BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL

Synthesis of molecular co-crystals in the solid phase and their structure analysis by single crystal X-ray diffraction

PhD Thesis

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1. Introduction

The bottle nack of the application of the single crystal X-ray diffraction is the preparation of good quality single crystals. The main force of the crystallisation is to reach an local or global energy minimum[1]. The outcome of a crystallization experiment can not be still predicted because of the conformational variability of the molecules and the huge number of possible intermolecular interactions.

The goal of this PhD thesis work is to develop crystallization techniques in order to obtain solid state crystalline molecular cocrystals. My aim was to crystallize three organic compound families with different crystallization techniques and cocrystal formers or potential guest molecules, then to determine and compare their structural properties. It reveals the typical conformations, the tendencies of inclusion formation and the characteristics of the secondary interactions.

Three families of organic compounds were investigated.

(1) The phenomenon of desmotrophy (*e.g*. tautomer polimorphy) was studied.

(2) The inclusion forming property of the API drotaverin was explored.

(3) The associate forming ability of organocatalysts was investigated.

2. Literature background

(1) In case it is possible to separate the tautomeric forms, *e.g.* it is possible to crystallize the tautomeric forms separately and they do not transform from one form to the other, they are called desmotropic pairs, the phenomenon is called desmotropy. Their structures can be determined by single crystal X-ray diffraction. Holczer *et al*[2] reported 12 desmotropic compounds in which cases one of the dezmotropic forms appears. Katritzky writes[3] 'it is impossible to correctly interpret the detailed mechanism of a reaction of tautomeric heterocycles without knowing the dominant tautomeric structures.' It draws attention to the fact that the structure analysis mostly proves the presence of the thermodinamically more stable form int he crystal lattice. The existence

[1] A. Bényei, V. Harmat, Röntgendiffrakciós szerkezetvizsgálat, Debreceni Egyetem, 2013.
[2] W. Holzer, R. M Claramunt, C. López, I. Alkorta, J. Elguero, *Solid State Nuclear Magnetic Resonance*, **2008**, 34, 68–76.
[3] A. R. Katritzky (editor), Advances in Hetrocyclic Chemistry, Academic Press, San Diego, 2000.

of the desmotropic pair of S-methyl-5,5-diphenyl-2-thiohydantoin[4] had been predicted based on their IR spectra (1964-1972), then their crystal structures were determined by single crystal X-ray diffraction (1973). Afterwards the characterization of desmotropy remained hindered by the fact, that only one of the tautomers crystallized in a form suitable for single crystal studies. The desmotropic pairs could be obtained only as polycrystalline materials (for example irbesartan[5]). Kubicki[5] reported a structure where both tautomers are present in the same crystals. Desmotropy was observed in case of compounds with six-membered ring[6]. The first reported evidence for desmotropy of condensed seven-membered heterocycles was in the course of the preparation of new isomers of 4,1-benzothiazepines[7]. We were able to fully characterize the structure of both desmotropic forms of three compound the first time.

(2) The good inclusion forming ability of drotaverin.hydrochloride has been described[8,9]: the solvent is always enclathrated into the crystal lattice. The volume of the cavitiy is about 10-20% in the unit cell. The drotaverin was produced by recrystallization from ethanol and benzene in the seventies. It is forbidden to use benzene and suggested to avoid ethanol in the current pharmacopoea. Four drotaverin containing crystal structures were published in due time[8,9]. Three of the four published structures are ctrystallized in the space group *P*-1, and contain solvent as guest in the unit cell. Anyhow, four structures are not enough to explore the conformational flexibility and the dominant intermolecular interactions of drotaverin.

(3) The new way of the biomimetic chemistry is the organocatalysis. The term "organocatalysis" describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound. It aims the metalfree catalysis simulating the working processes of the ensimes. The organocatalytic reactions are controlled by the secondary interactions. The organocatalysts govern the resolvation during the reaction.

