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Tritium labelling of pharmaceuticals by metal-catalysed exchange methods

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Metal-catalysed exchange with tritiated water and tritium gas has been extensively used to prepare a wide range of tritium-labelled compounds in support of pharmaceutical research. Examples of the utility of both heterogeneous and homogeneous metal catalysts to label a very broad range of structures will be discussed in this review.

Keywords: tritium; rhodium; ruthenium; iridium; platinum; nickel; exchange

Introduction

Methods that employ metal-catalysed exchange with tritiated water and tritium gas have been extensively used within our group since 1991, when we first began 'in house' preparation of ^{3}H-labelled compounds in support of new drug discovery. Although other methods of hydrogen isotope exchange have been employed by our group, such as acid- or base-catalysed methods and direct methods of synthesis such as catalytic reductions of olefins and aryl halides, metal-catalysed exchange has remained the single most important methodology employed. Of these metal-catalysed methods, both heterogeneous and homogeneous metal catalysts with either tritiated water or tritium gas have been used and will be illustrated through a number of specific examples in this review. Tritiated water reactions are typically run on a 0.5 Ci scale employing water at a specific activity of 900 mCi/mmol. Tritium gas reactions employ carrier free tritium and are typically run on a 0.5–1 Ci scale.

Heterogeneous metal-catalysed exchange with tritiated water

Platinum-catalysed exchange with tritiated water methodology has been extensively used to prepare a wide range of pharmaceutical structures, and we have previously reported several examples.[1–4] The Pt metal is freshly prepared by sodium borohydride reduction of an aqueous suspension of platinum oxide. It is most effective on structures containing aromatic or heteroaromatic rings devoid of the *ortho* deactivation effect as outlined by Garnett.[5] Furthermore in compounds that do not contain suitable directing groups for an *ortho*-mediated cyclometallation approach, this method can often be an attractive option. Raney Ni has on occasion been used as an alternative to Pt metal, particularly with molecules containing heteroaromatic ring systems.[1]

In the case of SCH A, the compound was treated with Pt and tritiated water as shown in Figure 1.

The reaction yielded 30 mCi of crude product at a radiochemical purity (RCP) of 53%, which was purified by HPLC to yield 15 mCi at a specific activity of 420 mCi/mmol. The ^{3}H NMR showed that the tritium was located exclusively in the monosubstituted phenyl ring in the non-sterically hindered *meta* and *para* positions. No incorporation was found in the 3,5-trifluoromethyl substituted ring, presumably due to steric hindrance.

Compound SCH B was labelled initially by Raney Ni-catalysed exchange as shown in Figure 2.

A high degree of selectivity for the position α to the pyridine nitrogen was seen, with the remaining 10% of the tritium located in the furan. The reaction was then repeated using Pt as catalyst (Figure 3).

A more general labelling distribution was observed by ^{3}H NMR data. In addition the overall specific activity and yield were more than doubled when using Pt as catalyst.

Raney Ni was also used to prepare [^{3}H]SCH C, with the initial tritiation carried out on the target molecule (Figure 4).

24 mCi of the compound was isolated from the tritiation with a RCP of 90%. After HPLC purification, a total of 18 mCi at a specific activity of 338 mCi/mmol was prepared. ^{3}H NMR analysis showed that the majority of the label was distributed in the pyrimidine ring. Subsequently a second batch was requested devoid of tritium in the pyrimidine ring. This was accomplished via Raney Ni-catalysed exchange with tritiated water on an advanced intermediate using the same labelling conditions previously described, and completion of the synthesis via the Medicinal Chemistry route as shown in Figure 5.

42 mCi of the product at 70% RCP was recovered from the tritiation. After purification on silica gel, the two remaining steps were carried out to generate a batch of 17 mCi at a specific activity of 568 mCi/mmol. ^{3}H NMR analysis showed that the tritium was broadly distributed across the pyridine and imidazopyridine rings.

