Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 459–462.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1194

JLCR

Short Research Article

Synthesis and analysis of tritiated camptothecin analogs with iridium-mediated ^3H exchange†

TAPAN RAY[1], AMY WU[1,*] and ALBAN J. ALLENTOFF[2]

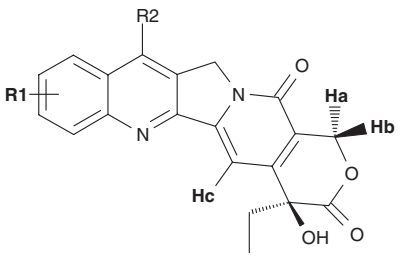
[1] Drug Metabolism Department, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ, USA
[2] Department of Chemical Synthesis-Radiochemistry, Bristol-Myers Squibb Company, USA

Received 28 July 2006; Revised 2 November 2006; Accepted 22 November 2006

Keywords: tritium; iridium; camptothecin; NMR

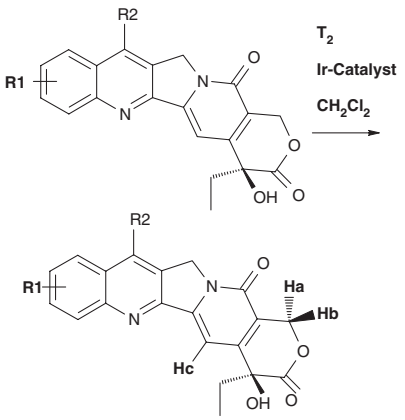
Introduction

In recent work to support a transporter study, we synthesized three tritiated camptothecin analogs[1,2] with high specific activity. Their rapid synthesis was achieved using tritium exchange mediated by the Iridium catalyst $(COD)Ir(PPh_3)_2PF_6$. Tritium NMR analysis of the labeled products indicated that in all three cases, the major site of tritium exchange took place on position c, with lesser incorporation on position b. NOESY experimentation established that the labeling on position b was stereospecific. A possible mechanism will be proposed to explain these results.

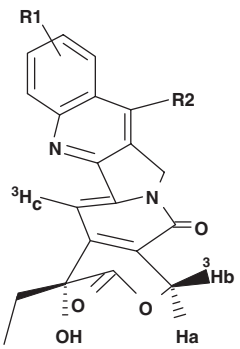


Results and discussion

All three tritium labeled compounds were prepared in a one-step process using an iridium-catalyzed direct tritiation reaction (H_b and H_c are the tritium locations).



For all of the three compounds, the tritium was incorporated mainly on the pyridone moiety and to some extent on the lactone ring system (Figures 1–3).



*Correspondence to: Amy Wu, Drug Metabolism Department, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ, USA. E-mail: amy.wu@novartis.com
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.

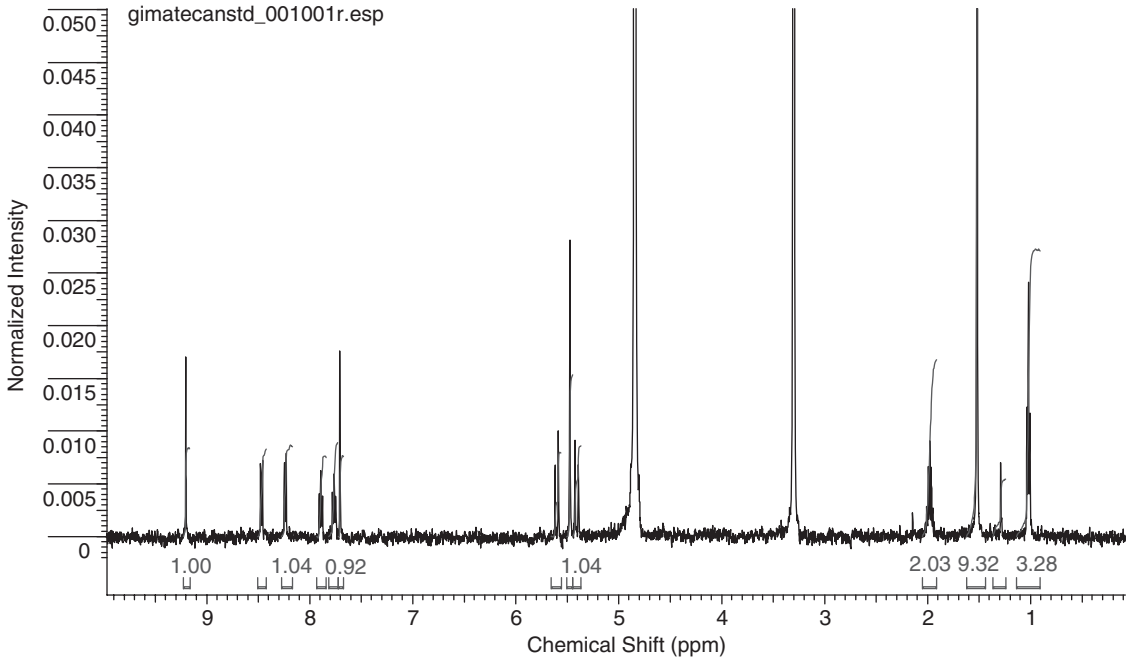


Figure 1 ^{1}H NMR of standard.

