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Synthesis, radiolabeling and animal studies of [^{131}I]MPPI: A 5-HT$_{1A}$ imaging agent

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Abstract The synthesis and biological evaluation of serotonin (5-HT$_{1A}$) imaging agent [^{131}I]-4-iodo-*N*-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]-ethyl}-*N*-pridin-2-yl-benzamide ([^{131}I]MPPI) are reported. The chemical structure of aimed compound and intermediates were confirmed by IR, ^{1}HNMR, and MS. Radiochemical purity was above 99% determined by TLC. Biodistribution of [^{131}I]MPPI in rats displayed high uptake in hippocampus and low uptake in cerebellum. The ratio of the uptake of [^{131}I]MPPI in hippocampus to that in cerebellum was 2.90 at 30 min post injection. The radioactivity in thyroid was 0.069 and 0.128% ID/g organ at 5 min and 120 min, respectively, and it was increased with time, which suggests that *in vivo* deiodination may be the major route of metabolism. *Ex vivo* autoradiography of brain section displayed significant decrease of radioactivity in hippocampus when pretreated with 8-OH-DPAT, a selective 5HT$_{1A}$ agonist, compared with control. These findings strongly suggested that ^{131}I-MPPI could be used as an *in vivo* marker for studies of pharmacology of the 5-HT$_{1A}$ receptor system in animals.

Keywords 5-HT$_{1A}$, [^{131}I]MPPI, Synthesis, Biological evaluation, Imaging agent, Biodistribution

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1 Introduction

In the last two decades, considerable progress has been made in the understanding of the central nervous system (CNS) serotonin system. It is an important neurotransmission network that regulates various physiological functions and behavior, including anxiety and affective states.[1-3] The family of receptors activated by the neurotransmitter serotonin has been divided into at least seven classes (5-HT$_{1-7}$), some of them further subdivided into different subtypes[4, 5]. Over the past few years, special attention has been paid to 5-HT$_{1A}$, which is certainly the most well-characterized subtype due to the availability of the *R* enantiomer of 8-OH-DPAT, a high selective 5HT$_{1A}$ agonist. 5HT$_{1A}$ receptor is involved in various physiological processes such as the regulation of mood, sleep, and sexual disorder as well as in psychiatric disorders such as anxiety and depression [6, 7]. To develop antagonist for *in vivo* evaluation of 5-HT$_{1A}$ receptors, a series of halogen substituted benzamido derivatives of 4-(2'-methoxyphenyl)-1-[2'(*N*-2''-pyridinylhalobenzamido) ethyl] piperazine were prepared.[8] Of these, the iodinated derivative (the *p*-iodobenzamido compound, [^{125}I]-*p*-MPPI) displayed high affinity and selectivity for 5-HT$_{1A}$ receptors. De-

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spite promising *in vivo* binding properties both in rats and baboons, *in vivo* application of ^{123}I-MPPI in human subjects is hampered by negligible ability to penetrate blood-brain-barrier (BBB). However, MPPI still has potential applications in drug screening in animal models and as an *in vivo* marker for studies of pharmacology of the 5-HT_{1A} receptor system in animals.

Herein, we report the synthesis, radiolabelling and preliminary evaluation of ^{131}I-MPPI as a 5-HT_{1A} imaging agent.

2 Materials and methods

2.1 General materials

All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. When reactions were worked up by extraction with dichoromethane (CH_2Cl_2), ethyl acetate (EtOAc) or ethyl ether (Et_2O), organic solutions were dried with anhydrous Na_2SO_4 and concentrated with a rotary evaporator under reduced pressure.

Melting points were determined on Yanadimoto apparatus and uncorrected. Column chromatography was performed using silica gel, 100—200 mesh. ^{1}HNMR spectra were recorded on an AM spectrometer at 400 MHz, with $CDCl_3$-*d* as solvent and tetramethylsilane (TMS) as the internal standard (0 ppm). Mass spectra were run on Varian MAT 2.2 spectrometer.

Rats (Sprague-Dawley, 200–250 g) were purchased from the Center of Experimental Animals of East China. They were allowed free access to food and water in the biodistribution study.

2.2 Synthesis of *p*-MPPI

The synthetic route is shown in Fig. 1.

2.2.1 2-chloro-*N*-pyridin-2-yl-acetamide (**3**)

To a solution of pyridin-2-ylamine (4.7 g, 0.05 mol) and triethylamine in CH_2Cl_2 (50 mL) chloro-acetyl chloride (4.7 mL) was added at low temperature (-78°C) under nitrogen. The mixture was stirred at 0°C for another 1 h, cold water (100 mL) was added and the organic layer was separated. The aqueous layer was adjusted to pH 10 with 50% sodium hydroxide followed by extraction with CH_2Cl_2 (50 mL×4). The combined organic layers were washed with H_2O, dried and concentrated under reduced pressure to give **3** (7.5g, 87%) as a gray solid, mp: 118~120°C. IR (KBr, cm^{-1}): 3226, 1685, 1581, 1542; ^{1}HNMR: δ4.20 (s, 2H), 7.10 (t, 1H), 7.73 (t, 1H), 8.19 (d, 1H), 8.32 (m, 1H), 8.95 (s, 1H); MS: 170 (M^+), 135 (M-Cl), 78 (M-$ClCH_2CONH$).

2.2.2 2-[4-(2-methoxy-phenyl)-piperazin-1-yl]-*N*-pyridin-2-yl-acetamide (**4**)

A mixture of product **3** (1 g, 5.86 mmol), 1-(2'-methoxy-)piperazine (1.3 g, 6.77 mmol) and K_2CO_3 (0.5 g, 3.6 mmol) in 50 mL DMF was stirred at room temperature. Twenty hours later, the reaction was quenched with water (200mL). The mixture was

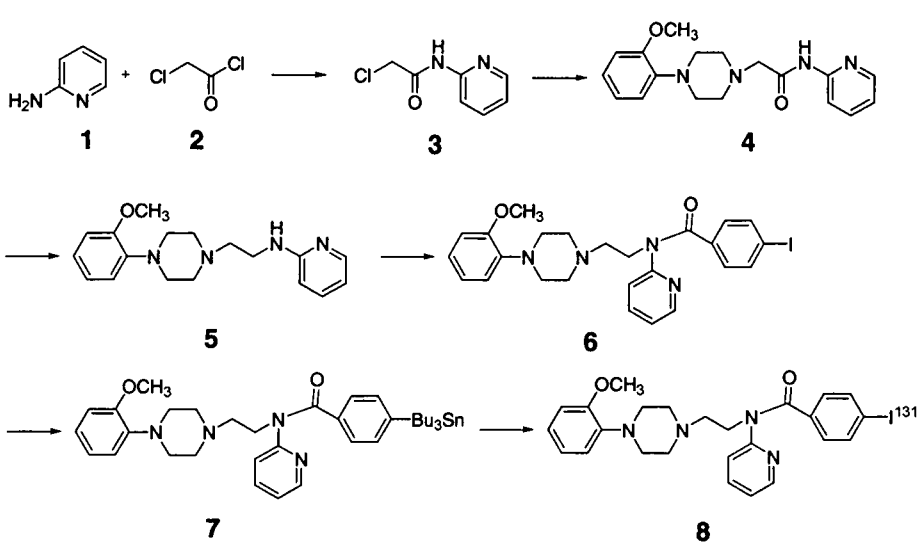

Fig. 1 Synthesis of MPPI.