Final report on the PD-121020 project titled „Quantumchemical calculations for studying stereochemistry and reaction mechanisms”

principal investigator: Attila Mándi

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In the frame of the PD-121020 project, the following research goals and activities were supported by the NKFI:

1) Elucidation of the absolute configuration of isolated natural products by combined application of chiroptical methods (ECD, VCD, OR). Versatile potent biologically active compounds are isolated by our international co-operation partners, for which the determination of absolute stereochemistry is fundamental.

2) Elucidation of the absolute configuration and conformation of synthetic derivatives by ECD and VCD analysis and computation of their spectra. Bioactive *O*- and *O*,*N*-heterocycles are prepared in our institute which also need to be characterized by chiroptical data in order to correlate the stereochemistry with the pharmacological activity.

3) Computation of spectroscopic properties focusing on NMR parameters applicable for elucidation of the relative configuration of novel heterocyclic scaffolds.

4) Mechanistic studies of synthetic derivatives. Focusing on the computation of activation parameters and energy surfaces.

5) Reducing molecular flexibility by chemical derivatization or application of solid-state techniques for conformationally flexible systems. Low flexibility usually means lower computational costs and higher reliability.

In the three-year period of the NKFI project, 27 ESI papers came out (7 out of these with open access) and 1 manuscript is under revision in the research topics specified above and with reference to the financial support of NKFI. The scientific achievements are detailed below.

1) Elucidation of the absolute configuration of isolated natural products by ECD, VCD and OR methods and their combination.

Chiroptical methods (ECD, VCD, OR) based on the interaction of linearly polarized light and non-racemic chiral matter can provide information for both configuration and conformation of the studied derivative, hence one can investigate absolute configuration by knowing conformation and vice versa. In silico computations can find the low-energy conformations and provide the spectroscopic data for the given conformers which can be utilized for comparison with experimental data to elucidate stereochemistry. In most cases the solution conformers have to be computed with different methods and subsequent chiroptical calculations of the conformers are also performed at various levels to check possible level and solvent dependencies and make a solid assignment. Combination of these chiroptical methods with each other or with further techniques can be also applied in cases where the results of a single technique are not enough for a safe determination. Sometimes chiroptical studies alone can elucidate also the relative configuration or lead to the revision of the absolute and / or relative configuration. In the case of racemic and scalemic mixtures the online HPLC-ECD technique is one of the best choice to elucidate stereochemistry of the stereoisomers.

Six natural products were isolated from the plant *Luzula luzuloides* from which the novel luzulin A was investigated by HPLC-ECD and TDDFT-ECD studies. The plant contains this compound in a non-racemic (scalemic) mixture and the absolute configuration of the major enantiomer could be determined as (*S*). Results were published in *Fitoterapia* **2017**, *116*, 131-138.

Two new lignan-iridoid glucoside diesters were isolated from the leaves of *Vaccinium bracteatum* and their relative and absolute configuration was determination by DFT NMR and TDDFT-ECD calculations. (Due to the NMR calculations this project also belongs to point 3.) 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 3 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.

Eight new hydroquinone derivatives were isolated from the marine-derived fungus *Gliomastix* sp. for three of which the absolute and relative configuration was elucidated by ECD, OR and NMR TDDFT and DFT calculations. (Due to the NMR calculations this project also belongs to point 3.) The ECD and OR methods were applied for all theoretically studied compounds, while computed C and H-NMR shift values were required for gliomastin A to verify the supposed relative configuration. The latter compound exhibited potent cytotoxic activity. The results were published in the *RSC Adv.* **2017**, *7*, 30640-30649. (open access)

Five fungal metabolites obtained by mixed fermentation of a fungus and a bacterium were investigated by ECD and TDDFT-ECD methods. In the case of chaetoisochorismin ECD alone was able to tell both the relative and the absolute configuration due to the comparable impact of the two chirality centers on the experimental ECD curve. The relative configuration established by ECD was in line with the NMR results. For three compounds solution ECD was able to elucidate the absolute configuration of the major enantiomer of non-racemic mixtures without application of any HPLC-ECD technique. Results were published in *Eur. J. Org. Chem.* **2017**, *2017*, 3256-3264.

