Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 25 April 2008, Revised 13 August 2008, Accepted 19 August 2008 Published online 7 October 2008 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1545

Synthesis of a ^{14}C-labeled FPTase inhibitor *via* a Pd-catalyzed cyanation with Zn(^{14}CN)$_2$ and *via* bromo[^{14}C]acetic acid

Jonathan Z. Ho,* Charles S. Elmore, and Matthew P. Braun

^{14}C-Labeled farnesyl-protein transferase inhibitor 1a was required for drug metabolism studies. The first approach was to synthesize ^{14}C-labeled 1b using Zn(^{14}CN)$_2$ in a Pd-catalyzed cyanation. A second approach was to prepare labeled 1c with the ^{14}C-label in the piperazine ring. All metabolites from 1b were non-radioactive whereas the same metabolites from 1c were all radioactive and quantifiable.

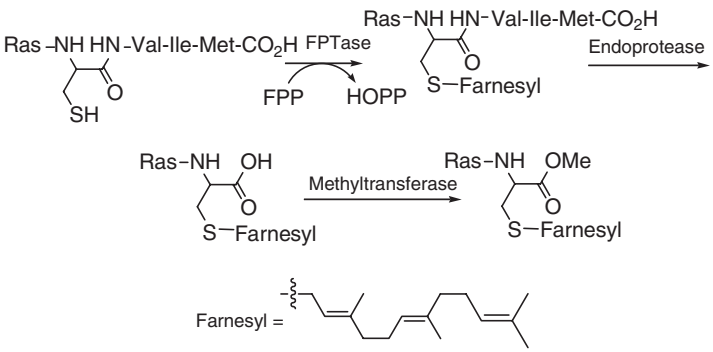
Keywords: ^{14}C-labeled ; cyanation ; Zn(^{14}CN)$_2$; bromo[^{14}C]acetic acid; FPTase

Introduction

Ras is a guanosine triphosphate (GTP) binding protein that cycles between the inactive guanosine diphosphate (GDP) binding conformation and the active GTP binding conformation. The protein exists primarily in the GDP binding conformation, but phosphorylation by receptor tyrosine kinases (e.g. the receptors of vascular endothelial and epidermal growth factors) leads to the GTP binding conformation. This form transfers growth signals from the receptor to the mitogen-activated protein kinase cascade, which puts Ras at the heart of the signaling pathway leading to cellular growth.[1] Ras mutations that result in a preference for the GTP binding form lead to unregulated cell growth and are observed in approximately 20–30% of human cancers.[2]

of the protein but are not required for activity.[6] Therefore, inhibition of FPTase represents a potential therapeutic target for anticancer efforts.[7]

FPTase is a heterodimeric, GTP-binding protein with subunits of 48 and 46 kDa. It selectively farnesylates Ras proteins with the amino acid sequence of CAAX at the carboxy terminus where C is cysteine, A is an aliphatic amino acid, and X is usually methionine or serine. Farnesylation occurs at the thiol of the cysteine and facilitates association of the peptide and the cellular membrane. This places it in close proximity to the tyrosine kinases of the cellular growth factor receptors.[6,7] Compound **1a** (Figure 1) was developed as a potent inhibitor of FPTase for treatment of cancer. For its preclinical metabolism study a radio-labeled tracer of **1a** was needed. Two ^{3}H-labeled tracers, with tritium label at different locations, were made



Scheme 1. Post-translational modifications of RAS required to give maximal enzymatic activity.

