Synthesis and characterization of novel cyclohexane-based molecular triskelions

PhD thesis outline

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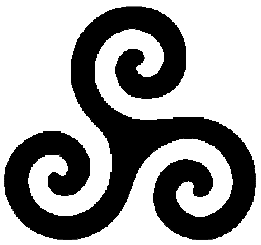
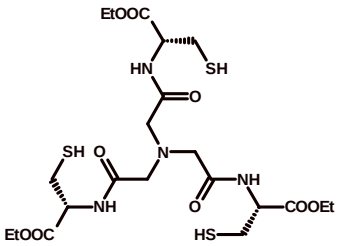
Introduction

Small molecules with receptor-like ion-binding properties, especially symmetric polydentate complexing agents are of great interest in medicinal and coordination chemistry, as shown by the large number of C_3 symmetric molecules (i.e. “molecular triskelions”) that have recently been synthesized.





Objectives

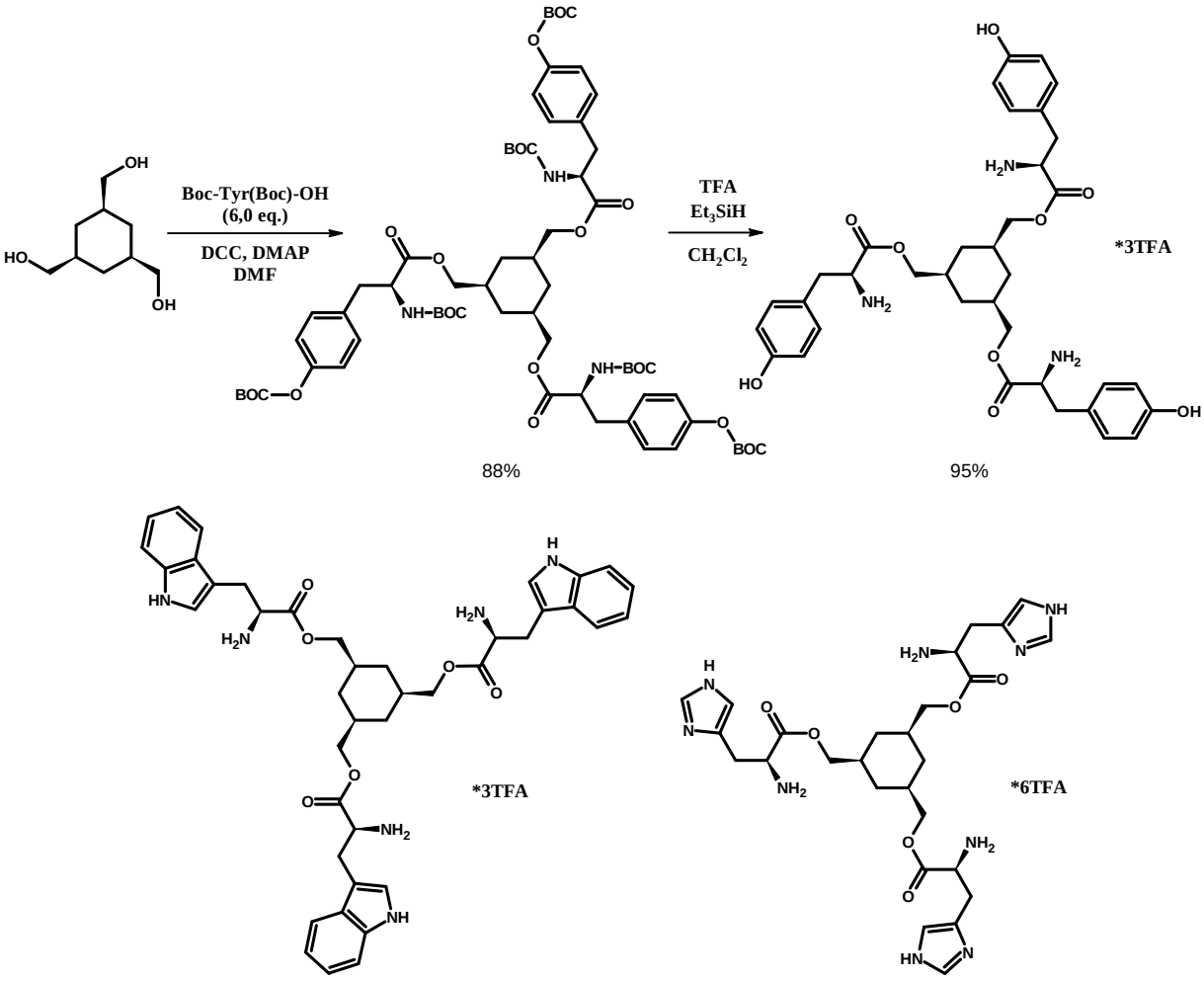
The aim of our work was to increase the variability, and characterize the newly synthesized entities. The main focus was on preparative organic synthesis of the compounds, while the characterization of their conformational behaviour and ion-binding properties was planned only by studying some specific aspects (e.g. NMR analysis, protonation, copper(I)-binding).

