Closing report for the K120181 research project titled "Stereochemisry and stereoselective synthesis of bioactive heterocycles"

In the five-year period of the project (2016.10.01.-2021.09.30.), we performed the synthesis of chiral *O*- and *O,N*-heterocycles such as isochromans, tetrahydroisoquinolines, pterocarpans, condensed 2-arylchroman or -2*H*-chromene derivatives and prepared several novel condensed heterocyclic scaffolds. Our efforts to explore the bioactivity of our heterocycles resulted in the identification of neuroprotective activity for isochroman-2*H*-chromen conjugates, antifungal and PTP1B inhibitory activity for chiral isochromans, antiproliferative activity for pterocarpans, condensed and spirocyclic novel heterocyclic scaffolds. A vibrational circular dichroism (VCD) spectrometer was acquired and installed with the support of a GINOP project in 2018. The measurement and calculation of VCD spectra were integrated in our stereochemical arsenal, and in combination with the calculation of OR, ECD and NMR parameters, we could efficiently address most of the stereochemical problems raised in the field of natural and synthetic derivatives.

With the support of the five-year project, 58 peer-reviewed SCI papers were published and four have been accepted for publication in international journals with a sum impact factor of 252.99. Moreover, there are two additional recently submitted manuscripts under review. In the following, I am discussing representative results of the project with the corresponding citations.

Racemic chiral *O,N*-heterocycles containing 2-arylchroman or 2-aryl-2*H*-chromene subunit condensed with morpholine, thiazole, or pyrrole moieties at the C-3-C-4 bond were synthesized with various substitution patterns of the aryl group by the cyclization of *cis*- or *trans*-3-aminoflavanone analogues. Antiproliferative activity of the condensed heterocycles and precursors was evaluated against A2780 and WM35 cancer cell lines. For a 3-(*N*-chloroacetylamino)-flavan-4-ol derivative, showing structural analogy with acyclic acid ceramidase inhibitors, 0.15 μM, 3.50 μM, and 6.06 μM IC_{50} values were measured against A2780, WM35, and HaCat cell lines, and apoptotic mechanism was confirmed. Low micromolar IC_{50} values down to 2.14 μM were identified for the thiazole- and pyrrole-condensed 2*H*-chromene derivatives. Enantiomers of the condensed heterocycles were separated by HPLC using chiral stationary phase, HPLC-ECD spectra were recorded and TDDFT-ECD calculations were performed to determine the absolute configuration and solution conformation. Results were published in *Biomolecules* (**2020**, *10*, 1462).

The Heck-oxyarylation domino cyclization of racemic 2-(1-naphthyl)- and 2-(2-naphthyl)-2*H*-chromene derivatives were carried out resulting diastereoselectively in (6*S**,6a*R**,11a*R**)-6-(1-naphthyl)- and 6-(2-naphthyl)-pterocarpans as major products and bridged (6*R**,12*R**)-6,12-methanodibenzo[d,g][1,3]dioxocine derivatives as minor products. Antiproliferative activity of two 6-naphthylpterocarpans was identified by MTT assay against A2780 and WM35 human cancer cell lines with low micromolar IC_{50} values. The measured 0.80 and 3.51 μM IC_{50} values of the (6*S**,6a*R**,11a*R**)-6-(1-naphthyl)pterocarpan derivative with 8,9-methylenedioxy substitution represent the best activities in the pterocarpan family. Enantiomers of the pterocarpan and dioxocine derivatives and their chiral 2-naphthylchroman-4-one and 2-naphthyl-2H-chromene precursors were separated by HPLC using chiral stationary phase. HPLC-ECD spectra were recorded and absolute configuration and low-energy solution conformations were determined by TDDFT-ECD calculations. Results were published in *Org. Biomol. Chem*. (**2020**, *18*, 2148).

