

## Supplemental material

# Chrysin Directing an Enhanced Solubility through the Formation of a Supramolecular Cyclodextrin–Calixarene Drug Delivery System: A Potential Strategy in Antifibrotic Diabetes Therapeutics

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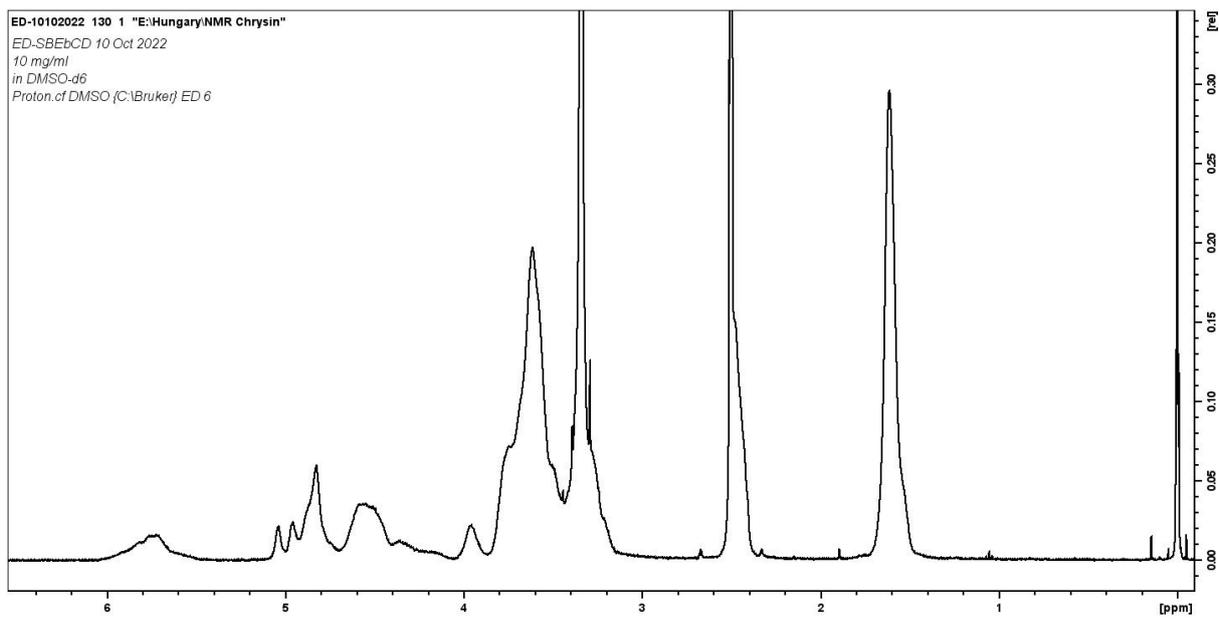


Figure S3.  $^1\text{H}$  NMR spectrum of SBECD in  $\text{DMSO-d}_6$ .

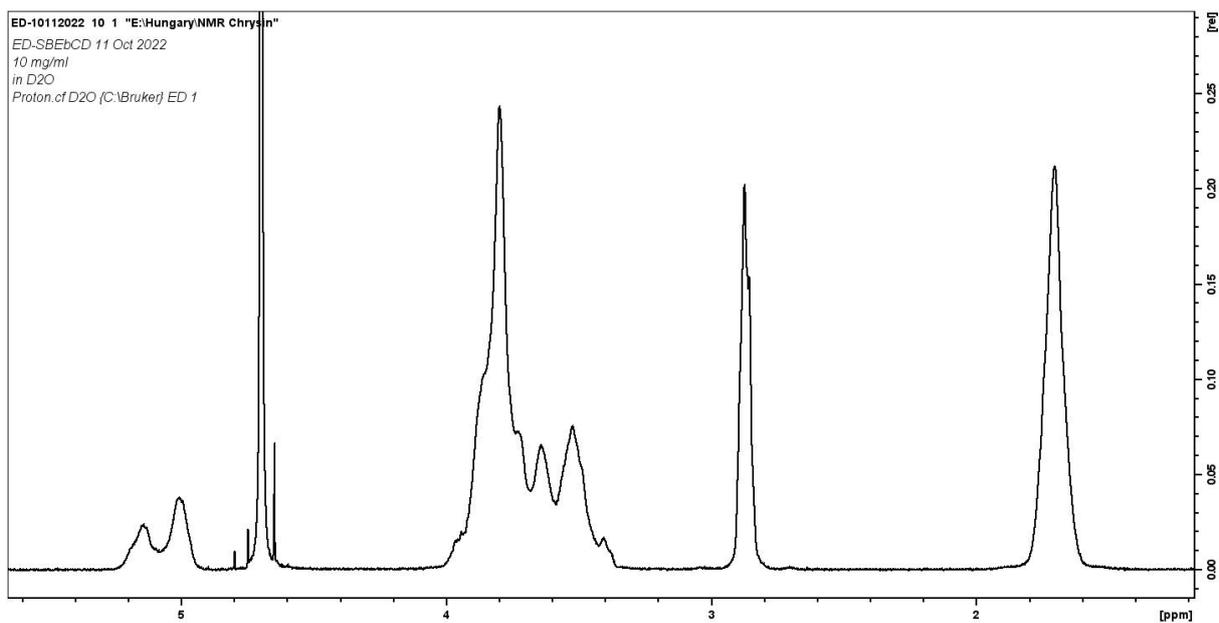


Figure S4.  $^1\text{H}$  NMR spectrum of SBECD in  $\text{D}_2\text{O}$ .

