Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 576–577.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1283

JLCR

Short Research Article

Synthesis of 1-(1-benzyl-2-ethylthio-2-^{14}C-5-imidazolyl)-4-{3-(1-*iso*propylamino)-2-pridyl} piperazine†

NADER SAEMIAN*, GHOLAMHOSSEIN SHIRVANI and HOJATOLLAH MATLOUBI

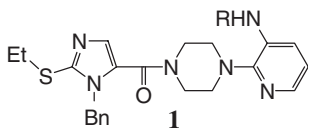
Nuclear Research Center/AEOI, Chemical Division, P.O. Box 11365-3486, Tehran, Iran

Received 21 June 2006; Revised 22 January 2007; Accepted 23 January 2007

Keywords: carbon-14; bis(heteroaryl) piperazines

Introduction

A variety of analogues of bis (heteroaryl) piperazines (BHAPs) (such as: U-80493E) were synthesized and evaluated for their inhibition of human immuodeficiency virus type1 (HIV-1) reverse transcriptase.[1] Sometimes replacement of the substituted aryl moiety with other various aromatic systems provided bis (heteroaryl) piperazines that were 10–100 fold more potent than U-80493E (for instance: Atevirdine).[2] According to previous structure and activity relationship studies on atevirdine, the compound **1** was synthesized by Hadizadeh and coworkers, in which 1-(3-alkylamino-2-pyridyl) piperazine part of the molecule was unchanged and 5-alkoxy-2-indolylcarbonyl part of the molecule was replaced by benzyl-2-alkylthio-imidazolylcarbonyl moiety.[3] Therefore, to further elucidate the mechanism of action and to support ongoing metabolism studies, there arose a need for analogs of this compound carbon-14 labelled in a biologically stable site.[4] In this paper, the synthesis of 1-(1-benzyl-2-ethylthio-2-[^{14}C]-5-imidazolyl)-4-{3-(1-*iso*propylamino)-2-pridyl} piperazine **1** is described.



1

R:isopropyl

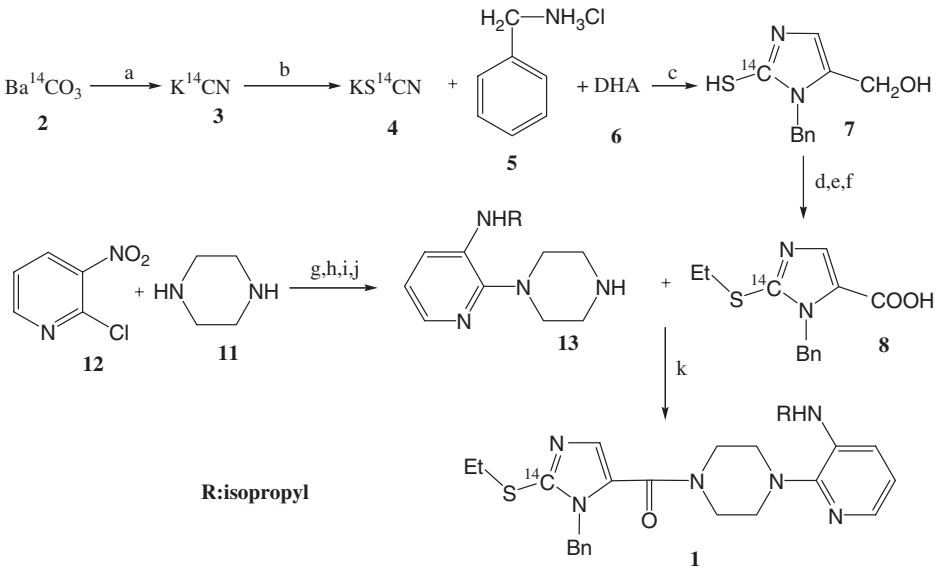
Results and discussion

In this approach, according to the synthetic pathway shown in Scheme 1, barium [^{14}C]carbonate **2** was converted to potassium [^{14}C]cyanide **3** according to standard procedure.[5]

Then potassium [^{14}C]thiocyanate **4** was obtained quantitatively via the reaction between potassium [^{14}C] cyanide **3** and sulfur in acetone.[6] Potassium [^{14}C] thiocyanate **4** was stirred with 1,3-dihydroxyacetone dimmer **6** and benzylamine hydrochloride **5** to give [2-^{14}C]-5-hydroxymethyl-2-mercapto-1-benzylimidazole **7**.[7] Subsequent alkylation of compound **7** with ethyl iodide and oxidation of the product with manganese dioxide and further oxidation of the latter product with alkaline solution of silver nitrate gave [2-^{14}C]-2-ethylthio-1-benzylimidazole-5-carboxylic acid **8**.[8–10] On the other hand, 1-[3-(1-*iso*propylamino)-2-pridyl] piperazine **13** has been synthesized as part of a 4-step sequence from piperazine **11** and 2-chloro-3-nitro pyridine **12**.[1] The final step coupling of **8** with **13** was accomplished utilizing 1,1′-sulfinyldiimidazole to afford the title compound 1-(1-benzyl-2-ethylthio-2-[^{14}C]-5-imidazolyl)-4-{3-(1-*iso*propylamino)-2-pridyl} piperazine **1**.

*Correspondence to: Nader Saemian, Nuclear Research Center/AEOI, Chemical Division, P.O. Box 11365-3486, Tehran, Iran.
E-mail: nsaemian@aeoi.org.ir

†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



Scheme 1 (a) K/KN_3, (b) S,acetone, (c) *n*-BuOH, AcOH, (d) EtI, (e) MnO_2, (f) Ag_2O, NaOH, (g) CH_2Cl_2, $(BOC)_2O$, (h) Pd/H_2, (i) acetone, $NaCNBH_3$, (j) TFA and (k) 1,1′-sulfinyldiimidazole.

REFERENCES

1. Rommero DL, Morge RA, Biles C, Berrios-pena N, May PD, Palmer JR, Johnson PD, Smith HW, Busso M, Tan CK, Voorman RL, Reusser F, Althaus IW, Downey KM, So AG, Resnick L, Tarpley WG, Aristoff PA. *J Med Chem* 1994; **37**: 999–1014.
2. Schafer W, Friebe WG, Lienert H, Mertens A, Poll T, Von der Saal W, Zilch H, Nuber B, Ziegler ML. *J Med Chem* 1993; **36**: 726–732.
3. Hadizadeh F, Mehrparvar A. *J Sci I R Iran* 2004; **15**: 131–134.
4. Saemian N, Shirvani G, Matloubi H. *J Label Compd Radiopharm* 2006; **49**: 71–76.
5. Perry CW, Burger W, Dlaney CM. *J Label Compd Radiopharm* 1978; **16**: 645–649.
6. Matloubi H, Ghandi M, Saemian N. *Appl Radiat Isot* 2002; **57**: 501–504.
7. Duncia JV, Chiu AT, Carini DJ, Gregory GB, Johnson AL, Price WA, Wells GJ, Wong PC, Calabrese JC, Timmermans PBMWM. *J Med Chem* 1990; **33**: 1312–1329.
8. Shafiee A, Hadizadeh F, Noori SB. *J Heterocyclic Chem* 2000; **37**: 1015–1018.
9. Shafiee A, Hadizadeh F. *J Heterocyclic Chem* 1997; **34**: 549–550.
10. Firoozi F, Javidnia K, Kamali M, Fooladi A, Foroumadi A, Shafiee A. *J Heterocyclic Chem* 1995; **32**: 123–128.

DOI: 10.1002.jlcr