Domino cyclization reactions of *N*-aryl-1,4- and 1,5-benzoxazepine derivatives involving [1,5]-hydride shift or C(sp^2)-H functionalization were investigated. Neuroprotective and acetylcholinesterase inhibitory activities of the products were studied. Domino Knoevenagel-[1,5]-hydride shift-cyclization reaction of *N*-aryl-1,4-benzoxazepine derivatives with 1,3-dicarbonyl reagents having active methylene group afforded the 1,2,8,9-tetrahydro-7b*H*-quinolino [1,2-*d*][1,4]benzoxazepine scaffold with different substitution pattern. The C(sp^3)-H activation step of the tertiary amine moiety occurred with complete regioselectivity and the 6-*endo* cyclization took place in a complete diastereoselective manner. In two cases, the enantiomers of the chiral condensed new 1,4-benzoxazepine systems were separated by chiral HPLC, HPLC-ECD spectra were recorded, and absolute configurations were determined by TDDFT-ECD calculations. In contrast, the analogue reaction of the regioisomeric *N*-aryl-1,5-benzoxazepine derivative did not follow the above mechanism but instead the Knoevenagel intermediate reacted in an S_EAr reaction [C(sp^2)-H functionalization] resulting in a condensed acridane derivative. The AChE inhibitory assays of the new derivatives revealed that the acridane derivative had a 6.98 μM IC_{50} value (*Molecules* **2020**, *25*, 1265).

We performed the stereoselective synthesis of a chiral non-racemic isochroman-2*H*-chromene conjugate containing three chirality centers by the oxa-Pictet-Spengler cyclization of an optically active 1-arylpropan-2-ol derivative with a 3-formyl-2*H*-chromene reagent, and confirmed the stereochemistry by TDDFT-ECD calculations. Our compound possessed superior neuroprotective effect against oxidative injuries. Pretreatment with the compound (1–

10 μM), concentration-dependently prevented H_2O_2-induced cell death in SH-SY5Y neuroblastoma cells and rat primary cortical neurons and significantly alleviated H_2O_2-induced apoptotic changes. We concluded that our compound exerts neuroprotection associated with dual regulative mechanisms and consequently activating cell survival and inhibiting apoptotic changes, which may provide important clues for the development of effective neuroprotective drug candidate. Results were reported in the *Acta Pharmacologica Sinica* (**2021**, 42:36–44) in collaboration with the Shanghai Institute of Materia Medica. All the other 7 stereoisomers of our isochroman-2*H*-chromene conjugate were prepared for further pharmacological studies and their stereochemistry was analyzed by ECD and VCD measurements and calculations. We are preparing a manuscript on the chiroptical analysis of the stereoisomers, which discuss X-ray diffraction analysis, VCD and ECD calculations and stereochemistry-activity relationships. Tetrahydroisoquinoline analogues with different substitution patterns were also synthesized by the Pictet-Spengler cyclization of the optically active amine derivatives and the VCD method was tested to distinguish the different stereoisomers. An additional paper on the synthesis, bioactivity and VCD analysis of optically active 1-arylisochroman is under construction as well.

Four different cyclization mechanisms were identified in the domino Knoevenagel-cyclization reaction of 2*H*-chromene derivatives containing an *o*-formyl-arylamine or ether side-chain and DFT calculations were performed to determine the the activation parameters and transition states and explain the observed stereoselectivites. We completed the DFT calculations to determine the mechanism of our new multistep domino reaction resulting in the formation of condensed hydroxyindole derivatives with antiproliferative activity. We have prepared a manuscript on the synthesis, stereochemical and cytostatic evaluation of 80 novel chiral condensed *O*,*N*-heterocycles representing new heterocyclic entities, which is to be submitted to the journal *Angew. Chem. Int. Ed.*. The diastereoselective domino-Knoevenagel-IMHDA reactions of 5,6-dihidro-2*H*-pyran derivatives containing an *o*-formylaryl amine or ether moiety were performed with active methylene reagents. In the spiro heterocyclic products representing a novel skeleton, a tetrahydroquinoline or chroman unit is fused with two pyran rings and the annulation points are chirality centers formed diastereoselectively. Depending on the substitution pattern, a domino Knoevenagel-[1,5]-hydride shift-cyclization sequence was identified as a competing pathway, which resulted in the formation of tetrahydroquinoline derivatives with a 5,6-dihydro-2*H*-pyran-3-yl substitutent. In 2021, the results were submitted to the special issue of the *Eur. J. Org. Chem*. dedicated to the memory of Prof. Ferenc Fülöp and it has been accepted for publication.

