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Analogues of WAY 100635 as Radiotracers for In Vivo Imaging of 5-HT_{1A} Receptors

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Summary

Two diastereoisomeric analogues of the potent 5-HT_{1A} antagonist WAY 100635 have been synthesized and radiolabelled with ^{11}C; namely trans- and cis-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)-cyclohexanecarboxamide (**3** and **4**). Both [^{11}C]-**3** and [^{11}C]-**4** were obtained in modest yields at high specific activities by O-[^{11}C]-alkylation of their respective alkoxide precursors with [^{11}C]-iodomethane. The labelled diastereoisomers were isolated by reverse-phase HPLC and isolated as radiochemically pure formulations for *in vivo* experiments. Biodistribution studies in rats showed moderate brain uptake for [^{11}C]-**4** with little differentiation of uptake between regions rich in 5-HT_{1A} receptors (e.g. hippocampus) and receptor poor regions (e.g. cerebellum). However the diastereoisomeric [^{11}C]-**3** possessed better brain uptake with moderate differentiation between 5-HT_{1A} receptor rich and poor regions at early time points (5-30 min post-injection). The results suggest that [^{11}C]-**3** may have potential as an *in vivo* imaging agent for 5-HT_{1A} receptors .

Key Words: carbon-11, WAY 100635, 5-HT_{1A}, positron emission tomography

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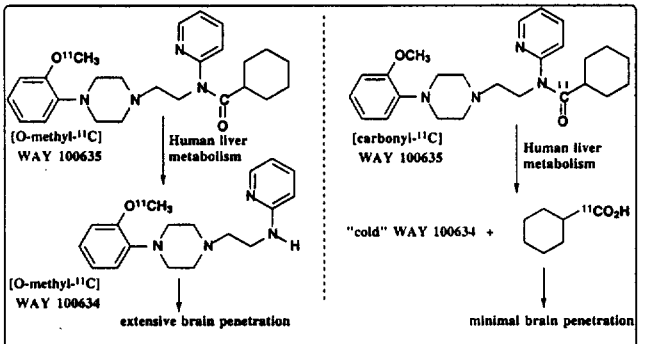
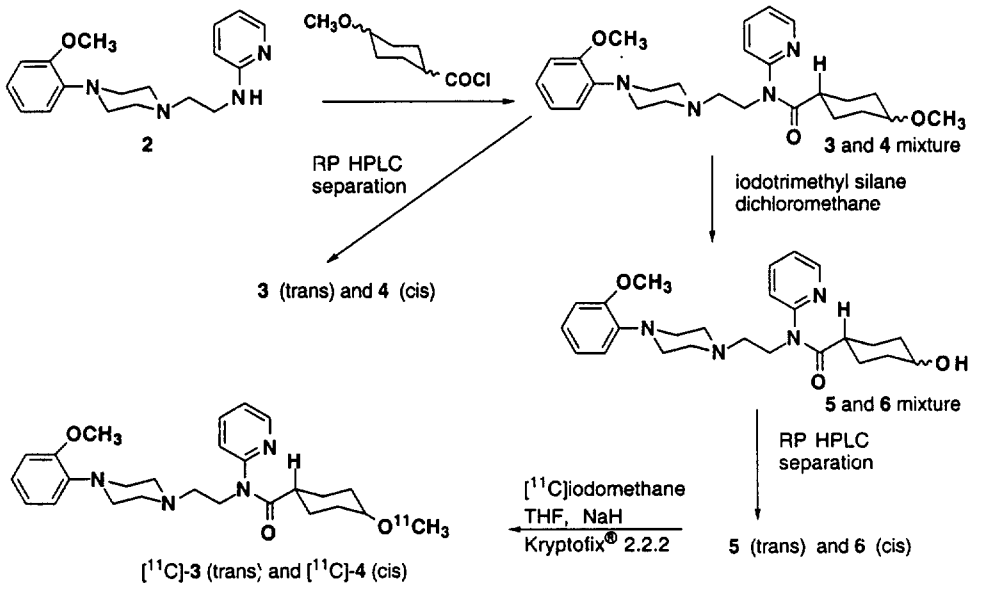
Introduction

