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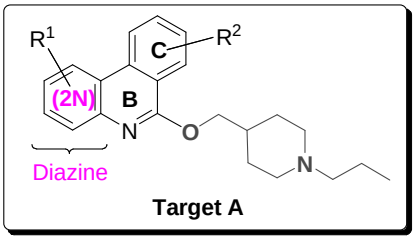
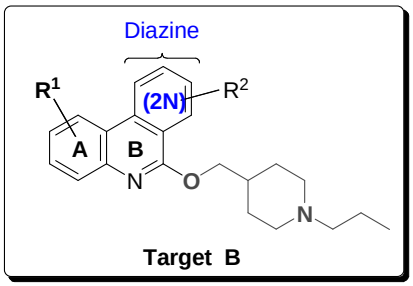
Synthesis of new fused fluorinated tricyclic diazine heterocycles and their use as ligands for 5-HT_4 serotoninergic receptors

Despite few symptomatic treatments, there is not at the present time a drug which is able to cure or stop the progression of Alzheimer's disease. Among the different approaches for the development of curative treatments, serotonin 5-HT_4 receptor (5-HT_4R) agonists have recently emerged as promising compounds. Recent works have allowed synthesizing 5-HT_4R ligands such as phenanthridines and benzonaphthyridines showing nanomolar affinity. Based on these results, we aimed at developing new fluorinated tricyclic ligands containing a diazine cycle in order to increase their affinity and selectivity toward 5-HT_4R and determinate their pharmacological profile.

Our targets **A** and **B** were prepared from the corresponding diazino[*c*](iso)quinolinones. Two different methodologies involving on a palladium cross-coupling (Suzuki or Stille) reaction and a KOH mediated anionic ring closure have been developed.



Target A



Target B

R^1, R^2 = H, Ph, OMe, Cl, F, I, CF_3

Thus, 20 final compounds were obtained in the three diazine series (pyrazine, pyrimidine and pyridazine) and evaluated on guinea pig and human 5-HT_4R. Pyrazino[2,3-*c*]isoquinoline derivatives showed a better affinity for 5-HT_4R than phenanthridines and benzonaphthyridines series and four selected targets were selective against others 5-HT receptors.

Keywords: Alzheimer's disease, Serotonin 5-HT_4 receptors, Diazines, Phenanthridines, nitrogen fused heterocycles.