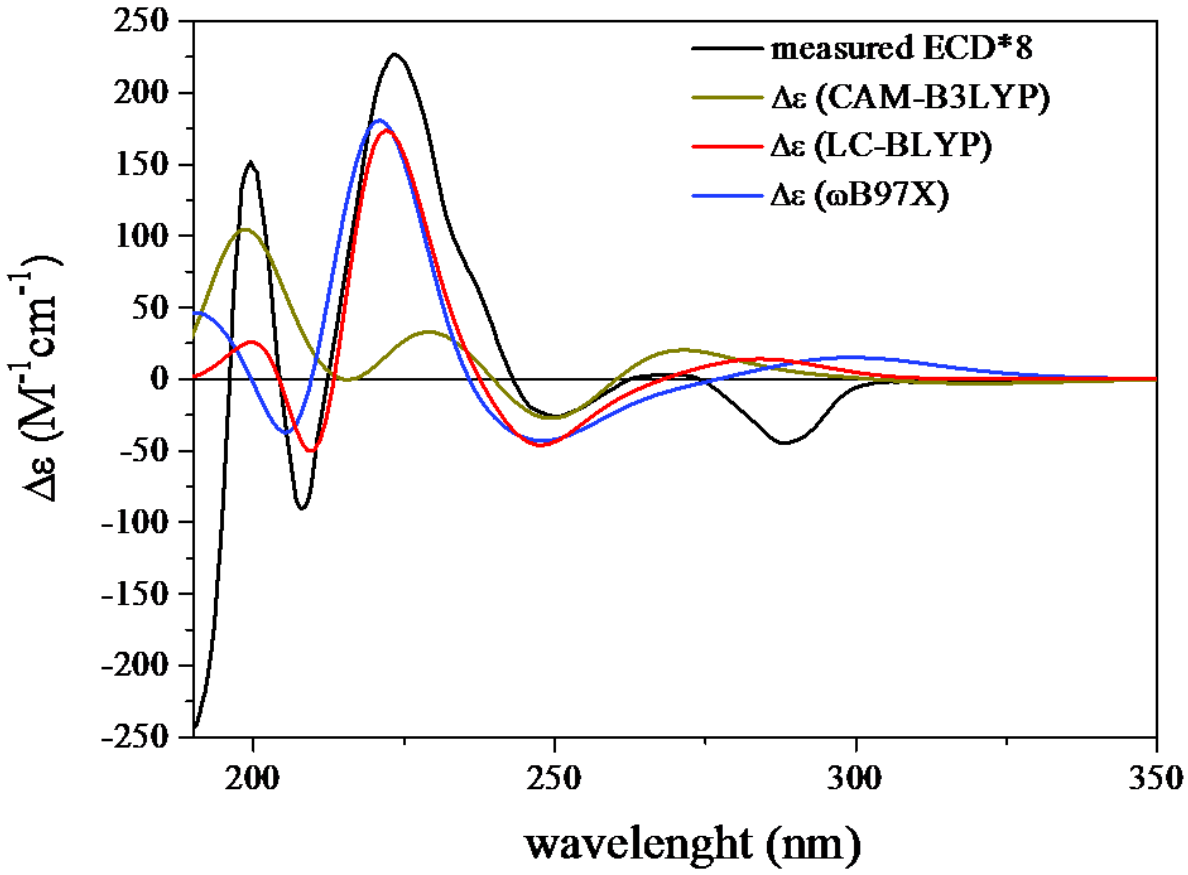


Figure 8: ECD spectra calculated with the sTDA method for 100 raw structures obtained from the aqueous molecular dynamics simulation of the low-energy EF *trans* conformer of teicoplanin-aglycon (**8**) compared to the experimental ECD spectrum measured in water

Although both calculations reproduced the measured spectrum better than the original ones, determination of the isomerism or the location of conformational differences is not possible as the ECD is primarily influenced by the conformation of the B, D, and F amino acids which is similar in both forms. However, based on the size and flexibility of the system, this study serves as a good example of the spectral reproduction improvement of the MD-based ECD method in a molecular size that is difficult to examine with conventional methods.