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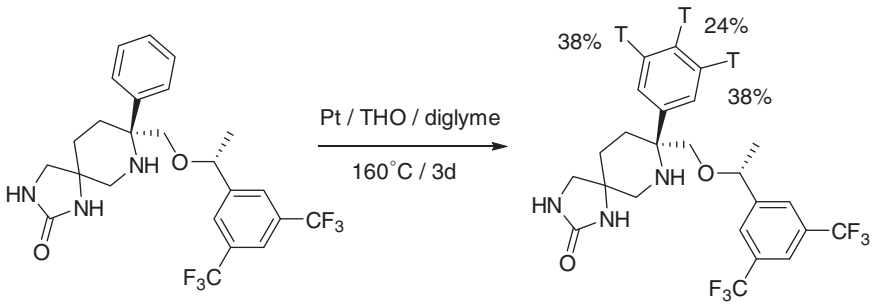

Figure 1. Synthesis of [^{3}H]SCH A. Reaction conditions: SCH A (20 mg), Pt metal (ca. 15 mg), diglyme (100 µl), THO (900 mCi/mmol, 10 µl, 0.5 Ci), 160°C, 3d.

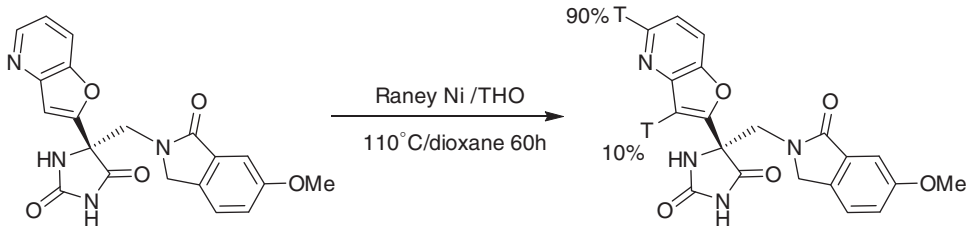

Figure 2. Synthesis of [^{3}H]SCH B by Raney Ni-catalysed exchange. Reaction conditions: SCH B (30 mg), Raney Ni (ca. 60 mg), dioxane (100 µl), THO (0.5 Ci), 110°C, 60 h.

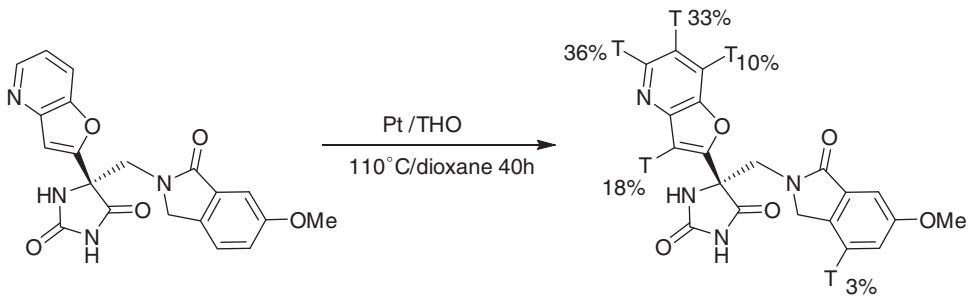

Figure 3. Synthesis of [^{3}H]SCH B by Pt-catalysed exchange. Reaction conditions: SCH B (30 mg), Pt metal (ca. 60 mg), dioxane (100 µl), THO, (0.5 Ci), 110°C, 40 h.

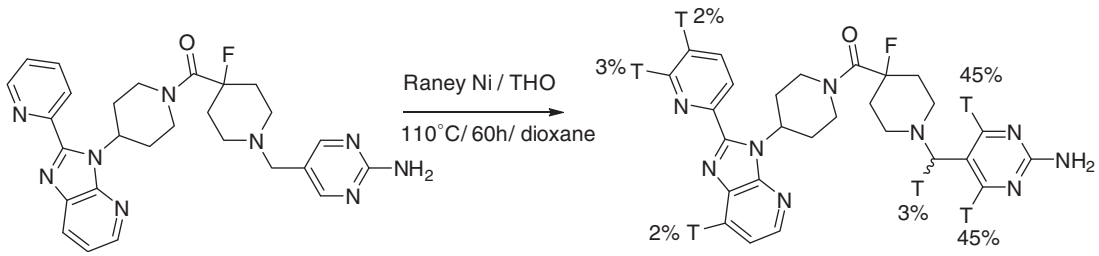

Figure 4. Synthesis of [^{3}H]SCH C by Raney Ni-catalysed exchange. Reaction conditions: SCH C (30 mg), Raney Ni (ca. 40 mg), dioxane (150 µl), THO (0.5 Ci), 110°C, 60 h.