Central 5-HT_{1A} receptors are thought to be intrinsically involved in a variety of psychiatric disorders such as schizophrenia, anxiety and depression (1-3). The identification of WAY 100635 (Scheme 1) as a potent, selective antagonist for 5-HT_{1A} receptors (4,5) led to its labelling with ^{11}C and its development as a radiotracer for positron emission tomography (PET) (6). Initially WAY 100635 was readily labelled with [^{11}C]-iodomethane in the 2-methoxy position (7) but further studies showed that liver metabolism in humans cleaved the amide bond and generated a [^{11}C]-labelled lipophilic metabolite, WAY 100634 (2), which crossed the blood-brain barrier, confounding the PET studies (Scheme 1) (8,9). This problem was circumvented by labelling WAY 100635 with ^{11}C in the carbonyl position (Scheme 1); the radiolabel now residing on the polar cyclohexanecarboxylic acid fragment upon metabolic cleavage of the amide bond(10,11).



Scheme 1. Metabolic fate of WAY 100635 labelled in different positions.

However, the radiosynthesis of [carbonyl-^{11}C]-WAY 100635 is very taxing, and many groups are exploring alternative routes to potential 5-HT_{1A} ligands which can be both radiolabelled more easily and which circumvent the human liver metabolism problem (12-17). To this end we explored the possibility of labelling analogues of WAY 100635 possessing methoxy groups on the 4- position of the cyclohexane ring (3 and 4 in Scheme 2). Such ligands can be labelled with the widely available and convenient [^{11}C]-iodomethane; furthermore, metabolic amide cleavage would result only in polar radiolabelled metabolites. We report here the synthesis of the two diastereoisomeric cis- and trans-4-methoxy derivatives (3) and (4). Both isomers were labelled with carbon-11 from their corresponding 4-hydroxy precursors (5) and (6) using [^{11}C]-iodomethane and tested *in vivo* in rats for their potential to image 5-HT_{1A} receptors.



Scheme 2. Synthesis and radiosynthesis of 4-methoxy analogues of WAY 100635.

Results

Chemistry. The synthesis of 4-methoxy analogues of WAY 100635 is shown in Scheme 2. Coupling of the commercially available mixture of cis- and trans-1, 4-methoxycyclohexanecarboxylic acid, via the acid chloride, to WAY 100634 (**2**) produced the diastereoisomeric mixture of **3** and **4**. No normal phase TLC conditions could be found to separate the diastereoisomers but they were easily resolved by reverse-phase HPLC. The precursors required for radiolabelling, the 4-hydroxy derivatives **5** and **6** were obtained by demethylation of the mixture of **3** and **4** using iodotrimethylsilane (Scheme 2). As expected, cleavage of the alkyl O-methoxy bond competed well with cleavage of the aryl O-methoxy bond (18), although numerous by products were evident by HPLC. Separation of the cis- and trans- diastereoisomers **5** and **6** was also effected by reverse-phase HPLC.

Radiochemistry. Reaction of **5** and **6** with [^{11}C]-iodomethane was carried out under Williamson ether type conditions with the alkoxide being generated *in situ* by sodium hydride. Radiochemical yields were only moderate under these conditions with large amounts of more polar (by reverse phase HPLC) radioactive by-products. A variety of other solvents (DMF, DMSO, acetone, HMPA) and bases (n-butyl lithium, BaO, TBAOH, DBU) were examined but best results were obtained with NaH in THF in the

presence of the aminopolyether Kriptofix®222. The 4-hydroxy precursors (**5** and **6**), chemical by-products, and radiochemical by-products were easily separated from the desired [^{11}C]-labelled products by reverse-phase HPLC to give chemically and radiochemically pure tracers (>97%) formulated for *in vivo* small animal experiments. Radiochemical yields (based on [^{11}C]-iodomethane, uncorrected) were 5-10% in a synthesis time of 26 min. Specific activities were 30-70 GBq /μmole at end-of-synthesis.