Six cladosporol derivatives were isolated from the marine algal-derived endophytic fungus *Cladosporium cladosporioides* the TDDFT-ECD and OR investigation of which resulted in the configurational revision of all previously reported cladosporol derivatives. Absolute and relative configuration of cladosporol A was elucidated in the literature by comparison of a distantly related natural product and ECCD technique without any proper knowledge on the conformational distribution of the target compound. ECD and OR results of the four theoretically investigated cladosporols (including the known cladosporol C) and the parent compound cladosporol A (described in the literature) unequivocally indicated (4’*S*) absolute configuration in the cladosporol family. These compounds also bear potent cytotoxic activities. The studies were reported in the *J. Org. Chem.* **2017**, *82*, 9946-9954.

Several butenolides, resorcylides, butenolide-resorcylide dimers and dihydroisocoumarin derivatives were isolated from the marine-derived fungus *Talaromyces rugulosus* living in the Mediterranean sponge *Axinella cannabina*. TDDFT-ECD calculations were performed for 3 derivatives and the results in combination with literature data allowed elucidation of the AC or that of the major enantiomer of the non-racemic isolated compounds. Some of the molecules exhibited potent cytotoxicity against the L5178Y murine lymphoma cell line. Results were published in *Mar. Drugs* **2017**, *15,* Article number 359. (open access)

Fourteen new polyketides with a *trans*-fused decalin ring system were isolated from the fermentation extract of a coral-derived *Libertasomyces* sp. fungus. Their stereochemistry was studied by TDDFT-ECD and OR calculations. Interestingly, the OR of the known aspermytins were found to have opposite signs in MeCN and $CHCl_3$, which was in agreement with the OR calculations producing alternating signs for the optical rotation depending on the applied conditions. Because the signs of the OR showed high solvent dependence, they may not be used alone to correlate the absolute configurations. ECD calculations performed on 5 derivatives gave consequent results and allowed unambiguous determination of the absolute configuration of the isolated series of compounds. Some of these molecules significantly induced the proliferation of $CD3^+$ T cells. This is the first report of immunoregulatory activity for metabolites of this kind. The studies were reported in the *J. Nat. Prod.* **2017**, *80*, 2930-2940.

Three new isocyanoditerpenes have been characterized from Australian nudibranch *Phyllidiella pustulosa*. The planar structure and absolute configuration was determined by experimental and computational NMR methods (the NMR calculations were performed by the partners) in combination with TDDFT-ECD calculations. A catalyst-controlled enantio- and diastereoselective total synthesis of the most likely diastereomeric candidates for the structure of pustulosaisonitrile-1 solidified its AC. (Due to the total synthesis this project also belongs to point 2.) The natural and some synthetic diastereomers showed high activity against *Plasmodium falciparum* malaria parasites. The results were published in the *J. Org. Chem.* **2017**, *82*, 13313-13323. The paper was selected into an ACS Select Virtual Issue showcasing a snapshot of the nicest works in total synthesis of natural products published in the Journal of the American Chemical Society, The Journal of Organic Chemistry, and Organic Letters in the last 18 months.

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 to elucidate the AC and *trans* annulation of the fused ten-membered ring system. Results were published in *Tetrahedron Lett.* **2018**, *59*, 632-636.

Two new biphenyl derivatives and one new dihydroquinolone were isolated from *Aspergillus versicolor*, an endophyte derived from leaves of the Egyptian water hyacinth *Eichhornia crassipes*, together with ten other known metabolites. The axial chirality of the isocoumarin 7,7′-homodimers was deduced by TDDFT-ECD calculations. Several tested compounds revealed significant cytotoxic activity against mouse lymphoma L5178Y cell line. The studies were reported in *Phytochem. Lett.* **2018**, *24*, 88-93.