Ras proteins must undergo a series of post-translational modifications to become active (Scheme 1). The first modification – addition of a 15 carbon isoprenoid unit, farnesol, to Ras – is catalyzed by farnesyl-protein transferase (FPTase).[3] Further modifications, such as hydrolysis of the three C-terminal amino acids[4] and esterification of the C-terminus,[5] increase the activity

Department of Process Research, Merck Research Laboratories, 126 E. Lincoln Avenue, PO Box 2000, RY80R-104, Rahway, New Jersey 07065, USA

**Correspondence to: Jonathan Z. Ho, Department of Process Research, Merck Research Laboratories, 126 E. Lincoln Avenue, PO Box 2000, RY80R-104, Rahway, NJ 07065, USA.*
E-mail: jonathan_ho@merck.com

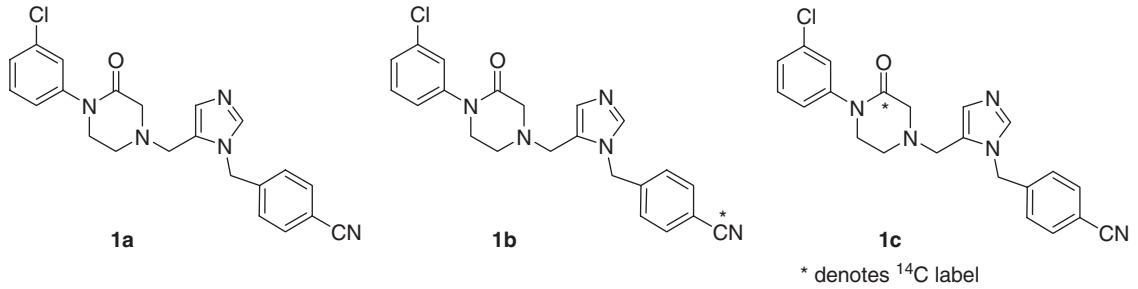


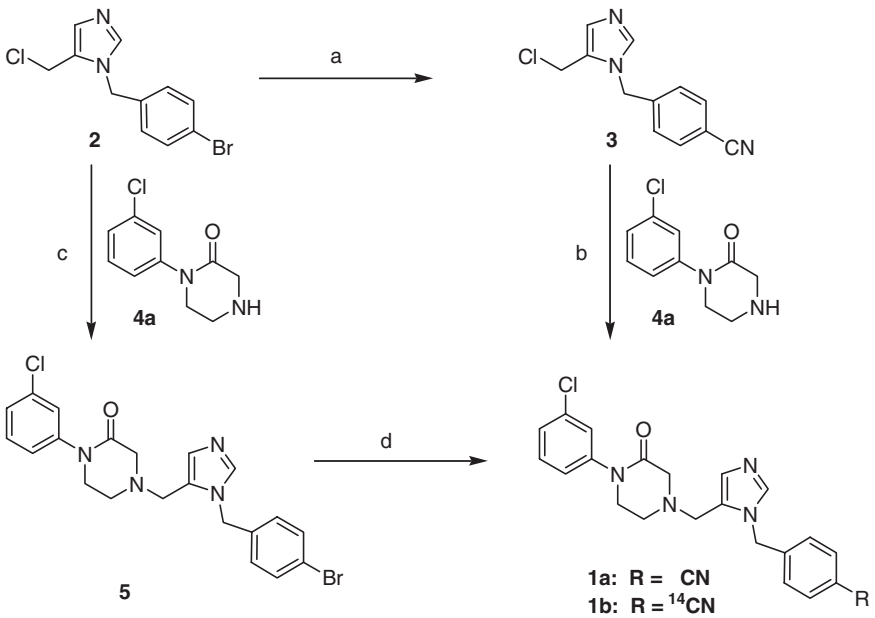
Figure 1A new FPTase inhibitor **1a**, 4-((5-((4-(3-chlorophenyl)-3-oxopiperazin-1-yl)methyl)-1*H*-imidazol-1-yl)methyl)benzonitrile.

initially but they all suffered with 2–3% of tritium loss during the microsone covalent binding (CV) studies. Consequently, a tracer labeled with ^{14}C was highly desired for required metabolic studies.[8] The details of preparation of ^{3}H-labeled tracers and related CV results are subjected to a separated publication.