The first organocatalytic experiments[10] were described in the 1970`s. At the beginning metal containing Lewis acid and organic base molecules were applied in asymmetric reactions. The functional groups of the organocathalysts ensuring the complex formation are separated by bulkiness and by rigid moiety. The first cinchona alkaloids

[4] K. Lempert, J. Nyitrai, K. Zauer, A. Kálmán, Gy. Argay, A. J. M. Duisenberg, P. Sohár, *Tetrahedron*, **1973**, 29, 3565–3569.
[5] M. Kubicki, *Acta Cryst.*, **2004**, B60, 191-196.
[6] G. R. Desiraju, *J. Chem. Soc., Perkin Trans.2.*, **1983**, 2, 1025–1030.
[7] P. Csomós, L. Fodor, J. Sinkkonen, K. Pihlaja, G. Bernáth, *Tetrahedron Lett.*, **2006**, 47, 5665–5667.
[8] K. Simon, A. Friesz, I. Hermecz, *Acta Pharm.Hung*. **1999**, 69, 24–29.
[9] Zs. Böcskei, K. Simon, *Acta Cryst*. **1995**, C51, 1587-1590.
[10] K. Hine, *Acc. Chem. Res.*, **1978**, 11, 1–7.

were used in Michael addition by Hiemstra and Wynberg[11] to synthesize chiral products. The next step in the development of organocatalysts was made in 1998 by Jacobsen and coworkers[12], and then in 2003 by Takemoto and coworkers[13]. Thiourea is the hydrogen donor in the organocatalyst, bis(trifluoromethyl)phenyl group on one of the nitrogen of thiourea is the electron withdrawing part of the catalyst. This way good yeald and enanthioselectivity is achieved.

In the organocatalyst developed by by Soós and co-workers[14] in 2005, cinchona-alkaloid having the chiral information is attached to the thiourea. The cinchona-alkaloid moiety contains two basic, hydrogen acceptor nitrogens. The more basic nitrogen belongs to the cimetidine, the less basic nitrogen belongs to the cinoline groups.

3. Experimental methods

Crystals were produced by the following techniques: solving by warming up – crystallisation by cooling down, precipitation, solvent evaporation and other diffusion based methods. The techniques were developed to have robust, reproducible methods. Intensity data were collected on a Rigaku R-AXIS-RAPID diffractometer equipped with graphite monochromator using CuKα λ = 1.54187 Å, MoKα λ = 0.71075 Å or AgKα λ=0.56089Å radiation at low temperature (93(2) K) and room temperature (294(2) K.

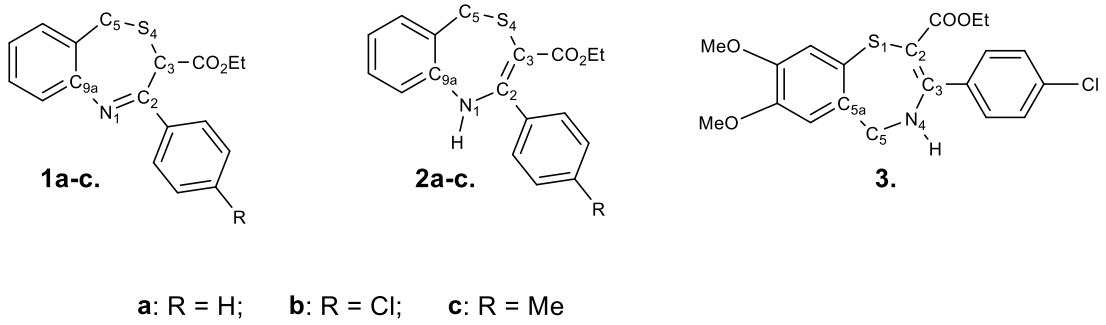
The software Crystal Clear (developed by Rigaku Company) and SORTAV (adopted by L. Párkányi) programs were used for data collection and refinement.

