Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 1570–1574
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Laboratory note

Synthesis of new carbon-11 labeled benzoxazole derivatives for PET imaging of 5-HT_3 receptor

Mingzhang Gao, Min Wang, Gary D. Hutchins, Qi-Huang Zheng*

Department of Radiology, Indiana University School of Medicine, 1345 West 16th Street, L3-208, Indianapolis, IN 46202-2111, USA

Received 19 September 2007; received in revised form 16 October 2007; accepted 17 October 2007
Available online 22 October 2007

Abstract

5-HT_3 receptor is an attractive target for the development of therapeutic agents for use in brain, heart and cancer diseases, and imaging agents for use in biomedical imaging technique PET. Benzoxazole derivatives are a novel class of 5-HT_3 receptor partial agonists with high binding affinity. Carbon-11 labeled benzoxazole derivatives have been synthesized as new potential PET radioligands for imaging 5-HT_3 receptor. The target tracers were prepared by N-[^{11}C]methylation of their corresponding precursors using [^{11}C]CH_3OTf and isolated by HPLC purification procedure in 40–50% radiochemical yields, which were decay corrected to the end of bombardment (EOB), based on [^{11}C]CO_2. The overall synthesis time was 20–25 min from EOB. The radiochemical purity was >99%, and specific activity was in a range of 74–111 GBq/μmol at the end of synthesis (EOS).

Keywords: Carbon-11; Benzoxazole derivatives; PET; 5-HT_3 receptor; Imaging

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) subtype 3 (5-HT_3) receptor is an important target for the development of therapeutic agents including 5-HT_3 receptor antagonists and agonists for various neurological and psychiatric disorders, heart and cancer diseases [1–6], since 5-HT_3 receptor is associated with a variety of biological pathways in central and peripheral nervous systems. Selective 5-HT_3 receptor antagonists have been effectively used in antiemetic therapy to prevent the nausea and vomiting for cancer patients who are undergoing chemotherapy or radiotherapy [6]. Recently a novel series of benzoxazole derivatives have been developed as 5-HT_3 receptor partial agonists for treatment of diarrhea-predominant irritable bowel syndrome [7–9]. A 5-HT_3 antagonist possesses potent antidiarrhetic efficacy, however, it has several side effects such as constipation. 5-HT_3 receptor partial agonists might control gastroenteric motility without completely blocking 5-HT_3-sensitized nerve function to avoid these side effects with regard to corresponding 5-HT_3 antagonists [7]. Four selected title compounds, 5-chloro-7-methyl-2-(4-methyl-1-piperazinyl)benzoxazole (**1b**), 5,7-dimethyl-2-(4-methyl-1-piperazinyl)benzoxazole (**1d**), 5-chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (**1f**) and 5,7-dimethyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (**1h**), exhibited a high binding affinity to 5-HT_3 receptor [7–9]. These 5-HT_3 receptor ligands possess *N*-methyl position amenable to labeling with a positron emitting radioisotope such as carbon-11 as 5-HT_3 receptor radioligands. These same properties are often beneficial in a diagnostic radiotracer. 5-HT_3 receptor also provides an attractive target for the *in vivo* biomedical imaging technique positron emission tomography (PET) to map 5-HT_3 receptor and its related diseases. Benzoxazole derivatives labeled with carbon-11 may enable non-invasive monitoring of 5-HT_3 receptor and its response to 5-HT_3 receptor antagonist and agonist treatment using PET. To translate therapeutic agent for diagnostic

Abbreviations: PET, Positron emission tomography; 5-HT_3, 5-Hydroxytryptamine subtype 3; EOB, End of bombardment; EOS, End of synthesis; TMS, Tetramethylsilane; RDS, Radionuclide delivery system; INGEN, Indiana Genomics Initiative.

* Corresponding author. Tel.: +1 317 278 4671; fax: +1 317 278 9711.
E-mail address: qzheng@iupui.edu (Q.-H. Zheng).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.10.017

use, we have designed and synthesized new carbon-11 labeled benzoxazole derivatives, 5-chloro-7-methyl-2-(4-[^{11}C]methyl-1-piperazinyl)benzoxazole ([^{11}C]**1b**), 5,7-dimethyl-2-(4-[^{11}C]methyl-1-piperazinyl)benzoxazole ([^{11}C]**1d**), 5-chloro-7-methyl-2-(4-[^{11}C]methyl-1-homopiperazinyl)benzoxazole ([^{11}C]**1f**) and 5,7-dimethyl-2-(4-[^{11}C]methyl-1-homopiperazinyl)benzoxazole ([^{11}C]**1h**), as potential PET radioligands for imaging of 5-HT$_3$ receptor.