In 2006, Tajc and Miller created a new pH-switchable molecule by coupling tyrosine and cyclohexane 1,3,5-trimethanol which possesses a closed conformation only in the range of 9.2 < pH < 10.5 and can also serve as ion-receptor in aqueous solution at high pH either for various anions (e.g. Cl^-, Br^-) or cations (e.g. Zn^{2+}, Cd^{2+}). We have decided to synthesize this compound for thorough characterization, and aimed at designing other receptor molecules with various amino acid ‘arms’ to alter the structure’s pH-dependent behavior. For the better understanding of their protonation properties all derivatives’ mono- and disubstituted analogues were also created.

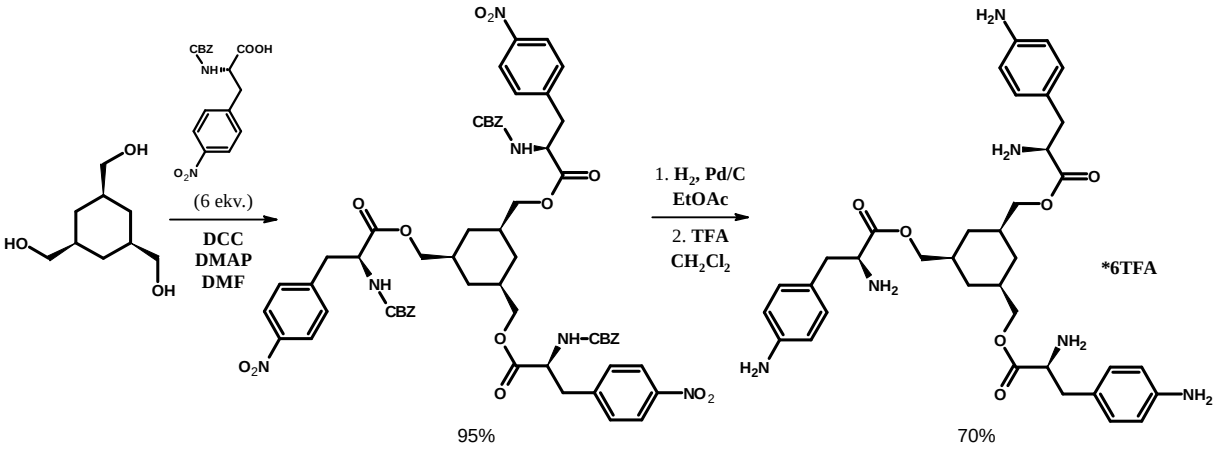
Further C_3 symmetric compounds were also planned to be synthesized by reversing the esterification procedure, and coupling cyclohexane 1,3,5-tricarboxylic acid with various alcohols (and amines). Designing the structures we focused on ion-binding functions, especially on 1,2,3-triazoles as building blocks by utilizing Cu(I) and Ru(II) catalysis. In the case of C_3 triazole derivatives we also decided to investigate their Cu(I)-binding capabilities.

