12th Asian Cyclodextrin Conference
in conjunction with the 41th National Cyclodextrin Symposium, Japan

A Versatile Intermediate for the Synthesis of Highly Functionalized β-Cyclodextrins

Eric J. Kuenstner,[1] Dora Ujj,[2] Gábor Benkovics,[3] and Dustin McMinn[1]

[1]*Beren Therapeutics, P.B.C., Thousand Oaks CA, USA,* [2]*ELTE, Budapest, Hungary,* [3]*Beren Therapeutics Kft. Budapest, Hungary*

(E-mail: ekuenstner@berentx.com)

Functionalized cyclodextrins offer unique opportunities for molecular recognition in medicinal chemistry.[1] Precise regio/chemo-selective manipulation of the sugar-unit alcohols can facilitate subtle host-guest binding interactions. During a recent campaign targeting bilirubin,[5] we employed methodological advances published by Sinaÿ and Sollogoub,[2] Bols,[3] and Ling[4] to achieve selective 6^A,6^D functionalization of β-cyclodextrin (β-CD). While remarkable binding of 6^A,6^D-derivatized β-CDs was achieved, the high lipophilicity of potency-enabling substituents led to decreased solubility of top bilirubin targeting compounds. We sought to redress this decreased solubility through low molecular weight structural changes. Replacement of sugar alcohols with methyl ethers is a purported strategy to rescue the solubility of derivatized β-CDs.[6] Since previous structure-activity relationships (SAR) indicated that functionalization of the 3-OH groups had a detrimental effect on binding interactions, we chose to investigate 2-OMe substituted variants of the 6^A,6^D analogs. We hypothesized that these species would have improved solubility while retaining complex supramolecular interactions. However, new synthetic methodology was required to efficiently access this previously unreported substitution pattern. We now report the synthesis and unambiguous regiochemical characterization by HPLC-CAD, HPLC-MS/MS, and cIM-MS of a per-2-OMe-β-CD derivative that is selectively functionalized at the 6^A,6^D positions. This synthetic advancement broadens the potential chemical diversity of synthetically accessible cyclodextrins enabling medicinal chemistry campaigns. Results from preliminary SAR investigations into the solubility of this scaffold will be reported.

REFERENCES

1. J.A. Adam, D.J. Bennett, A. Bom, J.K. Clark, H. Feilden, E.J. Hutchinson, R. Palin, A. Prosser, D.C. Rees, G.M. Rosair, D. Stevenson, G.J. Tarver, M.-Q. Zhang, Cyclodextrin-Derived Host Molecules as Reversal Agents for the Neuromuscular Blocker Rocuronium Bromide: Synthesis and Structure-Activity Relationships, *J. Med. Chem.*, **2002,** *45*, 1806–1816.
2. T. Lecourt, A. Herault, A.J. Pearce, M. Sollogoub, P. Sinaÿ, Triisobutylaluminum and Diisobutylaluminum Hydride as Molecular Scalpels: The Regioselective Stripping of Perbenzylated Sugars and Cyclodextrins, *Chem. Eur. J.,* **2004**, *10*, 2960–2971.
3. M. Petrillo, L. Marinescu, C. Rousseau, M. Bols, Selective Discrimination of Cyclodextrin Diols Using Cyclic Sulfates, *Org. Lett.,* **2009**, *11*, 1983–1985.
4. R. Ghosh, P. Zhang, A. Wang, C.-C. Ling, Diisobutylaluminum Hydride Mediated Regioselective O Desilylations: Access to Multisubstituted Cyclodextrins, *Angew. Chem. Int. Ed.,* **2012**, 51, 1548–1552.
5. S. Jo, B. Herberich, E. Kuenstner, Q. Cheng, J. Giani, D. McMinn, Readily Accessible Host Library and Screening Approach for High Binding Affinity Host-Guest Complex Formation: Case Study for Cyclodextrin-Bilirubin Complex, *EuroCD 2025*, Milan, Italy, 2025 September 9.
6. L. Szente, J. Szejtli, Highly Soluble Cyclodextrin Derivatives: Chemistry, Properties, and Trends in Development, *Adv. Drug Deliv. Rev.,* **1999**, *36*, 17–28.