3.3. Determination of the Structure of Lobatolide H and Development of NMR Chemical Shift Parameters for Exomethylene Derivatives

The computational challenges of the NMR chemical shift data of exomethylene derivatives are well-known in the literature. Therefore, in order to determine the structure of lobatolide H, which contains an exomethylene moiety, I sought functional pairs beyond the

commonly used and generally well-performing 3 combinations in our group that could be suitable for computing such derivatives. For this purpose 80 different functional pairs were tested on the volenol molecule to better reproduce the chemical shift values of carbon atoms close to the exomethylene moiety. The majority of the methods were selected based on the Cheshire database as of October 5, 2018, considering all essential available combinations primarily developed for experimental results measured in chloroform.

The functional pairs that performed best on volenol are shown in Table 1. These functional pairs were further tested on **21** (Table 2) and then I attempted to determine the relative configuration of lobatolide H using the most promising functional pairs identified here, namely the 2nd and 3rd functional pairs.

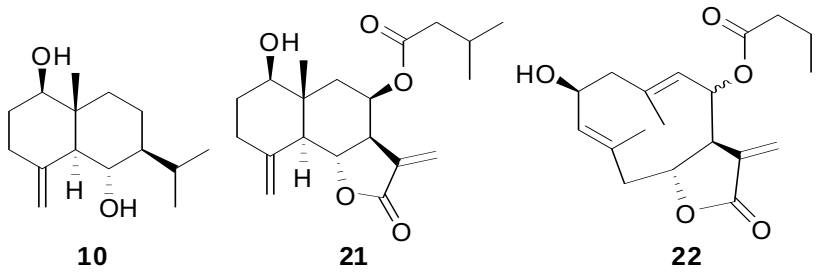


Figure 9: The structure of compounds investigated using statistical methods

	DFT optimization level	**NMR calculation level (GIAO)**	**MAE (ppm)**
1.	M06-2X/6-31G(d) *in vacuo*	mPW1PW91/6-31G(d) *in vacuo*	1.35
2.	M06-2X/6-31G(d) *in vacuo*	mPW1PW91/6-31G(d) SMD/$CHCl_3$	1.30
3.	B3LYP/6-31+G(d,p) *in vacuo*	M06/6-31G(d) *in vacuo*	1.32
4.	B3LYP/6-31+G(d,p) *in vacuo*	OPBE0/6-31G(d) *in vacuo*	1.51

Table 1: Functional pairs showing the smallest average chemical shift differences for the volenol molecule

	MAE ((1*R*,5*S*,6*R*,7*S*,8*R*,10*R*)-**21**; (1*R*,5*S*,6*R*,7*S*,8*S*,10*R*)-**21**)	**sDP4**+ ((1*R*,5*S*,6*R*,7*S*,8*R*,10*R*)-**21**; (1*R*,5*S*,6*R*,7*S*,8*S*,10*R*)-**21**)
1.	1,63;1,68	69,35%; 30,65%
2.	1,40; 1,54	93,58%; 6,42%
3.	1,68; 2,01	99,13%; 0,87%
4.	1,93; 2,35	99,79%; 0,21%

Table 2: Statistical evaluation derived from the comparison of ^{13}C NMR chemical shift values calculated with four functional pairs for the two epimers of **21** with experimental data

The relative configuration of lobatolide H could not be unambiguously determined using the best performing tested functional pairs (Table 3) or the functional pairs successfully applied in our research group (Table 4). Therefore, we decided for the development of new correction parameters.

	MAE ((2*S*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*S*)-**22**; (2*S*,6*R*,7*S*,8*S*)-**22**)	**sDP4+** ((2*S*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*S*)-**22**; (2*S*,6*R*,7*S*,8*S*)-**22**)
2	2,42; 2,59; 2,15; 2,85	90,66% 3,14% 5,16% 1,04%
3	3,12; 2,83; 3,19; 2,76	2,54%; 69,71%; 9,58%; 18,17%

Table 3: Statistical evaluation derived from the comparison of ^{13}C NMR chemical shift values calculated with the two best performing tested functional pairs for the four diastereomers of **22** with experimental data