2. Results and discussion

2.1. Chemistry

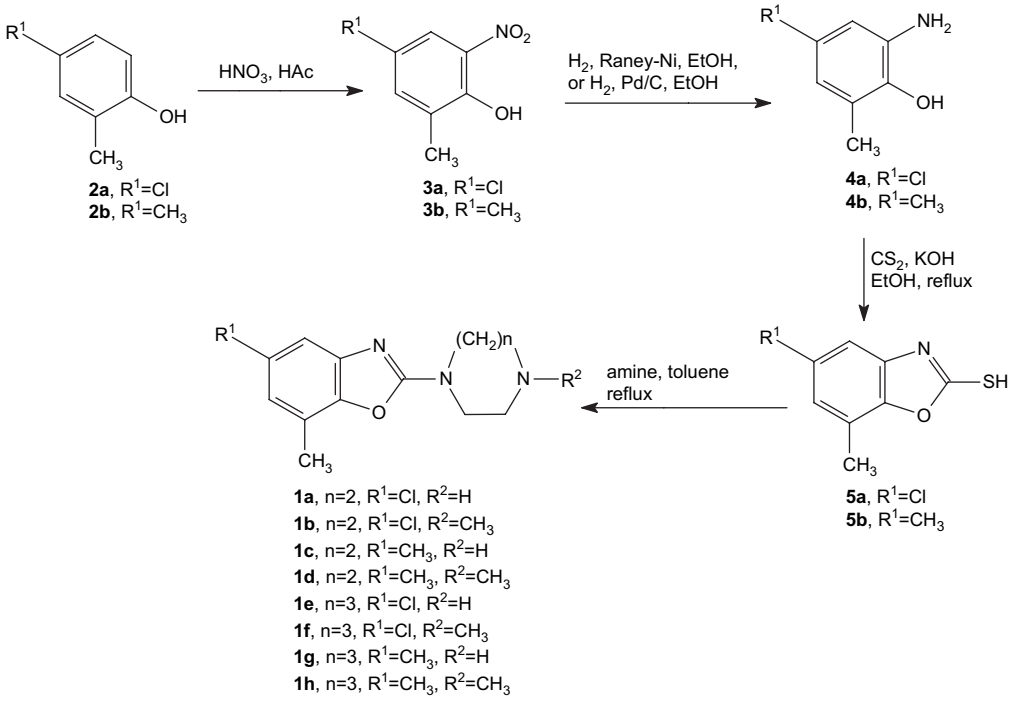
Synthesis of precursors and reference standards was accomplished using a modification of the previously reported procedures [7–9]. The synthetic approach is outlined in Scheme 1. The nitration of compounds **2a**,**b** with nitric acid in acetic acid provided compounds **3a**,**b** in 88% and 87% yield, respectively. The hydrogenation of the nitro group of compounds **3a**,**b** in the presence of H_2 with Raney-Ni and Pd–C as catalyst afforded compounds **4a**,**b** in 98% and 97% yield, respectively. Raney-Ni catalyst was more effective at reducing the nitro group of aromatic compounds with a halogen substituent. The cyclization of compounds **4a**,**b** with carbon disulfide and KOH produced cyclized thiol compounds **5a**,**b** in 91% and 92% yield, respectively. The coupling reaction of compounds **5a**,**b** with amines piperazine, 1-methylpiperazine, homopiperazine, and 1-methylhomopiperazine gave precursors 5-chloro-7-methyl-2-(1-piperazinyl)benzoxazole (**1a**), 5,7-dimethyl-2-(1-piperazinyl)benzoxazole (**1c**), 5-chloro-7-methyl-2-(1-homopiperazinyl)benzoxazole (**1e**) and 5,7-dimethyl-2-(1-homopiperazinyl)benzoxazole (**1g**), and reference standards **1b**, **1d**, **1f** and **1h** in moderate to excellent yields (60–80%).

