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Synthesis and evaluation of (*S*)-[^{18}F]fesetron in the rat brain as a potential PET imaging agent for serotonin 5-HT$_3$ receptors

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ABSTRACT

Serotonin 5-HT$_3$ receptors are involved in various brain functions including as an emesis target during cancer chemotherapy. We report here the development of (*S*)-2,3-dimethoxy-5-(3′-[^{18}F]fluoropropyl)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide ([^{18}F]fesetron) as a potential PET imaging agent for serotonin 5-HT$_3$ receptors. By radiolabeling((*S*)-2,3-dimethoxy-5-(3′-tosyloxypropyl)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzamide) with fluorine-18, (*S*)-[^{18}F]fesetron was obtained in 5 to 10% decay-corrected yields and with specific activities >74 GBq/μmol at the end of radiosynthesis. PET imaging in rats showed low uptake of [^{18}F]fesetron in the brain with retention of binding in the striatal and cerebellar regions. Using colliculi as a reference region, ratios were 3.4 for striata and 2.5 for cerebellum. Ex vivo brain PET analysis displayed binding of [^{18}F]fesetron in the hippocampus, striatum and cerebellar regions. Cerebellar regions corresponded to area postrema and nucleus tract solitaris known to contain 5-HT$_3$ receptors. Dorsal hippocampus showed the highest uptake with ratio of >17 with respect to colliculi, while area postrema and striata had ratios of >10. Thus, [^{18}F]fesetron exhibited a unique binding profile to rat brain regions known to contain significant amounts of serotonin 5-HT$_3$ receptors. However, the very low brain uptake limits its usefulness as a PET radiotracer in this animal model.

The serotonin 5-HT$_3$ receptor is a ligand-gated cation channel belonging to the nicotine/gamma-aminobutyrate (GABA) receptor super-family.[1] The 5-HT$_3$ receptors are found in the brain mainly in presynaptic regions associated with axons and nerve terminals (70–80%). In the hippocampus, they are predominately postsynaptic receptors located on somatodendritic regions.[2] They have been found at many central nervous system (CNS) locations and mostly on GABAergic neurons. The 5-HT$_3$ receptor is involved with pain processing, integration of the vomiting reflex (emesis), sensory transmission, the reward system, often associated with dopaminergic pathways, anxiety control and gastrointestinal disorders.[3,4] Therapeutically, antagonists have shown the most promise in chemotherapy induced nausea and vomiting (CINV). The 5-HT$_3$ receptor has also been investigated for its potential use in treating drug addiction.[4] Subtypes of 5-HT$_3$ receptor have been reported: 5-HT$_{3A}$, 5-HT$_{3B}$, 5-HT$_{3C}$, 5-HT$_{3D}$, and 5-HT$_{3E}$ of which the 5-HT$_{3A}$ subtype has been reported across species.[1,4]

Several ligands with high affinity and selectivity for the 5-HT$_3$ receptor, including zacopride have been reported (Fig. 1).[5] Zacopride is a 3-aminoquinuclidinyl derivative exhibiting antiemetic effects which were found to be greater for its (*S*)-isomer.[6–8] In

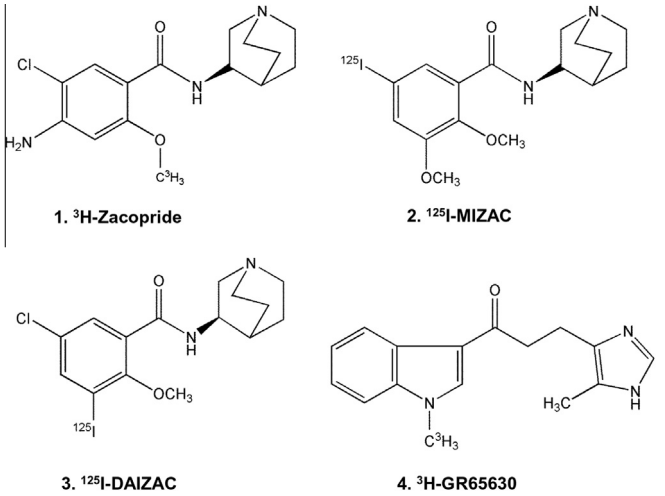

Figure 1. Chemical structures of 5-HT$_3$ radioligands: four radiolabeled derivatives with subnanomolar affinities for the 5-HT$_3$ receptor used for in vitro studies. 3-Aminoquinuclidine derivatives **1**. [^{3}H]Zacopride, **2**. [^{125}I]MIZAC, and **3**. [^{125}I]DAIZAC. Derivative without 3-aminoquinuclidine ring, **4**. [^{3}H]GR65630.