An enantioselective domino Michael addition-cyclization-dehydration sequence was performed in the reaction of a 3,4-dihydroisoquinolin-1(2*H*)-ylideneethanenitrile derivative and α,β-unsaturated aldehydes using cinchona- and diphenylprolinol-type organocatalyts. The resultant 6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolines was reduced by catalytic hydrogenation to produce benzo[c]quinolizidines diastereoselectively with three chirality centers, the skeleton of which is a comman structural motif in alkaloids. The stereochemistry of products was studied by single crystal X-ray diffraction and solution TDDFT-ECD and DFT-VCD approaches. With the aid of VCD and ECD calculations, characteristic VCD and ECD transitions were identified, which reported the absolute configuration of the tricyclic skeleton by simple comparison regardless the different C-2 substituents. The results have been submitted to *Eur. J. Org. Chem*. for publication.

VCD analysis of 16 diastereomeric pairs of NHC precursors containing two isolated chirality centers and different substitution patterns identified characteristic VCD transitions, which in contrast to ECD and OR, could be utilized to assign the two chirality centers separately by simple comparison, regardless of the type and position of achiral aromatic substituents. VCD, ECD and OR approaches were evaluated, and several carbene precursors were found, for which only the VCD method could distinguish the four stereoisomers. The manuscript has been submitted to *Org. Lett.* for publication.

By performing DFT NMR calculations of a fragment to determine the relative configuration, we contributed to the structural elucidation of the super-carbon-chain polyol-polyether natural product of the benthic dinoflagellate, *Amphidinium* sp., amphibenthol A, exhibiting antimalarial activity (*Chem. Sci*. **2021**, *12*, 10197).

The planar structure and absolute configurations of gibbosols A and B, super-carbon-chain natural products of marine dinoflagellates with thirty-seven stereogenic carbon centers, were determined by the combinations of chemical, spectroscopic, and computational approach including ^{13}C-NMR DFT calculations and DP4+ analysis of synthetic fragments. Results were dedicated to the memory of Prof. Koji Nakanishi and reported in *Angew. Chem. Int. Ed.* (**2020**, *59*, 13028-13036).

TDDFT-ECD calculations were utilized to explain the mirror image or different ECD spectra of previously reported homochiral natural products thaigranatins A-E and granatumin L, the simple comparison of which would result in a wrong stereochemical conclusion. Different conformations of the furan-2-yl-d-lactone subunit were found responsible for the mirror image

ECD spectra of the homochiral thaigranatins C–E. Two DFT ^{13}C NMR chemical shift calculation methods and DP4+ analysis were performed on the C-6 epimers of thaigranatin D, which together with the ECD calculation, could determine the absolute configuration of C-6 as (*R*). Results were reported in *RSC Advances* (**2020**, *10*, 32216).

Leucobryns A-E, axially chiral 9,10-phenanthrenequinone dimers, were isolated from *Paraleucobryum longifolium*. Leucobryns B and C were proved to be homodimeric atropodiastereomers containing both axial and central chirality elements, while leucobryns D and E were found to be heterodimeric atropodiastereomers containing central chirality in only one of the two monomeric units. Axial chirality of the compounds was determined by ECD measurements and sTDA ECD calculations, while the central chirality elements were assigned by TDDFT-SOR calculations (*J. Nat. Prod*., **2020**, *83*, 268-276).

With hypervalent iodine(III) oxidation of juncuenin B, eleven racemic semisynthetic compounds were produced, the majority containing an alkyl substituted *p*-quinol ring. Stereoisomers of the cytostatic derivatives were separated by chiral-phase HPLC and absolute configurations of the active compounds, 2,6-dioxo-1,8a-dimethoxy-1,7-dimethyl-8-vinyl-9,10-dihydrophenanthrenes, and 8a-ethoxy-1,7-dimethyl-6-oxo-8-vinyl-9,10-dihydrophenanthrene-2-ols were determined by ECD measurements and TDDFT-ECD calculations (*J. Nat. Prod*., **2020**, 83, 3250-3261).