2.2. Radiochemistry

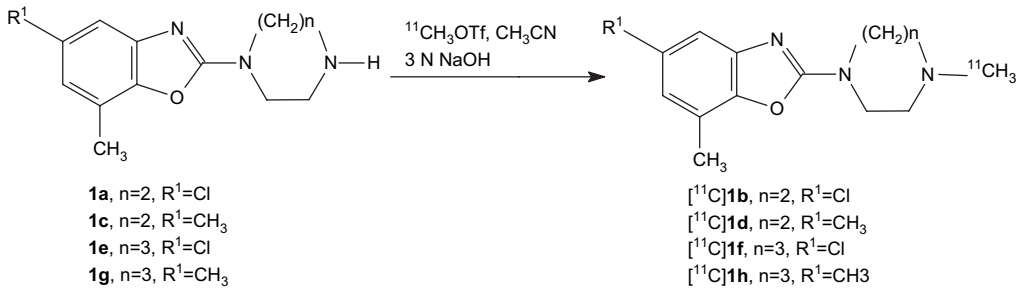
Synthesis of the target tracers, carbon-11 labeled benzoxazole derivatives [^{11}C]**1b**, [^{11}C]**1d**, [^{11}C]**1f** and [^{11}C]**1h**, is outlined in Scheme 2. The precursor **1a**, **1c**, **1e** or **1g** was labeled by [^{11}C]methyl triflate ([^{11}C]CH_3OTf) [10,11] through N-[^{11}C]methylation [12] and isolated by HPLC purification procedure [13] to produce corresponding pure target compound [^{11}C]**1b**, [^{11}C]**1d**, [^{11}C]**1f** or [^{11}C]**1h**. The radiochemical yields were 40–50%, based on [^{11}C]CO_2, decay corrected to end of bombardment (EOB). The radiosynthesis was performed in an automated multi-purpose ^{11}C-radiosynthesis module, allowing measurement of specific activity during synthesis [14,15]. Overall synthesis time was 20–25 min from EOB. The specific activity was in the range of 74–111 GBq/μmol at the end of synthesis (EOS). Chemical purity and radiochemical purity were determined by analytical HPLC method [16]. The chemical purity of precursors and reference standards was >95%. The radiochemical purity of target tracers was >99% and determined by radio-HPLC through γ-ray (NaI) flow detector, and the chemical purity of target tracers was >95% and determined by reversed-phase HPLC through UV flow detector.

3. Conclusion

An efficient and convenient synthesis of new carbon-11 labeled benzoxazole derivatives has been well-developed. The synthetic methodology employed classical organic chemistry



Scheme 1. Synthesis of benzoxazole derivatives.



1a, n=2, R^1=Cl
1c, n=2, R^1=CH_3
1e, n=3, R^1=Cl
1g, n=3, R^1=CH_3

[^{11}C]**1b**, n=2, R^1=Cl
[^{11}C]**1d**, n=2, R^1=CH_3
[^{11}C]**1f**, n=3, R^1=Cl
[^{11}C]**1h**, n=3, R^1=CH3

Scheme 2. Synthesis of carbon-11 labeled benzoxazole derivatives.

such as nitration, hydrogenation, reduction, cyclization and coupling reaction to synthesize unlabeled benzoxazole derivatives. Carbon-11 labeling at nitrogen position of the precursor through N-[^{11}C]methylation was incorporated efficiently using [^{11}C]CH_3OTf, a signature reaction of carbon-11 radiochemistry from our laboratory. Radiosynthesis produced new probes in amounts and purity suitable for the preclinical application in animal studies using PET. Labeled product suitable for injection, with the higher specific radioactivity in the range of 74–111 GBq/μmol at EOS, can be obtained within 25 min from EOB including HPLC purification and formulation. These chemistry results combined with the reported *in vitro* biological data encourage further *in vivo* biological evaluation of carbon-11 labeled benzoxazole derivatives as new potential PET radioligands for imaging of 5-HT_3 receptor.