Results and discussion

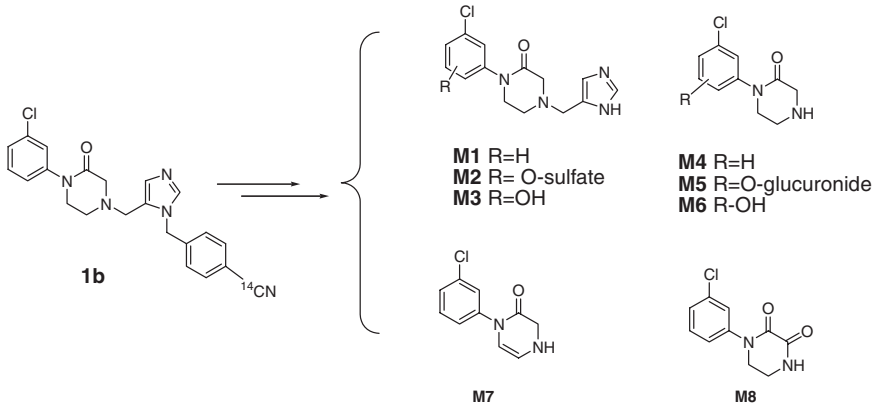
The classical ^{14}C-labeled cyanation procedure utilizes Cu^{14}CN as the source of ^{14}C-labeled cyanide.[9a] The cyanation reaction with CuCN is known as the Rosenmund von Braun reaction and is usually carried out at high temperatures (150–250°C) for long reaction times (24 h or more).[10] The development of a milder Zn(^{14}CN)$_2$ to be an attractive reagent for the preparation of the compound containing benzo[^{14}C]nitrile subunits for several reasons, including its commercial availability, low cost, good yields and tolerance of unprotected function groups. This strategy was adopted to label **1b** with ^{14}C since there would be only one radiochemical step with no protected functional groups.

The preparation of unlabeled 4-((5-((4-(3-chlorophenyl)-3-oxopiperazin-1-yl)methyl)-1*H*-imidazol-1-yl)methyl)benzonitrile (**1a**) was carried out by a Pd-catalyzed cyanation reaction of Zn(CN)$_2$ with 1-(4-bromobenzyl)-5-(chloromethyl)-1*H*-imidazole (2) (Scheme 2). The palladium catalyzed cyanation of aryl bromides with Zn(CN)$_2$ has been reported, and the reaction



Scheme 2. Reaction conditions: a) Zn(CN)$_2$, Pd(PPh$_3$)$_4$, DMF, 70 °C, 96%, b) *i*PrNEt, MeCN, rt, 73% for **1a**, c) *i*PrNEt, MeCN, rt, 69%, d) Zn(^{14}CN)$_2$, Pd(PPh$_3$)$_4$, DMF, 70 °C, chemical yield 88% and radiochemical yield 44% for **1b**.

and general route to access aryl cyanides in the presence of other sensitive functional groups would be highly desirable. In recent years, several transition-metal-mediated processes to transform an aryl halide to its cyanide have been developed with significant success; many of these use palladium or nickel complexes as catalysts together with inexpensive cyanide salts such as Zn(CN)$_2$ NaCN or KCN.[11] The aryl halides include iodide, bromide and even chloride.[12] Current methodology involving transition metal mediated cyanation reaction has been widely used in both organic and medicinal chemistry.[13] We found temperature was in the range of 120–150°C.[11b] We found that bromide **2** can be transformed to its cyanide **3** under a much milder (70°C) condition. Reaction of **3** with 1-(3-chlorophenyl)-piperazin-2-one (**4a**) is a known procedure[9b] and it provided the product **1a** in good overall yield. For the synthesis of ^{14}C-labeled 4-((5-((4-(3-chlorophenyl)-3-oxopiperazin-1-yl)methyl)-1*H*-imidazol-1-yl)methyl)-benzonitrile (**1b**), however, we adopted a different reaction sequence in which it consisted of only one radiochemical step (the last step) (Scheme 2). Treatment of **2** with 1-(3-chlorophenyl)piperazin-2-one (**4a**) gave bromide **5**.



