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Structural optimization of losartan as an approach to the design of new angiotensin II receptor antagonists

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Introduction. Arterial hypertension (AH) remains one of the leading causes of mortality worldwide. Even with the availability of effective medications, a considerable proportion of patients fail to achieve target blood pressure levels, which highlights the need for developing new molecules with improved therapeutic profiles [1]. One of the widely used agents for the treatment of hypertension is losartan – the first non-peptide antagonist of the angiotensin II type 1 receptor (AT_1). Since losartan requires metabolic activation, resulting in variability of the pharmacological effect, and other sartans (valsartan, candesartan, telmisartan) have their own drawbacks – such as low solubility, excessive lipophilicity, or limited bioavailability – this creates a strong rationale for rational structural optimization.
Materials and methods. Angiotensin II type 1 receptor antagonists (AT_1-blockers). BIOVIADraw and SwissADME software. Databases such as the Protein Data Bank (PDB) and DrugBank.
Results and discussion. Rational design was carried out in several directions. A bioisosteric replacement of the tetrazole ring with a triazole (LOZ-1) or 1,2,4-oxadiazole (LOZ-2) was performed to reduce the risks of tetrazole metabolism and idiosyncratic toxicity, and to fine-tune acidity and solubility. A bioisosteric substitution of the imidazole core with benzimidazole (telmisartan-like, LOZ-3) and 1,2,4-triazole (LOZ-4) was designed to enhance π-stacking within the receptor binding pocket, improve metabolic stability, and prolong the half-life. These modifications were made while maintaining the methylene bridge to the biphenyl fragment and introducing an ether linker ($–CH_2–O–$) to increase polarity (LOZ-5). A cyclopropyl group was introduced instead of the butyl substituent (LOZ-6), and a controlled biphenyl conformation was achieved by adding an ortho-fluoro substituent (LOZ-7) on the ring adjacent to the tetrazole to fix the non-planar twist that promotes optimal binding to the AT_1 site and may increase selectivity. An in silico analysis of seven rationally designed losartan derivatives was performed in comparison with the parent compound. The original losartan shows moderate solubility, a short duration of action, and CYP-mediated interaction risks. All designed analogues comply with Lipinski's rule of five and demonstrate acceptable pharmacokinetic properties. The molecular weight of the compounds ranges from 389 to 439 g/mol, and TPSA values from 90 to 110 $Å^2$. The best balance between lipophilicity and solubility was observed for LOZ-1 and LOZ-4 ($LogP \approx 3.3$; $LogS \approx -4.5$), whereas losartan has lower solubility (LogS −5.2). All compounds exhibit high gastrointestinal absorption and do not penetrate the blood–brain barrier. LOZ-1 and LOZ-2 do not inhibit CYP3A4, which reduces the risk of drug–drug interactions compared with losartan. LOZ-2 is characterized by the presence of a carboxylic acid fragment that may enhance AT_1 receptor affinity but slightly decreases solubility.
Conclusions. Among the obtained analogues, LOZ-1 shows the most favorable pharmacokinetic profile, while LOZ-2 exhibits higher potential activity due to the acidic fragment but lower solubility. Both compounds are promising candidates for further optimization and experimental evaluation.

References

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