The paper from Biscotti et al. describes the synthesis and the relaxometric characterization of five derivatives of Gd-DOTA and Gd-TTHA conjugated to hydroxylated and permethylated cyclodextrins. Even if not particularly innovative, the experiments are clearly explained and commented. Nevertheless, some integrations are suggested in order to better describe the systems and their relaxometric behavior. The authors should consider the following points:

1) For a better understanding of the experiments, the experimental section, which now is included in supporting material, should be moved to the main text.
2) Abstract, line 22: "various hydroxylated and permethylated 21 □-CDs via an amide linker" should be "….via an amide bond"
3) Figure 1: Gd-TTHA derivatives are erroneously labelled as compound 4 should have R1, R2= Me and compound 5 should have R1, R2=H
4) Line 210: "HTBU" is likely "HBTU"
5) Remove the concentrations from legends of figures 2 and 3 as the data are reported as relaxivities ($r1/mM^{-1}s^{-1}$) thus normalized to 1 mM concentrations. The concentrations of the solutions which were used for NMRD profiles acquisition should be indicated in the experimental part.
6) After complexation of the ligands with Gd(III), the absence of free Gd ions should be checked …especially with cyclodextrins containing systems which could retain metal ions weakly bound to OH groups
7) Supporting info, figure 2: in the legend of the figure it is written that the spectrum has been acquired in CD3CN while in the text it is stated that it was acquired in CDCl3
8) Relevant information (i.e. on the reorientational correlation time) could be obtained through the fitting of NMRD profiles, which is missing. For example, the authors assume that the size of the different systems is the same and thus the relaxivity is not influenced by this parameter. However, the presence or the absence of 14 Me groups (difference in MW of ca. 200 D) could have an influence on the global reorientational correlation time and fitting of NMRD profiles would highlight this kind of differences.
9) The variable temperature 17OR2 data and high resolution NMR on Eu-complexes should be better analyzed. For macrocyclic DOTA derivatives, the presence of two isomers (corresponding to SAP and TSAP structures) characterized by different exchange dynamics has long been appreciated since the end of the nineties, and it was ascertained that the water exchange kinetics of the TSAP isomer are 50−100 times faster than those of the SAP isomer. For the parent Gd-DOTA the ratio between SAP and TSAP structures is highly shifted toward the former (ca. 90:10). Here, inspection into 17O data, suggests that for Gd-DOTA-1 and Gd-DOTA-2 a higher amount of TSAP over SAP isomer, with respect to the parent Gd-DOTA, takes place. In my opinion, more information could be obtained from 1H NMR spectra of the corresponding Eu complexes simply trough a more accurate acquisition of the spectra. First of all, looking at figures 8 and 9 of supplementary, it seems that a lot of free ligand is present …the complexation should be better performed. Second, increasing the concentration of the Eu-complexes (I didn't find the concentration of the solutions used for 1H-NMR) or the number of acquisitions better spectra could be obtained which would allow for a rough estimation of the SAP/TSAP ratio. Moreover, to be thorough, 1H NMR of Eu-DOTA-3 should be included in the work. Once obtained this useful information from 1H-NMR, a complete analysis of 17O data could be done.