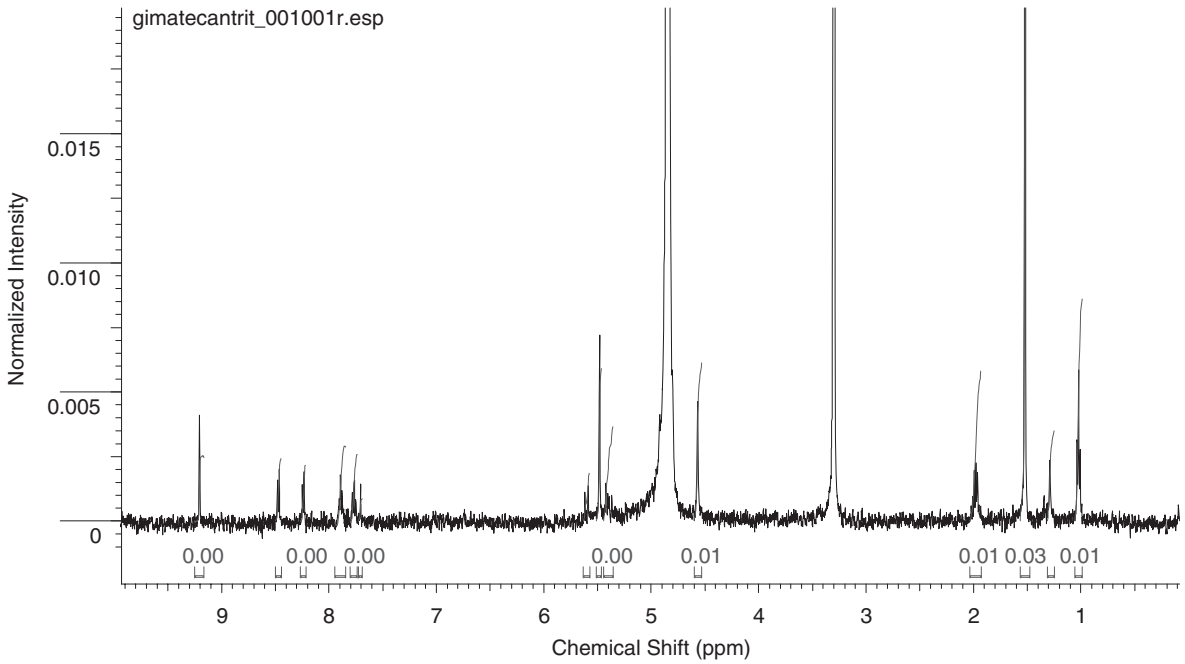


Figure 2 ^{1}H NMR of ^{3}H sample.

The tritium incorporation on the lactone ring was also stereospecific (we assigned position a and b via a NOESY spectrum of the standard material). The folding of the six-membered lactone ring then allowed the accessibility of the carbonyl-bound iridium complex exclusively to the beta-position on the lactone ring.

The conformation of the lactone ring is boat with the bulky ethyl group in the pseudo-equatorial position. This also eliminates the strain due to dipolar–OH and carbonyl interaction. In this configuration the insertion of iridium, to form planar five-membered ring, is only possible from pseudo-equatorial position.