The covalent coupling of hydrophobic carotenoids with hydrophilic flavonoids, such as daidzein and chrysin, was achieved, resulting in new amphipathic structures. ECD and UV-vis analysis of covalently linked zeaxanthin–flavonoid conjugates revealed that they form different optically active J-aggregates in acetone/water and tetrahydrofuran/water mixtures depending on the solvent ratio and type of the applied aprotic polar solvent, while the capsanthin derivatives showed no self-assembly. The zeaxanthin bis-triazole conjugates with daidzein and with chrysin, differing only in the position of a phenolic hydroxyl group, showed significantly different aggregation profile upon the addition of water (*Molecules*, **2020**, *25*, 636).

Fermentation of *C. sphaerospermum* on solid rice medium yielded three new hybrid polyketides, cladosins L-N (1e3), and a known derivative cladodionen. The absolute configurations of compounds were determined by Mosher's method and TDDFT-ECD calculations. Cladodionen exhibited cytotoxicity against the mouse lymphoma cell line L5178Y with an IC_{50} value of 3.7 μM, and also exhibited antifungal activity against *Ustilago maydis* and *Saccharomyces cerevisiae*, while cladosin L displayed week antibacterial activity against

Staphylococcus aureus ATCC 29213 and *S. aureus* ATCC 700699 with MIC values of 50 and 25 μM, respectively (*Eur. J. Med. Chem*., **2020**, *19*1, 112159).

Alternarin A, a rearranged drimane meroterpenoid characterized by a thioglycerate moiety, was isolated together with two known analogues from the coral-associated fungi *Alternaria sp*. ZH-15. Its structure was determined based on spectroscopic analysis, modified Mosher's method, and TDDFT-ECD calculations (*Org. Lett*., **2020**, *8*, 2995-2998).

Covering the period 2012-2018, our contribution to the configurational assignment of natural products by chiroptical methods were summarized in a *Natural Product Reports* review (**2019**, *36*, 889-918). The principles and applicability of optical rotation, and electronic and vibrational circular dichroism aided by quantum chemical calculations were presented to determine absolute con*fi*guration and conformation through examples of stereochemical analysis of natural products with emphasis on the possibility of combined analysis and pitfalls for natural product chemists.

The absolute configurations of a butenolide derivative, aflaquinolone I and terrestric acid hydrate, isolated from a marine-derived strain of the fungus *Metarhizium marquandii*, were determined by the combination of OR, ECD, and VCD measurements and calculations. The (*3R*,4*R*) absolute configuration of aflaquinolone I was found to be opposite of the (3*S*,4*S*) absolute configuration of the related aflaquinolones A-G, suggesting that the fungus *M. marquandii* produces aflaquinolone I with a different configuration *(J. Nat. Prod*., **2019**, *82*, 2460-2469).

Starting from a substituted 2*H*-chromene derivate, domino cyclization reactions were performed affording condensed *O*,*N*-heterocycles, *N*-substituted 1,2-dihydrochromeno[2,3-c]pyrrol-3-one derivatives. Isomerization of the double bond and the inherently labile stereogenic center was studied, and HPLC-ECD analysis of a chiral 1,2-dihydrochromeno[2,3-c]pyrrol-3(3a*H*)-one derivative aided by TDDFT-ECD calculation allowed configurational assignment of the separated enantiomers. Antiproliferative activity of the products was demonstrated on the CaCo-2 human epithelial colorectal adenocarcinoma cell line. (*Synlett,* **2019**, *30*, 799-802).

New cytotoxic brominated azaphilone stereoisomers were isolated from the fungus *Penicillium canescens*, the absolute configurations of which were determined by the sTDA ECD calculations (*J. Nat. Prod*., **2019**, *82*, 2159-2166).

The absolute configuration of dihydrolateropyrone, isolated from the co-culture of the fungus *Fusarium tricinctum* with *Streptomyces lividans*, was determined by TDDFT-ECD calculations of its two stereoisomers (*RSC Adv*., **2019**, *9*, 1491-1500).

Stereochemistry and ring tautomers of synthetic aryl-substituted glucopyranosylidene-spiro-imidazolinones, having glycogen phosphorylase inhibitory activity, were investigated by TDDFT-ECD and DFT-^{13}C NMR calculation to aid identifying structure-activity relationships (*J. Med. Chem*. **2019**, *62*, 6116-6136).

Spiro-configurations of synthetic glucopyranosylidene-spiro-benzo[b][1,4]oxazinones and -benzo[b][1,4]thiazinones with plant-growth inhibitory activity were determined by TDDFT-ECD calculations (*J. Agric. Food Chem*., **2019**, *67*, 6884-6891).