Heterogeneous metal-catalysed exchange with tritium gas

In 2006, the Lockley group reported Rh black, Ru black and 5% Rh/C were effective catalysts in the regiospecific α-deuteration of substituted pyridines.[6] As Rh black was identified as having the most general activity, we employed the method to prepare [^{3}H]SCH D with tritium gas (Figure 6).

The reaction was run with approximately two equivalents of Rh black catalyst relative to the substrate and two equivalents of tritium gas relative to the catalyst. These conditions employed 970 mCi of tritium gas, which resulted in the generation of 58 mCi crude product at an RCP of 68%. Use of higher amounts of catalyst led to lower yields, presumably due to absorption of tritium by the catalyst. An overall yield of 30 mCi of purified product was isolated from the reaction at a specific activity of 15 Ci/mmol. ^{3}H NMR analysis indicated complete selectivity for the 6-position in the pyrazine ring. This method and the recent advance reported by Schou[7] using the catalyst in combination with Crabtree's catalyst provides another option for labelling heteroaromatic systems, and is a particularly useful alternative to the previously reviewed heterogeneous Pt metal or Raney Ni methods, where there is concern about the thermal stability of the compound.

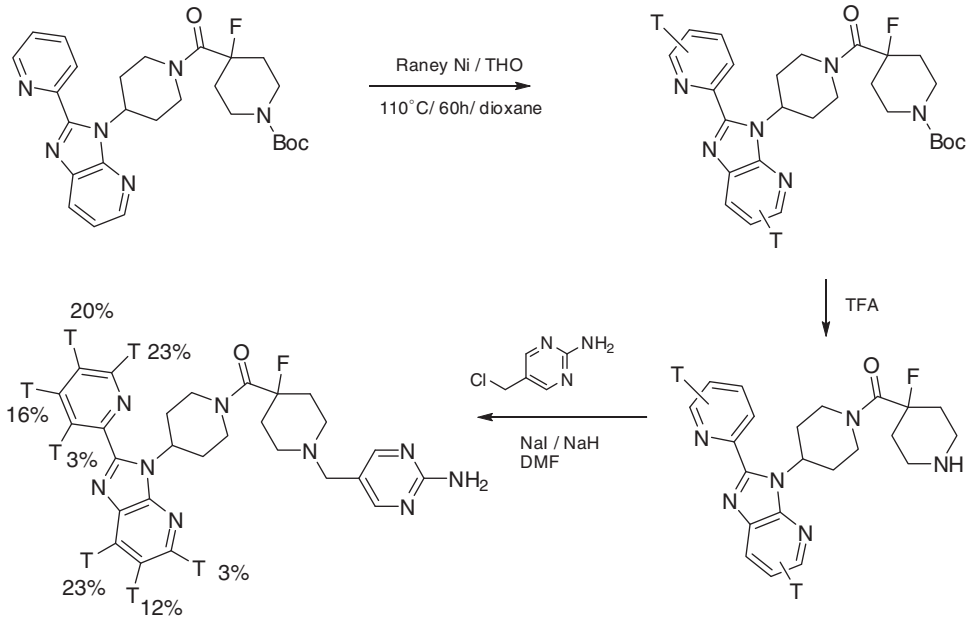

Figure 5. Synthesis of [^{3}H]SCH C by Raney Ni-catalysed exchange.

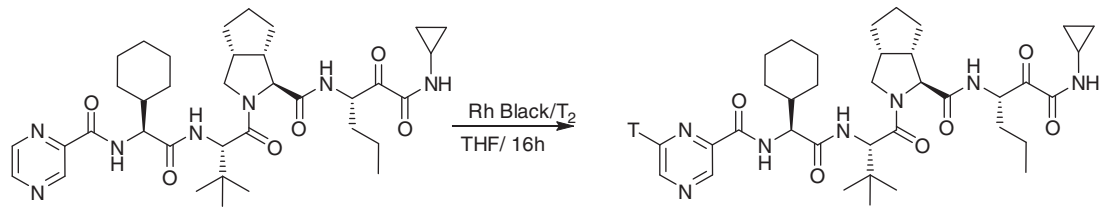

Figure 6. Synthesis of [^{3}H]SCH D by Rh black-catalysed exchange. Reaction conditions: SCH D (2.4 mg), Rh black (0.8 mg), THF (0.5 ml), T_2 (0.97 Ci), 16 h.