Methods

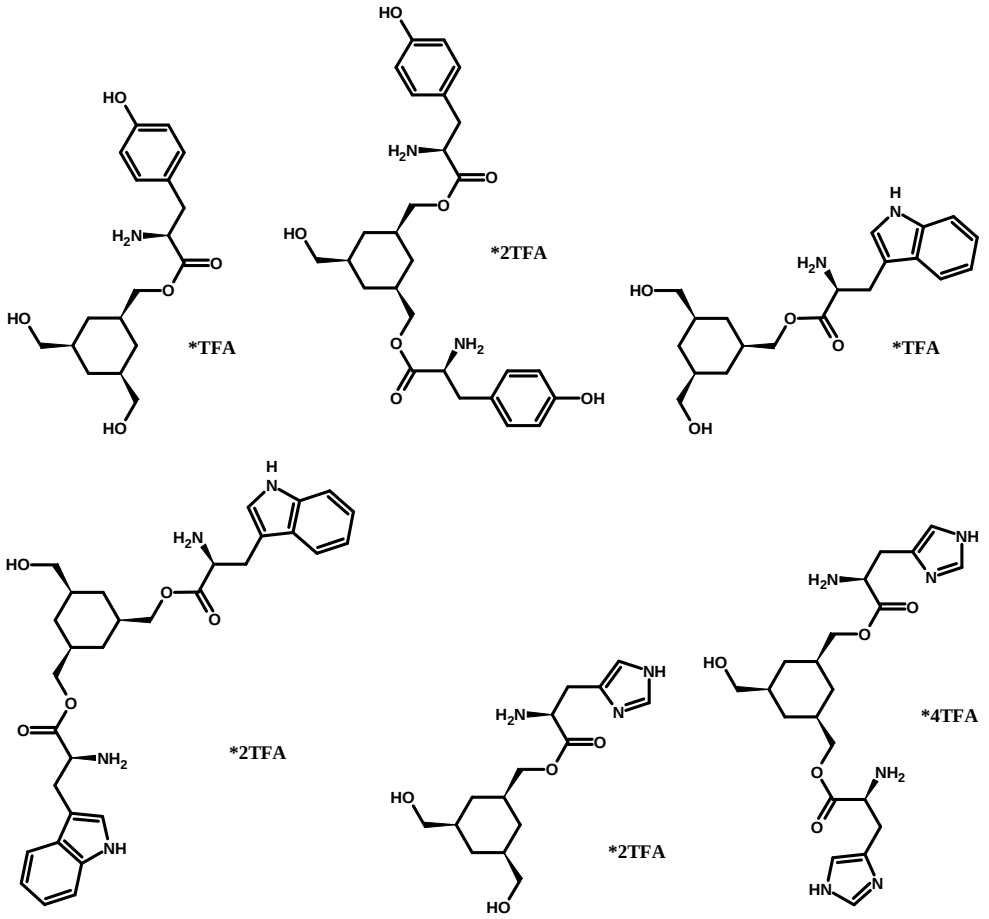
Cyclohexane 1,3,5-*cis*-trimethanol was coupled with a tert-butyloxycarbonyl protected amino acid (tyrosine, tryptophan, histidine) in the presence of *N*,*N'*-dicyclohexylcarbodiimide and 4-dimethylaminopyridine. After purification with column chromatography deprotection was accomplished with trifluoroacetic acid, yielding the final products as trifluoroacetate salts.

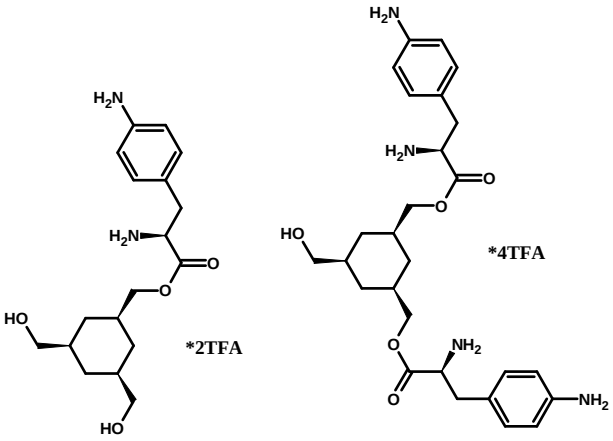


The derivative of the tyrosine analogue non-classical amino acid, *p*-amino phenylalanine was synthesized as well. The esterification step was carried out with carboxybenzyl-protected *p*-nitro phenylalanine; the deprotection was made with catalytic hydrogenation which reduced the nitro group simultaneously. Preventing the product from decomposition trifluoroacetate salt was formed with trifluoroacetic acid.

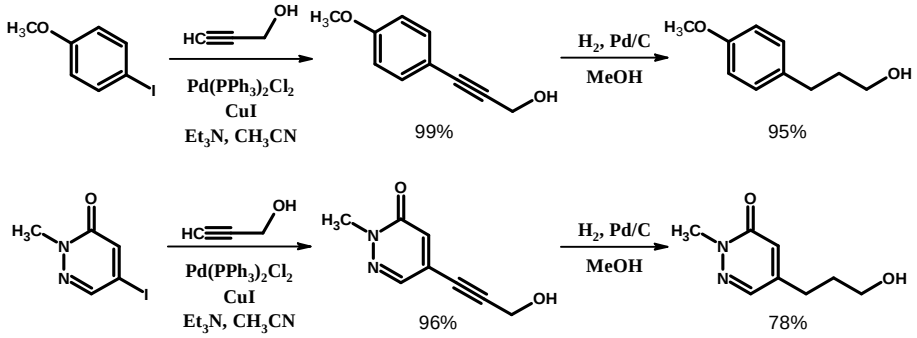


The mono- and disubstituted derivatives were also prepared for all above mentioned amino acid. Two equivalents of protected amino acid was used for the esterification step which produced the mixture of the protected mono- and disubstituted derivatives. After separation with column chromatography the protecting groups were removed, and trifluoroacetate salt products were formed.

