SYNTHESIS OF A NEW ANALOGUE OF ANTI-ALZHEIMER DRUG TACRINE

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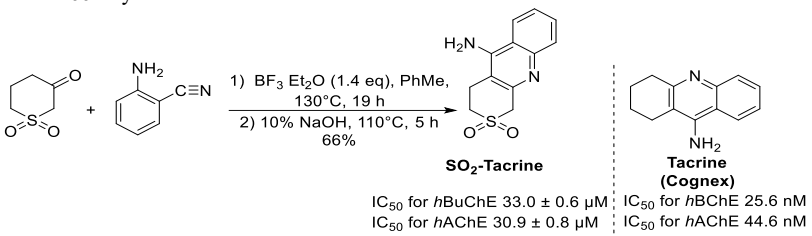
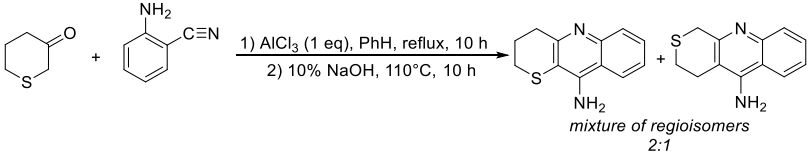
Alzheimer's disease (AD) is a severe age-dependent neurodegenerative brain disorder associated with progressive memory loss and decrease of cognitive functions. The absence of a cure so far and the expected dramatic incidence increase in the coming years, due to the population aging, place a huge burden on society, which has accounted for the current intensive studies aimed at preventing and treating AD. Tacrine (trade name Cognex®), the first clinically effective acetylcholinesterase inhibitor, was approved for the treatment of mild to moderate AD. Unfortunately, frequent adverse effects including peripheral cholinergic effects and hepatotoxicity limited its therapeutic potential. However, its high potency in cholinesterase inhibition, low molecular weight, and simple structure make tacrine a promising scaffold for developing new multi-target agents. In this work, we started our investigation on the development of sulfur-containing tacrine analogues.

Our interest in dihydro-2*H*-thiopyran-3(4*H*)-one 1,1-dioxide has arisen due to its high reactivity in multicomponent reactions (MCR) and wide applicability in the synthesis of various bioactive heterocycles. After a quick optimization, we found that the mentioned *β*-ketosulfone reacts with an equimolar amount of 2-aminobenzonitrile under $BF_3 \cdot Et_2O$ catalysis to form SO_2-tacrine in 66 % yield.



Our previous experiments with dihydro-2*H*-thiopyran-3(4*H*)-one and various Lewis acids ($AlCl_3$, $BF_3 \cdot Et_2O$ etc.) showed only an inseparable mixture of regioisomeric products.



Screening of the biological activity of SO_2-tacrine on human acetyl- and butyrylcholinesterase was performed by Dr. Manuela Bartolini (Alma Mater Studiorum University of Bologna, Italy). *In vitro* tests and evaluation of the half-maximal inhibitory concentration (IC_{50}) showed that the original tacrine drug is two orders of magnitude more potent than our SO_2-analogue. Thus, in the near future, we plan to modify SO_2-tacrine for fine-tuning pharmacodynamic and pharmacokinetic parameters of the molecule, and as a result, increasing the biological activity of human cholinesterases. In addition, we have screened *in silico* biological profile of SO_2-tacrine using free online tool https://www.molpredictx.ufpb.br (Laboratory of Cheminformatics, Federal University of Paraíba, Brazil). The prediction suggests high (60 % and more) probability levels of activity against *Acetylcholinesterase, C-albicans, Sars-Cov, Leishmania infantum – Promastigota, Alphis gossypii* and *Tripomastigote Chagas* species.

We believe that SO_2-tacrine is a promising compound for further investigation. The relevant results will be reported in due course.