	MAE ((2*S*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*S*)-**22**; (2*S*,6*R*,7*S*,8*S*)-**22**)	**sDP4+** ((2*S*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*S*)-**22**; (2*S*,6*R*,7*S*,8*S*)-**22**)
mPW1PW91/ 6-311+G(2d,p) // B3LYP/6-31+G(d,p)	2,32; 2,10; 2,57; 2,49	5,28%; 93,00%; 0,25%; 1,47%
mPW1PW91/ 6-311+G(2d,p) SMD/$CHCl_3$ // B3LYP/6-31+G(d,p)	2,06; 2,07; 2,16; 2,34	55,91%; 30,41%; 12,46%; 1,22%
mPW1PW91/ 6-311+G(2d,p) SMD/$CHCl_3$ // mPW1PW91/6-311+G(2d,p) SMD/$CHCl_3$	2,15; 1,89; 2,38; 2,41	3,40%; 96,26%; 0,19%; 0,16%

Table 4: Statistical evaluation derived from the comparison of ^{13}C NMR chemical shift values calculated with the functional pairs generally applied in our research group for the four diastereomers of **22** with experimental data.

To develop the correction parameters, conformational searches were performed for 11 compounds with known stereochemistry containing exomethylene moiety. Subsequently, I optimized the obtained MM conformers at the ωB97XD/6-31+G(d,p) *in vacuo* and the ωB97XD/6-31+G(d,p) SMD/$CHCl_3$ levels, followed by NMR shift calculations using the GIAO method at the mPW1PW91/6-311+G(2d,p) level both *in vacuo* and with SMD/$CHCl_3$ solvent model. The correction parameters were derived from the slopes and intercepts of the resulting lines by plotting the calculated chemical shifts against the measured ones.

To validate the developed parameters, I calculated the chemical shifts of **21** using the

two new level combinations and performed their statistical evaluation (Table 5). Subsequently, the calculation and evaluation of the stereoisomers of **22** were carried out using the two new functional pairs (Table 6), which suggests the (2*S**,6*R**,7*S**,8*R**) relative configuration.

	MAE ((1*R*,5*S*,6*R*,7*S*,8*R*,10*R*)-**21**; (1*R*,5*S*,6*R*,7*S*,8*S*,10*R*)-**21**)	**sDP4+** ((1*R*,5*S*,6*R*,7*S*,8*R*,10*R*)-**21**; (1*R*,5*S*,6*R*,7*S*,8*S*,10*R*)-**21**)
gas	1,82; 1,87	66,38%; 33,62%
SMD	1,60; 1,91	99,26%; 0,74%

Table 5: Statistical evaluation of the calculated ^{13}C chemical shifts of **21** using the new functional pairs

	MAE ((2*S*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*R*)-**22**; (2*R*,6*R*,7*S*,8*S*)-**22**; (2*S*,6*R*,7*S*,8*S*)-**22**)
gas	2,33; 2,48; 2,58; 3,11
SMD	2,26; 2,42; 2,48; 3,23

Table 6: Statistical evaluation of the calculated ^{13}C chemical shifts of **22** using the new functional pairs