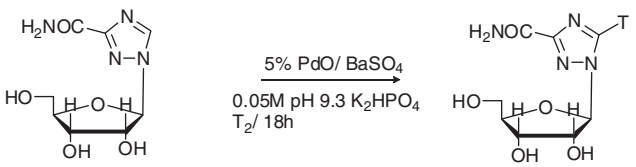

Figure 7. Synthesis of [^{3}H]ribavirin by PdO/$BaSO_4$-catalysed exchange. Reaction conditions: ribavirin (1 mg), 5% PdO/$BaSO_4$ (2 mg), 0.05 M pH 9.3 Aq. K_2HPO_4 (250 µl), T_2 (0.65 Ci), 18 h.

A more classical method was used to synthesize [^{3}H]ribavirin by tritium gas exchange over 5% PdO/$BaSO_4$ in pH 9.3 aqueous phosphate buffer (Figure 7).[8]

Under these conditions a specific activity of 24 Ci/mmol was obtained.

Homogeneous metal-catalysed exchange with tritiated water

While heterogeneous metal-catalysed exchange labelling methods have proven to be very useful in labelling a wide range of structures, most methods suffer from poor regiospecificity of labelling. Hence homogeneous catalysts, which frequently produce tritiated compounds labelled with a high degree of regiospecificity, are an attractive option. Thus, rhodium trichloride trihydrate is a well-known catalyst promoting *ortho* exchange in aromatic acids, amides, acetanilides and aralkylamines.[9] As previously reported[10] α-ethyl[^{3}H]benzylamine and *p*-chloro[^{3}H]benzylamine intermediates were prepared in the synthesis of [^{3}H]SCH E and [^{3}H]SCH F, respectively (Figure 8).

In both cases a rather modest yield of the [^{3}H]benzylamine was isolated from the tritiation; however, it was sufficiently pure after a simple acid/base extractive work-up to be incorporated in the synthesis without further purification. The development by Lockley[11] of (1,5-cyclooctadiene)(hexafluoroacetylacetonato) iridium(I) ($IrCODF_6AcAc$) as an improved catalyst for labelling aralkylamines was used in a more recent synthesis to prepare α-methyl[^{3}H]benzylamine with an approximately five-fold improvement in yield (Figure 9).

After a simple extractive workup, the α-methyl[^{3}H]benzylamine was incorporated into a multi-step synthesis which will be reported on in due course. Key to this synthesis was the careful manipulation and drying of the labelled intermediate which was accomplished by an azeotropic distillation with pentane.

$IrCODF_6AcAc$ was also used to prepare [^{3}H]SCH G utilizing the oxazole functionality as a directing group (Figure 10).[12]

32 mCi at a RCP of 20% was isolated from the reaction using 0.5 Ci of tritiated water. A second reaction on twice the scale yielded 57 mCi at 27% RCP. The combined batches were purified by chromatography on a silica gel SepPak® to provide a yield of 20 mCi, which was used in the remainder of the synthesis, which will be reported at a later date. ^{3}H NMR data confirmed the regiospecificity of tritium incorporation.

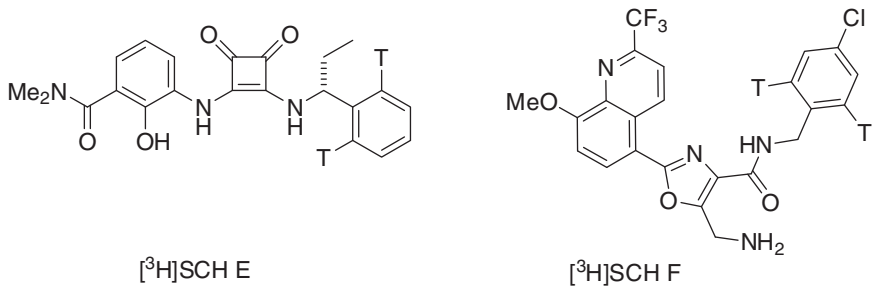

Figure 8. [^{3}H]SCH E and [^{3}H]SCH F. Labelling conditions: amine (ca. 20 mg), $RhCl_3.3H_2O$ (6 mg), DMF (100 µl), THO (0.5 Ci), 106°C, 16 h.