4. New scientific results

(**1**) The desmotropic pairs of 3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines (**1a–c**: 4-H, Cl, Me), 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzo thiazepines (**2a–c**: 4-H, Cl, Me) and 2-ethoxycarbonyl-3-(4-chlorophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine were crystallized separately, and their structures

[11] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.*, **1981**, 103, 417–430.
[12] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.*, **1998**, 120, 4901–4902.
[13] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.*, **2003**, 125, 12672–12673.
[14] B. Vakulya, Sz. Varga, A. Csámpai, T. Soós, *Organic Letters*, **2005**, 7, 1967–1969.

determined (Figure 1)[15]. Compound **3** proves the limitation of the occurance of desmotropy by the hindered conjugation.



a: R = H; **b**: R = Cl; **c**: R = Me

Figure 1. The desmotrophic pairs. **1a**: 3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepine, **2b**: 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzo thiazepine. **3**: 2-ethoxycarbonyl-3-(4-chlorophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine compound.

In the three desmotropic pairs (**1a**/**2a**, **1b**/**2b** and **1c**/**2c**), the bond lengths and angles of the puckered seven-membered heterocycles are clearly distinguishable and fairly consistent within each group of the desmotropes. The dominant desmotropic form is the imino form, with the flopping proton linked to the sp^3 carbon C3. The unusual feature of these new desmotropic pairs is that the protonation of C3 generates chirality, *i.e*. the flopping hydrogen may be placed either an equatorial (**1a**) or an axial (**2b–2c**) position.

In the structures of **1a-1c**, the bulky S4 atom links two C atoms through S(II)–C sp^3 single bonds each one is 1.82 Å in length. The change in the hybridization of C3 from sp^3 to sp^2 in **2a-2c** is also well indicated by the shortening of the S4–C3 bond lengths to 1.77(1) Å. The C3-C2 distences also depend on the hybridisation of the C3 atom (1.36(1) Å). The C2 sp^2 atom is linked to N1 by a double bond in the imino forms with a length of ca. 1.28(1) Å in **1a-1c**, while the C2-N1 distances in the enamine structures are 1.38(1) Å. However the proton flopping from C3 to N1 is demonstrated by the changes in the relevant bond lengths and angles, the C3 – S4 – C5 angle is similar (98(2)°) in the enamine and imino structures.

The proton migration from C3 to N1 alters the puckering of the heteroring in the enamines: they lose their *C*2 symmetry. The endo and exocyclic torsion angles for **2a** and **2c** are similar; only the conformations of the ethoxycarbonyl moieties differ. Presumably, these minor differences provoke, that **2a** and **2c** crystallize in different, but related polar space groups $P2_1$ and $P2_12_12_1$. Although, the conformation of the *p*-methyl derivative **2b** differs from that of **2c**, their unit cell parameters are very close (Π

[15] The label of atoms are indicated only, if it discussed int the text.

= 0.0194) and their space group symmetry $P2_12_12_1$ is the same. However, despite the similarities, they are not isostructural (I_v = 42%). The structures where the molecular placements are different in the unit cells with closely related dimensions are termed homomorphous.

The internal consistency of the relevant bond lengths and angles within the imino and enamin tautomeric forms (**1** *vs.* **2**) indicates that neither the electron-donating methyl nor the electron-withdrawing chloro substituent hinders their desmotropy. Desmotropy can be regarded as a phenomenon that is barely affected by the electron donating or withdrawing character of the substituent.

In contrast, with the migration of the endocyclic CH_2 moiety along the C5a–C9a bond of the condensed phenyl ring the 1,4-benzothiazepine derivative **3** does not exhibit tautomerism. The position of the tetrahedral CH_2 moiety seems to hinder the conjugation between the phenyl ring and the coplanar part of the heteroring.