Scheme 3. Metabolism of **1b** results in non-radioactive metabolites.

Subsequent Pd-catalyzed cyanation of **5** with $Zn(^{14}CN)_2$ afforded the desired ^{14}C-labeled tracer **1b**. In this reaction, two equivalents of $Zn(^{14}CN)_2$ were used. The chemical yield was 88% based on the limited starting material bromide **5**, and the radiochemical yield was 44% based on the excess $Zn(^{14}CN)_2$. After final purification with preparative HPLC, total of 4.7 mCi of **1b** (99.4% radiochemical purity) was obtained as a free base. To the best of our knowledge, this is the first example of palladium-catalyzed cyanation of an aryl bromide with ^{14}C-labeled $Zn(^{14}CN)_2$, although there are reports on cyanation of an aryl iodide with $Zn(^{14}CN)_2$ (or $K^{14}CN$) in the literature.[9c–d]

Metabolism of the tracer **1b** resulted in many non-radioactive metabolites (Scheme 3),[14] mainly arising from oxidative cleavage of the molecule between the imidazole and piperazinone rings. To quantify these metabolites, we need to synthesize another ^{14}C-labeled tracer where the ^{14}C label should be located in either the piperazinone ring or chlorophenyl group. Based on the availability of radiochemical starting materials and the evaluation of the synthetic strategies, we decided to put the ^{14}C label in piperazinone ring via the ^{14}C-labeled intermediate **4b** (Scheme 4).

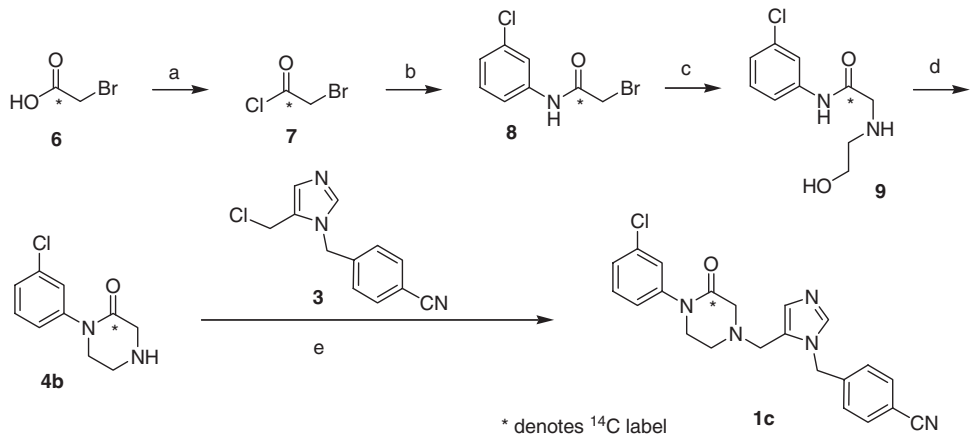
Our second synthesis began with the conversion of commercially available bromo[1-^{14}C]acid **6** into the corresponding bromo[1-^{14}C]acetyl chloride (7) (Scheme 4). After coupling **7** with 3-chloroaniline, the intermediate **8** was immediately reacted with ethanolamine to afford the aminoalcohol **9**. An intramolecular Mitsunobu reaction[15] and subsequent cyclization afforded the key intermediate **4b** with a ^{14}C label located at the carbonyl carbon. The same chemistry used to prepare **1a** from **4a** in Scheme 2 was followed to prepare ^{14}C-labeled **1c** from ^{14}C-labeled **4b**. After preparative HPLC purification, a total of 2.1 mCi of **1c** was obtained in 64% yield at 97.6% radiochemical purity.

In conclusion, we reported two radiochemical synthesis of a ^{14}C-labeled FPTase inhibitor **1b**. The first synthesis used a Pd-catalyzed coupling of aryl bromide **5** and $Zn(^{14}CN)_2$. A second synthesis with bromo[1-^{14}C]acetic acid provided labeled **1c,** which was suitable for quantification of the metabolites related to this program. The metabolite profile of FPTase inhibitor **1** will be addressed in a separate publication.