4. Experimental

4.1. General

All commercial reagents and solvents were used without further purification. [^{11}C]CH_3OTf was prepared according to a literature procedure [10]. Melting points were determined on a MEL-TEMP II capillary tube apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 200 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (ppm, δ scale) relative to internal standard TMS (δ 0.0), and coupling constants (J) were reported in hertz (Hz). The low resolution mass spectra (LRMS) were obtained using a Bruker Biflex III MALDI-TOF mass spectrometer. Chromatographic solvent proportions are indicated in a volume/volume ratio. Thin layer chromatography was run using Analtech silica gel GF uniplates (5×10 cm^2). Plates were visualized by UV light. Normal phase flash chromatography was carried out on EM Science silica gel 60 (230–400 mesh) with a forced flow of the indicated solvent system in the proportions described below. All moisture- and/or air-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Analytical HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 4.6×250 mm; 3:1:3 CH_3CN/MeOH/20 mM, pH 6.7 $KHPO_4^-$ (buffer solution) mobile phase; flow rate 1.5 mL/min and UV (254 nm) and γ-ray (NaI) flow detectors. Semi-preparative HPLC was performed using a YMC-Pack ODS-A, S-5 μm, 12 nm, 10×250 mm i.d. (Waters) C-18 column; 3:1:3 CH_3CN/MeOH/20 mM, pH 6.7 $KHPO_4^-$ mobile phase, 5.0 mL/min flow rate, UV (254 nm) and γ-ray (NaI) flow detectors. Sterile Millex-GS 0.22 μm vented filter unit was obtained from Millipore Corporation, Bedford, MA.

4.2. 4-Chloro-2-methyl-6-nitrophenol (*3a*)

Nitric acid (90%, 11.0 g, 157.1 mmol) was slowly added to a solution of 4-chloro-2-methylphenol (**2a**, 18.0 g, 126.2 mmol) in acetic acid (240 mL) at 5 °C. The reaction mixture was stirred for 40 min. Then ice-water (150 mL) was added in above mixture, the mixture was filtered, washed with cold water, and dried in air to give compound **3a** as a yellow solid (20.88 g, 88%), mp 108–110 °C, $R_f = 0.82$ (1:3 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 7.63 (d, $J = 2.6$ Hz, 1H, Ph-H), 7.85 (d, $J = 3.4$ Hz, 1H, Ph-H), 10.57 (s, 1H, OH).

4.3. 2,4-Dimethyl-6-nitrophenol (*3b*)

According to the procedure for preparation of compound **3a**, compound **3b** was prepared from 2,4-dimethylphenol (**2b**) in 87% yield as brownish solid, mp 64–66 °C, $R_f = 0.79$ (1:3 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 7.38 (d, $J = 1.6$ Hz, 1H, Ph-H), 7.64 (s, 1H, Ph-H), 10.20 (s, 1H, OH).

4.4. 2-Amino-4-chloro-6-methylphenol (*4a*)

Compound **3a** (8.0 g, 42.6 mmmol) was dissolved in ethanol (100 mL), and Raney-Ni (1.0 g, Aldrich) was added to the solution. The reaction mixture was stirred under a hydrogen atmosphere (56 psi) for 7 h, and the Raney-Ni was removed by filtration through celite. The solution was evaporated in vacuo to afford compound **4a** as a brown solid (6.58 g, 98%), mp 131–133 °C, $R_f = 0.71$ (1:1 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6) δ: 2.06 (s, 3H, CH_3), 4.77 (s, 2H, NH_2), 6.29 (s, 1H, Ph-H), 6.44 (s, 1H, Ph-H), 8.06 (s, 1H, OH).

4.5. 2-Amino-4,6-dimethylphenol (**4b**)

Compound **3b** (7.0 g, 41.9 mmmol) was dissolved in ethanol (100 mL), and 10% palladium–carbon (1.0 g, Aldrich) was added to the solution. The reaction mixture was stirred under a hydrogen atmosphere (57 psi) for 18 h, and the palladium–carbon was removed by filtration through Celite. The solution was concentrated in vacuo to afford compound **4b** as a brown solid (5.60 g, 97%), mp 127–129 °C, $R_f = 0.68$ (1:1 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6) δ: 2.04 (s, 6H, $2 \times CH_3$), 4.41 (s, 2H, NH_2), 6.10 (d, $J = 1.6$ Hz, 1H, Ph-H), 6.25 (d, $J = 1.6$ Hz, 1H, Ph-H), 7.53 (s, 1H, OH).