(**2**) 18 new crystals containing 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline (drotaverine) (Figure 2.)[15] were prepared and their structures were analysed. The guestfree drotaverin HCl salt was successfully crystallised. In 14 crystals the guests were 1-propanol, 2-propanol, 1-buthanol, 2-methyl-2-buthanol, 1-buthanol and 1-penthanol, 2-penthanol, ethylene glycol, urea, fluoroacetic acid, bromoacetic acid, propionic acid, lactic acid, p-xylene-hydroperoxide or mixture of acetic acid and water. The chloride anion was exchanged into maleate anion (maleic acid pK_a: 1.9, oxalate anion (oxalic acid pK_a: 1.3), trifluoroacetate anion (trifluoroacetic acid pK_a: 0.2) with low *p*Ka value in three crystals, where the anionic and neutral forms of the acids are observated within the same asymmetric unit.

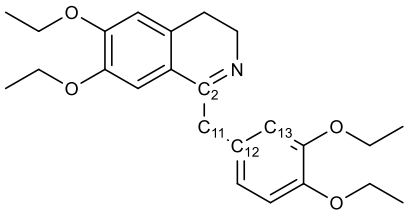


Figure 2. The 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline (drotaverine) molecule.

Nine drotaverine structures are isostructural in the space group *P*-1 and three are isostructutal in the space group $P2_1/c$. The isostructurality indexes are between (I_v=) 63-94%, the cell simetricities are between (Π=) 0.003-0.041. In spite of the different space groups the placement of the cavities are similar in the crystal lattices.

The good inclusion forming ability of drotaverin HCl salt was observed with solvents and solid compounds. The crystallisation of drotaverine with salycilic acid led successfully to the guest free form. Two dimensions of the unit cells of drotaverine and salycilic acid are similar. Because of the partial isostructurality of the two compounds, the drotaverine crystallizes on the surface of the salycilic acid crystal without enclathrating any guest molecule. The drotaverin molecules arrange in "herring bone" pattern in this lattice. This is not the typical way of packing of the clathrates. There are 28 drotaverine molecules in the asymmetric unit of the 18 analysed clathrate structures. In 25 drotaverine molecules out of the 28 π … π and bifurcal C-H…O intermolecular interactions occur between the isoquinoline groups in head to tail arrangement. Oxalic acid and trifluoroacetic acid guests break this motif.

The C2-C11-C12-C13 torsion angle describes the angle of the rigid phenyl and dihydroisoquinolin groups connected by the CH_2. The torsion angle is around 148(13)° where the asymmetric unit contains one drotaverin molecule. In the trifluoroacetic acid containing crystal the torsion angle is 102(1)° because of the O ... π intramolecular interaction between the etheric oxygen and the phenyl group. When there are two drotaverin molecules in the asymmetric unit the conformation of one of the molecules remains, while the torsion angle is 55(3)° in the other molecule. The only exception is the maleic acid containing crystals, where two drotaverin molecules have similar conformations in the asymmetric unit.

The sum of the C2-C11-C12-C13 torsion angles is 208(21)^o in all the 10 cases where two drotaverins are in the asymmetric unit. It means the plane of two phenyl groups has a nearly reverse placement in the crystal.

The ethoxy substituents of the drotaverin have high flexibility. In most of the cases, the terminal ethoxy groups are found in the plane of the phenyl ring or in the plane of the isoquinoline ring. If the guest molecule does not fit into the void of the drotaverine lattice because of its length or branches, the therminal ethoxy groups of the isoquinoline ring turns out of the plane of the aromatic ring in 5 cases of the 18 structures.

(**3**) 18 new crystals were grown from the 1-(3,5-bis(trifluoromethyl)phenyl)-3-((6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)thiourea organocatalyst (Figure 3)[15] with guest molecules having different functional groups being solvents or solid partners. 24 single crystal X-ray diffraction measurements were performed to

investigate their structures changing in time.

