

Point 1: My only question is what the authors think the next optimization action would be. For instance, even the most selective molecule in this series has an S1R/S2R of less than 100-fold. Would it be a concern for the toxicity of those lead compounds?

Response 1: We would like to thank the reviewer for his/her positive comments and for giving us the opportunity to explain our strategy.

We really think that our molecules are worthy of further investigation and we will work for giving them a future. Currently, we cannot do precise correlations between the structure of the best promising compounds and an eventual further improvement of their profile of cytotoxicity. However, as already reported in the paper, we already evaluated the cytotoxicity against human neuroblastoma cells SHSY-5Y revealing a safe profile and, considering also their antioxidant properties, their behavior is consistent with that of S1R agonist/partial agonist. However, it will be important to extend the study to other cell lines of different tissue origin, and then proceed with animal tests. Only after completing these *in vitro* and *in vivo* characterizations, a clearer picture of the toxicity profiles linked to the structure of the chosen lead compounds will be attainable. To sum up, this work is not the end of the story, but it is only the beginning.