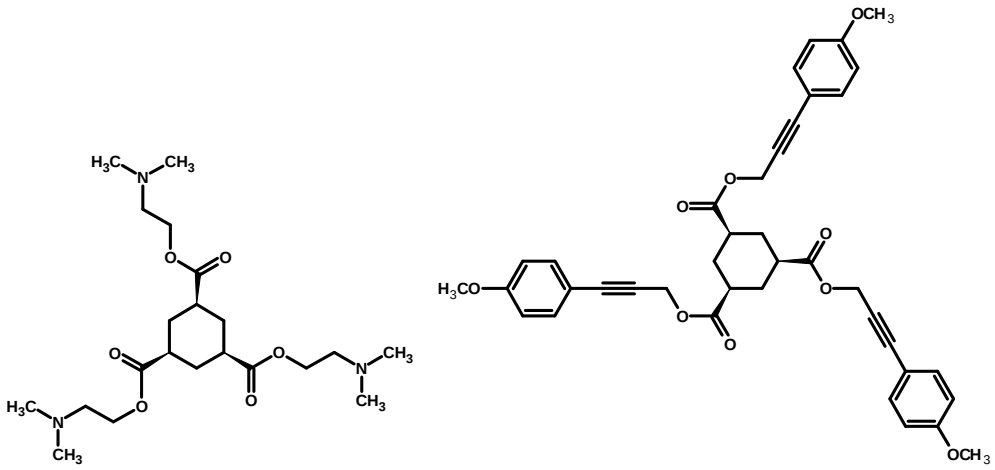


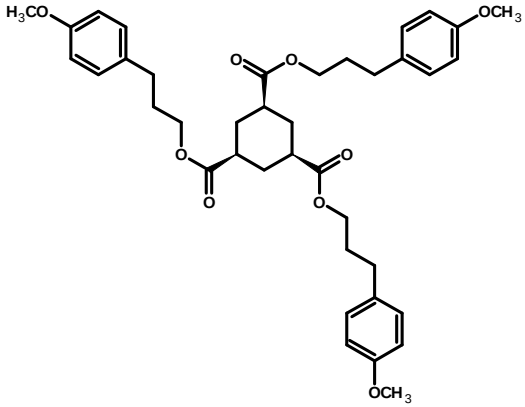


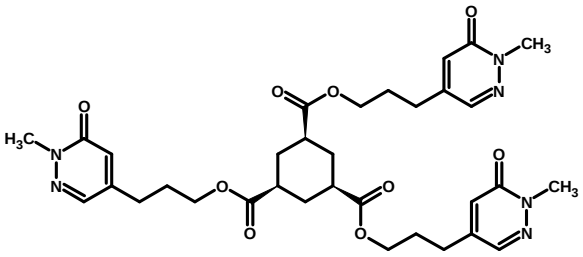
For further esters several saturated and unsaturated alcohols was prepared in Sonogashira reaction and in a subsequent catalytic hydrogenation step from 4-iodoanisole or 5-iodo-2-methylpyridazin-3(2*H*)one. The effect of the solvent on the Sonogashira reaction was also tested.

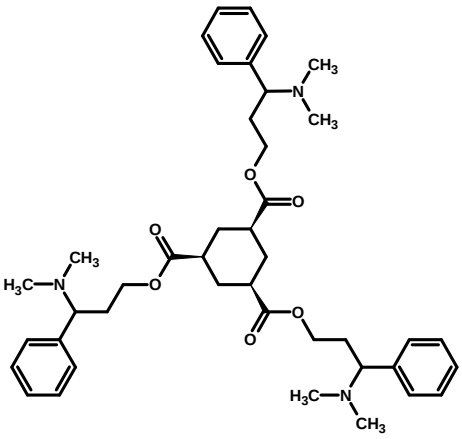


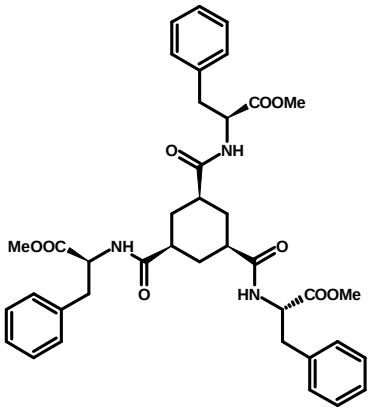
Reversing the previous esterification reaction, cyclohexane 1,3,5-*cis*-tricarboxylic acid was converted into acyl chloride and reacted with several alcohols and amines (obtained from commercial suppliers or synthesized previously).