Absolute configuration of the separated enantiomers of the racemic cytotoxic natural product, cryptomeriolide, was determined by TDDFT-ECD calculations (*J. Nat. Prod.,* **2018**, *81*, 2667-2672).

The solution TDDFT-ECD approach was applied to determine the absolute configurations of three new compounds as well as that of the previously reported bulgarialactone B, for which the absolute configuration was unknown so far. TDDFT-ECD analysis also allowed determining the absolute configuration of (+)-epicocconone, which had an enantiomeric absolute configuration in the tricyclic moiety compared to that of the related bulgarialactone B (*RSC Adv*., **2019**, *9*, 25119-25132).

A combination of TDDFT-ECD, TDDFT-SOR, DFT-VCD and DFT-NMR calculations were applied to determine the absolute and relative configurations of a new sesquiterpene derivative and a cytotoxic bismacrolactone derivative isolated from the co-cultivation of T*richocladium* sp. with *Bacillus subtilis* (*RSC Adv*., **2019**, *9*, 27279-27288).

Absolute configurations of natural products, isolated from the coral-associated fungus *Pseudallescheria boydii* TW-1024-3, including the sulfur stereogenic center of a sulfoxide moiety, were determined by comparison of experimental ECD spectra to TDDFT-ECD calculations. Epimeric chiral sulfoxides differing in the absolute configuration of the sulfur chirality center could be efficiently distinguished and assigned by comparing the experimental ECD to those of calculations for the sulfur epimers (*J. Nat. Prod*. **2019**, *82*, 1274-1282).

The absolute configuration of a chiral tetralone derivative, isolated from fruit peel of *Elaeagnus rhamnoides*, was determined by TDDFT-ECD calculations allowing evaluation of the tetralone helicity rule (*Tetrahedron*, **2019**, *75*, 1364-1370).

The solution TDDFT-ECD approach was utilized to determine the absolute configuration of five optically active epoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl)chromone derivatives and a

tricyclic prezizaane-type sesquiterpenoid isolated from the Chinese agarwood (*Fitoterapia*, 2019, 134, 182-187, *Fitoterapia*, **2019**, *138*, 104301).

The stereochemisry of a dimeric natural product from the aerial parts of *Helichrysum italicum*, containg α- and γ-pyrone unit, was investigated by ECD calculations (*Fitoterapia*, **2019**, *133*, 80-84).

TDDFT-ECD calculations of 22-epi-aflaquinolone B and two new anthraquinones, isolated from the co-culture of the sponge-associated fungus *Aspergillus versicolor* with *Bacillus subtilis*, were performed allowing their configurational assignment (*Planta Med.*, **2019**, *85*, 503-512).

The contribution of the unstructured secondary structure elements were estimated by ECD measurements and deconvolution of the fuzzy proteins c-Fos, c-Jun, their complex and mutants of c-Fos to assess the impact of the mutations on c-Fos structure in the free form and in complex with full-length c-Jun (*J. Mol. Biol*., **2019**, *431*, 1700-1707).

Fourteen new natural products were isolated from the marine-derived fungus *Talaromyces rugulosus* living in the Mediterranean sponge *Axinella cannabina* containing three butenolides, seven resorcylide derivatives, two butenolide-resorcylide dimers and two dihydroisocoumarin derivatives. The butenolide-resorcylide dimers talarodilactones A and B exhibited potent cytotoxicity against the L5178Y murine lymphoma cell line with IC_{50} values of 3.9 and 1.3 μM, respectively. Their absolute configuration was determined by TDDFT-ECD calculations carried out on butenolide and resorcylide derivatives. For the configurational assignment of the two dihydrocoumarin derivatives, ECD calculation was performed on a truncated model compound, which not only afforded the absolute configuration but also allowed evaluating the correlation between the n-π* Cotton effect and the helicity of the condensed heteroring (helicity rule). Results were published in *Mar. Drugs* **2017**, *15*, 359.

