Synthesis of novel WAY 100635 derivatives containing a norbornene group and radiofluoroination of [^{18}F]AH1.MZ, as a Serotonin 5-HT$_{1A}$ Receptor Antagonist for molecular Imaging

Herth M, Kramer V and Rösch F
Institute of Nuclear Chemistry, Johannes Gutenberg-Universitaet Mainz, Mainz, Germany

Introduction:

5-HT$_{1A}$ receptors are involved in a variety of psychiatric disorders and *in vivo* molecular imaging of the 5-HT$_{1A}$ status represents an important approach to analyze and to treat these disorders. Recently, Fiorino et al.[1] synthesized new arylpiperazines containing a norbornene group as 5-HT$_{1A}$ receptor antagonists and reported their outstanding *in vitro* selectivity for the 5-HT$_{1A}$ receptor. Therefore, we decided to slightly modify promising ligands by replacing a methoxy- by a fluoroethoxy group for labelling purposes, to alter the position of the fluoroethoxy group within the phenylic ring and to determine the affinities of the new compounds towards several 5-HT receptor subtypes. Also, we report the optimized labelling and purification procedure of the a promising candidate [^{18}F]AH1.MZ.

Methods:

Organic synthesis of WAY 100635 derivatives containing a norbornene group has been described by Fiorino et al.. Due to the necessary structural replacement of a methoxy- by a fluoroethoxy group for labelling purposes, a similar synthesis route was applied, but hydroxyphenylpiperazines were used as starting materials for both precursors and reference compounds. Moreover, the ^{18}F-labelling was carried out similar to the one reported in Herth et al. (2008) and the *in vitro* receptor profile was provided by PDSP.

Results:

Three potential 5-HT$_{1A}$ antagonists could be synthesized in total yields of 15%. In vitro affinites of the htree compounds were in a low to moderate nanomolar range for AH1.MZ (**1**) (K_i = 4.2 nM) and AH2.MZ (**2**) (K_i = 30 nM), whereas AH3.MZ (**3**) shows no affinity towards the 5-HT$_{1A}$ receptors (Figure 1). Moreover, AH1.MZ and AH2.MZ showed a reasonable *in vitro* affinity profile and should enable the imagining of the 5-HT$_{1A}$ receptor by PET.

The [^{18}F]fluoroalkylation was optimized only due to temperature variation resulting in radiochemical yields of > 70%. Final reaction conditions were 120 °C, 7 mmol precursor and 7 mmol 5 N NaOH dissolved in 1 mL of dry DMSO with a reaction time of 20 minutes.

Conclusion:

Fiorino et al. reported about a outstanding high affine (K_i = 0.021 nM) and selective compound. By replacing the methoxy- by a fluoroethoxy group of the parent compound, three different reference compounds (**1**)-(**3**) were obtained enabling a labeling strategy with [^{18}F]FETos. *In vitro* evaluation of these ligands showed high to moderate affinities to the 5-HT$_{1A}$ receptor for AH1.MZ and AH2.MZ, but no affinity of AH.3MZ toward the 5-HT$_{1A}$ receptor of the p-substituted fluoroethylated compound. The receptor profile of AH1.MZ and AH2.MZ demonstrates selectivity within the 5-HT system. However, the outstanding affinity and selectivity of the literature reference compound is mainly lost by introducing a fluoroethyl group. Nevertheless, compounds AH1.MZ and AH2.MZ may provide potential for molecular imaging the 5-HT$_{1A}$ receptor system.
^{18}F-labelling via [^{18}F]FETos was carried out and optimized up to RCY of > 70%.

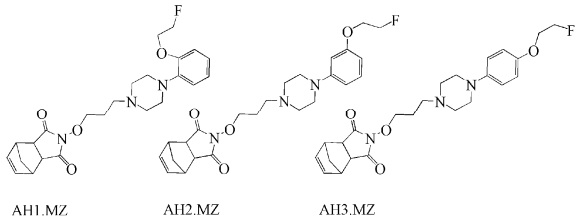

Figure 1:Structures of novel WAY 100635 derivatives

References:

[1] Fiorino et al.; J. Med. Chem. 2005**,** *48,* 5495-5503