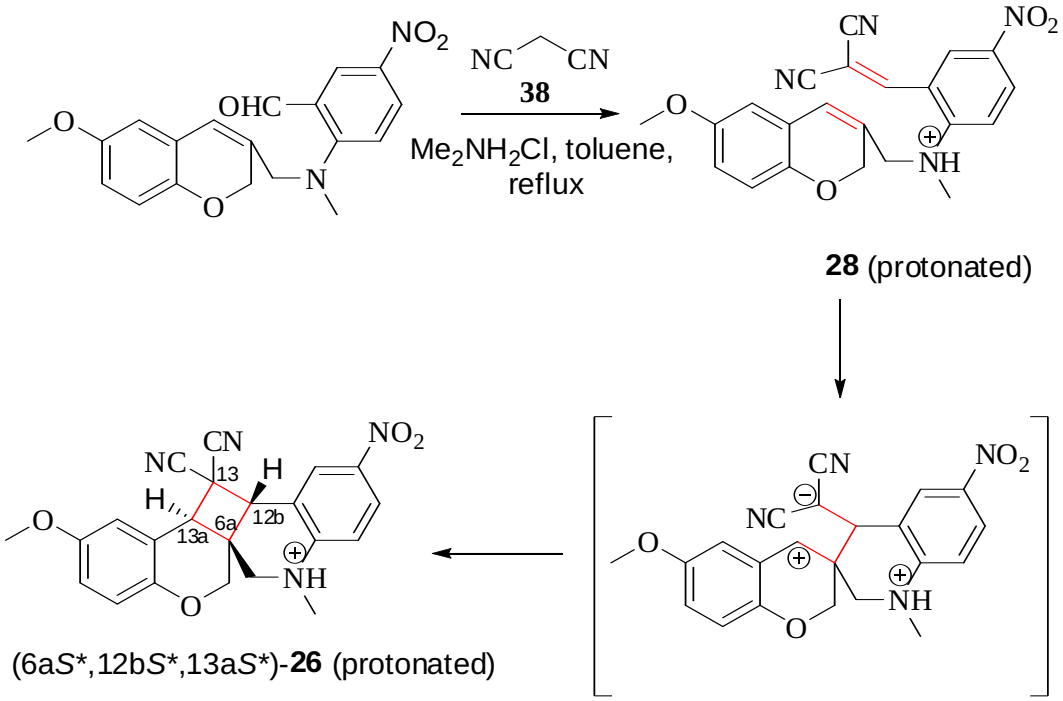
The suggested relative configuration based on the new combinations was verified by coupling constant calculations. Additionally, ECD calculations provided evidence for the homochirality of the conserved C-6 and C-7 centers in lobatin and lobatolide compounds. The absolute configuration of lobatolide H could be determined as (2*S*,6*R*,7*S*,8*S*).

3.4. Study of Reaction Mechanisms

The theoretical study of reaction mechanisms is crucial for understanding both the formation and stereochemistry of compounds, as well as for the refinement of the syntheses. In my dissertation, I investigated the mechanisms of two pathways of the Domino Knoevenagel-ringclosure reaction.

In one of the reactions a cyclobutane-condensed derivative is formed in two steps. The process of compound formation is depicted in Scheme 1. During the mechanism investigation I initially performed a 2D scan with non-protonated nitrogen, but the reaction energy barrier was unrealistically high. Therefore, the corresponding scan was also performed with protonated nitrogen, resulting in a realistic energy barrier. TS calculation was performed at

the saddle point of the scan, and then the obtained transition state was investigated using the IRC method, which led to the discovery of an intermediate. Starting from the intermediate, I also identified the other transition state of the reaction. The energy profile of the reaction is shown in Figure 10.



