NEW 2,3-BENZODIAZEPINES AS NONCOMPETITIVE AMPA RECEPTOR ANTAGONISTS

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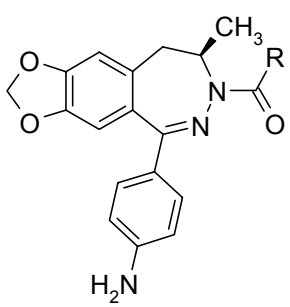
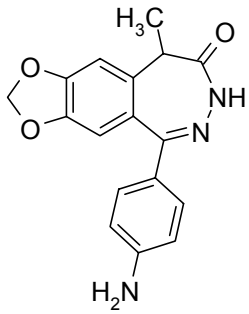
The discovery of GYKI 52466 as the prototype of the noncompetitive AMPA receptor antagonists endowed with anticonvulsant and neuroprotective properties, induced wide-ranging research activities focused on 2,3-benzodiazepines [1]. Highly active analogs of GYKI 52466 have been found such as 3,4-dihydro-3-*N*-methylcarbamoyl (GYKI 53655) and 3,4-dihydro-3-*N*-acetyl (GYKI 53405) derivatives. In particular, the 4-*R* enantiomer of GYKI 53405 was chosen as a drug candidate and is now in clinical trial as LY 300164 (Talampanel) [2].

On these basis we planned the synthesis and resolution of 3,5-dihydro-5-methyl-7,8-methylenedioxy-4*H*-2,3-benzodiazepin-4-one (±)-**1**. The enantioselective interaction of (±)-**1** with the 2,3-benzodiazepine binding site of the AMPA receptor complex was demonstrated by the difference in affinity in favour of the *S*-(-)-**1** enantiomer with respect to the racemate.

Furthermore, we designed new 3,5-dihydro-7,8-ethylenedioxy-4*H*-2,3-benzodiazepin-4-ones (**2**), in order to check how the replacement of the dioxole nucleus with the dioxane moiety affects the AMPA antagonist activity. Binding data and functional assays indicate a selective antagonism at the AMPA receptor complex higher than that displayed by GYKI 52466.



Talampanel



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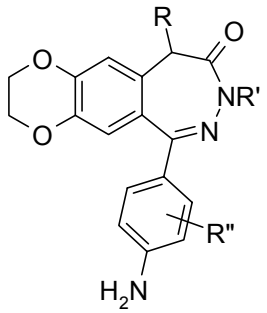

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[1] (a) Zappalà, M.; Grasso, S.; Micale, N.; Polimeni, S.; De Micheli, C. Synthesis and structure-activity relationship of 2,3-benzodiazepines AMPA receptor antagonists *Mini Reviews in Medicinal Chemistry* **2001**, *1*, 243. (b) Sólyom, S.; Tarnawa, I. Non-competitive AMPA antagonists of 2,3-benzodiazepine type *Curr. Pharm. Design* **2002**, *8*, 913.

[2] Chappell, A.S.; Sander, J.W.; Brodie, M.J.; Chadwick, D.; Liedo, A.; Zhang, D.; Bjerke, J.; Kiesler, G.M.; Arroyo, S. A crossover, add-on trial of talampanel in patients with refractory partial seizures. *Neurology* **2002**, *58*, 1680.