Experimental part

General

$Na^{14}CN$ was obtained from NEN, $Zn(^{14}CN)_2$ and Bromo[1-^{14}C]acetic acid were obtained from American Radiolabeled Chemicals. Tetrakistriphenylphosphinepalladium ($Pd(PPh_3)_4$) was obtained from Aldrich. Anhydrous solvents were obtained from Aldrich and were dried over 4 Å molecular sieves for at least 24 h prior to use. ^{1}H NMR spectra were recorded on a Varian U-400 spectrometer in CD_3CN, which was referenced to 1.93 ppm. Analytical HPLC was performed using a Shimadzu



Scheme 4. Reaction conditions: (a) Oxalyl chloride, CH_2Cl_2-DMF, 60%; (b) 3-Chloroaniline, $KHCO_3$, *i*PrOAc-H_2O; (c) Ethanolamine, *i*PrOAc, 99% over 2 steps; (d) PBu_3, EtOAc, Diisopropyl azodicarboxylate (DIAD), 65%; (e) Hunig's base, MeCN, Preparative HPLC, 64%.

HPLC system with LC-10ATVP pumps, a SPD-10AVP UV detector, a CTO-10ASVP column oven heated to 30°C, a SCL-10A controller and a Packard Radiomatic™ 150TR flow monitor. The radioactive products were identified by HPLC comparison with unlabeled reference material using either method A (30–100% MeCN-0.1% aq. trifluoroacetic acid over 30 min, ODS-AM) or method B (50% MeOH-0.1% aq. NEt_3 over 45 min, Zorbax RX C8). All HPLC analyses were concluded with a 10 min wash of 100% organic solvent.

Zinc [^{14}C]cyanide ($Zn(^{14}CN)_2$)

Although this reagent is a commercially available one, it can be easily made as follows. Aqueous solution of $MgCl_2$ (150 μL, 0.36 g/mL 0.58 mmol) was added to a solution of $Na^{14}CN$ (87 mg, 1.7 mmol, 69 mCi, 40.6 mCi/mmol) in deionized water (1 mL). After stirring for 5 min, a small amount of white precipitate was formed and filtered. The filtrate was added to a solution of $ZnCl_2$ (251 mg, 1.84 mmol) in a mixed solvent of H_2O (0.5 mL) and EtOH (0.5 mL). White precipitate started to form after stirring for 0.5 h. Additional H_2O (5 mL) was added to this suspension, and the mixture was stirred at room temperature for another 0.5 h. Solid was collected by vacuum filtration, washed with EtOH (1 mL) then Et_2O (2 mL), and dried at ambient temperature under a high vacuum (less than 1 mm of Hg) for 16 h to give $Zn(^{14}CN)_2$ (75 mg, 75%) as a white solid.

*4-(1-[(4-bromophenyl)methyl]imidazol-5-ylmethyl)-1-(3-chlorophenyl)-piperazin-2-one (**5**)*

Hunig's base (0.83 mL, 4.76 mmol) was added dropwise over 30 min to a suspension of piperazinone **4a** (441 mg, 1.64 mmol) and chloride **2** (421 mg, 1.54 mmol) in MeCN (2 mL) at 0°C. The resulting solution was warmed to rt and stirred overnight. The solution was concentrated to afford a yellow oil, which was purified by flash column chromatography on silica gel with 2% MeOH in CH_2Cl_2 as an eluant. Product containing fractions were combined, and solvent was removed under vacuum to give **5** (347 mg, 69%) as a white solid. The radiochemical purity was 99.4% determined by HPLC (method A). ^{1}H NMR: δ 7.61 (s, 1H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.37 (t, 1H, *J* = 7.9), 7.31 (t, 1H, *J* = 1.9 Hz), 7.27 (d, 1H *J* = 8.0 Hz), 7.18 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 2H, *J* = 8.4 Hz), 6.91 (s, 1H), 5.23 (s, 2H), 3.42 (s, 2H), 3.34 (t, 2H, *J* = 5.2 Hz), 3.06 (s, 2H), 2.62 (t, 2H, *J* = 5.6 Hz).