Scheme 1: Scheme of the formation of **26**

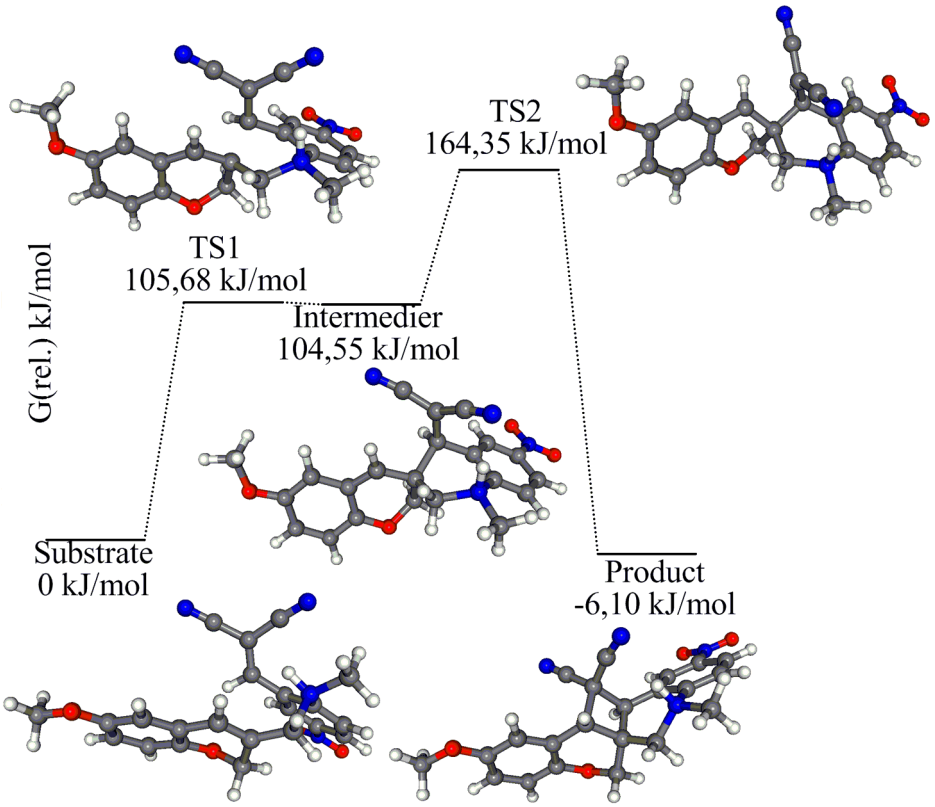


Figure 10: Potential energy diagram of the formation of **26**

The second examined reaction involves a multi-step reaction mechanism consisting of cyclization, protonation and deprotonation steps. The reaction scheme and energetic relationships are depicted in Figure 11. Step ii occurs spontaneously after protonation of the oxygen. The hydroxyindole ring closure takes place in a reaction sequence involving complex deprotonation and protonation steps.

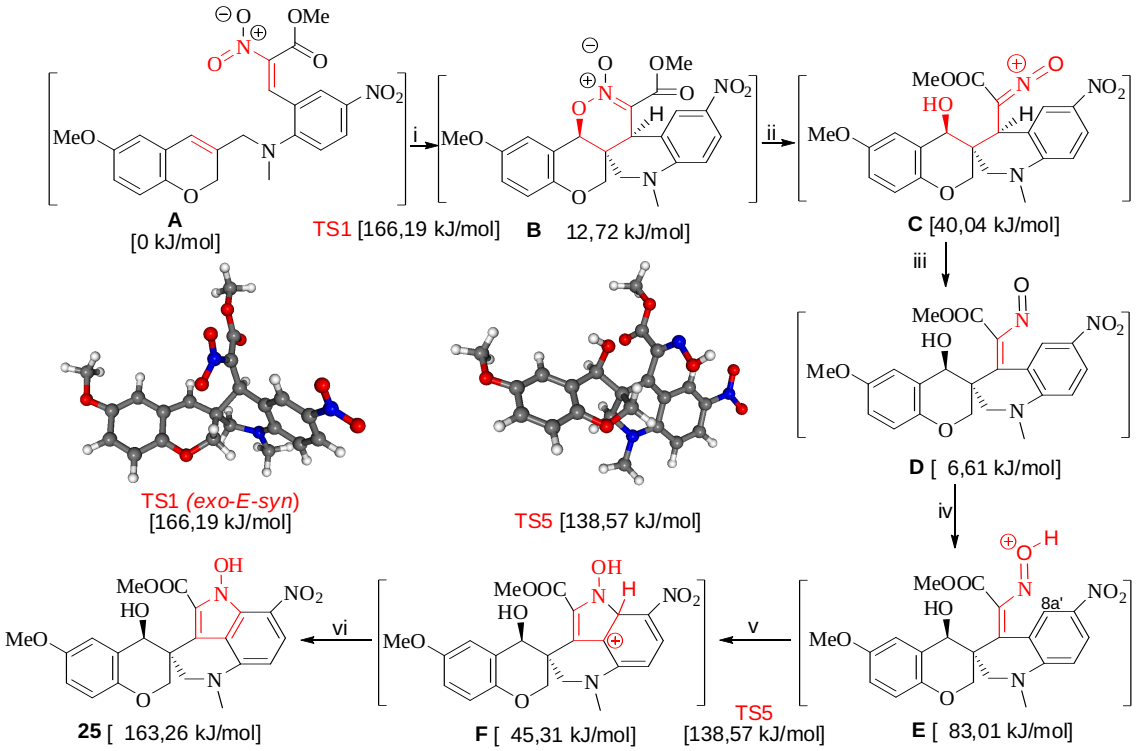


Figure 11: Mechanism of the formation of **25** and its energetics calculated at the B3LYP/6-31G(d) level

4. Possible applications of the Results

The results of the thesis can be applied in the future for the structural analysis of previously unknown compounds.