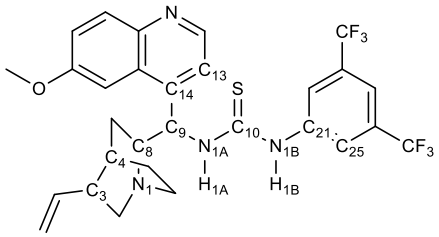


Figure 3. The 1-(3,5-bis(trifluoromethyl)phenyl)-3-((6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)thiourea organocatalyst.

The crystals of the organocatalyst contain enclathrated one or two water molecules, ethanol, ethylene glycol, 1-propanol, 2-propanol, acetylacetone, ethylacetate, 2-acethylbutirolactone and acetone, as well as phtalic acid, 2,3-naphthalene dicarboxylic acid, and 2,6- pyridine dicarboxylic acid as solid cocrystal formers.

The supramolecular interactions were explored in the crystals and the major interactions were compared. The thiourea is the hydrogen donor of the organocatalyst, while the nitrogens of the quinuclidine and of the quinoline groups are hydrogen acceptors. π interactions (C-H...π, π...π, etc.) were found between the phenyl substituted with electron withdrawing alkylfluoride and guest molecules.

The thiourea group forms hydrogen bonds in all structures, the quinoline forms hydrogen bonds in 16 cases (where solvents are hydrogen donor in 12 cases) and quinuclidine forms hydrogen bonds in 11 cases (where carboxylic acids are hydrogen donor in 6 cases). The thiourea and quinoline moieties are in intramolecular hydrogen bond in one structure. π interactions are found between the bis(trifluoromethyl)phenyl group and the guest molecules in 8 crystals, five of them are π ... π interactions, 3 of them are interactions with double bonds. π ... π interaction was observed between the phenyl and quinoline groups of neighbour molecules in two structures. The quinoline group contribute to the settling of the guest molecule in the crystal lattice in three structures. The apolar bis(trifluoromethyl)phenyl group turns out from the polar molecular parts.

Significant differences are found in the conformation of the organocatalyst molecule in the different crystal lattices. The turn of the phenyl group of the organocatalyst is described with the torsion angle of the $C10_{\text{ thiourea}}$ - $N1_{B\text{ thiourea}}$ - $C21_{\text{ phenyl}}$ - $C25_{\text{ phenyl}}$ atoms. Its value is in a wide range of ±61° and ±119°.

The turn of the quinoline groups is described with the torsion angle of the $N1_{A\text{ thiourea}}$ - C9 - $C14_{\text{ quinoline}}$ - $C13_{\text{ quinoline}}$ atoms, the extreme is 66°. The torsion of the isoquinolin

moiety is assisted by the C9 – $N1_A$ sp^3 single bond also. The extreme of the $C10_{thiourea}$ - $N1_{A\ thiourea}$ - C9 - $C14_{quinoline}$ torsion angle is 54°. The "cavity" size is described with the $N1_{quinuclidine}$ - $C8_{quinuclidine}$ - C9 - $N1_{A\ thiourea}$ torsion angle indirectly. The two extreme differences of $N1_{quinuclidine}$ - $C8_{quinuclidine}$ - C9 - $N1_{A\ thiourea}$ torsion angle are just 28°.

5. Thesis

1. I have verified the phenomenon of desmotrophy with ethyl 3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines and 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzo thiazepines β-lactam compounds and derivatives. [1-4]
2. I have prepared 11 new inclusion complexes of 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline. The non-covalent syntheses were performed succesfuly by anion metathesis. I succeeded to crystallize the 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline HCl salt the first time without any enclathrated molecule.
3. I have determined the typical conformations, the intermolecular interactions and the size of the cavities in the crystals of 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline salts.
4. I have established the typical conformations, the intermolecular interactions with solvents and different guest molecules (with double bond, phenyl group, dicarboxylic acid, ketone and alcohol function group), and the size of the cavities in their crystal lattices of the 1-(3,5-bis(trifluoromethyl)phenyl)-3-((6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)thiourea organocatalyst.
5. I have stated, that in spite of the expectations the C=S …H-N type thiourea … thiourea intermolecular hydrogen bonds are not typical in the crystal structures of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)thiourea, this kind of interaction occurs only once out of the determined structures.