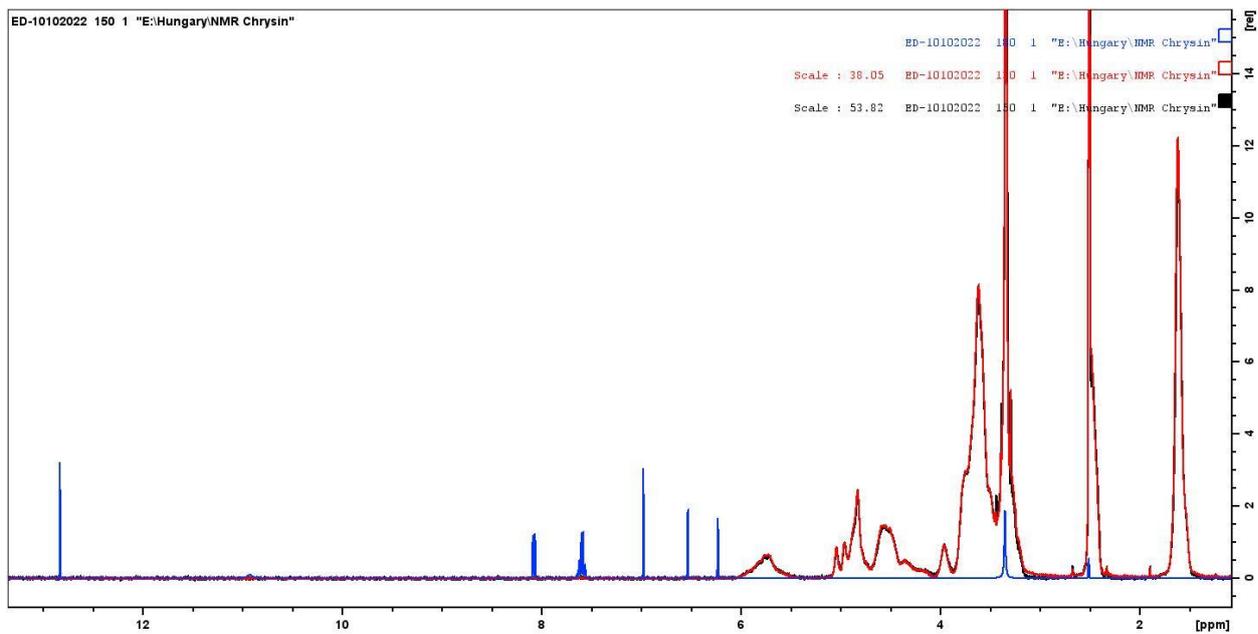


Figure S5.  $^1\text{H}$  NMR spectra of CHR-SBECD mixture (black line), CHR (Blue line) and SBECD (Red line) in  $\text{DMSO-d}_6$ .

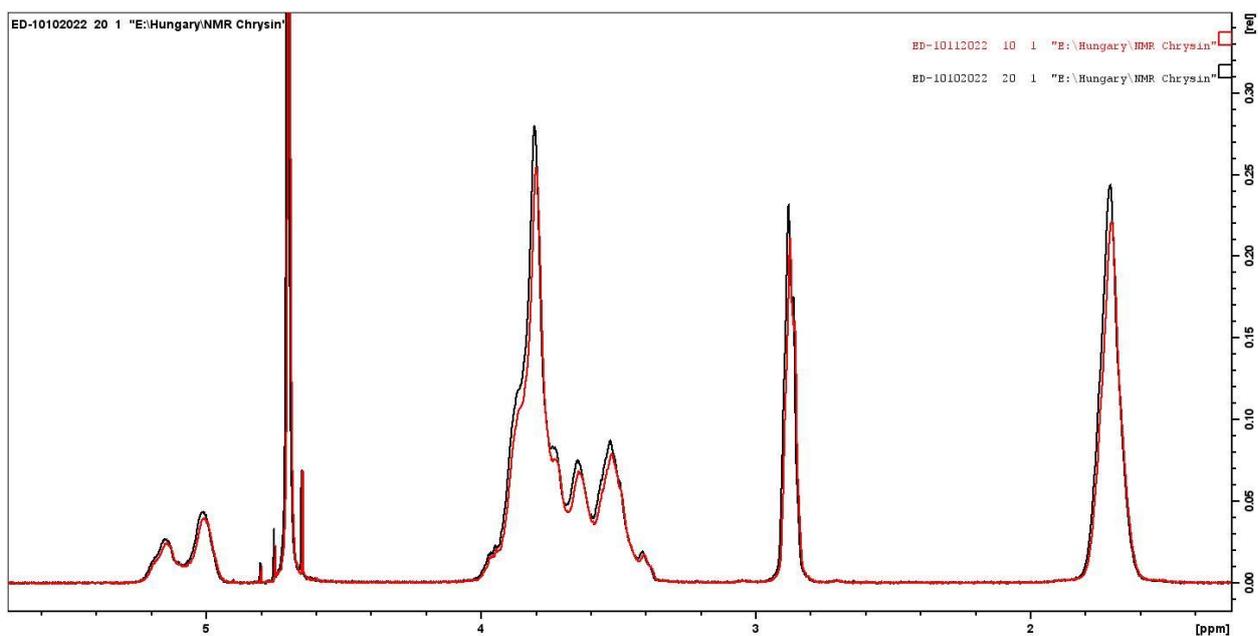


Figure S6.  $^1\text{H}$  NMR spectra of CHR-SBECD mixture (black line) and SBECD (Red line) in  $\text{D}_2\text{O}$ .

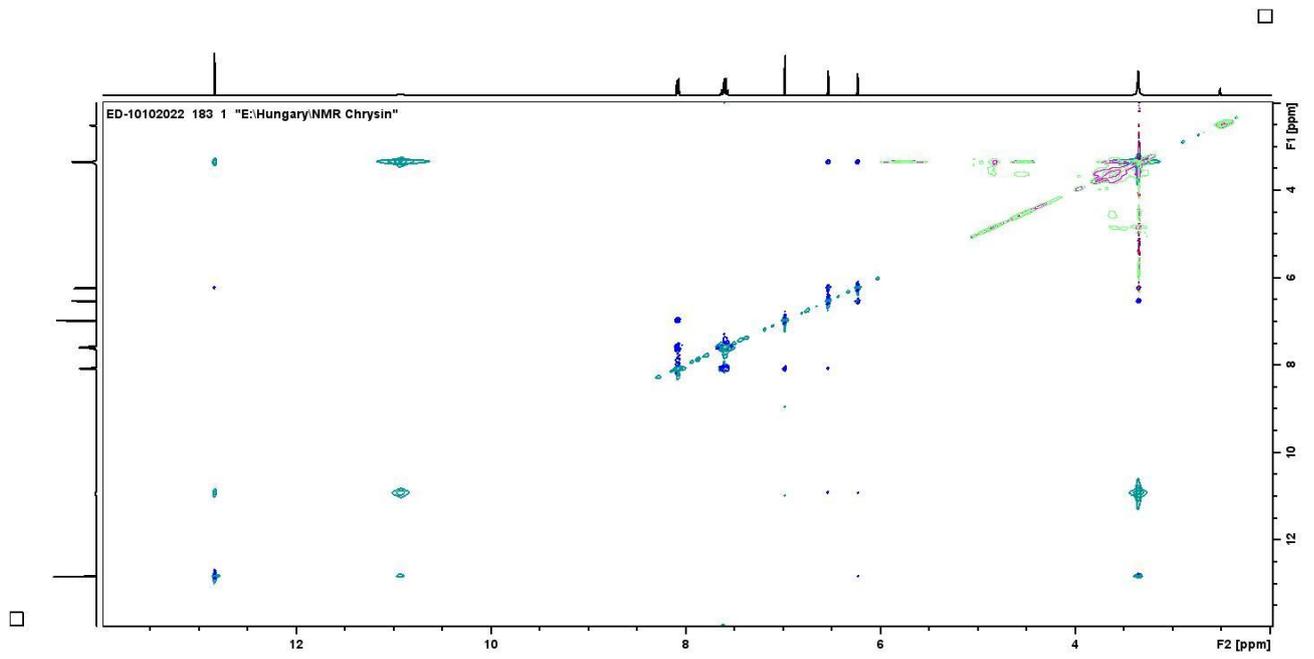


Figure S7. NOESY NMR spectra of CHR (Blue/Dark green line), CHR-SBECD mixture (Purple line) and SBECD (Light green line) in DMSO-d<sub>6</sub>.

