Syntheses of WAY 100635 derivatives as 5-HT_{1A} antagonists

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Introduction: Depression is a mood disorder, which affects an estimated 121 million people worldwide. In the U.S. alone, depression has a monetary impact in the tens of billions of dollars per year in medical costs and lost productivity, and an immeasurable toll on quality of life. The molecular basis for depression is not fully understood; however, deficits in the activity of serotonin-mediated neurons in the brain are clearly central to the disease. In particular, the 5-HT_{1A} receptor, found in high concentration in the limbic system, where it is thought to play a role in emotional processes, is a major target for neurobiological research and drug development. Its activation leads to a number of physiological changes.
New arylpiperazine derivatives were prepared by Fiorino et al 2005[2] to identify highly selective and potent ligands for the 5-hydroxytryptamine 1A (5-HT1A) receptor as potential pharmacological tools in studies of central nervous system (CNS) disorders. Therein, 4-[3-[4-(*o*-methoxyphenyl) piperazin-1-yl]propoxy]-4-aza-tricyclo-[5.2.1.02,6] dec-8-ene-3,5-dione showed the highest selectivity and a K_i of 0.021 nM.

Aim: The aim of this study was to develop new 5-HT_{1A} agents with high affinity and selectivity over other serotoninergic, dopaminergic, and adrenergic receptors with the possibility to label them with flourine-18. Arylpiperazines similar to those published by Fiorino et al.[2] were chosen as a starting point. Substituting a methoxy- by a fluoro-ethoxygroup should be appropriate for introducing a fluorine.

Experimental/Discussion: We have analyzed a set of arylpiperazine-*N*-alkyl derivatives with a novel exo-*N*-oxy-5-norbornene-2,3-dicarboximide fragment as the terminal part of the long-chain arylpiperazines, which contains an oxygen atom in the spacer (Fig 1).

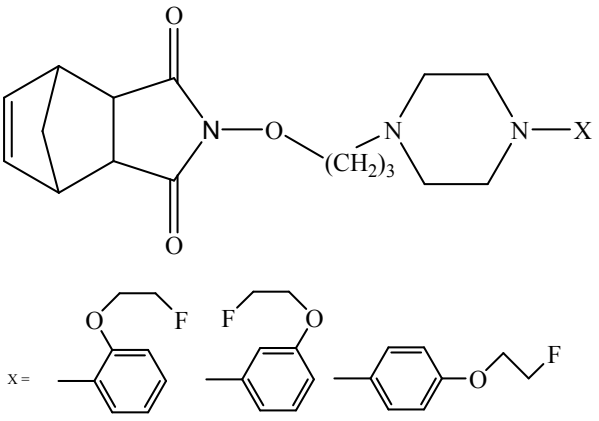

Fig.1: General structures

The general strategy for the synthesis of the target compounds is summarized in fig. 2. The general procedure is as follows: alkylation of the heterocycle endo-*N*-hydroxy-5-norbornene-2,3-dicarboximide with 1-bromo-2-chloroethane or 1-bromo- 3-chloro-propane in the presence of NaOH in absolute ethanol gave the corresponding chloro-alkyl norbornene derivatives **1**. Subsequent condensation of compounds **1** with the desired 4-X-substituted piperazines, performed in CH_3CN in the presence of K_2CO_3 and NaI under reflux, provided the final compounds, respectively.

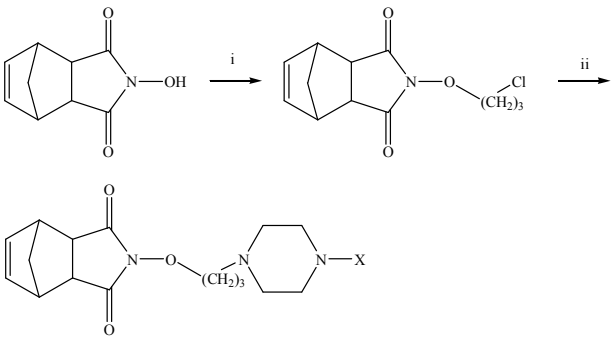

Fig 2: Reagents and conditions: (i) $Br(CH_2)_3Cl$, NaOH, absolute EtOH, 70 °C, 24 h; (ii) 4-X-substituted piperazine, K_2CO_3, NaI, CH_3CN, reflux, 24 h

Conclusion: To verify the potential of those new WAY 100635 arylpiperazine derivatives *in vitro* experiments are planed.

References:

[1] World Health Organization WHO Fact Sheet Number 265; The World Health Organization: Geneva, Switzerland, 2001
[2] Fiorino et al.; J. Med. Chem. 2005, *48,* 5495-5503