4.6. 5-Chloro-7-methylbenzoxazole-2-thiol (**5a**)

Compound **4a** (5.0 g, 31.7 mmol) was refluxed with potassium hydroxide (4.26 g, 76 mmol) and carbon disulfide (30 mL) in ethanol (100 mL) for 8 h. The reaction mixture was evaporated in vacuo, and aqueous hydrochloric acid (2 N, 38 mL, 76 mmol) was added to the residue. The mixture was filtered, washed with water, and dried in air to give compound **5a** as a brown solid (5.76 g, 91%), mp 230 °C (dec.), $R_f = 0.78$ (1:1 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 3.45 (s, 1H, SH), 7.09 (d, $J = 2.2$ Hz, 1H, Ph-H), 7.17–7.18 (m, 1H, Ph-H).

4.7. 5,7-Dimethylbenzoxazole-2-thiol (**5b**)

According to the procedure for preparation of compound **5a**, compound **5b** was prepared from compound **4b** in 92% yield as brown solid, mp 228 °C (dec.), $R_f = 0.80$ (1:1 EtOAc/hexanes). ^{1}H NMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.32 (s, 1H, SH), 6.85 (s, 1H, Ph-H), 6.88 (s, 1H, Ph-H).

4.8. General procedure for synthesis of benzoxazole derivatives (**1a–h**)

Compound **5** (2 mmol) with amine piperazine, 1-methylpiperazine, homopiperazine, or 1-methylhomopiperazine (4 mmol) were dissolved in dry toluene (25 mL), and mixture was refluxed for 16 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel with MeOH/CH_2Cl_2 as eluent (2–8%) to give compound **1** in 60–80% yield as a brown solid.

4.8.1. 5-Chloro-7-methyl-2-(1-piperazinyl)benzoxazole (**1a**)

Mp 60–62 °C, $R_f = 0.42$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 2.98 (t, $J = 5.2$ Hz, 4H, CH_2), 3.67 (t, $J = 5.2$ Hz, 4H, CH_2), 6.80 (dd, $J = 0.6$, 1.8 Hz, 1H, Ph-H), 7.13 (d, $J = 1.8$ Hz, 1H, Ph-H). MS (ESI): 252 ($[M + H]^+$, 100%).

4.8.2. 5-Chloro-7-methyl-2-(4-methyl-1-piperazinyl) benzoxazole (**1b**)

Mp 64–66 °C (lit [8], mp 62–64 °C), $R_f = 0.57$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.52 (t, $J = 5.2$ Hz, 4H, CH_2), 3.72 (t, $J = 5.2$ Hz, 4H, CH_2), 6.80 (dd, $J = 0.6$, 1.8 Hz, 1H, Ph-H), 7.13 (d, $J = 1.8$ Hz, 1H, Ph-H). MS (ESI): 266 ($[M + H]^+$, 100%).

4.8.3. 5,7-Dimethyl-2-(1-piperazinyl)benzoxazole (**1c**)

Mp 78–80 °C (lit [7], mp 68–70 °C), $R_f = 0.27$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 1H, NH), 2.93 (s, 3H, CH_3), 2.94 (s, 3H, CH_3), 3.57 (t, $J = 5.2$ Hz, 4H, CH_2), 4.25 (t, $J = 5.2$ Hz, 4H, CH_2), 7.22 (s, 1H, Ph-H), 7.56 (s, 1H, Ph-H). MS (ESI): 232 ($[M + H]^+$, 100%).

4.8.4. 5,7-Dimethyl-2-(4-methyl-1-piperazinyl) benzoxazole (**1d**)

Mp 49–51 °C, $R_f = 0.55$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.52 (t, $J = 5.2$ Hz, 4H, CH_2), 3.71 (t, $J = 5.2$ Hz, 4H, CH_2), 6.64 (s, 1H, Ph-H), 6.98 (s, 1H, Ph-H). MS (ESI): 246 ($[M + H]^+$, 100%).

4.8.5. 5-Chloro-7-methyl-2-(1-homopiperazinyl) benzoxazole (**1e**)

Mp 88–90 °C (lit [7], mp 68–70 °C), $R_f = 0.18$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.92–2.03 (m, 2H, $CH_2CH_2CH_2$), 2.27 (s, 1H, NH), 2.37 (s, 3H, CH_3), 2.95 (t, $J = 6.0$ Hz, 2H, CH_2), 3.07–3.12 (m, 2H, CH_2), 3.77–3.84 (m, 4H, CH_2), 6.78 (d, $J = 1.6$ Hz, 1H, Ph-H), 7.12 (d, $J = 2.0$ Hz, Ph-H). MS (ESI): 266 ($[M + H]^+$, 100%).

