Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 416–417.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1167

JLCR

Short Research Article

Synthesis of (^{3}H)doxorubicin by isotope exchange with tritiated water†

VALERII P. SHEVCHENKO[1,*], IGOR YU. NAGAEV[1], NIKOLAY F. MYASOEDOV[1] and ALEX B. SUSAN[2]

[1] Institute of Molecular Genetics, RAS, Moscow, Russia, pl. Kurchatova, 2, 123182 Moscow, Russia
[2] International Isotope Clearing House, Inc., 9110 Lee Blv. /P.O. Box 6986, Leawood, KS 66206, USA

Received 4 July 2006; Revised 10 November 2006; Accepted 17 November 2006

Keywords: tritium; doxorubicin; isotope exchange; tritiated water

Introduction

Doxorubicin is a chemotherapy drug that is used in the treatment of various forms of cancer. Doxorubicin is an extremely unstable compound that decomposes easily in both acidic and basic pH, and even more so after heating. Different modifications of liquid and solid state methods were employed for the optimization of the tritium labeling process and both doxorubicin and its silyl derivatives were used as the starting compounds. The labeling of Doxorubicine succeeded using the mildest version of isotope exchange with tritiated water. The latter was prepared *in situ* via the reduction of palladium oxide with tritium gas.

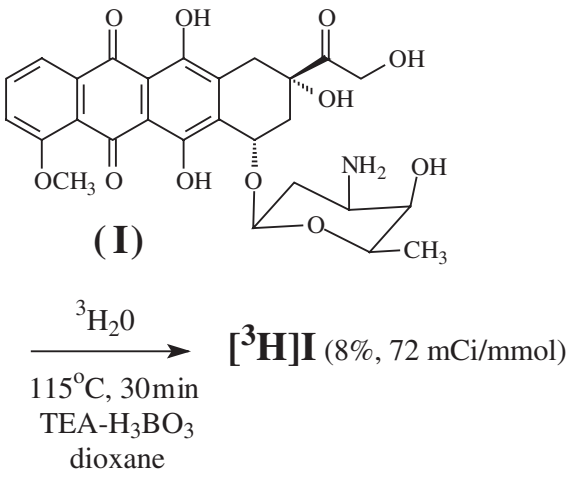
There are several common methods of isotope exchange with tritiated water.[1,2]

Results and discussion

One of the most common ways is treatment of a mixture of palladium oxide and a heterogeneous catalyst with tritium gas *in situ* leading to tritiated water and a catalyst activated with tritium. After the removal of excess tritium, the reaction of isotopic exchange is carried out by heating of the substrate solution in an aprotic solvent (dioxane) with addition of triethylamine. The specific activity of the resulting labelled compounds can reach as much as 10–30 Ci/mmol. Thus, labelled alprazolam with specific activity of 27 Ci/mmol was reported.[2]

A milder method is the heterogeneous isotopic exchange with tritiated water in solution at room temperature using non-activated catalyst (Figure 1). This method was successfully used to prepare an unstable compound containing an acetylenic fragment (pargyline, specific activity of 0.54 Ci/mmol).[1]

However, in the case of doxorubicin both methods failed due to the instability of the compound in the presence of triethylamine. So, the exchange procedure was carried out in the presence of triethylamine borate both as a buffering additive and a catalyst:



The HPLC analysis (Kromasil 100C_{18}, 4.0 × 150 mm, 6.0 μm, flow rate 1.0 ml/min, eluent methanol–water–acetic acid, 40:60:0.1, retention time –5.23 min) showed that 8% of the total label was present in the doxorubicin. After a two stage HPLC purification procedure, doxorubicin with specific activity of

*Correspondence to: V. P. Shevchenko, Institute of Molecular Genetics, RAS, Moscow, Russia, pl. Kurchatova, 2, 123182 Moscow, Russia. E-mail: atcarma@mail.ru
Contract/grant sponsor: Scientific Schools; contract/grant number: 2150.2003.4
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.

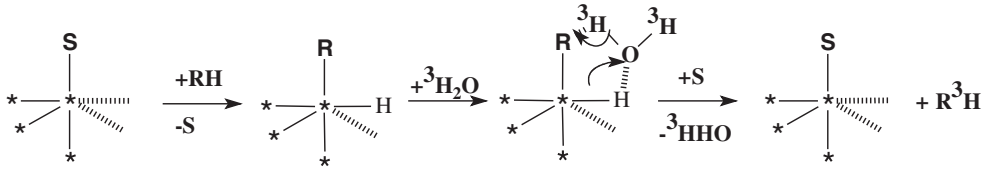


Figure 1 Isotope exchange on catalyst active centers without activation with tritium gas.

72 mCi/mmol and radiochemical purity of 98% was isolated.

Acknowledgements

This work was supported from 'Scientific schools No. 2150.2003.4', Russia and from the 'Molecular and Cell Biology' Program of Fundamental Research, Presidium of the RAS.

REFERENCES

1. Shevchenko VP, Nagaev IY, Myasoedov NF. *Lipophilic Compounds Labelled With Tritium*. Nauka: Moscow, 2003.
2. Shevchenko VP, Nagaev IY, Shevchenko KV, Myasoedov NF. Synthesis of tritium labelled biologically active compounds for research of actual problems in biology and medicine. In *Isotopes in Medicine*, vol. 2, Baranov VY (ed.). PhysMatLit: Moscow, 2005; 484–538.