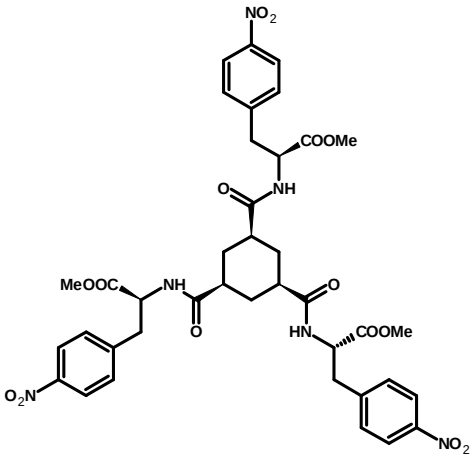


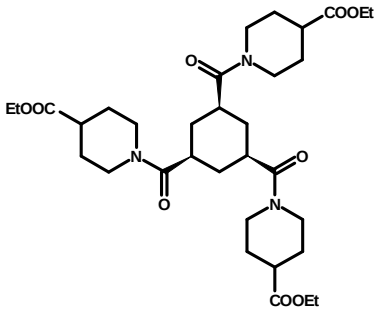


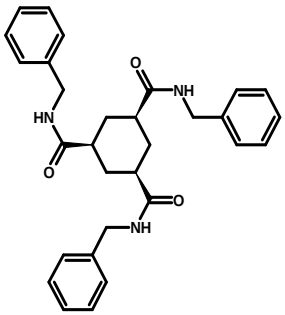


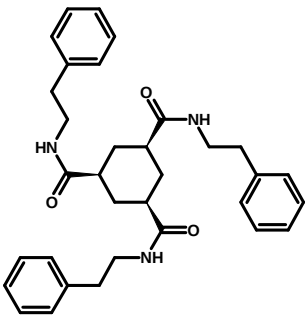


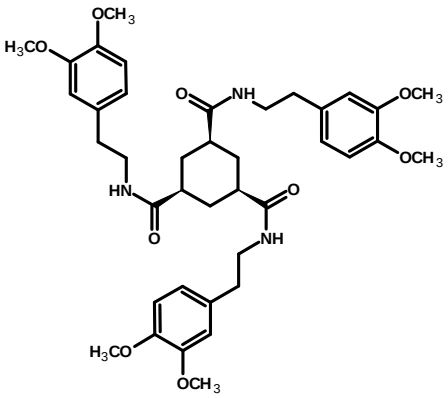




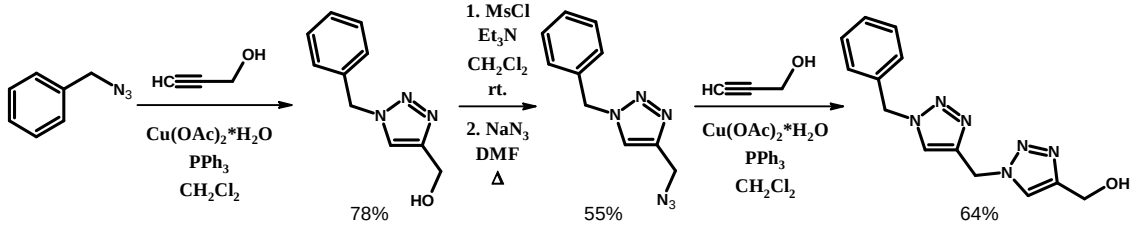


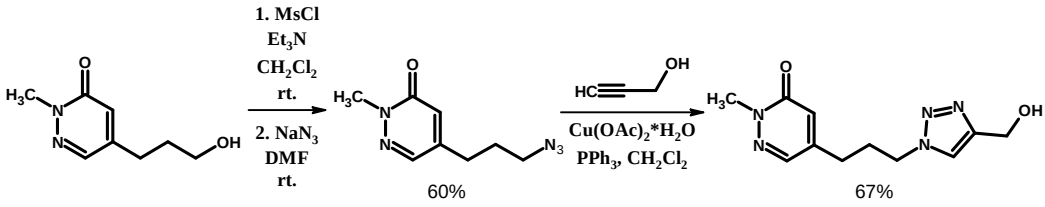


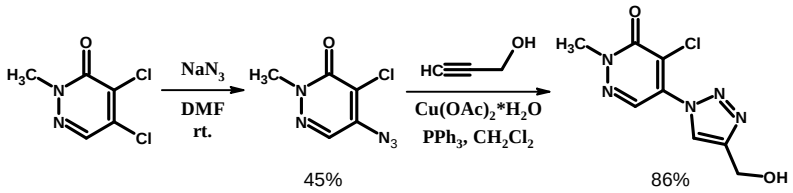


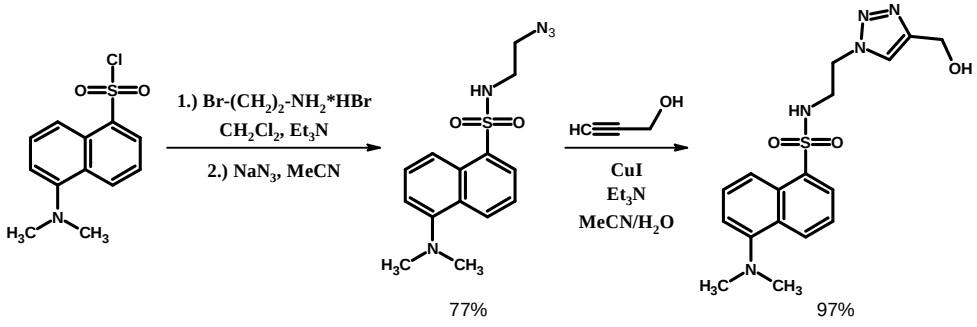


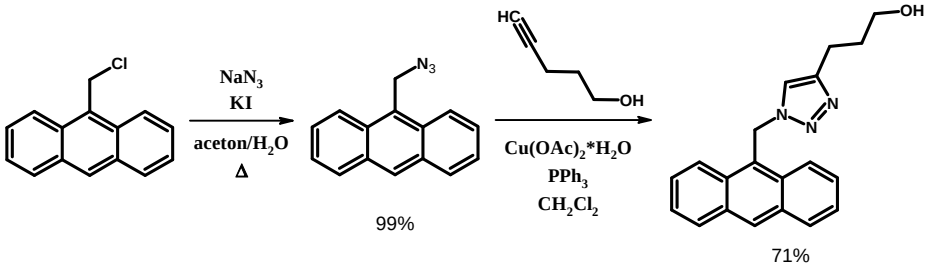
Due to solubility problems of the obtained amides, synthesis of the C_3 symmetric triazole derivatives was carried out solely by coupling cyclohexane 1,3,5-*cis*-tricarboxylic acid with an appropriate alcohol. The required triazole alcohols were synthesized from an azide and a terminal alkyne in copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) reaction.