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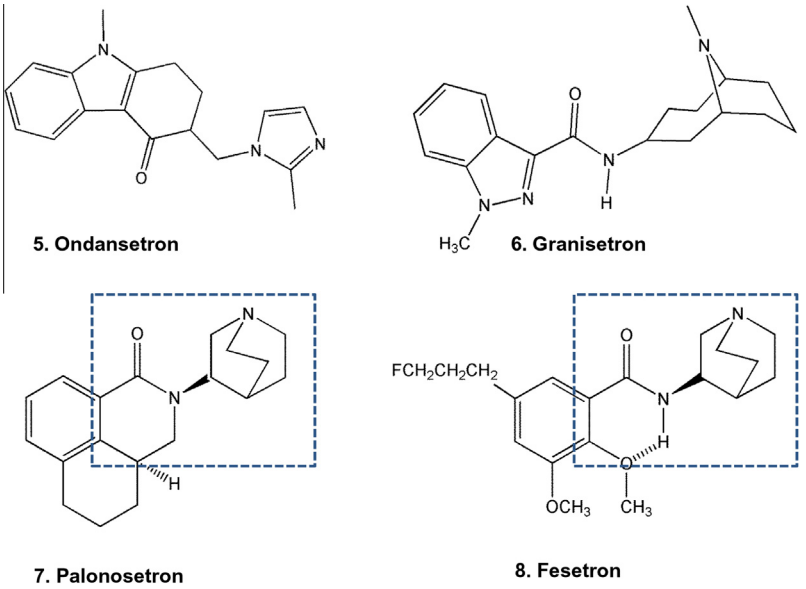

Figure 2. Chemical structures of 5-HT_3 ligands: the 'setron' drugs used as antiemetic agents: **5**. Ondansetron, **6**. Granisetron, and **7**. Palonosetron. Palonosetron contains the 3-aminoquinuclidine ring structure (blue dashed box in **7**). Based on the structures of MIZAC and Palonosetron, Fesetron **8** was developed as a potential PET radiotracer for 5-HT_3 receptors and is reported in this Letter.

order to study the distribution of these receptors, [^{3}H]zacopride,[9] related radioiodinated derivatives, [^{125}I]DAIZAC[10] and [^{125}I]MIZAC[11] and other compounds without the 3-aminoquinuclidinyl moiety as in [^{3}H]GR65630[12] have been synthesized (Fig. 1). Although in vitro studies have been reported with these radioligands, no in vivo studies are available.[10] Additionally, positron emission tomography (PET) imaging agents with high affinity such as [^{18}F]MR18445[13] and [^{11}C]MDL72222[14] were not successful in vivo for selective binding to 5-HT_3 receptors.

The 'setron' drugs (defined as selective serotonin 5-HT_3 receptor antagonists) were first used because of their effects on CINV due to high affinity for the 5-HT_3 receptor (Fig. 2). They belong to the same substance class because of their binding to the orthosteric ligand binding site on the receptor protein.[15] Although only granisetron and palonosetron are selective to the 5-HT_3 receptor,[16,17] all the setron drugs are equally capable of inhibiting Ca^{2+} influx.[4] Palonosetron, being the 'newer' setron drug, seems to show a longer plasma half-life and a higher affinity to 5-HT_3 receptors when compared to the other setron drugs.[16,18] Also, palonosetron has shown to be effective not only in treating acute CINV but also delayed CINV.[18] Because of its apparent advantages, we took an interest in palonosetron and looked closely at its chemical

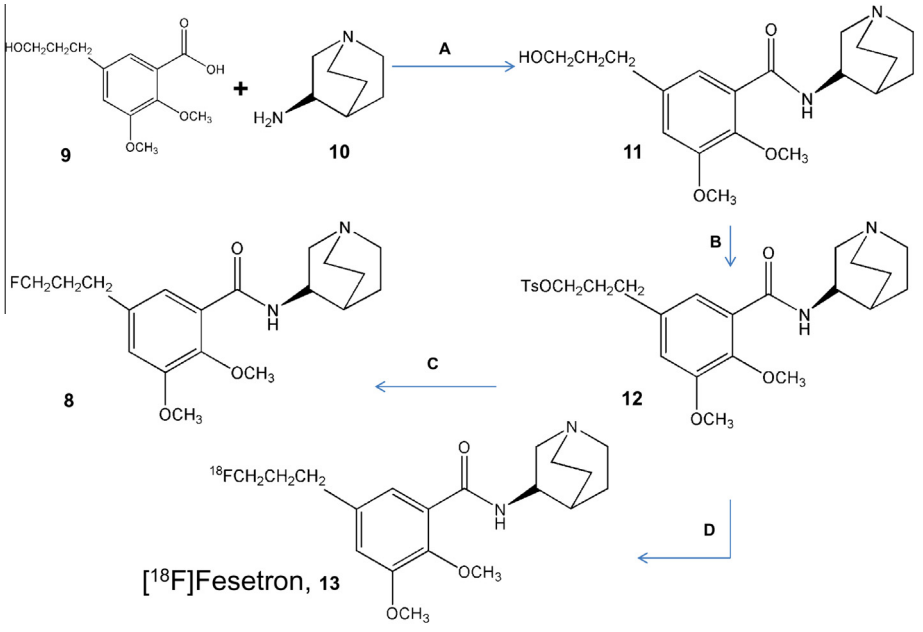

Figure 3. Synthesis of fesetron **8** and [^{18}F]fesetron **13**. Step A: coupling of carboxylic acid **9** with amine **10** to provide the substituted amide **11** (BOP: benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate; Et_3N: triethylamine; CH_3CN: acetonitrile). Step B: tosylation of alcohol **11** to the tosylate **12** (TsCl: *p*-toluenesulfonyl chloride; CH_2Cl_2: dichloromethane). Step C: nucleophilic displacement of tosylate with fluoride to provide fesetron **8** (Bu_4NF: tetrabutylammonium fluoride; THF: tetrahydrofuran). Step D: radiolabeling of tosylate **12** with K[^{18}F]Kryptofix in CH_3CN to provide [^{18}F]fesetron which was purified by HPLC.