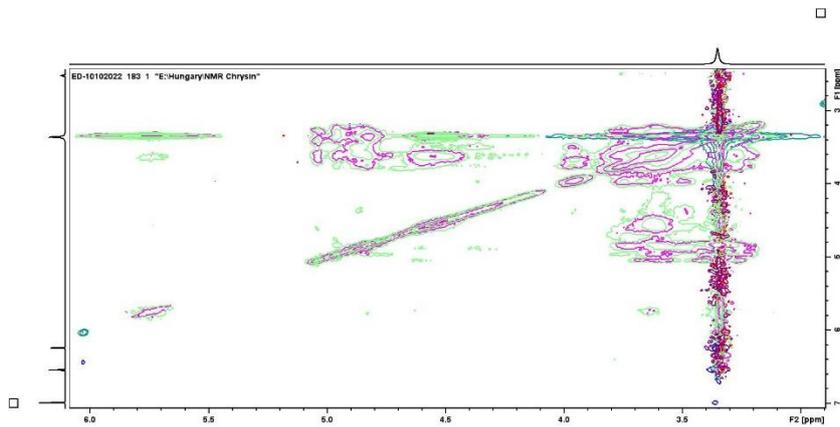


Figure S8. Expanded area of the NOESY spectra Figure S7.

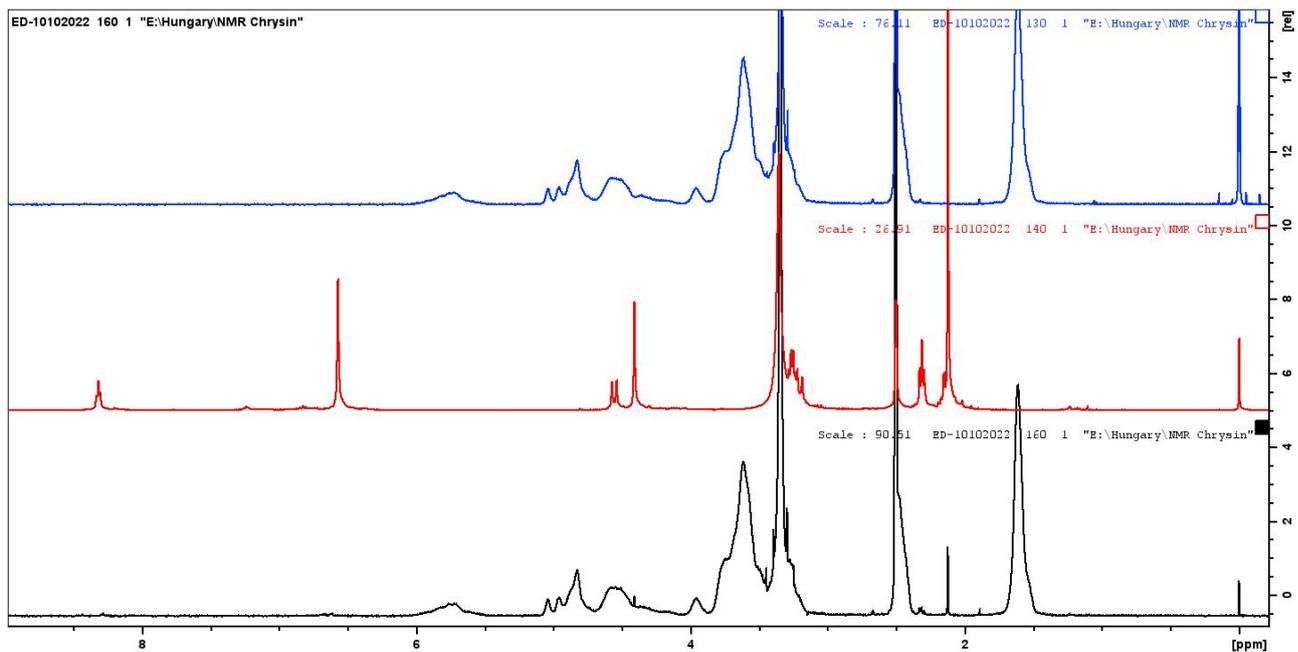


Figure S9. <sup>1</sup>H NMR spectra of OTX008-SBECD mixture (Black line), OTX008 (Red line) and SBECD (Blue line) in DMSO-d<sub>6</sub>.