4.8.6. 5-Chloro-7-methyl-2-(4-methyl-1-homopiperazinyl) benzoxazole (**1f**)

Mp 113–115 °C (lit [8], mp 116–117 °C), $R_f = 0.46$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.97–2.09 (m, 2H, $CH_2CH_2CH_2$), 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.62 (t, $J = 5.2$ Hz, CH_2), 2.71–2.76 (m, 2H, CH_2), 3.75–3.86 (m, 4H, CH_2), 6.76 (dd, $J = 0.6$, 2.0 Hz, 1H, Ph-H), 7.11 (d, $J = 1.6$ Hz, 1H, Ph-H). MS (ESI): 280 ($[M + H]^+$, 100%).

4.8.7. 5,7-Dimethyl-2-(1-homopiperazinyl)benzoxazole (**1g**)

Mp 99–101 °C, $R_f = 0.21$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.90–2.02 (m, 2H, $CH_2CH_2CH_2$), 2.03 (s, 1H, NH), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.92 (t, $J = 5.6$ Hz, 2H, CH_2), 3.05–3.10 (m, 2H, CH_2), 3.73–3.84 (m, 4H, CH_2), 6.61 (s, 1H, Ph-H), 6.97 (s, 1H, Ph-H). MS (ESI): 246 ($[M + H]^+$, 100%).

4.8.8. 5,7-Dimethyl-2-(4-methyl-1-homopiperazinyl) benzoxazole (**1h**)

Mp 56–58 °C, $R_f = 0.41$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ: 1.98–2.10 (m, 2H, $CH_2CH_2CH_2$), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.60–2.65 (m, 2H, CH_2), 2.72–2.77 (m, 2H, CH_2), 3.76–3.87 (m, 4H, CH_2), 6.61 (t, $J = 0.8$ Hz, 1H, Ph-H), 6.97 (s, 1H, Ph-H). MS (ESI): 260 ($[M + H]^+$, 100%).

*4.9. General method for the preparation of carbon-11 labeled benzoxazole derivatives, 5-chloro-7-methyl-2-(4-[^{11}C]methyl-1-piperazinyl)benzoxazole ([^{11}C]**1b**), 5,7-dimethyl-2-(4-[^{11}C]methyl-1-piperazinyl) benzoxazole ([^{11}C]**1d**), 5-chloro-7-methyl-2-(4-[^{11}C] methyl-1-homopiperazinyl)benzoxazole ([^{11}C]**1f**) and 5,7-dimethyl-2-(4-[^{11}C]methyl-1-homopiperazinyl)benzoxazole ([^{11}C]**1h**)*

[^{11}C]CO_2 was produced by the ^{14}N(p,α)^{11}C nuclear reaction in small volume (9.5 cm^3) aluminum gas target (CTI) from 11 MeV proton cyclotron on research purity nitrogen (+1% O_2) in a Siemens radionuclide delivery system (Eclipse RDS-111). The precursor **1a**, **1c**, **1e** or **1g** (0.1–0.3 mg, 0.4–1.1 μM) was dissolved in CH_3CN (300 μL). To this solution was added 3 N NaOH (2 μL, 6 μM). The mixture was transferred to a small reaction vial. No carrier-added (high specific activity) [^{11}C]CH_3OTf that was produced by the gas-phase production method [10] from [^{11}C]CO_2 through [^{11}C]CH_4 and [^{11}C]CH_3Br with silver triflate (AgOTf) column was passed into the reaction vial, which was cooled to 0 °C, until radioactivity reached a maximum (~2 min), and then the reaction vial was isolated and heated at 80 °C for 3 min. The contents of the reaction tube were diluted with $NaHCO_3$ (1 mL, 0.1 M) and water (0.5 mL), and injected onto the semi-preparative HPLC column with 2 mL injection loop. The product fraction was collected, the solvent was removed by rotatory evaporation under vacuum, and the final product [^{11}C]**1b**, [^{11}C]**1d**, [^{11}C]**1f** or [^{11}C]**1h** was formulated in saline, sterile-filtered through a sterile vented Millex-GS 0.22 μm cellulose acetate membrane and collected into a sterile vial. Total radioactivity was assayed and total volume was noted. The overall synthesis, purification and formulation time was 20–25 min from EOB. Retention times in the analytical HPLC system were: t_R **1a** = 2.22 min, t_R **1b** = 2.42 min, t_R [^{11}C]**1b** = 2.42 min; t_R **1c** = 2.13 min, t_R **1d** = 2.44 min, t_R [^{11}C]**1d** = 2.44 min; t_R **1e** = 2.26 min, t_R **1f** = 3.35 min, t_R [^{11}C]**1f** = 3.35 min; and t_R **1g** = 1.89 min, t_R **1h** = 3.47 min, t_R [^{11}C]**1h** = 3.47 min. Retention times in the semi-preparative HPLC system were: t_R **1a** = 3.30 min, t_R **1b** = 4.58 min, t_R [^{11}C]**1b** = 4.58 min; t_R **1c** = 3.23 min, t_R **1d** = 4.91 min, t_R [^{11}C]**1d** = 4.91 min; t_R **1e** = 3.67 min, t_R **1f** = 5.17 min, t_R [^{11}C]**1f** = 5.17 min; and t_R **1g** = 3.10 min, t_R **1h** = 5.89 min, t_R [^{11}C]**1h** = 5.89 min. The radiochemical yields were 40–50% decay corrected to EOB from [^{11}C]CO_2 and 20–25% at EOS, respectively.

