**Hírlevél**

**MTA Szénhidrát, Nukleinsav és Antibiotikumkémiai Munkabizottság**

**2017. február**

1.) A 2017. évi munkabizottsági ülés időpontja: **2017. 05. 31. (szerda) - 2017. 06. 02. (péntek), Mátraháza**

A munkabizottsági ülésre bejelentette részvételi szándékát **Prof. Jindrich Jindrich** (Charles Egyetem, Prága) és hallgatói is.

2.) A Munkabizottság tagjainak legújabb eredményei, megjelent közlemények kivonatai (a teljesség igénye nélkül):

**Efficient mechanochemical synthesis of regioselective persubstituted cyclodextrins**

Laszlo Jicsinszky\*, Marina Caporaso, Katia Martina, Emanuela Calcio Gaudino and Giancarlo Cravotto\*

*Beilstein Journal of Organic Chemistry* 12(1):2364–2371 · November 2016; DOI: 10.3762/bjoc.12.230

**Abstract**

A number of per-6-substituted cyclodextrin derivative syntheses have been effectively carried out in a planetary ball mill under solventless conditions. The preparation of Bridion® and important per-6-amino/thio-cyclodextrin intermediates without polar aprotic solvents a source of by-products and persistent impurities could be eliminated. Isolation and purification processes could also be simplified. Considerably lower alkylthiol/halide ratios were necessary to reach the complete reaction in comparison with thiourea or azide reactions. While the presented mechanochemical syntheses were carried out on the millimolar scale, they are easily scalable.

**Unprecedented β-manno type thiodisaccharides with a C-glycosylic function by photoinitiated hydrothiolation of 1-C-substituted glycals.**

László Lázár, László Juhász, Gyula Batta, Anikó Borbás and László Somsák

*New J. Chem*., 2017, 41, 1284 – 1292 DOI: 10.1039/c6nj03751h

**Abstract**

Free-radical hydrothiolation of O-peracylated 1-C-(carbamoyl-, methoxycarbonyl- and cyano) substituted glycals with a range of sugar derived thiols gave the corresponding β-manno type 3-deoxy-3-S-disaccharides with full regio- and stereoselectivity. The configuration of the glycals (arabino vs. lyxo) and the size of the protecting groups had no significant effect on the outcome of the transformations. Formation of by-products was tracked down by LCMS studies and correlated with the electron density of the double bonds to show that the reactions were synthetically useful with a COOMe and especially with a CONH2 group as the 1-C-substituent.

**Coupling of anhydro-aldose tosylhydrazones with hydroxy compounds and carboxylic acids: a new route for the synthesis of C-β-D-glycopyranosylmethyl ethers and esters**

Tímea Kaszás, Marietta Tóth, Sándor Kun and László Somsák

*RSC Adv*., 2017, 7, 10454–10462.

**Abstract:**

Cross couplings of O-peracylated 2,6-anhydro-aldose tosylhydrazones (C-(β-D-glycopyranosyl)formaldehyde tosylhydrazones) with alcohols, phenols, and carboxylic acids were studied underthermic or photolytic conditions in the presence of K3PO4 or LiOtBu. The reactions failed with EtOH, BnOH, or tBuOH, however, (CF3)2CHOH, electron poor phenols and carboxylic acids gave the corresponding C-β-D-glycopyranosylmethyl ethers and esters, respectively, representing a new access to these glycomimetic compounds.

**MALANGA, M., SZEMÁN, J., FENYVESI, É., PUSKÁS, I., CSABAI, K., GYÉMÁNT, GY., FENYVESI, F., SZENTE, L.**

“Back to the Future”: A New Look at Hydroxypropyl Beta-Cyclodextrins.

Journal of Pharmaceutical Sciences, 105(9), 2921–2931 (2016)

**Abstract:**

Since the discovery about 30 years ago (2-hydroxypropyl) beta-cyclodextrin, a highly soluble derivative of beta-cyclodextrin, has become an approved excipient of drug formulations included both in the US and European Pharmacopoeias. It is recommended to use as solubilizer and stabilizer for oral and parenteral formulations. Recently its pharmacological activity has been recognized in various diseases. The increasing applications require a closer look to the structure – activity relationship. As HPBCD is always a mixture of isomers with various degrees and pattern of hydroxypropylation, no wonder that the products of different manufacturers are often different. Several (2-hydroxypropyl)-beta-cyclodextrins were compared applying a battery of analytical tools including TLC, HPLC, HPLC-MS and MALDI MS. We studied how the average degree of substitution affects the aggregation behavior, the toxicity and the solubilizing effect on poorly soluble drugs. We found that the products with low average degree of substitution are more prone to aggregation. The samples studied are non-toxic to Caco-2 cells and have low hemolytic activity. The solubility enhancement of poorly soluble drugs decreases or increases with increasing degree of substitution or shows a maximum curve depending on the properties of the guest.

**SZENTE, L., FENYVESI, É.**

Cyclodextrin-Lipid Complexes: Cavity Size Matters.

*Structural Chemistry* DOI: 10.1007/s11224-016-0884-9 (2016)

**Abstract** :

Lipids being hydrophobic or amphiphilic can be encapsulated by cyclodextrin complexation. Among the various groups of lipids cholesterol, fatty acids, phospholipids and sphingolipids are overviewed concerning the structural requirements for both the lipid and the cyclodextrin component of the complexes. The chain length and the number and position of the double bonds in the fatty acids, the polarity of the head-group in the phospholipids and sphingolipids are important factors. Concerning the cyclodextrins, in addition to the most crucial cavity size also the chemical microenvironment of cavity entrances determine the interaction with lipids. While fatty acids, phospholipids and sphingolipids prefer the alpha-cyclodextrin cavity, cholesterol is complexed first of all by the beta-cyclodextrin and its derivatives. Methylated beta-cyclodextrin has extreme affinity to all of these lipids, which are common constituents of cell membranes. Based on the knowledge on the specific cyclodextrin-lipid interactions, cyclodextrin derivatives are able to selectively remove certain lipid components from model and biological membranes and can be selected making possible to modulate the lipid profile in such membranes.