Swinhoeisterols C-F, four new steroids having a rearranged 6/6/5/7 ring system, were isolated from the sponge *Theonella swinhoei*, and combination of TDDFT-ECD and OR calculations was applied to elucidate the absolute configuration, since one of the compounds exhibited oppositely signed specific rotation from those of other swinhoeisterols. The chiroptical study verified the homochirality of the family supposed upon biogenetic considerations. In an *in vitro* assay, swinhoeisterols C showed potent (h)p300 inhibitory activity with an IC_{50} value of 8.8 μM. Results were published in the *J. Nat. Prod.* **2018**, *81*, 1645-1650.

Three new cytotoxic 2-methoxy acetylenic acids and three new natural pyrazole alkaloids were isolated from an Indonesian marine sponge of the genus *Cinachyrella*. The absolute

configuration of the acetylenic acid derivatives was established by ECD spectroscopy and results were published in *Mar. Drugs* **2017**, 15, 356.

A novel 10-membered macrolactone, hypoxylide, was isolated from the endophytic fungus *Annulohypoxylon* sp. obtained from the Mangrove plant *Rhizophora racemosa*. TDDFT-ECD calculations were applied on two stereoisomers to determine the absolute configuration and confirm the *trans* annulation of the fused ten-membered ring system. Results were published in *Tetrahedron Lett.* **2018**, *59*, 632-636.

Two new axially chiral biaryl and one cytotoxic dihydroquinolone derivatives were isolated from *Aspergillus versicolor*, an endophyte derived from leaves of the Egyptian water hyacinth *Eichhornia crassipes*. The axial chirality of the 7,7′-linked isocoumarin homodimers was deduced by TDDFT-ECD calculations. The studies were reported in *Phytochem. Lett.* **2018**, *24*, 88-93.

Synthesis of eight racemic hexahydropyrrolo[1,2-a]quinoline derivatives was performed by utilizing the Knoevenagel-[1,5]-hydride shift-cyclization domino reaction, from which one possessed moderate acetylcholinesterase inhibitory activity, while another derivative showed neuroprotective activity in oxygen-glucose deprivation-induced neurotoxicity in human neuroblastoma SH-SY5Y cells. Separation of the enantiomers of the chiral products was carried out by chiral HPLC, and online HPLC-ECD spectra were recorded to elucidate the absolute configuration by comparing the experimental and TDDFT-ECD spectra obtained at various theoretical levels. The results were published in a special issue dedicated to the Chirality conference 2017 held in Rennes (*Chirality* **2018**, *30*, 866-874).

Two new cryptic 3,4-dihydronaphthalen-(2*H*)-1-one (1-tetralone) derivatives, aspvanicin A and its epimer aspvanicin B, were obtained from the ethyl acetate extract of the co-culture of the endophytic fungus *Aspergillus versicolor* KU258497 with the bacterium *Bacillus subtilis* 168 trpC2 on solid rice medium. Their relative and absolute configurations were determined by the combination of NMR and electronic circular dichroism (ECD) analysis aided by DFT conformational analysis and TDDFT-ECD calculations. The ECD calculations revealed that although the sign of the blue-shifted overlapping n-pi* transition follows the helicity rule of cyclic aryl ketones, the calculation of low-energy conformers and ECD spectra were necessary to determine the stereochemistry. One of the new diastereomers showed moderate cytotoxic activity against the mouse lymphoma cell line L5178Y. The results were published in *Tetrahedron Lett.* **2018**, *59*, 2647-2652.

Allene carotenoids such as neoxanthin, (9’Z)-neoxanthin and capsoneoxanthin were isolated from the fruit of red mamey (*Pouteria sapota*) in milligram amounts and with high purity, which

allowed their spectroscopic characterization. ECD spectra for the neoxanthin isomers were in good accordance with literature data, whereas the ECD spectrum of capsoneoxanthin suggested aggregate formation in n-hexane solution. The results were published in *J. Food Compos. Anal*. **2018**, *65*, 1-5.

Luzulin A, a new 1,6-dihydroxy-2-keto-1,7-dimethyl-8-vinyl-1,2- dihydrophenanthrene derivative isolated from the plant *Luzula luzuloides*, was investigated by chiral HPLC, online HPLC-ECD and TDDFT-ECD studies. The plant contains this compound as a scalemic mixture and the absolute configuration of the major enantiomer could be determined as (*S*). Results were published in the paper *Fitoterapia* **2017**, *116*, 131-138.