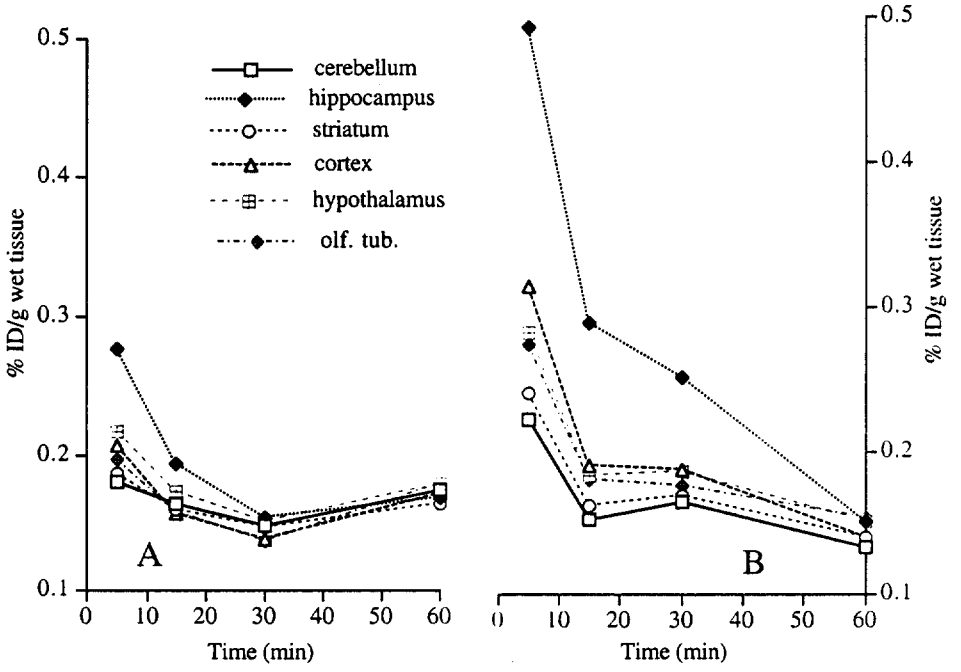


Figure 1. Biodistribution of the ^{11}C-labelled 4-methoxy analogues of WAY 100635 upon tail vein injection in rats. Standard deviations of 10% of values were typical — error bars are ommited for purposes of clarity. **A** —[^{11}C]-**4**. **B** — [^{11}C]-**3**.

In Vivo Biodistribution Studies and In Vitro Binding Assays . Upon tail vein injection of [^{11}C]-**4**, low to moderate regional brain uptake was observed after 5 min (Fig. 1A). Some differentiation of uptake of radioactivity was seen in areas rich in 5-HT$_{1A}$ receptors such as the hippocampus compared with the cerebellum, a region with few or no 5-HT$_{1A}$ receptors (19). However washout was quick from all brain regions examined, leading to a homogeneous distribution at 30 min post-injection. The trans-diastereoisomer, [^{11}C]-**3**, displayed a qualitatively different distributon pattern (Fig. 1B). Regional brain uptake was higher at earlier time points with a more heterogeneous

distribution of radioactivity. Hippocampus to cerebellum ratios were 2.2, 1.9 and 1.5 at 5, 15, and 30 min respectively, suggesting specific uptake in 5-HT$_{1A}$ rich brain regions. At 60 min post-injection the distribution of activity was uniformly low.

Measurement of the inhibition of binding of [^{3}H]-8-OH-DPAT to bovine hippocampal tissues gave K_i values of 2.6 nM and 24 nM for **3** and **4** respectively.

Discussion

Recent structure-affinity studies have shown that a variety of different alkyl and aryl substituents can replace the cyclohexyl ring of WAY 100635 with little or no deleterious effect on 5-HT$_{1A}$ receptor binding (13,20-22). This tolerance encouraged us that the 4-methoxy analogues of WAY 100635 would possess high affinity for 5-HT$_{1A}$ receptors *in vivo*, while providing a handle with which to effect radiolabelling with ^{11}C in a facile manner. The synthesis of the 4-methoxy analogues, and the 4-hydroxy derivatives required as radiolabelling precursors, proceeded using conventional chemistry (Scheme 2) although HPLC was required to effect the separation of the diastereoisomers. Demethylation at the 2-methoxy position of the phenyl ring was a competing reaction with iodotrimethylsilane induced demethylation at the 4-methoxy position on the cyclohexane ring but was slow enough that sufficient quantities of the 4-hydroxy precursors could be obtained for our purposes.