DOI: 10.1002.jlcr

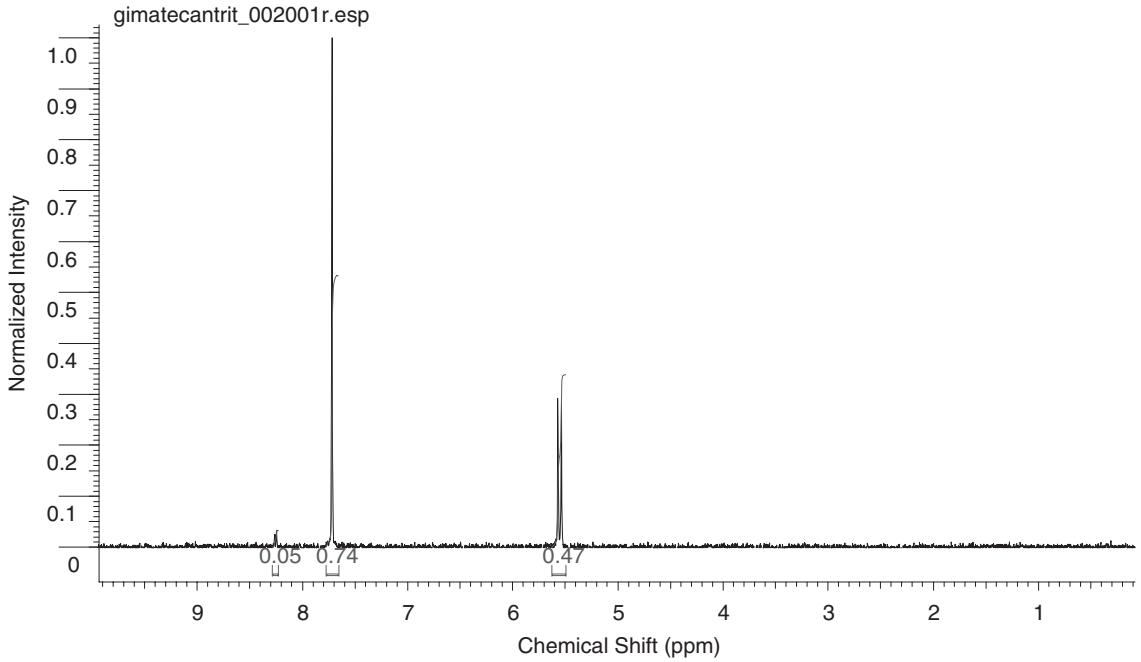
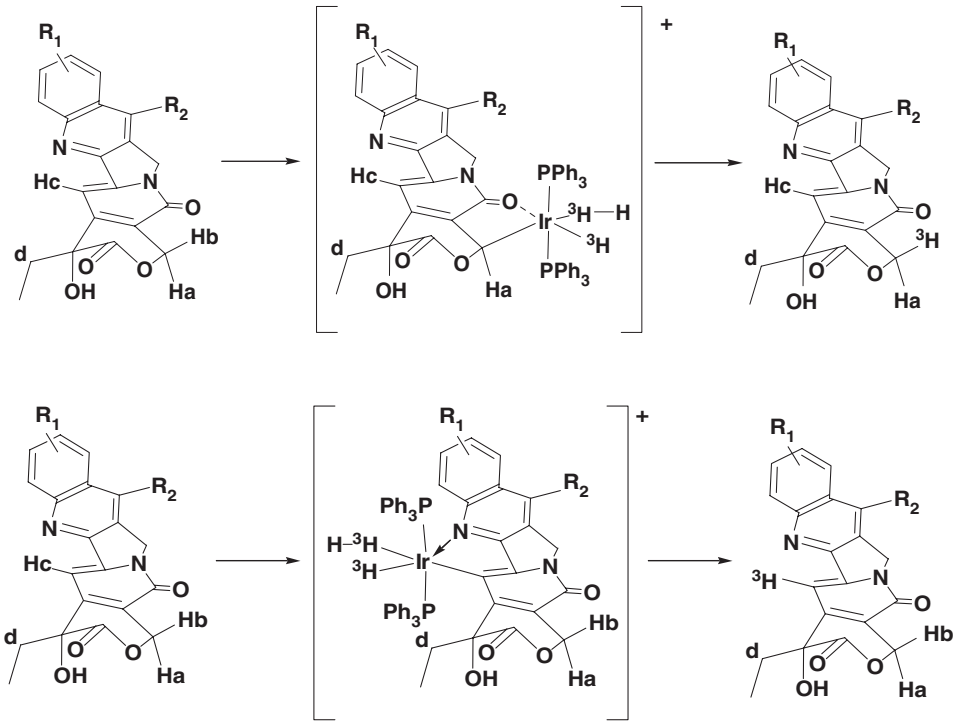


Figure 3 ^{3}H NMR of ^{3}H sample.

The insertion of tritium on the pyridone ring can be explained by considering the five membered planar iridium intermediate where iridium is inserted into the C–H bond by oxidative addition and subsequent reductive elimination releasing tritiated product (Scheme 1).



Scheme 1

DOI: 10.1002.jlcr

All three compounds were purified by semi prep HPLC using C18 column with acetonitrile and water as mobile phase. The specific activities measured by LC/MS varied from 2 to 34 Ci/mmol. The difference among the specific activities is most likely caused by the dilution of tritium gas and are not structure related.

Acknowledgements

The authors would like to thank Mr K. Gunderson from Novartis Biomedical Research Discovery Technology for his support on ^{3}H NMR experiments.

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