*4-[(5-[4-(3-chlorophenyl)-3-oxopiperazinyl]methylimidazolyl)-methyl]-benzenecarbo-[^{14}C]-nitrile hydrochloride (**1b**)*

A thoroughly degassed suspension of $Zn(^{14}CN)_2$ (26 mg, 0.21 mmol, 11 mCi, 110 mCi/mmol), bromide **5** (129 mg, 0.21 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in DMF (0.5 mL) was heated at 70°C for 20 h. The reaction progress was monitored by HPLC (method A). After being cooled to rt, solvent was removed under vacuum and the residue was dissolved in MeCN (2 mL) to give crude **1b** (7.4 mCi) with 95% radiochemical purity (method B). The sample was purified by preparative HPLC (ODS-AM column, 22.1 × 250 mm, 20 mL/min, isocratic, 31% MeCN-69% H_2O with 0.1% TFA) and the product containing fractions were combined. MeCN was removed under vacuum. After its pH was adjusted to 10 with saturated aqueous Na_2CO_3, the solution was extracted with benzene (10 mL × 3). The combined organic layers were concentrated to provide **1b** (4.7 mCi) with 99.5% radiochemical purity. Unlabeled **1a**^{14} (48 mg) and ^{14}C labeled **1b** (4.7 mCi) were dissolved in benzene (10 mL) to form a clear solution, to which a solution of HCl in EtOH (1 mL, 7% w/w) was added. After removal of solvent, the solid was re-crystallized from EtOAc (4.5 mL) and EtOH (0.5 mL) to give **1b** (74 mg, 0.19 mmol, 3.72 mCi) as a white solid. The specific activity was determined to be 25.1 mCi/mmol by gravimetric determination. HPLC analysis showed a radiochemical purity of 99.4% (Method B). ^{1}H NMR: δ 7.67 (d, 2H, *J* = 8.3 Hz), 7.63 (s, 1H), 7.37 (t, 1H, *J* = 8.1), 7.29 (t, 1H, *J* = 2.0 Hz), 7.26 (d, 1H, 8.1 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 7.15 (d, 1H, *J* = 8.1), 6.93 (s, 1H), 5.34 (s, 2H), 3.41 (s, 2H), 3.32 (t, 2H, *J* = 5.4), 3.03 (s, 2H), 2.61 (t, 2H, *J* = 5.5 Hz).

N-*(3-chlorophenyl)-2-[(2-hydroxyethyl)amino][1-^{14}C]acetamide (**9**)*

A solution of oxalyl chloride (59 mg, 0.47 mmol) in DMF (10 μL) was added to a suspension of bromo[1-^{14}C]acetic acid (21 mCi, 0.39 mmol, 54.3 mCi/mmol) in CH_2Cl_2 (1 mL). The resulting suspension was stirred at rt for 16 h to provide bromo[1-^{14}C]acetyl chloride, and it was used immediately without further purification.

A biphasic mixture of K_2CO_3 (66 mg, 0.66 mmol) in water (1 mL) and 3-chloroaniline (60 mg, 0.47 mmol) in *i*PrOAc (3 mL) was stirred at 0°C as above mentioned [^{14}C]bromoacetyl chloride (21 mCi) in CH_2Cl_2 (1 mL) was added. The progress of the reaction was followed by HPLC and was judged complete after 15 min. The aqueous layer was removed and ethanolamine (95 mg, 1.56 mmol) in *i*PrOAc (0.3 mL) was added. The reaction mixture was stirred at 60°C for 3 h, then water (1 mL) was added at 60°C. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated to give **9** as a solid (91 mg, 21 mCi). ^{1}H NMR:δ7.45 (s, 1H), 7.41 (t, 1H, *J* = 8.0 Hz), 7.38 (d, 1H, *J* = 8.9 Hz) 7.28 (d, 1H, *J* = 7.9 Hz) 3.99 (s, 2H), 3.94 (t, 2H, *J* = 5.5 Hz), 3.66 (t, 2H, 5.5 Hz), 3.55 (br s, 2H).