Assignment of stereochemistries of **3/4** and **5/6** were based on a multiplet pattern analysis of their ^{1}HNMR spectra (23). Chemical shift information also provides evidence of stereochemistry: For **5**, the chemical shift (δ in ppm relative to TMS) of the hydrogen at the 4- position of the cyclohexane ring is 3.57 compared to 3.90 for **6** implying that the protons are in the axial and equatorial positions respectively. On the assumption that the bulky moiety at the 1- position of the cyclohexane ring assumes the equatorial position (24), this assigns the trans- and cis- stereochemistry to **5** and **6** respectively. Analagous examination of the chemical shifts in the **3/4** pair and the conversion of **3** to **5** and **4** to **6** with iodomethane reinforces these assignments. In addition the ^{13}C chemical shifts of the carbon at position 4 in **3/4** and **5/6** are fully consistent with the assigned axial/ equatorial positions (25).

In vitro binding assays demonstrated that the trans diastereoisomer **3** (K_i 2.6 nM) has significantly higher affinity for the 5-HT$_{1A}$ receptor than the cis isomer **4** (K_i 24 nM). Given the reported tolerance of the 5-HT$_{1A}$ receptor for changes at the cyclohexyl position of WAY 100635 analogues, this order of magnitude difference of the binding

affinities for the two diastereoisomers was unexpected. The biodistribution results were also rather surprising (Figure 1). The cis-diastereoisomer, [^{11}C]-**4**, displayed an almost homogeneous distribution in rat brain except at the earliest time point examined (5 min post-injection). The trans-diastereoisomer. [^{11}C]-**3**, gave a more differentiated pattern of distribution, consistent with 5-HT$_{1A}$ receptor binding and the higher affinity of **3** compared with **4**. However, compared to the biodistribution of [^{11}C]- or [^{3}H]- WAY 100635 in rats (6,26), [^{11}C]-**3** displays a much faster washout from 5-HT$_{1A}$ receptor rich tissues such as cortex and hippocampus with much lower peak signal to noise ratios — 2.2 at 5 min post injection for **3** compared with 16 at 60 min post injection for WAY 100635. In light of the high affinity of **3** for the 5-HT$_{1A}$ receptor *in vitro*, the rapid washout of the radiotracer from receptor rich rat brain regions is puzzling. Metabolism of the radiotracer might be the simplest explanation but a shift from an antagonist to a full or partial agonist (by the 4-methoxy perturbation) could also be invoked (26) (27).

Speculatively, the rapid washout of [^{11}C]-**3** from 5-HT$_{1A}$ receptor rich regions could also indicate a sensitivity of the radiotracer to endogenous serotonin levels; WAY 100635 has been shown to be insensitive to changes in endogenous levels of serotonin (28). Thus [^{11}C]-**3** may be of use as an imaging tool for measuring changes in endogenous serotonin levels in response to pharmacological or other challenges (20,29). However given the low (2.2) signal to noise ratios, it would be anticipated that only large changes in *in vivo* binding could be detected reliably.

Experimental

Purification and analyses of radioactive mixtures by HPLC were performed with an in-line uv (254 nm) detector in series with a NaI crystal radioactivity detector. HPLC columns used were: A, Waters Novapak C_{18} (300 x 19 mm); B, Phenomenex Prodigy C_{18} (250 mm x 10 mm, 10μ); or C, Alltech Econosil C_{18} (250 mm x 4.6 mm, 10 μ). Peak areas were measured using Hewlett-Packard 3396 and Waters 746 recording integrators. Isolated radiochemical yields were determined with a dose-calibrator (Capintec CRC-712M). THF was freshly distilled under nitrogen from $LiAlH_4$ and DMF was distilled from BaO and stored over 4 Å molecular sieves. All other chemicals were obtained from commercial sources. NMR were run at 500 MHz (^{1}H) or 127.5 MHz (^{13}C) in $CDCl_3$ with TMS as internal standard. All new compounds gave satisfactory elemental analyses (C, H, N, ±0.4%) - Atlantic Microlabs (Georgia).