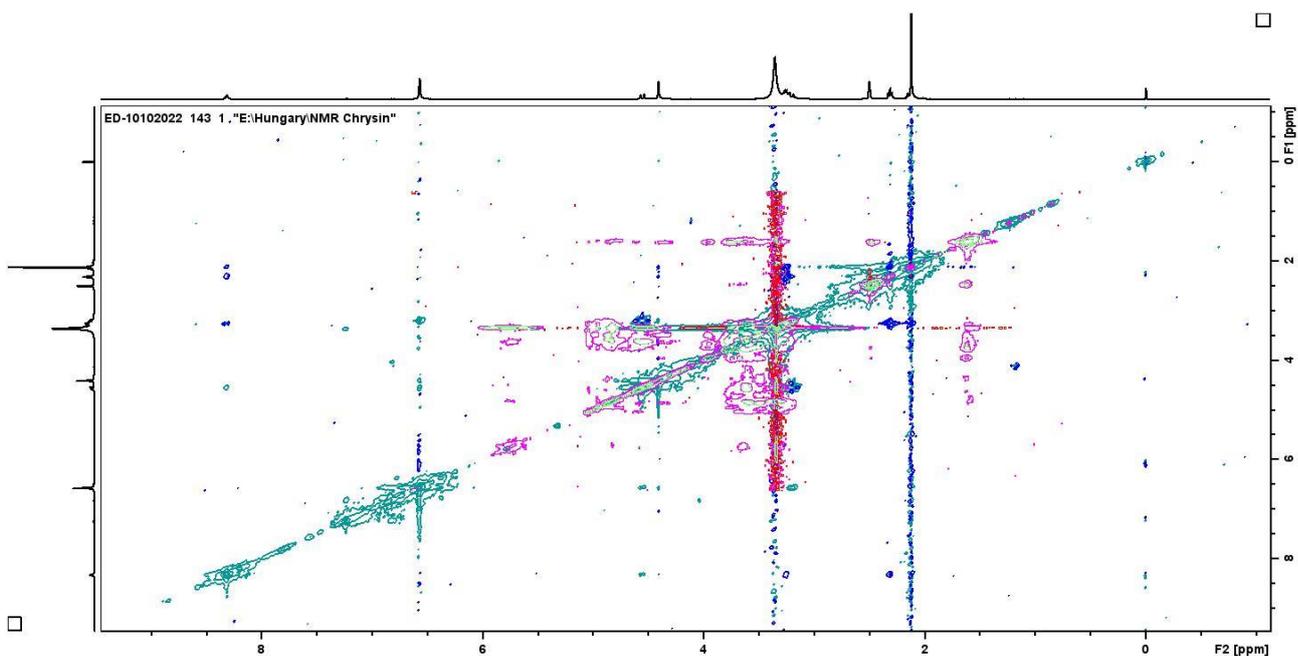


Figure S10. NOESY spectra of OTX008-SBECD mixture (Black line), OTX008 (Red line) and SBECD (Blue line) in DMSO-d<sub>6</sub>.

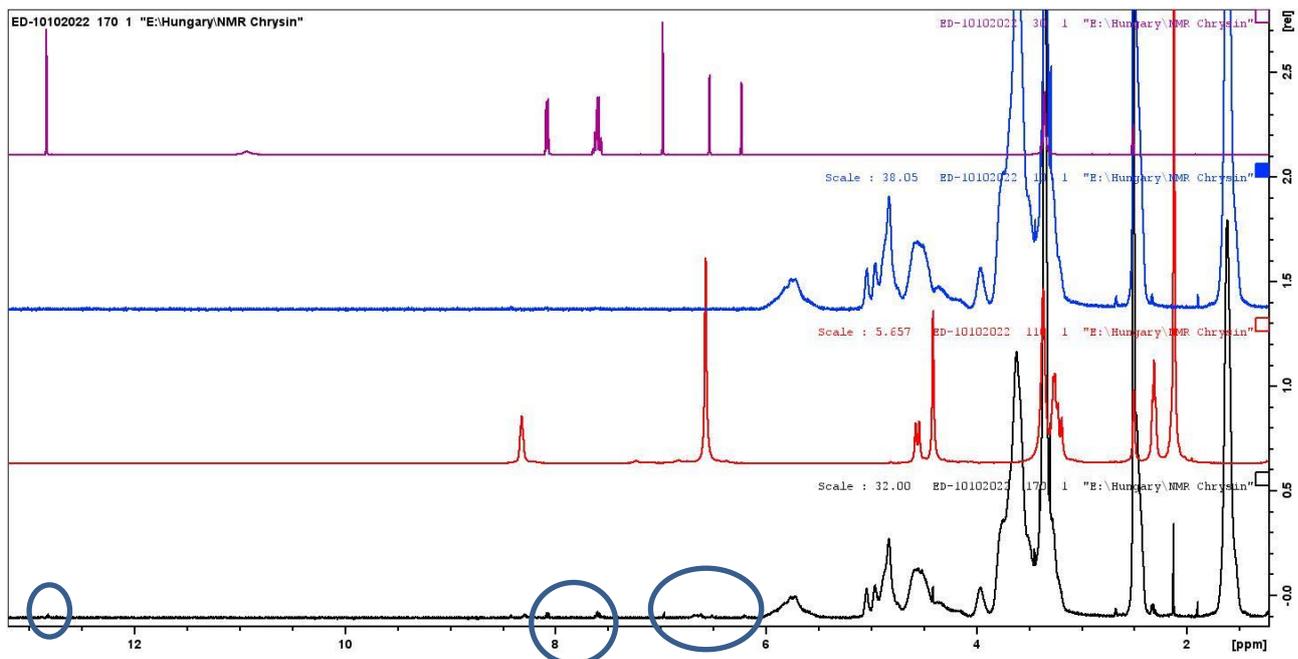


Figure S11.  $^1\text{H}$  NMR spectra of CHR-OTX008-SBECd mixture (Black line), OTX008 (Red line) SBECd (B, Blue line) and CHR (Purple line) in  $\text{DMSO-d}_6$ .