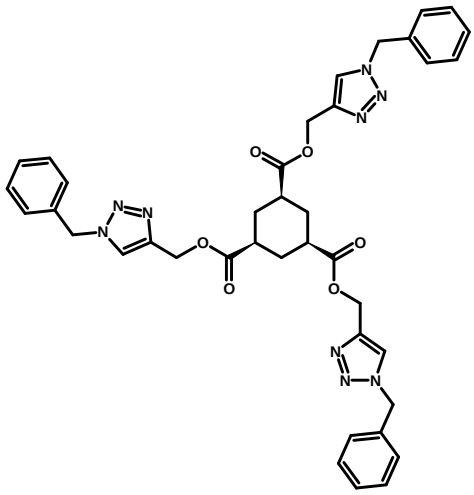


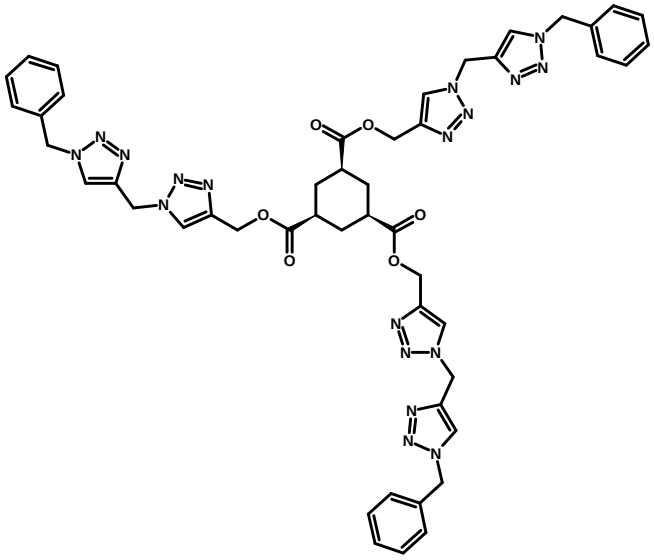


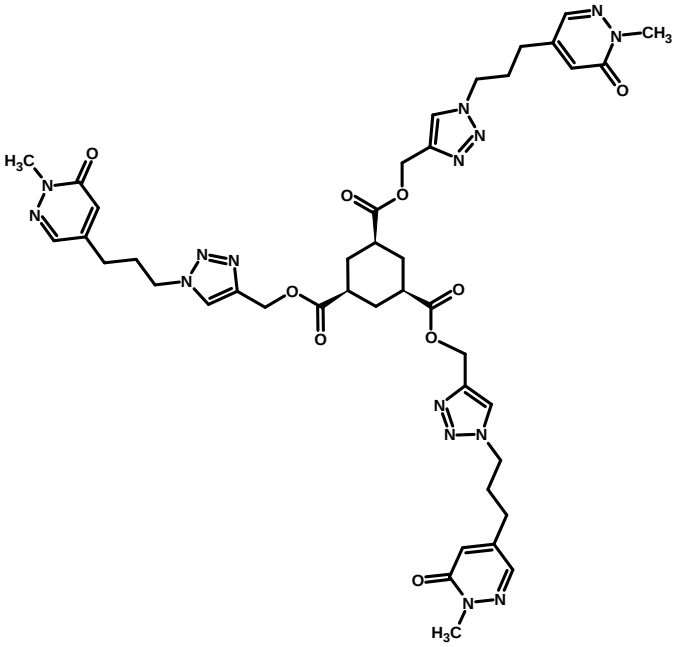


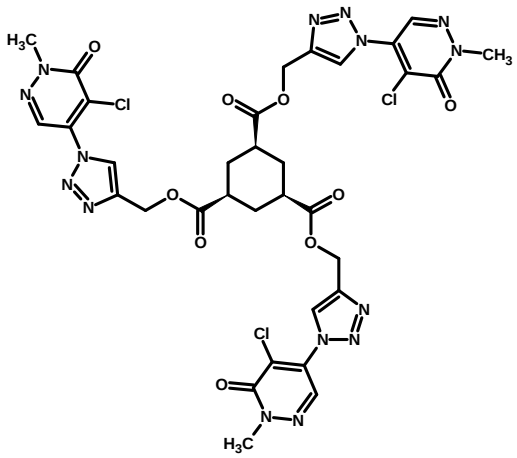


