Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 593–594.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1294

JLCR

Short Research Article

Synthesis of radio- and stable-labelled LAF237(Galvus, Vildagliptin)†

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Received 25 August 2006; Revised 22 January 2007; Accepted 31 January 2007

Keywords: Radio-labelled; stable-labelled; LAF237 (Galvus,Vildagliptin)

Introduction

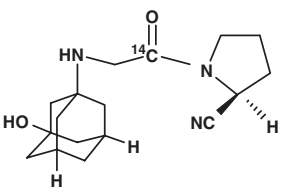
LAF237 (Galvus, Vildagliptin) is the first in a new class of oral dipeptidyl peptidase 4 (DPP4) anti-diabetes agents. It significantly improves glycemic control in patients with type-2 diabetes and is potentially the first therapeutical agent to modulate glucagons-like peptide-1 (GLP-1), which selectively controls blood sugar levels. Radiolabelled LAF237 was required to support the animal and human ADME studies. Stable-labelled (with an appropriately high number of labelled mass units) was also needed as an LC/MS internal standard for use in bioanalytical assays. [^{14}C]LAF237 was labelled in two positions (carbonyl-^{14}C and methylene-^{14}C). Stable-labelled LAF237 was prepared with five-^{13}C and ^{15}N incorporated in the L-proline moiety.

Results and discussion

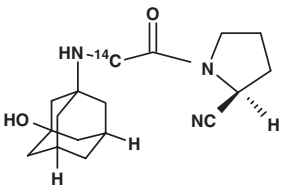
The procedures used for the preparation of [^{14}C]LAF237 and [$^{13}C_5$, ^{15}N]LAF237 were modifications of synthetic routes developed by Novartis Chemical & Analytical Development[1] and Discovery Research[2] chemists.

Preparation of (^{14}C) LAF237

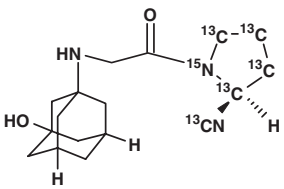
Proline amide **1** was acylated with either [1-^{14}C] or [2-^{14}C]- bromo-acetyl bromide and the resulting bromide **2** was dehydrated using Burgess reagent[3] to afford bromonitrile **3**. Treatment of **3** with 3-amino-1-adamantanol in the presence of base under anhydrous conditions yielded the crude drug substance, which was purified by flash chromatography affording [^{14}C] LAF237. The radiochemical purity and chemical identity of the drug substance were determined by HPLC, TLC, MS, IR, and differential scanning calorimetry.



[^{14}C]LAF237
labeled at carbonyl-^{14}C
position



[^{14}C]LAF237
labeled at methylene-^{14}C
position



[M+6]LAF237
[$^{13}C_5$, ^{15}N]

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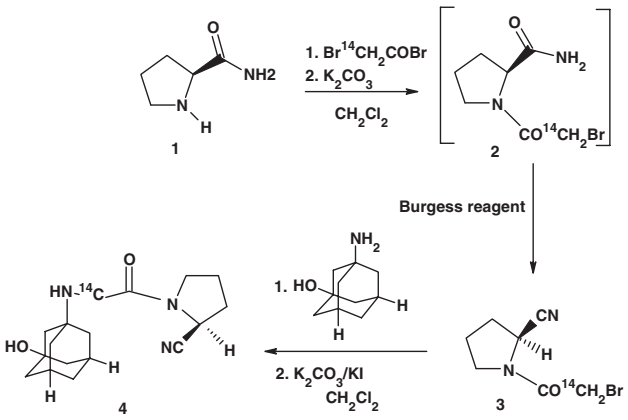
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



Synthesis of (M+6) LAF237

[$^{13}C_5$, ^{15}N]L-Proline, was adsorbed on Amberlyst-15 ion exchange resin (cation exchange resin) in methanol. On the resin surface, adsorbed [M + 6]L-proline was converted to the ester and then amidated using ammonia gas affording [M + 6]L-prolinamide. The conclusion of the synthesis was performed using analogous chemistry to that described for the preparation of [^{14}C]LAF237.

Summary

[^{14}C]LAF237 labelled at the 1 or 2 position of the acetyl moiety were efficiently prepared in three-step syntheses starting from bromo-1-[^{14}C]acetyl bromide or bromo-2-[^{14}C]acetyl bromide with 12 and 42% yields, respectively, with radiochemical purity >97%.

[$^{13}C_5$, ^{15}N]LAF237 labelled at the L-proline moiety was prepared in a five-step synthesis with 40% overall yield. For [M + 6]LAF237, no parent peak was detected by mass spectrometry (MS).

Acknowledgements

The authors would like to thank our Colleagues from Novartis Chemical and Analytical Development and Discovery Research for sharing their synthesis and analysis procedures and for providing intermediates and standards.

REFERENCES

1. Vilhauer E, Naderi G. NVP-LAF237-NX-2 synthesis sheet 06-Oct-1998.
2. Kappa P, Loeser E. Laboratory Process Description, 15-April-1999.
3. Claremon D, Philips B. *Tetrahedron Lett* 1998; **29**: 2155–2158.