Two new cryptic 3,4-dihydronaphthalen-(2*H*)-1-one derivatives and several known cryptic metabolites 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. When *A. versicolor* was cultured axenically in liquid Wickerham medium supplemented with 3.5% DMSO, additional three known secondary metabolites were isolated that were lacking when the fungus was fermented on rice medium. The AC of the two new tetralones was determined by 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-π^* transition follows the helicity rule of cyclic aryl ketones, the calculation of low-energy conformers and ECD spectra was 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.

Four new steroids (swinhoeisterols C-F) having a rearranged 6/6/5/7 ring system, were isolated from the sponge *Theonella swinhoei*, together with a known analogue. A combination of TDDFT-ECD and OR calculations was applied to elucidate AC since one of the compounds exhibited opposite sign OR than all other swinhoeisterols. The chiroptical study verified the homochirality of the family supposed upon biogenetic considerations. In an *in vitro* assay, one compound showed potent inhibitory effect on (h)p300. Results were published in the *J. Nat. Prod.* **2018**, *81*, 1645-1650.

(±)-Cryptomeriolide, a pair of racemic bis-*seco*-abietane diterpenoids, were isolated from the bark of *Cryptomeria fortunei*. The separation of enantiomers was achieved by using chiral HPLC. The absolute configuration of the stereoisomers was determined by solution TDDFT-ECD and OR methods. Calculations were also carried out for the X-ray conformers but these gave nearly opposite spectra to the solution results due to the different conformation in solid-state and solution. Since solid-state spectra were not recorded, only the solution results could be taken into consideration. Since the investigated compound is rather flexible, a solid-state measurement and calculation could have result in saving a lot of computational time and a much faster way for elucidation of the absolute configuration. (That is it would have been a nice candidate for point 5.) Both enantiomers were prepared in a bioinspired one-pot synthesis starting from sugiol. (Due to the synthesis this project also belongs to point 2.) The results were described in *J. Nat. Prod.* **2018**, *81*, 2667-2672.

Co-cultivation of the endophytic fungus *Fusarium tricinctum* with *Streptomyces lividans* on solid rice medium led to the production of four new naphthoquinone dimers, fusatricinones A–D, and a new lateropyrone derivative, dihydrolateropyrone, that were not detected in axenic fungal controls. The relative and absolute configuration of dihydrolateropyrone was elucidated by TDDFT-ECD calculations. Computed ECD spectra obtained for the *cis* isomer at various combinations of applied levels gave a mismatch while the *trans* isomer gave moderate to good agreement with the experimental spectrum. In line with some of our previous results the small experimental coupling constant can derive also from *trans*-diaxial orientation of the large substituents. The co-operation partners checked the rotational energy barrier of the naphthoquinone dimers on a model compound. Results were published in *RSC Adv.* **2019**, *9*, 1491-1500. (open access)

Two new 14-noreudesmane sesquiterpenes, one new phenylpropane heterodimer, caulilexin C, and uvaol were isolated from fruit peel of *Elaeagnus rhamnoides*. The absolute configuration of 6,9-dihydroxy-1-oxo-14-noreudesm-5,7,9-triene was determined by the TDDFT-ECD method since application of the semi-empirical 1-tetralone rule was questionable due to a chelating 9-OH group and an additional auxochrome 6-OH, and the equatorial/axial orientation of the 15-CH_3 group was not evident from the NMR data. All combinations of the applied methods gave moderate to good agreement allowing elucidation of the absolute configuration and indicated that indeed, the n-π* transition was not the first one and overlapped with a π-π* transition discouraging application of the semi-empirical rule for similar systems. Some of the isolated compounds showed promising antiviral activity against *Herpes simplex* virus type 2 (HSV-2). The results were described in *Tetrahedron* **2019**, *75*, 1364-1370.

A new cyclic pentapeptide, cotteslosin C, a new aflaquinolone, 22-epi-aflaquinolone B, and two new anthraquinones, along with thirty known compounds were isolated from a co-culture of the sponge-associated fungus *Aspergillus versicolor* with *Bacillus subtilis*. The new metabolites were only detected in the co-culture extract, but not when the fungus was grown under axenic conditions. Furthermore, the co-culture extract exhibited an enhanced accumulation of some of the known constituents. The absolute configuration of three compounds was determined by ECD analysis aided by TDDFT-ECD calculations. For one derivative a simple comparison with a previously known derivative was sufficient while conformational analysis and several combinations of theoretical levels were applied for the other two compounds. The nice mirror-image agreements and consistent results allowed elucidation of the absolute configuration with high confidence. Several compounds exhibited strong to moderate cytotoxic activity against the mouse lymphoma cell line L5178Y. Results were published in *Planta Med.* **2019**, *85*, 503-512.