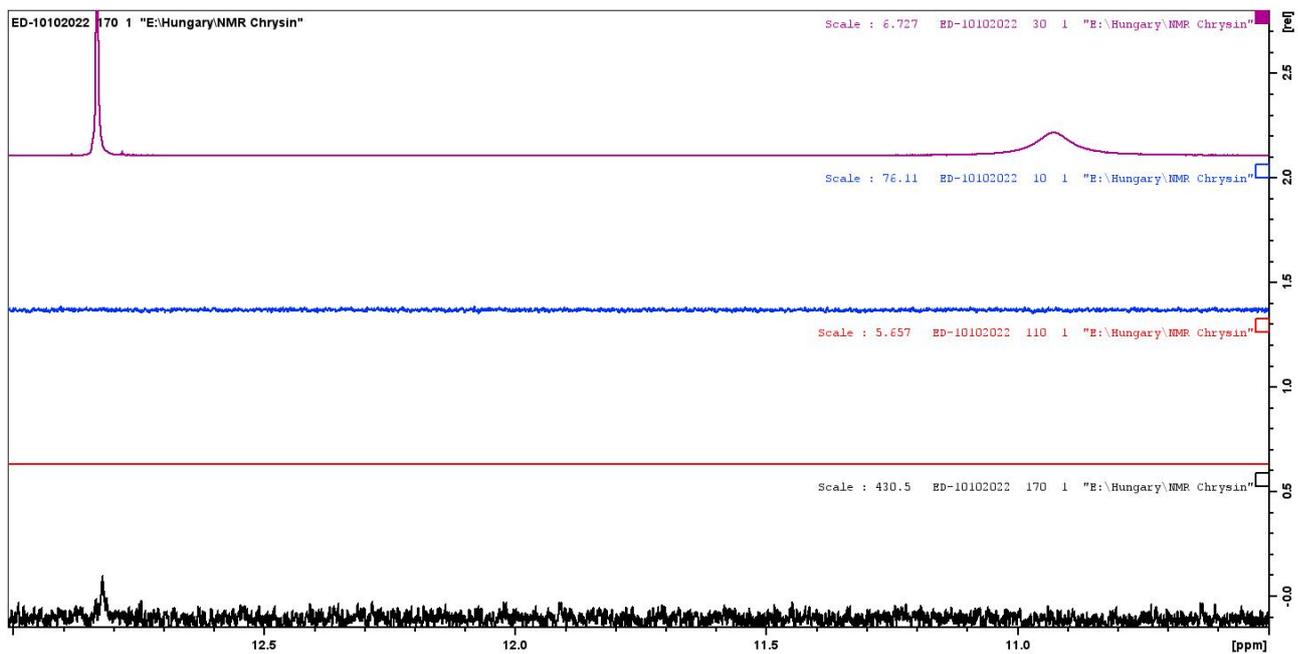


Figure S12. Expanded area of  $^1\text{H}$  NMR spectra of CHR-OTX008-SBECd mixture (Black line), OTX008 (Red line) SBECd (B, Blue line) and CHR (Purple line) in  $\text{DMSO-d}_6$ .

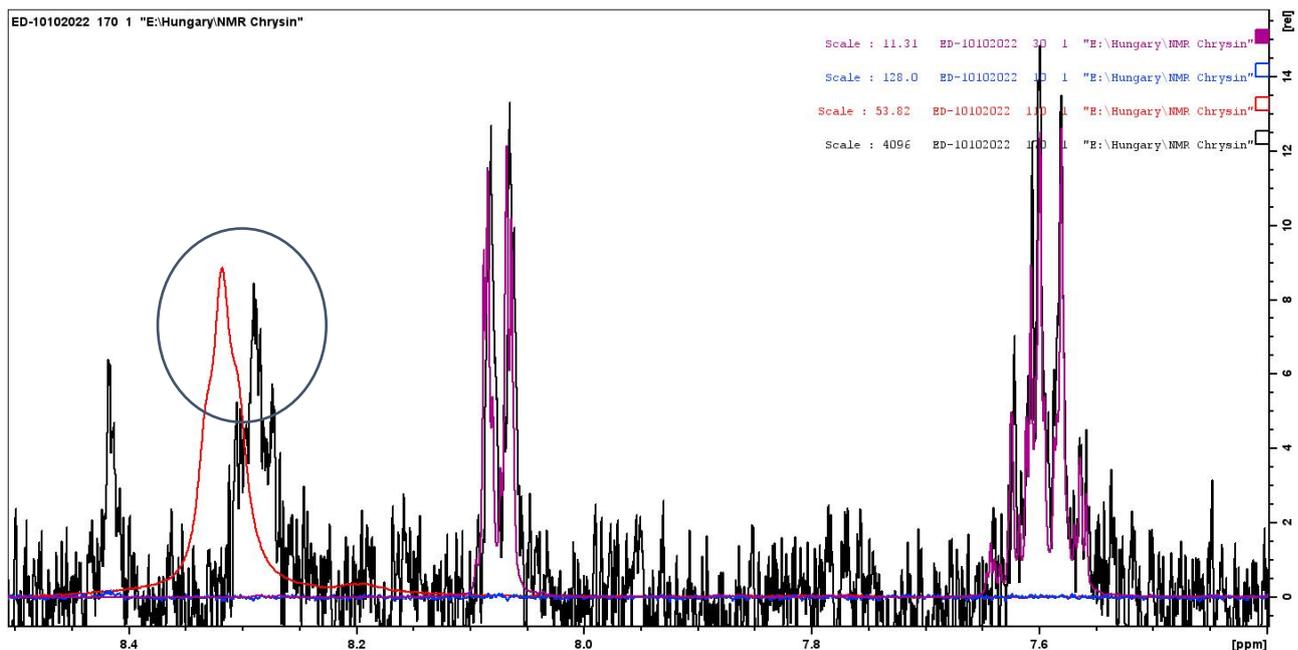


Figure S13. Expanded area of  $^1\text{H}$  NMR spectra of CHR-OTX008-SBECD mixture (Black line), OTX008 (Red line) SBECD (B, Blue line) and CHR (Purple line) in  $\text{DMSO-d}_6$ .

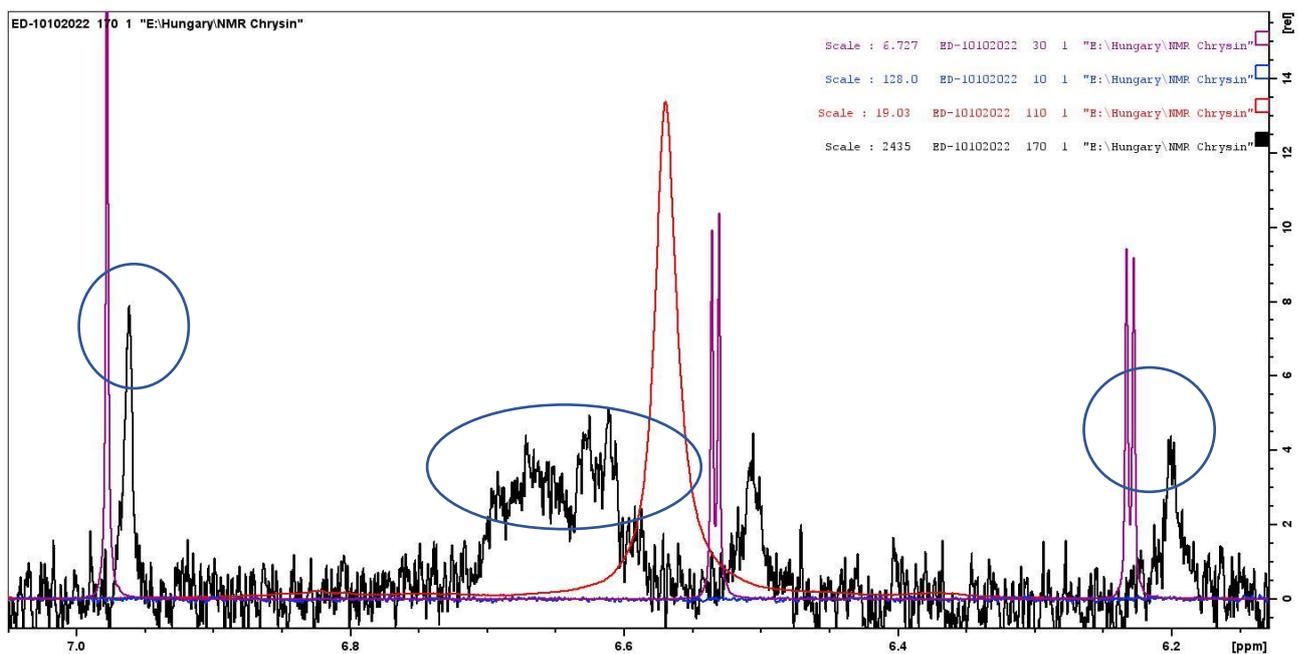


Figure S14. Expanded area of  $^1\text{H}$  NMR spectra of CHR-OTX008-SBECD mixture (Black line), OTX008 (Red line) SBECD (B, Blue line) and CHR (Purple line) in  $\text{DMSO-d}_6$ .