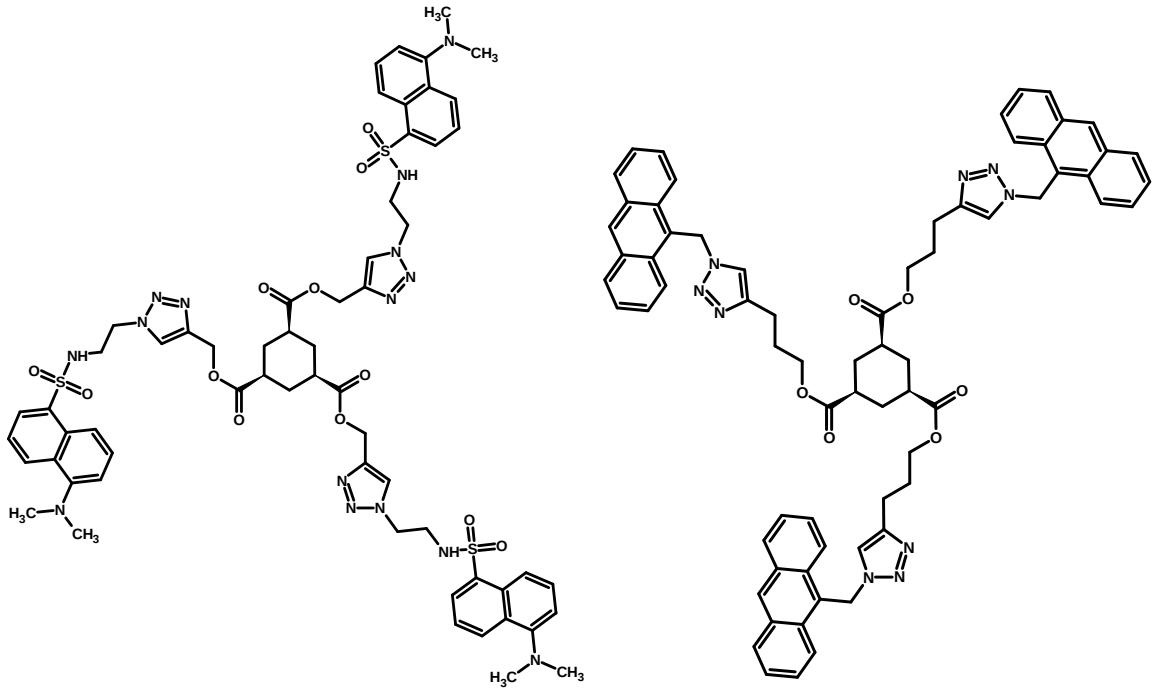
Coupling cyclohexane 1,3,5-*cis*-tricarboxylic acid with the obtained triazole alcohol yielded the expected tripodal derivatives.