*1-(3-chlorophenyl)-[2-^{14}C]-piperazin-2-one (**4b**)*

A solution of ethanolamine **9** (5 mCi), Bu_3P (109 mg) and diisopropyl azodicarboxylate (DIAD, 109 mg) in EtOAc (0.5 mL) was stirred at 0°C. The progress of the reaction was monitored by HPLC (method A), which indicated that this reaction was completed in 0.5 h. MeOH (2 mL) was added and the reaction mixture concentrated to near dryness. The residue was purified by flash chromatography on silica gel (flash elute 40S column, 6% MeOH in CH_2Cl_2 with 0.1% of triethyl amine) to give desired product **4b** (3.3 mCi, 65%). ^{1}H NMR:δ7.43 (s, 1H), 7.43 (t, 1H, *J* = 8.0 Hz), 7.36 (d, 1H, *J* = 8.9 Hz) 7.29 (d, 1H, *J* = 7.9 Hz) 3.99 (s, 2H), 3.94 (t, 2H, *J* = 5.5 Hz), 3.66 (t, 2H, 5.5 Hz), 1.61 (br s, 1H).

*4-[(5-[4-(3-chlorophenyl)-[3-^{14}C]-3-oxopiperazinyl]methylimidazolyl)-methyl]-benzenecarbonitrile hydrochloride (**1c**)*

A solution of **4b** (3.3 mCi), chloroimidazole **3** (18 mg, 0.7 mmol) and diisopropylethyl amine (17 mg) in MeCN (1 mL) was stirred at rt for 4 days. Solvent was removed under vacuum and the residue was dissolved in MeCN-H_2O-TFA (2, 2 and 0.1 mL, respectively). The mixture was purified by preparative HPLC (MeCN:H_2O:TFA = 30:70:0.1; Zorbax RX C8 column 22.1 × 250 mm, 20 mL/min). The product containing fractions were combined, and aqueous $NaHCO_3$ (2 mL) was used to adjust the pH to 6.50. MeCN was removed under vacuum and the

aqueous solution was extracted with EtOAc (50 mL × 3) to give **1c** (2.1 mCi, 64%). EtOAc was removed, and EtOH (10 mL) was added. Final purity analysis showed the compound to have 97.6% radiochemical purity (Method B). ^{1}H NMR: δ 7.67 (d, 2H, J = 8.3 Hz), 7.63 (s, 1H), 7.37 (t, 1H, J = 8.1), 7.29 (t, 1H, J = 2.0 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.15 (d, 1H, J = 8.1), 6.93 (s, 1H), 5.34 (s, 2H), 3.41 (s, 2H), 3.32 (t, 2H, J = 5.4), 3.03 (s, 2H), 2.61 (t, 2H, J = 5.5 Hz).

Acknowledgement

J. Z. H. dedicates this paper to his Ph.D. advisor, Professor Robert M. Coates, Ph.D., Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA, on the occasion of his 70th birthday. The authors thank Mr. Steven Staskiewicz for analytical support, and Dr Romi Singh and Dr Lixia Jin for performing the metabolism studies reported herein. We thank Dr David Schenk for proof reading of the manuscript.