Acknowledgments

This work was partially supported by the Indiana Genomics Initiative (INGEN) of Indiana University, which is supported in part by Lilly Endowment Inc. The authors would like to thank Dr. Bruce H. Mock, and Barbara E. Glick-Wilson for their assistance in production of [^{11}C]CH_3OTf. The referees' criticisms and editor's comments for the revision of the manuscript are greatly appreciated.

References

[1] R. Suzuki, A. Dickenson, Neurosignals 14 (2005) 175–181.
[2] W. Rahman, R. Suzuki, L.J. Rygh, A.H. Dickenson, Neurosci. Lett. 361 (2004) 229–231.
[3] K. Okamoto, H. Imbe, A. Tashiro, S. Kumabe, E. Senba, Neurosci. Lett. 367 (2004) 259–263.
[4] B. Kopczynska, M. Szereda-Przestaszewska, Life Sci. 75 (2004) 2281–2290.
[5] M. Camilleri, E.A. Mayer, D.A. Drossman, A. Heath, G.E. Dukes, D. McSorley, S. Kong, A.W. Mangel, A.R. Northcutt, Aliment. Pharmacol. Ther. 13 (1999) 1149–1159.
[6] R.J. Gralla, R. de Wit, J. Herrstedt, A.D. Carides, J. Ianus, J. Guoguang-Ma, J.K. Evans, K.J. Horgan, Cancer 104 (2005) 864–868.
[7] S. Yoshida, S. Shiokawa, K.-i. Kawano, T. Ito, H. Murakami, H. Suzuki, Y. Sato, J. Med. Chem. 48 (2005) 7075–7079.
[8] Y. Sato, M. Yamada, S. Yoshida, T. Soneda, M. Ishikawa, T. Nizato, K. Suzuki, F. Konno, J. Med. Chem. 41 (1998) 3015–3021.
[9] Y. Sato, M. Yamada, K. Kobayashi, K. Iwamatsu, F. Konno, K. Shudo, Eur. Pat. Appl. EP 0806419A1, 1997, 25 pp.
[10] B.H. Mock, G.K. Mulholland, M.T. Vavrek, Nucl. Med. Biol. 26 (1999) 467–471.
[11] D.M. Jewett, Appl. Radiat. Isot. 43 (1992) 1383–1385.
[12] M. Wang, G. Lacy, M. Gao, K.D. Miller, G.W. Sledge, Q.-H. Zheng, Bioorg. Med. Chem. Lett. 17 (2007) 332–336.
[13] X. Fei, J.-Q. Wang, K.D. Miller, G.W. Sledge, G.D. Hutchins, Q.-H. Zheng, Nucl. Med. Biol. 31 (2004) 1033–1041.
[14] B.H. Mock, Q.-H. Zheng, T.R. DeGrado, J. Labelled Comp. Radiopharm. 48 (2005) S225.
[15] B.H. Mock, B.E. Glick-Wilson, Q.-H. Zheng, T.R. DeGrado, J. Labelled Comp. Radiopharm. 48 (2005) S224.
[16] Q.-H. Zheng, B.H. Mock, Biomed. Chromatogr. 19 (2005) 671–676.