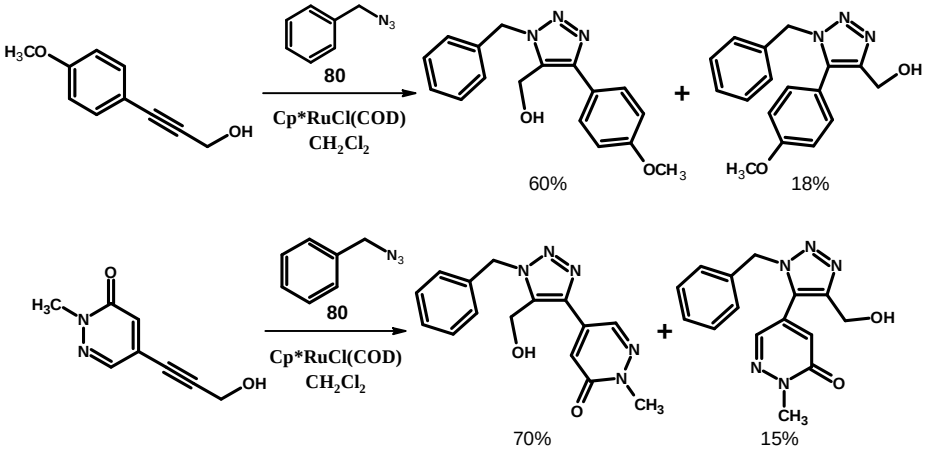


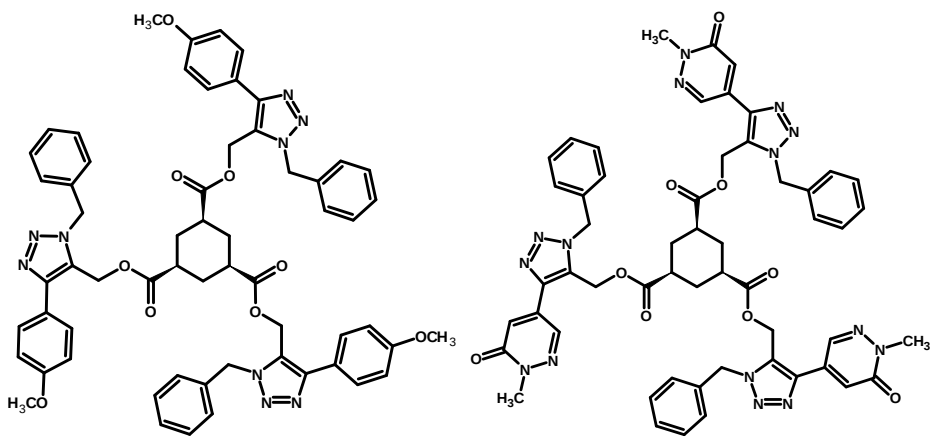






Internal alkynes from the Sonogashira reaction (see above) were reacted with benzyl azide in ruthenium(II)-catalyzed azide-alkyne cycloaddition resulting 1,4,5-substituted triazoles. In these reactions the two regioisomers were formed, after purification the main product was used for the esterification.





Results

The protonation constants of the amino acid derivatives were determined by ^{1}H NMR-pH titration for all tyrosine and *p*-amino phenylalanine derivatives, and for the trihistidine product as well. (The tritryptophane derivative was not soluble enough for the titration.)

Compound	logK_1	logK_2
3xTyr	10.12±0,01	7.11±0,01
2xTyr	10.04±0,01	7.17±0,01
1xTyr	9.90±0,01	7.22±0,01
3x*p*AmPhe	7.19±0,01	3.90±0,01
2x*p*AmPhe	7.24±0,01	3.99±0,01
1x*p*AmPhe	7.31±0,01	4.12±0,01
3xHis	7.19±0,01	5.06±0,01
3xTrp	N/A	N/A

For the investigation of the C_3 triazoles' copper(I)-binding ability three different approaches were used. In the first experiment, the possible chelators were tested as ligands in a model CuAAC reaction, where any improvement in the conversion meant to reflect copper(I) complexation. The second experiment was the study of Cu(I) binding by ^{1}H NMR, while mass spectrometry was utilized to confirm the binding event in the gas phase as well. The conclusion of these tests was that the tripodal derivatives formed 1:1 complexes with copper(I), and the symmetrical structure was crucial for the formation of the stabile complex.

Conclusions

In our organic synthetic work we have created 27 novel C_3 symmetric, 8 novel amino acid and 12 novel triazole alcohol derivatives. All structures were verified with 1D and 2D NMR techniques and with HRMS. We have determined the protonation constants of the amino acid derivatives by ^{1}H NMR-pH titrations. Six tripodal triazole derivatives' Cu(I)-binding capability in model CuAAC reaction was also investigated and the binding event was also confirmed by both NMR and MS experiments.

Bibliography of the Candidate's Publications

Publications related to the theme of the PhD thesis:

Neumajer, G.; Sohajda, T.; Darcsi, A.; Tóth, G.; Szente, L.; Noszál, B.; Béni, Sz. (2012) Chiral recognition of dapoxetine enantiomers with methylated-gamma-cyclodextrin: A validated capillary electrophoresis method. J Pharm Biomed Anal, 62: 42-47. *IF: 2.947*

Neumajer, G.; Tóth, G.; Béni, Sz.; Noszál, B. (2014) Novel ion-binding C3 symmetric tripodal triazoles: synthesis and characterization. Cent Eur J Chem, 12: 115-125. *IF: 1.329 (2013)*

Other publications:

Monsieurs, K.; Tapolcsányi, P.; Loones, K. T. J.; Neumajer, G.; De Ridder, D.; Goubitz, K.; Lemière, G. L. F.; Dommisse, R. A.; Mátyus, P.; Maes, B. U. W. (2007) Is samoquasine A indeed benzo[*f*]phthalazin-4(3*H*)-one? Unambiguous, straightforward synthesis of benzo[*f*]phthalazin-4(3*H*)-one and its regioisomer benzo[*f*]phthalazin-1(2*H*)-one. Tetrahedron, 63: 3870-3881. *IF: 2.869*

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