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Synthesis and biological evaluation of potential 5-HT$_7$ receptor PET radiotracers

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ABSTRACT

Brain serotonin 7 receptor (5-HT$_7$) is involved in several mood disorders and drug candidates targeting this subtype are currently in development. Positron emission tomography (PET) is a molecular imaging modality offering great promise for accelerating the process from preclinical discovery to clinical phases. As no PET radiopharmaceutical has yet been used successfully to study the 5-HT$_7$ receptor *in vivo*, our objective is to develop the first 5-HT$_7$ fluorine-18 labeled radiotracer.

Four structural analogs of **SB269970**, a specific 5-HT$_7$ receptor antagonist, divided in FP3 series and FPMP series were synthesized. Their antagonist effects were investigated by cellular functional assay. Nitro-precursors of these analogs were radiolabeled via a [^{18}F$^-$]nucleophilic substitution and *in vitro* autoradiographies were performed in rat brain.

Chemical and radiochemical purities of fluorine radiotracers were >99% with specific activities in 40 −129 GBq/μmole range. The four derivates presented antagonism potencies toward 5-HT$_7$ receptors (pK_B) between 7.8 and 8.8. The four PET radiotracers had suitable characteristic for 5-HT$_7$ receptor probing *in vitro* even if the FP3 series seemed to be more specific for this receptor. These results encourage us to pursue *in vivo* studies.