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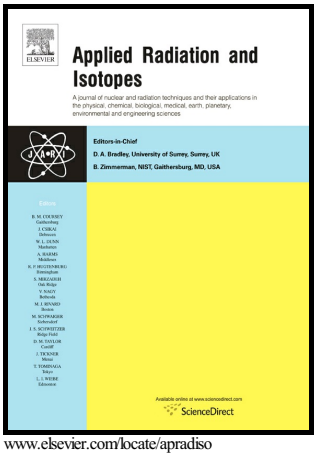

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Automated radiosynthesis and purification of [^{18}F]flumazenil with solid phase extraction

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Abstract

This paper describes the novel approach for preparation of [^{18}F]flumazenil ([^{18}F]FMZ), well known radioligand for assessment of $GABA_A$ receptors by PET. The optimized reaction conditions allowed us to implement commercially available SPE cartridges for [^{18}F]FMZ purification avoiding HPLC. All procedures were performed with TRACERlab FX N Pro synthesizer in 53 min. Developed approach provided [^{18}F]FMZ with high RCP (>97%) and low level of chemical impurities (< 5 μg/ml). FMZ was routinely synthesized in 6.4±0.7 % RCY at EOS (not decay corrected, n=8) and the molar radioactivity was >185 GBq/μmol.

Key words: Fluorine-18, [^{18}F]flumazenil, benzodiazepine receptors, positron emission tomography, solid phase extraction, automated GE TRACERlab FX N Pro synthesizer

1. Introduction

Gamma amino butyric acid (GABA)-receptors is part of the major inhibitory neurotransmitter system. They are located on neuronal membranes and have specific sites for the binding of GABA and some other modulators. Benzodiazepines are the most important allosteric modulators enhancing the GABA impact on the $GABA_A$ receptor via the benzodiazepine binding sites (Sigel et al., 2012). These receptors play an important role in many neurological and psychiatric disorders, such as epilepsy, panic disorder, dementia, acute stroke, alcoholism. The highest density of $GABA_A$ receptors was observed in cerebral cortex, the medium density in hippocampus and a relatively low in the pons and medulla (Andersson et al., 2013). Flumazenil (ethyl 8-fluoro-5, 6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5a][1,4] benzodiazepine-3-carboxylate) has the highest selectivity and affinity for $GABA_A$ receptors (*K*i~1 n*M*) in comparison with other benzodiazepines and competitively inhibits the effects of benzodiazepines. Therefore, flumazenil has been used as an antidote for the treatment of benzodiazepine overdose (Doyle et al., 1998).

Radiolabeled analogs of flumazenil are important radiopharmaceuticals for the assessment of the $GABA_A$ receptors density by positron emission tomography (PET) that provides information which allows detecting epileptic foci (Vivash et al., 2014) and cortical damage after stroke or trauma (Geeraerts et al., 2011). It has also been used to examine patients with disorders such as Alzheimer's disease, degenerative disorders of the basal ganglia and cerebellum, ischemic stroke (Heiss et al., 2007) and to support drug development (Declercq et al., 2016).

Flumazenil labeled with carbon-11 ([^{11}C]FMZ) was the first radioligand for PET imaging of the $GABA_A$ system (Mazière et al., 1984) and the gold reference for $GABA_A$ receptors evaluation, but short half-life of carbon-11 ($T_{1/2}$=20.4 min) imposes requirements upon the duration of the radiochemical synthesis and following PET study. Application of relatively long-lived isotope, fluorine-18 ($T_{1/2}$= 109.8 min) allows overcoming these limitations. Introduction of