SYNTHESIS AND RADIOLABELLING OF N^5-[^{18}F]FLUOROETHYL-PIRENZEPINE AND ITS METABOLITE N^5-[^{18}F]FLUOROETHYL-LS 75

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Introduction:
Pirenzepine **3**, namely 11-[2-(4-methyl-piperazin-1-yl)-acetyl]-5,11-dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one has originally been developed as M_1 selective muscarinergic antagonist. In vivo, **3** is metabolised to LS-75 **4** 5,11-dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one. The latter compound was found to be a moderate inhibitor of PARP, an enzyme directly related to e.g. neuronal signal transduction and in particular to the regulation of key events in apoptotic cascades. Moreover we were interested to investigate this second Pirenzepine-related mode of action on a physiological level[2]. Our aim was to synthetise appropriate ^{18}F-fluorinated analogues of **3** and **4** in order to provide the tools for an in vivo PET-study in healthy Sprague-Dawley rats of these potentially beneficial side effects of **3**, which are beyond pure M_1 antagonism.

Experimental:
3 and **4** were prepared via a modified procedure published elsewhere[1]. Alkylation with 2-fluoroethyl bromide afforded reference compounds **1** and **2**. **3** and **4** were labeled with 2-[^{18}F]fluoroethyl tosylate. [^{18}F]-**1** and [^{18}F]-**2** were isolated, purified by HPLC and formulated in PBS prior to application.
For autoradiography, brain sections from adult, male Sprague-Dawley rats were used. Sections were preincubated in assay buffer (50 mM Tris/HCl buffer, pH 7.5, containing 120 mM NaCl). Nonspecific binding was determined using 100 µM of pirenzepine.

Results and Discussion:
3 and **4** were synthetised and labeled with 2-[^{18}F]fluoroethyltosylate in radiochemical yields of 30 ±5 % after 20 min. Autoradiographic studies on rat brain sections showed high unspecific binding. Assay conditions therefore need further refinement. Nonetheless, specific uptake in the thalamus could be detected. Displacement of [^{18}F]-**1** by 100 µM pirenzepine hints on no significant deviation in binding by fluoroalkyl-derivatives compared to the parent compound.

Conclusion:
After autoradiographic evaluation, [^{18}F]-**1** and [^{18}F]-**2** can now be utilised in small animal PET studies using Sprague-Dawley rats.

Acknowledgement:
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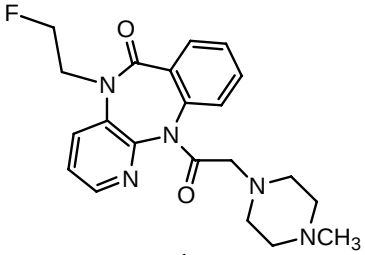
References
1 Holzgrabe U. et al. Tetrahedron 59 (2003) 781 ff
2 Schrattenholz A. et al. Current Topics in Medicinal Chemistry 6 (2006), 663 ff



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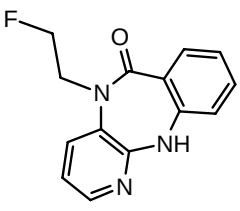

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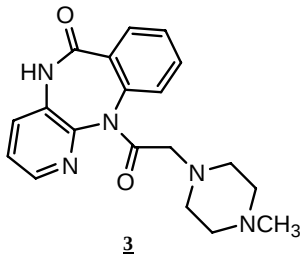

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