References

[1] D. R. Lowry, B. M. Willumsen, *Ann. Rev. Biochem.* **1993**, *62*, 851–891.
[2] G. Bollag, F. McCormick, *Ann. Rev. Cell Biol.* **1991**, *7*, 601–632.
[3] P. J. Casey, P. A. Solski, C. J. Der, J. E. Buss, *Proc. Nat. Acad. Sci. USA* **1989**, *86*, 8323–8327.
[4] M. N. Ashby, D. S. King, J. Rine, *Proc. Nat. Acad. Sci. USA* **1992**, *89*, 4613–4617.
[5] S. Clarke, J. P. Vogel, R. J. Deschenes, J. Stock, *Proc. Nat. Acad. Sci. USA* **1988**, *85*, 4643–4647.
[6] D. M. Leonard, *J. Med. Chem.* **1997**, *40*, 2971–2990.
[7] A. Oliff, *Biochim. Biophys. Acta* **1999**, *1423*(3), c19–c30.
[8] (a) R. Singh, I-W. Chen, L. Jin, M. V. Silva, B. H. Arison, J. H. Lin, B. K. Wong, *Drug Metab. Disp.* **2001**, *29*, 1578–1587. (b) K. E. McCarthy, *Curr. Pharm. Des.* **2000**, *6*, 1057–1083.
[9] (a) H. Matloubi, A. Shafiee, N. Saemian, G. Shirvani, F. J. Daha, *J. Label Compd. Radiopharm.* **2004**, *47*, 31–36. (b) P. E. Maligres, M.S. Waters, S. A. Weissman, J. C. McWilliams, S. Lewis, J. Cowen, R. A. Reamer, R. P. Volante, R. J. Reider, D. Askin, *J. Heterocycl. Chem.* **2003**, *40*(3), 229–241. (c) K. M. Cable, G. N. Wells, D. R. Sutherland, *J. Label Compd. Radiopharm.* **2000**, *43*, 29–45. (d) A. J. Allentoff, B. Markus, T. Duelfer, A. Wu, L. Jones, G. Ciszewska, T. Ray, *J. Label Compd. Radiopharm.* **2000**, *43*, 1075–1085.
[10] (a) K. W. Rothemund, E. Struck, *Berichte der Deutschen Chemischen Gesellschaft* **1916**, *52*, 1749–1750. (b) J. von Braun, G. Manz, *Justus Liebig's Annalen der Chemie* **1931**, *488*, 111–113. (c) D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189–283. (d) G. P. Ellis, T. M. Romney-Alexander, *Chem. Rev.* **1987**, *87*, 779–794.
[11] (a) M. Sundermeier, A. Zapf, M. Beller, *Angew. Chem. Int. Ed.* **2003**, *42*, 1661–1664. (b) P. E. Maligres, M. S. Waters, F. Fleitz, D. Askin, *Tetrahedron Lett.* **1999**, *40*, 8193–8195.
[12] K. M. Marcantonio, L. F. Frey, Y. Liu, Y. Chen, J. Strine, B. Phenix, D. J. Wallace, C. Chen, *Org. Lett.* **2004**, *6*, 3723–3725.
[13] (a) N. H. Khan, R. I. Kureshy, S. H. R. Abdi, S. Agrawal, R. V. Jasra, *Coord. Chem. Rev.* **2008**, *252*, 593–623. (b) M. Sundermeier, A. Zapf, M. Beller, *Eur. J. Inorg. Chem.* **2003**, *19*, 3513–3526. (c) A. Murray III, D. L. Williams, *Organic Synthesis With Isotopes*, Interscience Publishers Inc., New York, **1958**, pp. 38–39. (d) R. Adams, I. Levine, *J. Am. Chem. Soc.* **1923**, *45*, 2373–2377.
[14] (a) C. J. Dinsmore, C. B. Zartman, W. F. Baginsky, T. J. O'Neill, K. S. Koblan, I-W. Chen, D. A. McLoughlin, T. V. Olah, J. R. Huff, *Org. Lett.* **2000**, *2*, 3473–3476. (b) H. D. Burns, W. S. Eng, R. E. Gibson, *World Patent* 1999, WO **99**:00654. (c) J. P. Davide, R. B. Lobell, *World Patent* 2000, WO **00**:70083.
[15] S. Weissman, S. Lewis, D. Askin, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **1998**, *39*, 7459–7462.

