Synthesis and structure-activity-relationships of new 5-HT_{2A} receptor antagonists combining the structure of (R)-MH.MZ, altanserin and SR 46349B

Kramer V[1], Herth M[1], Palner M[2], Knudsen G[2], F Rösch
[1]Institute of Nuclear Chemistry, Johannes Gutenberg-University, Mainz, Germany
[2]Center for Integrated Molecular Brain Imaging, Rigshospitalet, Copenhagen, Denmark

Objectives: ^{18}F-labeled 4-benzoylpiperidine derivatives such as [^{18}F]MH.MZ and [^{18}F]altanserin play an important role as imaging agents to determine the 5-HT_{2A} receptor status *in vivo* using positron emission tomography (PET)[1]. Both radioligands can be well accommodated to the binding model published by Anderson et al[2]. This binding model provides two possible directions in which 4-benzoylpiperidine derivatives can bind to the receptor binding site. The aim of this work was to develop new derivatives containing structure elements of both ligands, [^{18}F]MH.MZ and [^{18}F]altanserin, to clearify in which way they bind to the binding site. With this background it should be possible to deduce structures for new high affine ligands or to optimize established tracers.

Methods: Three new ligands were synthesised containing a 4-benzoylpiperidine moiety as lead structure. Therefore the phenolic hydroxylgroup of ketone (1) was deprotected and reacted with 1-brom-2-fluoroethane. The resulting compound (3) was deprotected and reduced with $NaBH_4$ to obtain the intermediate compounds (3a) and (3b) (Fig. 1).

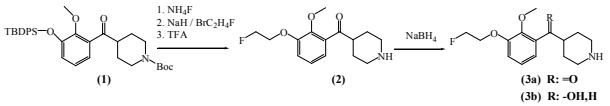

Figure 1: Synthesis of amine (3a) and (3b)

Reaction with boc-protected bromethylamine, deprotection and ringclosure with 2-thiocyanatobezoic acid results in compounds (6a) and (6b) (Fig. 2).

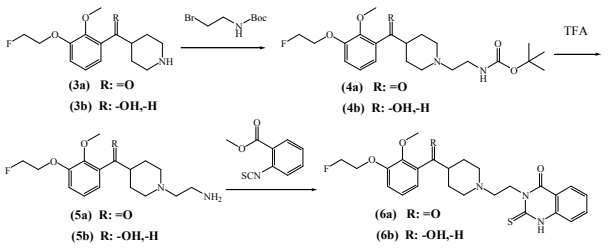

Figure 2: Synthesis of reference compounds (6a) and (6b)

For compound 6a the p-fluorophenyl ring of altanserin was replaced by the 3-fluorethoxy-2-methoxyphenyl ring present in the structure of MH.MZ. Compound 6b contains a quinazolinone ring instead of the p-fluorophenyl substituent in the structure of MH.MZ. The O-dimethylaminoethyloxim residue present in the structure of SR 46349B, was introduced in compound 9 to study if it may improve its affinity (Fig 3).

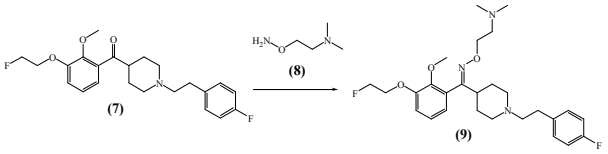

Figure 3: Synthesis of reference compound (9)

The *in vitro*-affinity for compounds (6a), (6b) and (9) was determined by a [^{3}H]MDL 100,907 binding assay with GF-62 cells, expressing high amounts of the 5-HT_{2A} receptor.

Results: Altanserin binds to the 5-HT_{2A} receptor with the p-fluorObenzoyl moiety in a hydrophobic binding pocket and with a subnanomolar affinity. The remarkable reduced affinity of compound 1 and 2 indicates that the additional space required by the fluorethoxy group and the methoxy group is not tolerated (Tab 1).

Table 1: Affinities to the 5-HT_{2A}-receptor

compound	K_i [nM]	compound	K_i [nM]
MH.MZ	9.03	(6a)	411
Altanserin	0.3	(6b)	390
SR46349B	1.3	(9)	57

These results demonstrate that [^{18}F]MH.MZ can only bind to the 5-HT_{2A} receptor with the p-fluorphenylethyl residue in the hydrophobic binding pocket. By varying size and hydrophobic properties of the substituent in the para position it should be possible to improve the binding characteristics of the radioligand. The moderate affinity of compound (9) indicates that the O-dimethylaminoethyloxim residue requires to much additional space and lowers the affinity.

Conclusions: This work demonstrates that [^{18}F]MH.MZ binds to the 5-HT_{2A} receptor with the p-fluorophenylethyl residue in a sterically restricted hydrophobic binding pocket. Structure-activity relationship (SAR) studies of derivatives with different p-substituents of [^{18}F]MH.MZ were also performed[3].

Literatur:

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[3] Herth MM, Kramer V, Piel M, Palner M, Riss PJ, Knudsen GM, Rösch F, (**2009**); Bioorg. Med. Chem. (submitted)