6. Application possibilities

The investigation of β-laktam structures initiated the recognition of the phenomenon of desmotrophy. The alteration of the physical-chemical properties of the prototroph ctystals supplies important information for the exploration of structure – property relationship and for crystal engineering.

The prepared and investigated numerous clathrates of 1-(3,4-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinoline HCl salt supply possible alternative ways for industrial crystallisation. Because of the various guest molecules in the determined structures the prediction of the crystallization experiment with a new guest molecule is made easier by the knowledge of the size, shape and functional groups of the selected guest molecule. We have successfully crystallized the drotaverine salt without enclathration of any additional molecule what was seaked by the industry for the last four decades.

The mapping of the supramolecular interactions of the organocatalyst contributes to the reveal of the theory of reaction mechanisms and to the development of new catalysts.

The research of molecular conformation and configuration, as well as the secondary interactions can be well applied in preparation of new compounds with desired properties, in crystal structure prediction, and also in the investigations of reaction pathways.

7. Publications

7.1. Paper in international peer reviewed journals:

1. Fodor, L., Csomós, P., Bernáth, G., Sohár, P., **Holczbauer, T.**, Kálmán, A. *Monatsh Chem.* **2010**, 141, 431–436. IF.: 1.312 C.: 3 (independent C: 2)
   „Reactions of 1,3-benzothiazines and 1,4-benzothiazepines with dimethyl acetylenedicarboxylate”
2. Fodor, L., Csomós, P**., Holczbauer, T.**, Kálmán, A., Csámpai, A., Sohár, P. *Tetrahedron Lett.* **2011**, 52, 224–227. IF.: 2.683 C.: 14 (independent C: 10)
   „Expected and unexpected reactions of 1,3-benzothiazine derivatives, I. Ring transformation of b-lactam-condensed 1,3-benzothiazines into 4,5-dihydro-1,4-benzothiazepines and indolo-1,4-benzothiazepines”

3. Fodor, L., Csomós, P., Csámpai, A., Sohár, P. **Holczbauer, T.**, Kálmán, A. *Tetrahedron Lett.* **2011**, 52, 592-594. IF.: 2.683 C.: 3 (independence C: 3)
„Expected and unexpected reactions of 1,3-benzothiazine derivatives, II. Formation of isomeric 5,6-dihydro-1,5-benzothiazocines"

4. **Holczbauer, T.**, Fábián, L., Csomós, P., Fodor, L., Kálmán, A. *CrystEngComm*. **2010**, 12, 1712–1717. IF.: 4.006 C.: 4 (independence C: 4)
„Annular desmotropy of three pairs of seven-membered heterocycles confirmed by X-ray crystallography"

