Design of new telmisartan analogues without AT1 receptor antagonistic activity

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INTRODUCTION

Telmisartan is an antihypertensive drug that acts as angiotensin 1 receptor (AT1R) antagonist and a partial peroxisome proliferator activating receptor γ (PPARγ) agonist. Unlike other AT1R antagonists, telmisartan possesses antiproliferative activity, but the exact mechanism is still not completely understood [1]. Therefore, elimination of AT1R antagonistic activity, with retained antiproliferative activity, would provide deeper insight into this mechanism and enable development of antiproliferative drugs without antihypertensive side effect.

THE AIM OF THE STUDY

The aim of this study was to design novel telmisartan derivatives without AT1R antagonistic activity using molecular docking.

MOLECULAR DOCKING

KEY BINDING INTERACTIONS

Molecular docking analyses were performed in FRED 3.2.0.2 software [2-4]. Telmisartan was docked into the active site of AT1R (pdb code: 4yay) and key binding interactions were identified: hydrogen bonds with Arg167 and Tyr35, as well as hydrophobic interactions with Tyr92 and Trp84 (Figure 1).

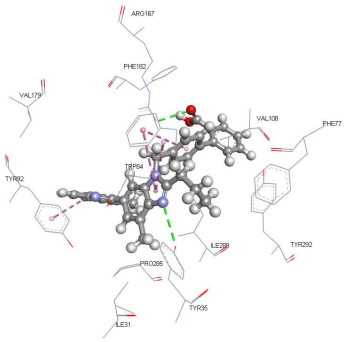

Figure 1. Interactions between telmisartan and AT1R

Elimination of key binding interactions

DESIGNED COMPOUNDS

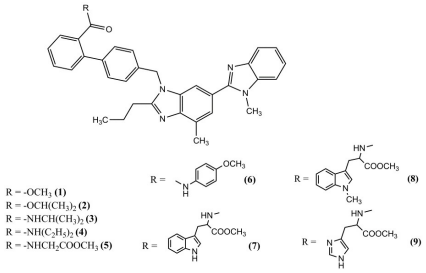

Figure 2. Chemical structures of designed compounds

CONCLUSION

New telmisartan derivatives were designed by modification of carboxilic group (amides and esters). Nine derivatives, from which lack of AT1R antagonistic activity could be expected, were selected. The first group (compounds 1 - 5, Figure 2) showed different interactions and similar binding energies as telmisartan (Figure 3). The second group (compounds 6 - 9, Figure 2) formed unfavourable interactions with the receptor and possessed significantly higher binding energies than telmisartan.

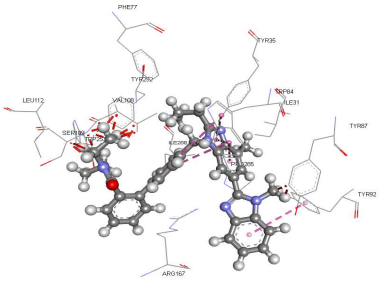

Figure 3. Interactions between compound 4 and AT1R

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