Five new natural products were isolated from the endophytic fungus *Bulgaria inquinans* living in mistletoe (*Viscum album*), while subsequent application of the OSMAC strategy on this strain by the addition of a mixture of salts induced the accumulation of nine additional new secondary metabolites. The TDDFT-ECD method was applied to determine the absolute configurations of four new compounds including the previously reported bulgarialactone B, for which the absolute configuration was unknown so far. TDDFT-ECD analysis also allowed determining the absolute configuration of the close relative compound (+)-epicocconone, which had an enantiomeric absolute configuration in the tricyclic moiety compared to that of bulgarialactone B. Interestingly the AC of epicocconone was mistakenly indicated by the SciFinder while the papers published before elucidated only the RC applying both experimental and computational methods. One of the new metabolites possess strong cytotoxic activity against the murine lymphoma cell line L5178Y. The results were described in *RSC Adv.* **2019**, *9*, 25119-25132. (open access)

Ten new tricyclic prezizaane type sesquiterpenoids were isolated from agarwood originated from *Aquilaria* sp. The absolute configuration of 3 derivatives was determined by single-crystal X-ray diffraction, while TDDFT-ECD method was applied on 1 compound. Since the investigated compound was very rigid and various combinations of the applied methods gave similar ECD spectra, the AC could be elucidated with high confidence. Two derivatives displayed significant inhibitory activities toward α-glucosidase. Results were published in *Fitoterapia* **2019**, *138*, 104301.

The endophytic fungus *Trichocladium* sp. isolated from roots of *Houttuynia cordata* was cultured on solid rice medium, yielding two new natural products together with eight known compounds. Co-cultivation of *Trichocladium* sp. with *Bacillus subtilis* resulted in induction of a further new compound. When the fungus was cultivated on peas instead of rice, a new sesquiterpene derivative and two known compounds were obtained. Addition of 2% tryptophan to rice medium led to the isolation of a new bismacrolactone. A combination of TDDFT-ECD, TDDFT-SOR, DFT-VCD and DFT-NMR calculations were applied to determine the absolute and relative configurations of the new sesquiterpene and bismacrolactone. Both compounds contains 4 stereogenic centers and the RC of only 3 could be deduced from experimental data that is for both derivatived 2 diastereomers were investigated theoretically. While for the sesquiterpene it is likely that the experimental Boltzmann distribution could not be reproduced even by the application of several DFT functionals and solvent models, for the bismacrolactone all computed data tend to support the same absolute and relative configuration allowing elucidation of the stereochemistry. Several compounds exhibited strong cytotoxicity against the L5178Y mouse lymphoma cell line. The results were described in *RSC Adv.* **2019**, *9*, 27279-27288. (open access)

Trigonostemons G and H, two novel dimeric dinorditerpenoids, were isolated from the stem barks of *Trigonostemon chinensis*. Torsional scan and computation of the transition states were carried out to estimate the rotational energy barrier and the axial chirality was determined by TDDFT-ECD calculations. The manuscript is under revision in the Chirality journal.

The principles and applicability of OR, ECD and VCD techniques combined with conformational analysis and DFT/TDDFT calculations and other techniques in the field of natural products were summarized and demonstrated on instructive examples from the last years focusing mainly on the time span 2012-2018. The review also shows several pitfalls of the application of chiroptical methods. It discusses the results of 244 references in 30 pages. The review was published in *Nat. Prod. Rep.* **2019**, *36*, 889-918. (Since possibilities of reducing molecular flexibility by derivatization and solid-state methods were included, it also belongs to point 5.)

2) Elucidation of the absolute configuration of synthetic derivatives by ECD and VCD methods.