**Szente, L., Szemán, J., Sohajda, T.**

Analytical characterization of cyclodextrins: History, official methods and recommended new techniques.

*Journal of Pharmaceutical and Biomedical Analysis,.* 130, 347–365, doi:10.1016/j.jpba.2016.05.009 (2016)

**Abstract:**

The main goal of this review is to provide a comprehensive overview on the methods used for analysis of cyclodextrins (CDs) and CD-derivatives. The paper intends to act as a guide for the readers in looking around the classical and modern instrumental analytical methods suitable for identification, characterization and determination of CDs themselves, CDs in finished products or even in biological samples. At present, in the European and United States Pharmacopoeias, the three parent CDs and two synthetic derivatives, namely the (2-hydroxypropyl)-beta-CD and sulfobutylether-beta-CD Na salt are official. Besides these modified CDs, two other derivatives are approved as excipients in human pharmaceutical products: the (2-hydroxypropyl)-gamma-CD and the randomly methylated-beta-CD. Although most of the official analysis methods in the pharmacopoeias have been well used for decades, new aspects of the functional excipient CD characterization suggest a need to revisit compendial methods. Comparison of strengths and weaknesses of current official methods with new improved techniques intends to help analysts to decide on changing traditional analytical methods with improved new ones. This review also deals with the analytical aspects of the first single isomer CD derivative approved as a drug active (Sugammadex/Bridion®) as well as analytical considerations of using CDs themselves as active pharmaceutical ingredients. Stability-indicating instrumental methods suitable to adequately follow chemical- and enzymatic degradation of CDs will also be discussed. Challenges in the determination of CDs in different biological matrices will be illustrated on real pharmaco- and toxicokinetic studies of CD-enabled drug formulations.

**Zsolt Szűcs, Ilona Bereczki, Magdolna Csávás, Erzsébet Rőth, Anikó Borbás, Gyula, Batta, Eszter Ostorházi, Réka Szatmári, Pál Herczegh:**

Lipophilic teicoplanin pseudoaglycon derivatives active against vancomycin and teicoplanin resistant enterococci

*Journal of Antibiotics* (2017) doi: 10.1038/ja.2017.2

**Abstract:**

A selection of nine derivatives of teicoplanin pseudoaglycon were tested in vitro against clinical vancomycin-resistant Enterococcus strains possessing vanA, vanB or both genes. The bacteria were characterized by PCR for the identification of their resistance genes. The tested compounds contain lipoic acid, different carbohydrates and aryl groups as lipophilic moieties. About one-third of the teicoplanin-resistant strains were shown to be susceptible to one or more of the glycopeptide derivatives.

**α‑Arylation of α‑Amino Acid Derivatives with Arynes via Memory of Chirality: Asymmetric Synthesis of Benzocyclobutenones with Tetrasubstituted Carbon**

Koji Kasamatsu, Tomoyuki Yoshimura, Attila Mándi, Tohru Taniguchi, Kenji Monde, Takumi Furuta, Takeo Kawabata

*Organic Letters* **2017**, *19*, 352-355.

Abstract: A method for asymmetric α-arylation of α-amino acid derivatives via memory of chirality has been developed. Addition of axially chiral enolates, generated from α-amino acid derivatives, to in situ generated arynes, followed by intramolecular C-acylation of the resulting aryl metallic species, gave benzocyclobutenones with a tetrasubstituted carbon with retention of configuration in up to 99% ee.

**Daldinone derivatives from the mangrove-derived endophytic fungus *Annulohypoxylon* sp.**

Yang Liu, Fabian Stuhldreier, Tibor Kurtán, Attila Mándi, Sathishkumar Arumugam, Wenhan Lin, Björn Stork, Sebastian Wesselborg, Horst Weber, Birgit Henrich, Georgios Daletos, Peter Proksch

*RSC Advances* **2017**, *7*, 5381-5393. (Open access)

Abstract: Two new benzo[j]fluoranthene metabolites, daldinones H, J (1 and 3), and the likewise undescribed artefact, daldinone I (2), along with six known compounds (4–9) were isolated from the endophytic fungus Annulohypoxylon sp. that was obtained from the Mangrove plant Rhizophora racemosa collected in Cameroon. The structures of the new compounds were elucidated by 1D and 2D NMR as well as by HRESIMS and ECD spectra analysis. Co-cultivation of this fungus with the actinomycetes Streptomyces lividans or with Streptomyces coelicolor resulted in an up to 38-fold increase of 1-hydroxy-8-methoxynaphthalene (9), while no significant induction was detected when the fungus was co-cultivated either with Bacillus subtilis or with Bacillus cereus. Compound 2 exhibited strong to moderate cytotoxicity against Ramos and Jurkat J16 cells with IC50 values of 6.6 and 14.1 mM, respectively. Mechanistic studies indicated that compound 2 induces apoptotic cell death caused by induction of intrinsic apoptosis. Moreover, 2 potently blocks autophagy, a potential pro-survival pathway for cancer cells. Feeding experiments with 1,8-dihydroxynaphthalene (DHN) led to an enhanced accumulation of daldinone B (6), which supported the proposed biogenetic pathway.

*A havi rendszerességű hírlevélben megjelentetni kívánt anyagot kérjük minden hónap utolsó napjáig elküldeni a* [*csavas.magdolna@science.unideb.hu*](mailto:csavas.magdolna@science.unideb.hu) *email címre.*

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2017. február 28.