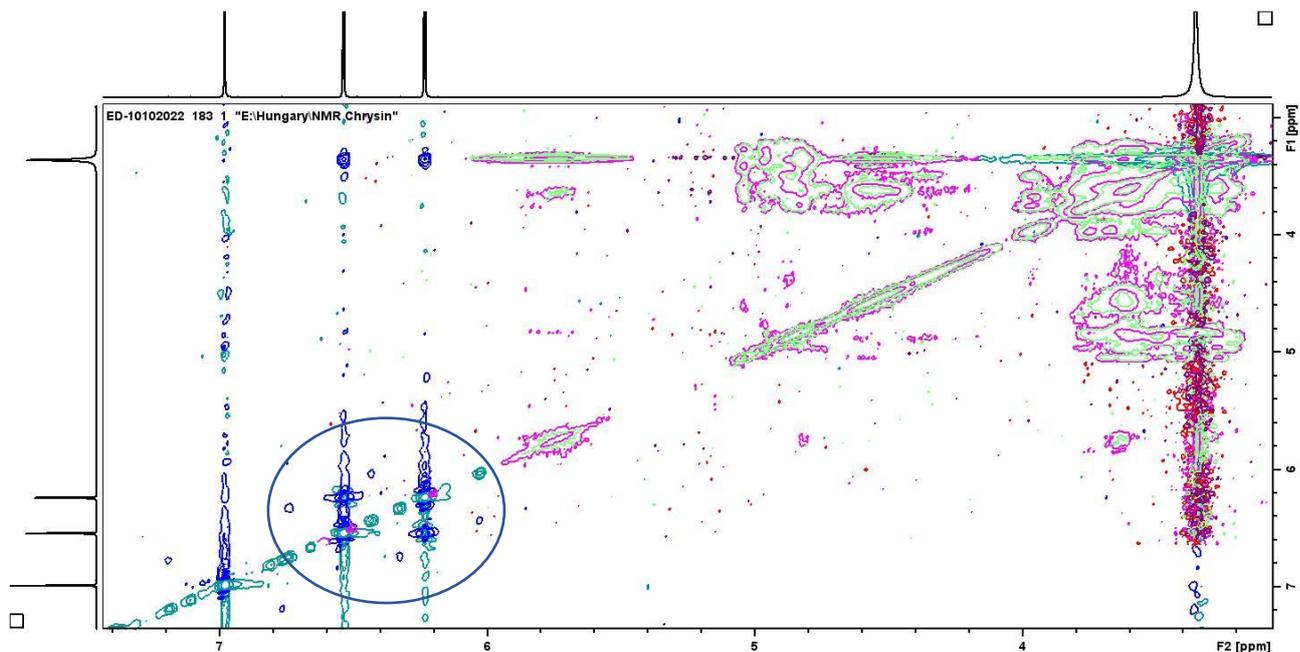


Figure S15. Comparison of NOESY spectra of CHR (Blue/Dark green line), CHR-OTX008-SBECD mixture (purple line) and binary CHR-SBECD mixture (Light green line) in DMSO- $d_6$ . The framed parts of the spectrum shown the presense of CHR molecules in a different situation when it is in ternary mixture.

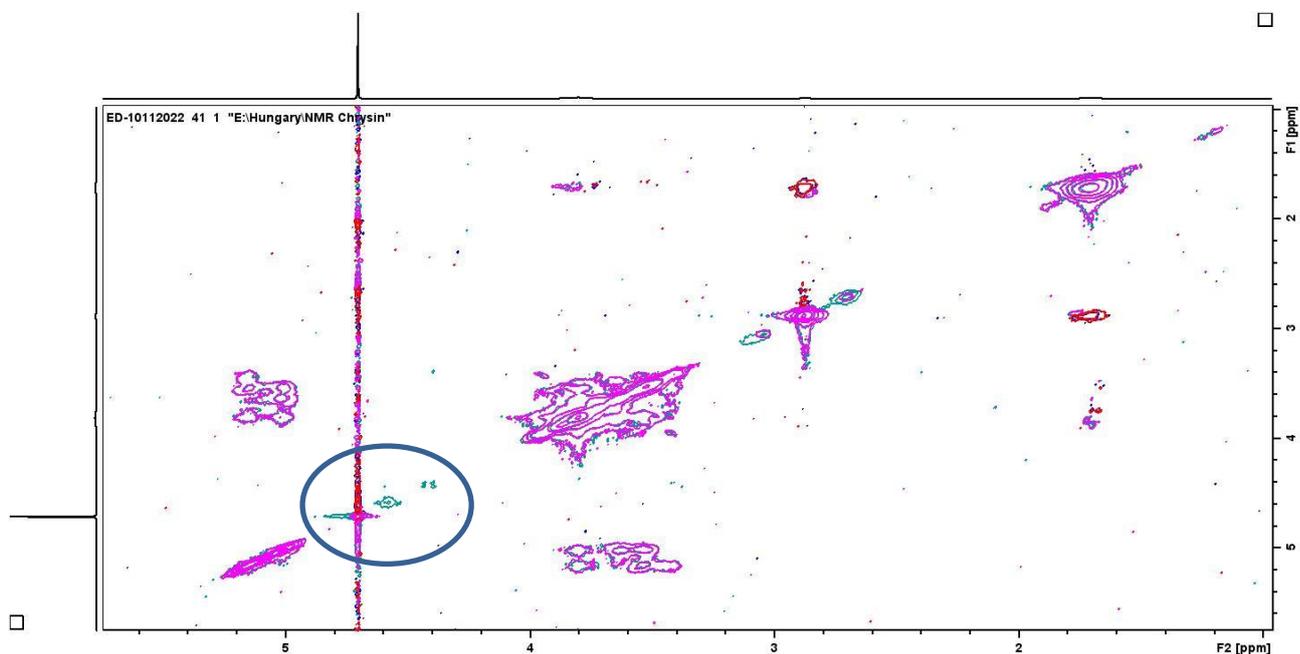


Figure S16. NOESY spectra CHR-OTX008-SBECD mixture (Black line) and SBECD (Red line) in  $D_2O$  showing the presense of CHR and OTX008 in the ternary structure.

