Answers to reviewers' comments

We thanks both reviewers for all the comments that helped us to improve this manuscript. We've corrected the manuscript following the several points mentioned here, and answered point by point to your questions to provide as much context as possible.

Reviewer 1

Comments and Suggestions for Authors

1. In the introduction, the development of current inhibitors and representative drugs can be introduced.

   We have added a small up-to-date point about current state of AT1 inhibitors and representative molecules in a new figure 1.

2. In the second and third paragraphs of the introduction, the author introduces the design of losartan-based compounds, such as the binding status between losartan and proteins. If a protein interaction diagram and the design scheme are added to the main text, it will be easier for readers to understand, for instance, why the author chose this parent nucleus.

   It was indeed not so easy to follow without models, so we have added a map of main residues involved with the binding of sartan, from the RX of losartan.

3. Does the R1 and R2 mentioned by the author in line 75 of the main text correspond to those in Scheme 1?

   They are the same indeed, with R1 being on the biphenyl and R2 in the scheme 1 being either the methoxy or the MOM moiety.

4. What is the design basis of the compounds in Scheme 1 proposed by the author? Why are the structural formulas of 4a-b and 4c completely different? In 4a-b: methoxy substitution is adopted, and the R1 position is substituted with biphenyl; in 4c, methyl ether substitution is used, and the biphenyl group at the R1 position has structural changes.

   The structural diversity observed between compounds 4a-b and 4c mainly reflects the synthetic pathway rather than a deliberate break in the medicinal chemistry design. Series 3 compounds were first generated from aldehyde intermediates, and series 4 compounds were subsequently obtained through Grignard reactions on these precursors. Therefore, the differences in methoxy/methyl ether substitution

patterns and in the biphenyl moiety originate from the specific synthetic intermediates and transformations used in each case.

5. The superscript notations for Ki and IC50 in Table 1 should be a and b.

   It was corrected.

6. The text first discusses the structure-activity relationship (Table 1), followed by the molecular docking results (Figure 1). Please reverse the order of these two sections.

   While we understand the rationale for reversing these two sections, in the present study molecular docking was not used as a predictive tool, but rather as a structural interpretation of the SAR derived from the binding assay results. For this reason, we believe that presenting the SAR first and the docking analysis afterwards provides a more logical progression, as the docking data are intended to rationalize and deepen the experimentally observed SAR.

7. Line 194 shows the docking result of 4b, but it is not displayed in the main text. Please provide it.

   We have added 4b to the now figure 2, as well as reference it in the text.