The absolute and relative configurations of the biomimetically synthesized dracocephins A and B were investigated by HPLC-ECD and TDDFT-ECD studies. A number of theoretical levels were tested for the parent compound naringenin and for the 4-4 stereoisomers of the two target compounds both at the DFT optimization and the ECD calculation levels. While the (2*R*) absolute configuration could be unambiguously elucidated for the 1st and 4th eluting diastereomers and consequently (2*S*) for the 2nd and 3rd ones of dracocephin A the absolute configuration of the other chirality center (C-5’’) tended to be opposite to the literature data, but the agreements found were not solid enough for a structural revision. The same tendency was found for dracocephin B. The results were published in the *Beilstein J. Org. Chem.* **2016**, *12*, 2523-2534. (open access)

New glucopyranosylidene-spiro-thiazolinones were synthesized at our department and relative and absolute configurations at C-1’ and C-2 were elucidated by TDDFT-ECD method. As expected by similarly protected monosaccharide examples from the literature, ECD spectra are mainly influenced by the aglycon part, *i.e.* the AC of C-1’ can be elucidated with high certainty. In the other case where the aglycon part contained an additional chirality center (C-2), both centers were similarly decisive for the ECD and

AC of both could be elucidated successfully. The results were published in *Molecules* **2017**, *22*, Article number 1760. (open access)

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 resulting in similar gas-phase and PCM ECD results further justifying the absolute configuration. The results were published in the *Eur. J. Org. Chem.* **2017**, *2017*, 4713-4718.

Synthesis of 8 racemic hexahydropyrrolo[1,2-a]quinoline derivatives was performed by utilizing the Knoevenagel-[1,5]-hydride shift-cyclization domino reaction. 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. For 1 of the products, the calculations allowed determining both the relative and the absolute configuration by distinguishing the 4 stereoisomers. One of the compounds possessed moderate acetylcholinesterase inhibitory activity, while an another derivative showed neuroprotective activity in oxygen-glucose deprivation-induced neurotoxicity in human neuroblastoma SH-SY5Y cells. The results were published in a special issue dedicated for the Chirality conference 2016 held in Rennes where I was a speaker and accordingly I was the major corresponding author of this paper. *Chirality* **2018**, *30*, 866-874.

Glucopyranosylidene-spiro-benzo[b][1,4]oxazinones were obtained via the corresponding 2-nitrophenyl glycosides obtained by two methods. Catalytic hydrogenation or partial reduction of the 2-nitro groups led to spirobenzo[b][1,4]oxazinones and spiro-benzo[b][1,4]-4-hydroxyoxazinones by spontaneous ring closure of the intermediate 2-aminophenyl or 2-hydroxylamino glycosides, respectively. The analogous 2-aminophenyl thioglycosides, prepared by reactions of *O*-perbenzoylated methyl (α-D-gluculopyranosyl bromide)heptonate with 2-aminothiophenols, were cyclized in m-xylene at reflux temperature to the corresponding spiro-benzo[b][1,4]thiazinones. Spiro-configurations were determined by NMR and TDDFT-ECD methods. The most interesting stereochemical finding of the study was that without any notable geometrical differences the *O*- and *S* series gave more or less opposite ECD spectra discouraging the reader to apply simple comparison of experimental ECD spectra to elucidate the absolute configuration even by closely related *O*- vs. *S*-containing heterocycles. Inhibition assays with rabbit muscle glycogen phosphorylase b and plant growth tests with white mustard and garden cress were tested with moderate effects. The results were published in the *J. Agric. Food Chem.* **2019**, *67*, 6884-6891.

Ethyl-3-formyl-6-methoxy-(2*H*)-chromene-2-carboxylate was transformed to *N*-substituted 1,2-dihydrochromeno[2,3-c]pyrrol-3-ones in a domino reductive amination-lactamization reaction. 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. The investigated compound was rather rigid and various combinations of levels gave consistent result resembling very well the experimental spectrum allowing an unambiguous elucidation of the AC. Antiproliferative activity of the products was demonstrated on the CaCo-2 human epithelial colorectal adenocarcinoma cell line. Results were reported in *Synlett* **2019**, *30*, 799-802.