7.2. Lectures

1. **Holczbauer, T.**, Czugler, M., Kardos, Gy., Varga, Sz., Soós, T.
XII. Doktoráns Iskola Kémiai kutatóközpont, 20-21 April 2009, Mátraháza
2. **Holczbauer, T.**, Németh, Cs., Pfeiffer, É., Mink, J., Kerényi, A., Keglevich, Gy., Czugler, M.
Anyagszerkezeti konferencia, 14-15 May 2009, Mátrafüred
3. **Holczbauer, T.**, Párkányi, L., Kudar, V., Kardos, Gy., Varga, Sz., Soós, T., Czugler, M.
Kutatóközponti Tudományos Napok, 24-26 November 2009, Budapest
4. **Holczbauer, T.**, Kálmán, A.
Fiatal Analitikusok Előadóülése, MKE, 25 February 2010, Budapest
5. **Holczbauer, T.**, Czugler, M., Kardos, Gy., Varga, Sz., Soós, T.
XIII. Doktoráns Iskola Kémiai Kutatóközpont, 21-23 April 2010, Balatonkenese
6. **Holczbauer, T.**, Fodor, L., Kálmán, A.
Vegyészkonferencia, 30 June - 2 July 2010, Hajdúszoboszló
7. **Holczbauer, T.**, Czugler, M., Párkányi, L., Kardos, Gy., Varga, Sz., Soós, T.
Kutatóközponti Tudományos Napok, 23-25 November 2010, Budapest
8. **Holczbauer, T.**, Czugler, M., Kardos, Gy., Varga, Sz., Soós, T.
XIV. Kálmán Erika Doktori Konferencia, 26 May 2011, Budapest
9. **Holczbauer, T.**, Czugler, M., Kardos, Gy., Varga, Sz., Soós, T.
XV. Kálmán Erika Doktori Konferencia, 18-20 September 2012, Mátraháza
10. **Holczbauer, T.**, Szabó, M., Tóth, V. R., Czugler, M.
A Szervetlen és Fémorganikus Kémiai Munkabizottság és az Anyag- és Molekulaszerkezeti Munkabizottság Közös Munkabizottsági Ülése, 12-14 October 2012, Szedres
11. **Holczbauer, T.**, Szabó, M., Tóth, V. R., Czugler, M.
Magyar Kémikusok Egyesülete Kristályosítási és Gyógyszerformulálási Szakosztály: Kristályosítási technológiák méretnövelése és hatásuk a gyógyszerformulálásra, 26-27 October 2012, Balatonszemes
12. **Holczbauer, T.**, Szabó, M., Czugler, M.
The 28th European Crystallography Meeting, 25-30 August 2013, Warwick, Anglia
13. **Holczbauer, T.**, Czugler, M., Varga, Sz., Kardos, Gy., Soós, T.
Magyar Kémikusok Egyesülete Kristályosítási és Gyógyszerformulálási Szakosztály, 6-7 September 2013, Balatonalmádi
14. **Holczbauer, T.**, Szabó, M., Tóth, V. R., Czugler, M.
MTA TTK Doktori Konferencia, 10-12 December 2014, Budapest
15. **Holczbauer, T.**, Szabó, M., Czugler, M.

Szerves Kémiai Szemináriumok, 18 February 2015, Budapest

16. **Holczbauer, T.**, Szabó, M., Czugler, M.
Akadémiai Anyag- és Molekulaszerkezeti Munkabizottság éves ülése, 27-28 February 2015, Mátrafüred
17. **Holczbauer, T.**
MKE Kristályosítási és Gyógyszerformulálási Szakosztály: Tavaszi előadói nap és MTA TTK intézetlátogatás, 12 March 2015, Budapest
18. **Holczbauer, T.**, Czugler, M.
Német-Magyar Szerves és Szerkezeti Tavaszi Szimpózium, 17 April 2015, Budapest

7.3. Posters

1. **Holczbauer, T.**, Németh, Cs., Pfeifer, É., Mink, J., Kerényi, A., Keglevich, Gy., Czugler, M.
25th European Crystallograpy Meeting, 16-21 August 2009, Istanbul
2. **Holczbauer, T.**, Czugler, M., Kardos, Gy., Varga, Sz., Soós, T.
4th European Conference on Chemistry for Life Sciences, 31 August - 3 September 2011, Budapest
3. **Holczbauer, T.**, Szabó, M., Czugler, M.
28th European Crystallograpy Meeting, 25-30 August 2013, Warwick
4. **Holczbauer, T.**, Szabó, M., Czugler, M.
Oláh György Doktori Iskola XI. Konferenciája, 6 February 2014, Budapest
5. **Holczbauer, T.**, Szabó, M., Czugler, M.
29th European Crystallograpy Meeting, 23-28 August 2015, Rovinj

7.4. Other publications

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