The absolute configurations of two shikimic acid analogues and a butenolide derivative, isolated from mixed fermentation of the fungal endophyte *Chaetomium* sp. with an autoclaved culture of the bacterium *Pseudomonas aeruginosa* on solid rice medium, were determined by TDDFT-ECD calculations and the modified Mosher's method. Results were published in the *Eur. J. Org. Chem.* **2017**, 3256-3264.

Four new antibacterial cladosporol derivatives, cladosporols F-I, the known cladosporol C, and its new epimer, cladosporol J, were isolated and identified from the marine algal-derived endophytic fungus *Cladosporium cladosporioides*. Their structures were determined by detailed interpretation of NMR and MS data, and the absolute configurations were established on the basis of TDDFT-ECD and OR calculations. The configurational assignment of cladosporols F and G showed that the previously reported absolute configuration of cladosporol A and all the related cladosporols need to be revised from (4′*R*) to (4′*S*). The results were published in the *Journal of Organic Chemistry* (**2017**, *82*, 9946-9954).

The absolute configurations of the spirocyclic glucopyranosylidene-spiro-thiazolin-4-one and its methanol adduct were studied by TDDFT-ECD calculations, which was found suitable to distinguish the epimers having different absolute configuration at the spiro heterocyclic ring. The results were published in the *Molecules* **2017**, *22*, 1760.

Eight new hydroquinone derivatives, gliomastins A–D, 9-O-methylgliomastin C, acremonin A 1-O-beta-D-glucopyranoside, gliomastin E 1-O-beta-D-glucopyranoside, and 6'-O-acetyl-isohomoarbutin, together with seven known analogues were isolated from the marine-derived fungus *Gliomastix sp*. Their structures were elucidated by extensive spectroscopic analysis including 1D and 2D NMR measurements aided by DFT NMR calculations as well as MS data. TDDFT-ECD and OR calculations were performed to determine the absolute configurations of gliomastins A and the aglycones acremonin A and gliomastin E. Results were published in the *RSC Adv*. **2017**, *7*, 30640-30649.

Dynamic kinetic resolution of ethyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate was performed by different hydrolases and the absolute configuration of the corresponding acids were elucidated by TDDFT-ECD and OR methods. Interestingly, computed ECD spectra of the cationic form of the amino acid containing the charge in the ring displayed nearly mirror-image computed ECD spectra in the gas-phase and the PCM calculations. OR calculations verified the more sophisticated solvent model results. By computing for the anionic species obtained by addition of NaOH, the charge was taken away from the ring affording similar gas-phase and PCM ECD results justifying the absolute configuration. The results were published in the *Eur. J. Org. Chem.* **2017**, *2017*, 4713-4718.

Fourteen new polyketides with a *trans*-fused decalin ring system, libertalides A−N, together with two known analogues, aspermytin A and its acetate, were isolated from the fermentation extract of a coral-derived *Libertasomyces sp.* fungus. Their relative configurations were elucidated on the basis of detailed spectroscopic analysis, and the absolute configurations were determined by TDDFT-ECD and optical rotation (OR) calculations. Results were accepted for publication in the *J. Nat. Prod*. (doi: 10.1021/acs.jnatprod.7b00463).

Two new lignan-iridoid glucoside diesters, together with their putative biosynthetic precursor 10-O-*trans*-caffeoyl-6alfa-hydroxyl-dihydromonotropein, were characterized from the leaves of *Vaccinium bracteatum*. Their planar structures and relative configuration were elucidated by spectroscopic measurements and DFT C-NMR calculations, and their absolute configurations were determined by time-dependent density functional theory (TDDFT) electronic circular dichroism (ECD) calculations. Since high-wavelength region of the two dimers were almost in mirror-image relationship and the monomer has only transitions below 280 nm, the first three transitions could be attributed to the newly formed two chirality centers allowing application of model compounds for the ECD and NMR calculations. While ECD calculations unambiguously determined the absolute configuration of C-2", they gave no information about the C-3" center. Relative configuration and absolute configuration of the latter one was established by DFT calculations of the carbon NMR shift values. The studies were reported in the *Tetrahedron* **2017**, *73*, 3213-3219.