Table S1. Results of thermal analysis.

Samples and mixtures	T <sub>m</sub>	T <sub>d</sub>
CHR	290	-
OTX1008	218	306
SBECD	272	281
Binary CHR- SBECD	272, 362	281
Binary OTX008- SBECD	290, 362	299
Ternary mixture CHR- OTX008- SBECD	293	300

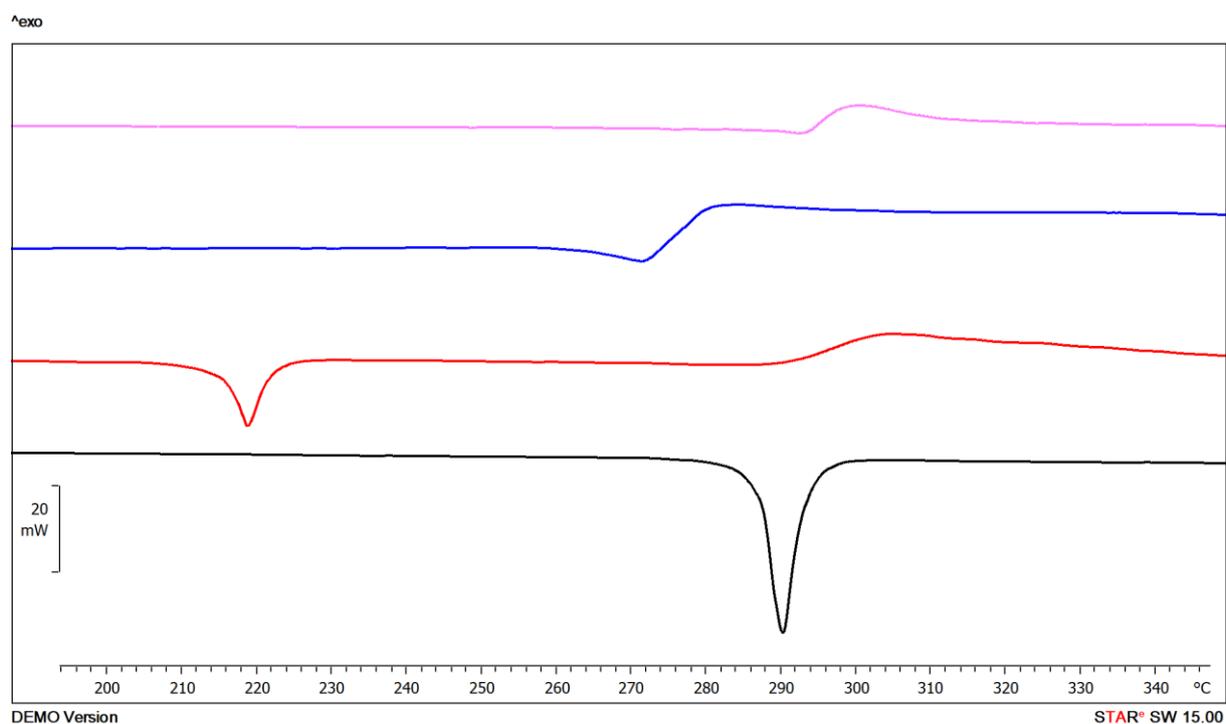


Figure S17. Zoomed view of DSC thermograms of CHR (Black line), OTX008 (Red line), SBECD (Blue line) CHR-OTX008-SBECD (Purple line), at 190-350 °C, 10 °C/min, inert N<sub>2</sub>.

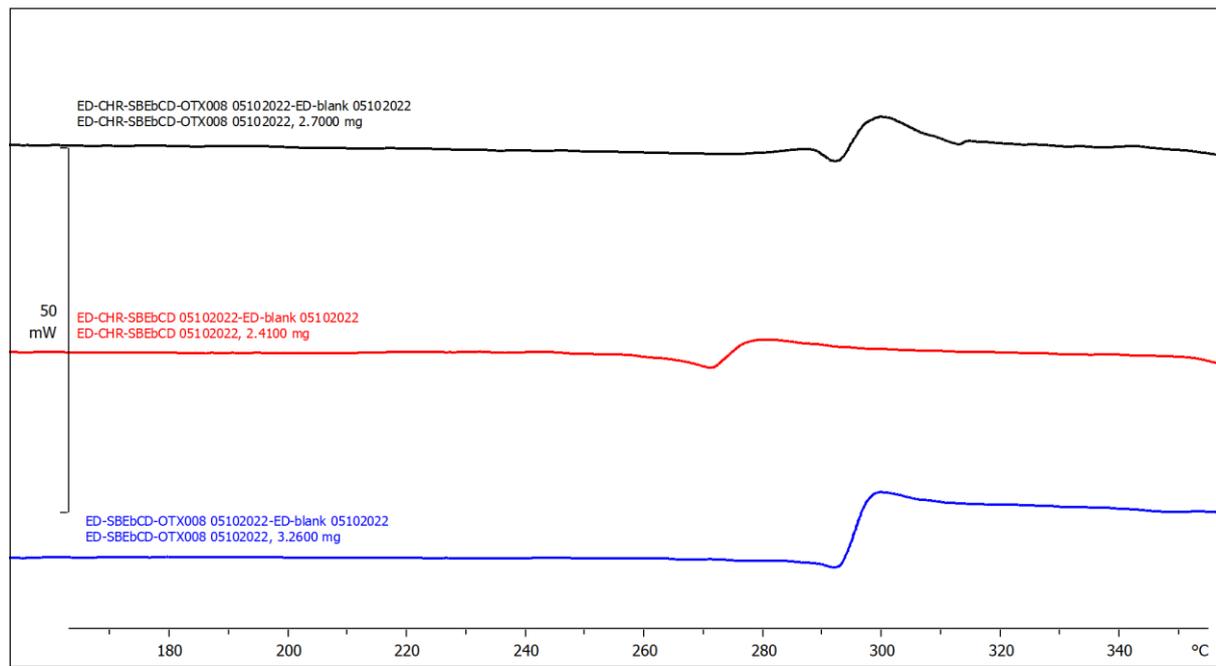


Figure S18. Comparison of zoomed areas of DSC thermograms of SBECD-OTX008 mixture (Blue line), SBECD-CHR mixture (Red line) and CHR-SBECD-OTX008 mixture (Black line), at 160-350 °C, 10 °C/min, inert N<sub>2</sub>.