The investigations of isochroman-2*H*-chromene derivatives can potentially be used in the future for the determination of the absolute configuration of similar new compounds without the need for further calculations.

With the test of the novel raw MD trajectory-based sTDA calculations on large systems it becomes possible to perform ECD calculations for compounds falling into a size range that are hard to investigate with the classical TDDFT-ECD method. These calculations can be carried out with moderate computational resources and provide better reproduction of experimental results compared to spectra calculated with small basis sets or at semi-empirical levels due to the limitations imposed by size.

In my dissertation I tested the performance of 80 functional pairs and the corresponding NMR scaling factors for compounds containing exomethylene moieties. These data may assist in the selection of functional pairs applicable for NMR calculations in rigid cases for similar compounds in the future. Additionally, I developed new scaling factors for two level combinations, which may be also suitable for determining the structure of flexible exomethylene derivatives. Furthermore, I presented an example that can be used in the future for the combined application of NMR shift, coupling constant, and ECD calculations.

Finally, the mechanism calculations provide an opportunity to explain the mechanism and stereochemical course of similar reactions, and based on these, optimize the experimental yields.

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Registry number: DEENK/1/2024.PL
Subject: PhD Publication List

Candidate: Tibor Kovács
Doctoral School: Doctoral School of Chemistry
MTMT ID: 10067933

List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. **Kovács, T.**, Lajter, I., Kúsz, N., Schelz, Z., Bózsity-Faragó, N., Borbás, A., Zupkó, I., Krupitza, G., Frisch, R., Hohmann, J., Vasas, A., Mándi, A.: Isolation and NMR Scaling Factors for the Structure Determination of Lobatolide H, a Flexible Sesquiterpene from Neurolaena lobata.
Int. J. Mol. Sci. 24 (6), 1-19, 2023. EISSN: 1422-0067.
DOI: http://dx.doi.org/10.3390/ijms24065841
IF: 5.6 (2022)

2. Király, S. B., Tóth, L., **Kovács, T.**, Bényei, A., Lisztes, E., Tóth, I. B., Bíró, T., Kiss-Szikszai, A., Kövér, K. E., Mándi, A., Kurtán, T.: Multifaceted Domino Knoevenagel-Cyclization Reactions; Four Movements for 2H-Chromenes and Chromans.
Adv. Synth. Catal. 365, 1-20, 2023. ISSN: 1615-4150.
DOI: http://dx.doi.org/10.1002/adsc.202300083
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List of other publications

Foreign language scientific articles in international journals (6)

3. Kopatz, V., Wen, K., **Kovács, T.**, Keimowitz, A. S., Pichler, V., Widder, J., Vethaak, A. D., Hollóczki, O., Kenner, L.: Micro- and Nanoplastics Breach the Blood-Brain Barrier (BBB): Biomolecular Corona`s Role Revealed.
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4. Alekszi-Kaszás, A., Käfer, B. K., Varga, T. R., Bényei, A., **Kovács, T.**, Mándi, A., Kurtán, T., Simon, A., Nemes, P.: Regio- and Stereoselective Synthesis of Benzoquinolizidines.
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5. Szabó, Z., Paczal, A., **Kovács, T.**, Mándi, A., Kotschy, A., Kurtán, T.: Synthesis and Vibrational Circular Dichroism Analysis of N-Heterocyclic Carbene Precursors Containing Remote Chirality Centers.
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DOI: http://dx.doi.org/10.3390/pharmaceutics13122088
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Chirality. 30 (7), 866-874, 2018. ISSN: 0899-0042.
DOI: http://dx.doi.org/10.1002/chir.22969
IF: 1.927

Total IF of journals (all publications): 39,621
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Lectures and Posters Related to the Ph.D. Thesis

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[24] T. Kurtán, S. Király, T. Kovács., M. Kajtár, A. Mándi., S. Antus: (2*H*)-kromén származékok sztereoszelektív gyűrűzárási reakciói, Vegyészkonferencia 2017, **2017**, Hajdúszoboszló, Hungary. (L)

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