Synthesis of 1,3-disubstituted tetrahydroisoquinoline and tetrahydroisochromane derivatives was successfully achieved in optically active form in our research group and neuroprotective activities were identified in some cases against oxidative injuries in human neuroblastoma SH-SY5Y cells. The stereochemistry (AC and conformation) has been studied by conformational analysis and a combination of solution ECD and VCD techniques. A manuscript from the results is in preparation.

In 2 papers summarized in point 1 the investigated natural products were prepared also synthetically, thus they belong also to this point.

3) Elucidation of the relative configuration by computation of NMR parameters.

A new class of heterocycles (called tricyclanos) containing three new chirality centers were synthesized at our university by substrate-controlled asymmetric synthesis with very high diastereoselectivity. Conventional NMR experiments alone were not able to tell the relative and absolute configuration of the new scaffold due to a dynamic equilibrium of conformers with equatorial and axial protons. NMR calculations were performed in the case of 2 derivatives for all possible 8 diastereomers and the most plausible one in the further cases. The results were verified by an X-ray experiment and H-H distances obtained from a new ROESY NMR method. The manuscript became a cover story and was published in the *Org. Biomol. Chem.* **2018**, *16,* 393-401.
2 papers summarized in point 1 contain also NMR calculations performed by me and thus belonging also to this point. In 1 further paper addressed in point 1 NMR calculations were performed by the co-operation partners (indicated above).

4) Mechanistic studies

Potential energy surfaces of the intended intramolecular Knoevenagel-hetero-Diels-Alder reaction leading to the experimental product and a plausible diastereomer were mapped and stationary points were identified with DFT calculations. The results show that the experimental product is both kinetically and thermodynamically preferential in line with the single isolated product. ECD calculations were also performed to elucidate the absolute configuration of the enantiomers. (The reaction was diastereoselective but not enantioselective.) Depending on the substituents two further types of heterocycles were also formed in the experiments carried out since the starting of this project. We are aiming to map also the mechanism of these new reactions in the future and plan a comprehensive paper on the intramolecular Knoevenagel-hetero-Diels-Alder reaction and it’s side reactions.

5) Reducing molecular flexibility by chemical derivatization or application of solid-state techniques

Optically active 1-aryl-propane-2-ol molecules were connected through a dicarboxylic acid linker and a biaryl bond was established under different reaction conditions which resulted in conformationally restricted biaryls containing both central and axial chirality elements. The central and axial chirality elements are studied by solution and solid-state ECD and VCD methods.

A natural product example described in point 1 was a nice candidate for solid-state studies with existing X-ray structures. The solid-state ECD spectrum, however, unfortunately could not be recorded for this molecule thus the AC was elucidated by the conventional solution ECD method.

The chiroptical review pictured in point 1 belongs also to this point since it describes possibilities of flexibility reduction by derivatization and solid-state methods.

Role in the project / published papers: Isolation of the natural products and biological tests were performed by the co-operation partners. I performed all the conformational analyses, DFT and TDDFT calculations described above except for 2 cases (addressed in point 1), in one case the DFT-NMR calculations and in an another one the torsional scans were carried out by the co-operation partners while the chiroptical studies were performed by me also in those cases. (The yearly CPU usage spent for this project was ca. 1 M CPU hours provided by the Governmental Information-Technology Development Agency (KIFÜ).) All of the VCD (mostly overnight measurements) and the non-routine ECD experiments were performed by me. The stereochemical part of all above mentioned papers were written by me and Prof. Tibor Kurtán together who is also a participant of this project. Both of us were involved in all parts of the chiroptical review but I was mainly focusing on the computational part, possibilities of simplifications (truncation, reclustering, chemical derivatization, applied theory, solid-state method etc.), combined applications and VCD (that is, mostly the second half of the review). C.a. half of the synthetic work connecting to point 2 was performed in our research group lead by Prof. Tibor Kurtán and the remaining half by the co-operation partners. Synthesis connecting to points 4 and 5 was also performed in our research group.