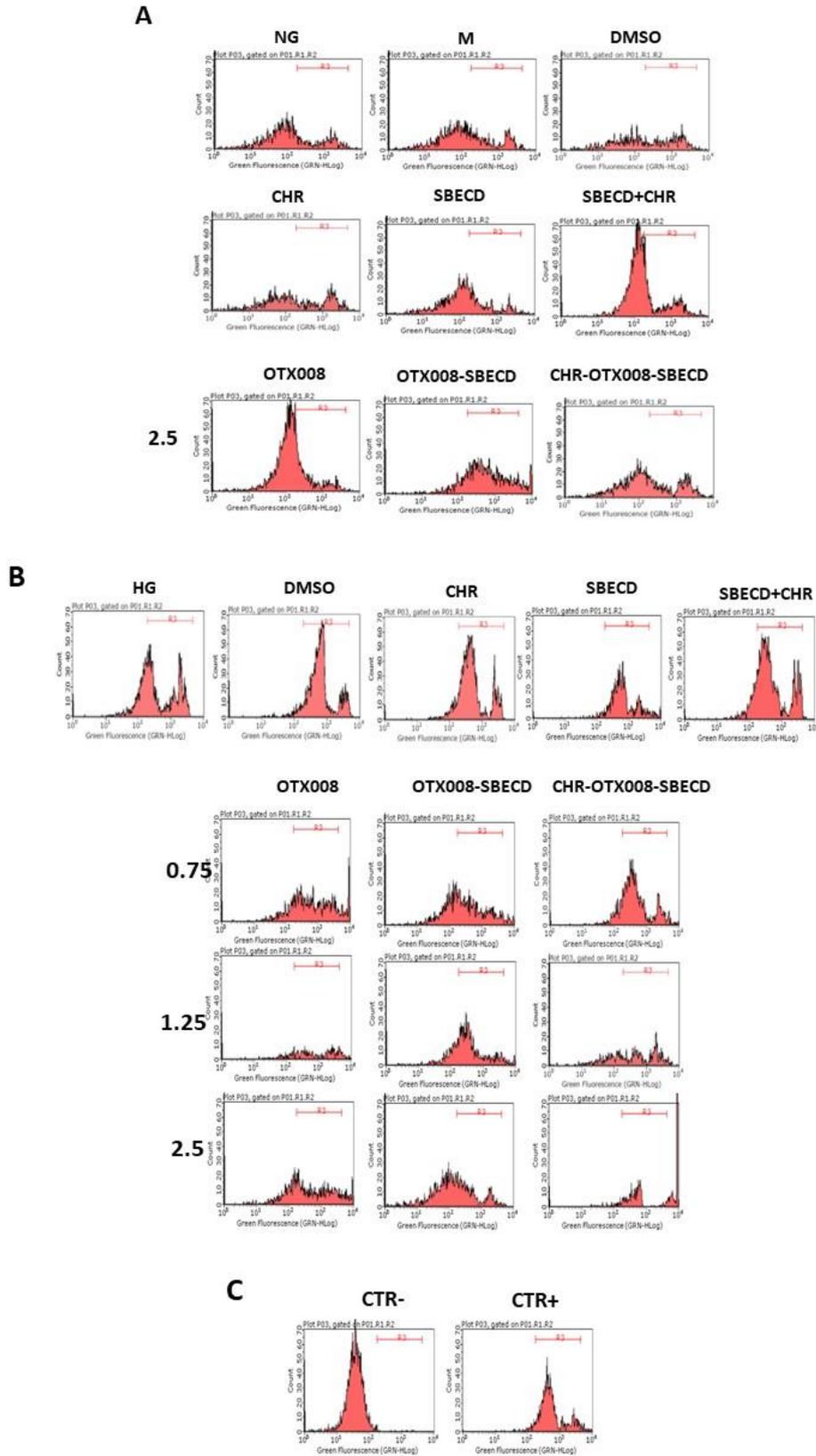


Figure S19. (A) Representative flow cytometer measures of total intracellular ROS levels assayed with DCFH-DA probe in NG or (B) HG medium. In NG cells, OTX008 was tested at

the maximum dose of 2.5  $\mu\text{M}$ . In HG cells, OTX008 was tested at the doses of 2.5-1.25-0.75  $\mu\text{M}$ ; (C) CTR<sup>-</sup> = negative control (5% FBS without DCFH-DA); CTR<sup>+</sup> = positive control (H<sub>2</sub>O<sub>2</sub> 100  $\mu\text{M}$ ). R3 region = DCFH-DA-positive cells.

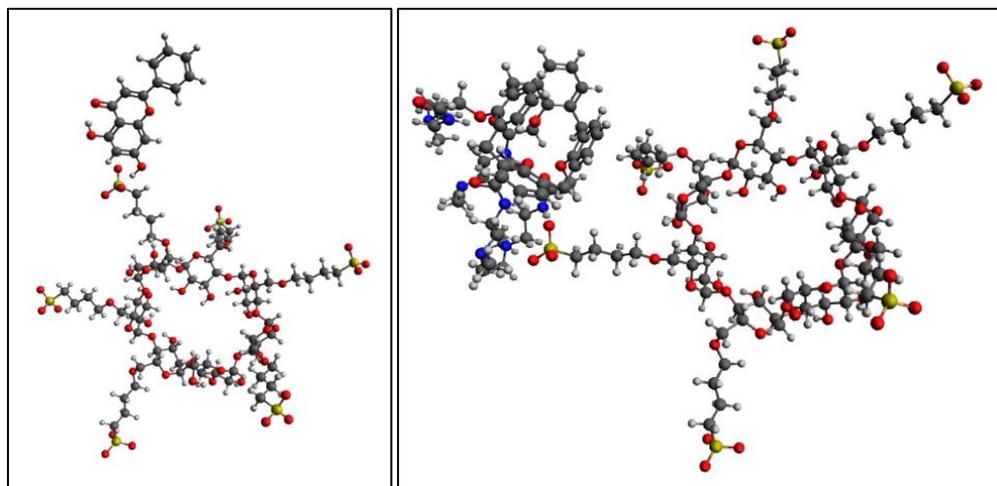


Figure S20. Interactions between SBECD and CHR (A). Interaction between OTX008 and SBECD (B).