trans- and cis-N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide (3 and 4). A solution of 4-methoxy-cyclohexanecarboxylic acid (mixture of cis and trans, 0.5 g, 3.16 mmol), and DMF (50 μL) in CH_2Cl_2 (10 mL) was stirred under N_2 at 0 °C whilst oxalyl chloride (2 mL, 2N in CH_2Cl_2) was added dropwise. The solution was stirred at ambient temperature for 30 min and evaporated to remove volatiles. The residue was taken up in CH_2Cl_2 (10 mL), stirred under N_2 at 0 °C, and treated with a solution of WAY 100634 (**2**, 0.5 g, 1.6 mmol) (22) and triethylamine (0.5 mL) in CH_2Cl_2 (10 mL) dropwise. The mixture was stirred at ambient temperature for 1 hr, diluted with ethyl acetate (30 mL) and washed with aqueous $NaHCO_3$ (sat., 2 x 50 mL). The organic solution was dried (K_2CO_3), filtered, and evaporated to dryness to give a brown viscous oil (1.01 g). Flash chromatography (silica, EtOAc:Et_3N 95:5) gave a tan oil (0.49 g, 68%) of a mixture of the cis- and trans- isomers. The individual isomers were resolved by multiple runs using HPLC (column A, 40% CH_3CN:60% H_2O + 0.1N NH_4HCO_2, 9 mL/min). Combined fractions were partially evaporated to remove acetonitrile, made basic with aq. NaOH (1N), and extracted twice with CH_2Cl_2. The organic fractions were dried (K_2CO_3), filtered, and volatiles removed to leave pure **3** (0.13 g) and **4** (0.11 g) as colourless oils:

3; ^{1}HNMR δ 0.88-1.01 (m, 2H), 1.56-1.66 (m, 2H), 1.84 (br d, 2H), 2.20 (br d, 2H), 2.18 (br d, 1H), 2.61 (m, 6H), 2.99 (br s, 4H), 3.07-3.14 (m, 1H), 3.30 (s, 3H), 3.84 (s, 3H), 3.98 (t, 2H), 6.83-6.99 (m, 4H), 7.23-7.33 (m, 2H), 7.77 (dt, 1H), 8.53 (m, 1H); ^{13}CNMR δ 175.6, 155.6, 152.1, 149.2, 141.2, 138.1, 122.7, 122.3, 122.1, 120.8, 118.0, 111.1, 78.4, 56.1, 55.6, 55.3, 53.3, 50.5, 45.2, 41.5, 31.0, 27.7.

4; ^{1}HNMR δ 1.18 (t, 2H), 1.5 (br d, 2H), 1.85-1.96 (m, 4H), 2.32 (m, 1H), 2.61 (m, 6H), 2.98 (br s, 4H), 3.27 (s, 3H), 3.34 (br s, 1H), 3.82 (s, 3H), 3.99 (t, 2H), 6.83-7.01 (m, 4H), 7.22-7.34 (m, 2H), 7.76 (dt, 1H), 8.52 (m, 1H); ^{13}CNMR δ 175.7, 155.9, 152.1, 149.1, 141.3, 138.0, 122.7, 122.1, 122.0, 120.9, 118.0, 111.1, 73.8, 56.2, 55.3, 53.3, 50.5, 45.2, 41.5, 28.5, 23.6.

trans- and cis-N-[2-[4-(2-Hydroxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide (5 and 6). A mixture of **3** and **4** (0.35 g, 0.77 mmol) in CH_2Cl_2 (10 mL) was treated with iodotrimethylsilane (1.3 mL, 9.1 mmol) and stirred at ambient temperature for 7 days. Methanol (2 mL) was added with stirring for 30 min, then aqueous $NaHCO_3$ (sat., 100 mL) added and stirred for a further 1 hr. The mixture was filtered through diatomaceous earth, and extracted with EtOAc (2 x 30 mL). The organic fractions were dried (K_2CO_3), filtered, and volatiles removed to leave a brown oil (0.30

g). The products were isolated by HPLC (column A, 30% CH_3CN:70% H_2O + 0.1N NH_4HCO_2, 9 mL/min) as described for **3** and **4** above to give **5** (60.1 mg, 17.7%) and **6** (27.3 mg, 8.5%) as colourless oils:

5; ^{1}HNMR δ= 0.95-1.08 (m, 2H), 1.55-2.01 (m, 7H), 2.17 (br s, 1H), 2.60 (m, 6H), 2.98 (br s, 4H), 3.57 (m, 1H), 3.84 (s, 3H), 3.97 (t, 2H), 6.83-7.02 (m, 4H), 7.24-34 (m, 2H), 7.77 (dt, 1H), 8.53 (m, 1H); ^{13}CNMR δ= 175.6, 155.7, 152.1, 149.2, 141.2, 138.2, 122.8, 122.3, 122.1, 120.8, 118.0, 111.1, 69.7, 56.0, 55.2, 53.3, 50.5, 45.2, 41.2, 34.6, 27.8.

6; ^{1}HNMR δ= 1.35-2.02 (m, 8H), 2.32 (br t, 1H), 2.62 (m, 6H), 2.98 (br s, 4H), 3.84 (s, 3H), 3.90 (m, 1H), 3.99 (t, 2H), 6.83-7.03 (m, 4H), 7.22-7.34 (m, 2H), 7.76 (dt, 1H), 8.52 (m, 1H); ^{13}CNMR δ= 175.7, 155.9, 152.2, 149.2, 141.3, 138.1, 122.8, 122.2 (+sh), 120.9, 118.0, 111.2, 65.6, 56.1, 55.3, 53.3, 50.55, 45.3, 41.0, 31.7, 23.3.

[^{11}C]-**3**. A solution of **5** (1.5 mg) in THF (200 μL) containing NaH (60%, 0.6 mg) and Kriptofix®222 (4.5 mg) was stirred for 15 min at 0 °C prior to end of bombardment. [^{11}C]-iodomethane, produced from $^{11}CO_2$ as described previously (30), was swept by a flow of N_2 gas (20 mL/min) into the precursor solution at 0 °C. When radioactivity had peaked the solution was heated to 70 °C for 3 min and quenched with HPLC buffer (0.5 mL). The mixture was purified by semi-prep HPLC; Column B, 35% CH_3CN:65% H_2O + 0.1N NH_4HCO_2, 10 mL/min. The desired fraction was collected, evaporated to dryness, and the residue taken up in 10 mL of sterile saline. This was passed through a sterile 0.22 μm filter into a sterile, pyrogen-free bottle containing aqueous sodium bicarbonate (1 mL, 8.4%). The radiochemical purity and specific activity of the final solution were determined by analytical HPLC; Column C, 40% CH_3CN:60% H_2O + 0.1N NH_4HCO_2, 4 mL/min. As formulated, [^{11}C]-**3** showed no radiolysis products over a 45 min period. [^{11}C]-**4** was synthesized in an identical manner to [^{11}C]-**3**. Yields were comparable.

Biodistribution Studies All animal experiments were carried out under humane conditions, with approval from the Animal Care Committee at the Clarke Institute and in accordance with the guidelines set forth by the Canadian Council on Animal Care. Animals were kept on a 12-hr light / 12-hr dark cycle and allowed food and water *ad libitum*. Male Sprague-Dawley rats (210-230 g), in a restraining box, received 3-30 MBq of high specific activity radiotracer (350-450 ng) in 0.3 mL of buffered saline via the tail vein, vasodilated in a warm water bath. A previously described method was used to determine the biodistribution of radioactivity (31). Experiments were conducted on groups of three rats per time point with results shown as the % injected dose per gram of wet tissue (%ID/g).

Competition Binding Studies were performed by Novascreen® (Hanover Maryland) using bovine hippocampal tissue with [^{3}H]-8-OH-DPAT and 12 concentrations of displacer compound (50 pM to 10 μM). Experiments were performed in duplicate. Under the assay conditions, 8-OH-DPAT had a K_i of 1.7 nM.

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