SEARCH FOR SELECTIVE ANTAGONISTS AT A_1-ADRENORECEPTOR SUBTYPES: WB-4101 RELATED COMPOUNDS

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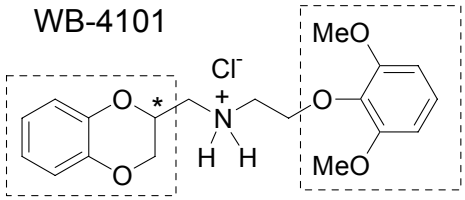
The development of subtype selective α_1 ligands is intensively pursued in order to obtain more effective and safer agents for the treatment of cardiovascular pathologies such as hypertension and arrhythmia, but also and particularly of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). One of the oldest and most potent α_1 antagonists is represented by WB-4101, a 2-aminomethyl-1,4-benzodioxane derivative which is slightly selective for α_{1A} and, to a minor extent, for α_{1D}-ARs with respect to α_{1B}-AR and 5-HT_{1A} serotoninergic receptor. Many structural modifications of WB-4101 have been done to improve both affinity and selectivity [1-4]. Some evidences, resulting from mutagenesis and docking studies, suggest that the benzodioxane moiety and the 2,6-dimethoxyphenoxy residue of WB-4101 are, respectively, involved in conferring α_{1a} selectivity and high α_1 affinity. Consistently with these findings, our recent researches have demonstrated that removal of one or both *ortho*-methoxy substituents adversely affects the affinity for the three α_1-AR subtypes, but not that for the 5-HT_{1A} receptor [3]. On the basis of these indications, we synthesized a number of *S* and *R* analogues of WB-4101, characterized by different substitutions at the benzodioxane and/or phenoxy fragment, in order to modulate and, hopefully, to improve the activity and selectivity profile of the parent compound. In particular, we considered derivatives with benzodioxane 8-substituted with F [4], Cl, OH or OMe [4] or fused with a cyclohexane to give a tetrahydronaphthodioxane polycycle [2]. On the other hand, 2,6-dimethoxyphenyl residue was replaced by *ortho* methoxy substituted 1-naphthyl [2] or biphenyl systems. Finally, hybrid structures were designed combining some of the above modifications. After binding assays, which demonstrated the better α_{1a}, α_{1b}, α_{1d} and 5-HT_{1A} affinity of the *S* enantiomers, these latter were tested in functional assays on isolated tissues, finding that almost all were able to discriminate among the α_1-AR subtypes.



[1] Bolognesi M.L., Budriesi R., Cavalli A., Chiarini A., Gotti R., Leonardi A., Minarini A., Poggesi E., Recanatini M., Rosini M., Tumiatti V., Melchiorre C. *J.Med.Chem.* **1999**, *42*, 4214-4224.
[2] Bolchi C., Catalano P., Fumagalli L., Gobbi M., Pallavicini M., Pedretti A., Villa L., Vistoli G., Valoti E. *Bioorg.Med.Chem.* **2004**, *12*, 4937-51.
[3] Fumagalli L., Bolchi C., Colleoni S., Gobbi M., Moroni B., Pallavicini M., Pedretti A., Villa L., Vistoli G., Valoti E. *Bioorg.Med.Chem.* **2005**, *13*, 2547-2559.
[4] Valoti E., Pallavicini M., Villa L., Pezzetta D. *J.Org.Chem.* **2001**, *66*, 1018-1025.