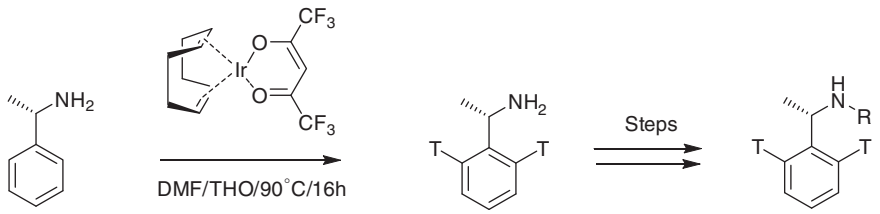

Figure 9. Synthesis of α-methyl[^{3}H]benzylamine catalysed by $IrCODF_6AcAc$. Reaction conditions: (S)-α-methylbenzylamine (30 mg), $IrCODF_6AcAc$ (7 mg), DMF (100 µl), THO (0.5 Ci), 90°C, 16 h.

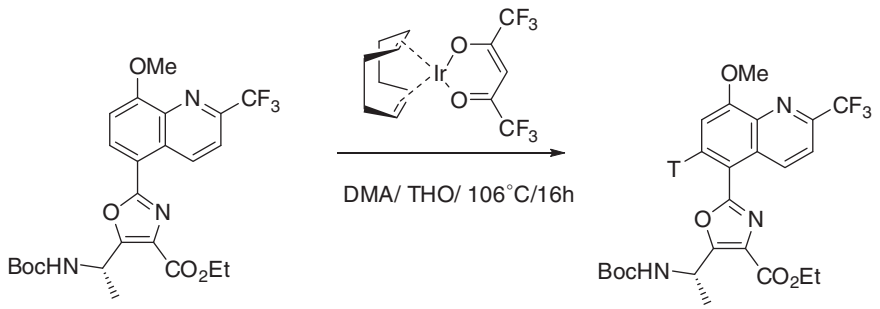

Figure 10. Synthesis of [^{3}H]SCH G intermediate catalysed by $IrCODF_6AcAc$. Reaction conditions: SCH G intermediate (19.8 mg), $IrCODF_6AcAc$ (10.9 mg), DMA (100 µl), THO (0.5 Ci), 106°C, 16 h.

In the case of SCH H, IrCODAcAc was chosen to prepare *p*-chloro[^{3}H]sulphonamide, which is not effectively labelled with rhodium trichloride trihydrate. The labelling reaction was optimized 'in house' and sent to Amersham for scale up because the number of steps in the route required that approximately 1 Ci of *p*-chloro[^{3}H]benzenesulphonamide would be needed to generate a sufficient quantity of [^{3}H]SCH H. Upon receipt of 1 Ci from Amersham, the 77% pure product was purified by HPLC and then converted to [^{3}H]SCH H as shown in Figure 11.

The key steps in the route were the conversion to the sulphonyl chloride and the Kulinkovich cyclopropanation,[13] the latter accomplished in 54% yield after HPLC purification. A total of 15 mCi of [^{3}H]SCH H was prepared.

Ir CODAcAc was also used in the preparation of [^{3}H]SCH I,[10] with the intention of labelling the molecule in the aromatic positions *ortho* to the urea and in the pyridine ring *ortho* to the amide (arrows in Figure 12).

However ^{3}H NMR analysis showed that 98.5% of the tritium was located in the urea *N*-methyl group with the remaining 1.5% in the 6-position in the pyridine ring. *N*-methyl labelling of *N*-methyl amides and amines has been previously observed with iridium (I) catalysts with tritium gas but is usually accompanied by a high degree of *ortho* exchange in these cases.[14–16] Clearly the near complete selectivity for *N*-methyl urea incorporation observed with this example is worthy of further investigation.

$Ru(Ph_3P)_3Cl_2$ has seen extensively used as a catalyst for the tritiation of piperidine and piperazine containing structures, examples of which have been previously reported.[4,10] In a more recent example, the catalyst was employed to label the intermediate of SCH J (Figure 13).

About 130 mCi of crude product at 85% RCP was isolated from the tritiation, which was purified on silica gel and coupled to the freshly prepared tricyclic chloride to give approximately a 20% yield of the desired diastereomer. A total batch of 15 mCi of [^{3}H]SCH J at a specific activity of 670 mCi/mmole was prepared.

The catalyst was also used to prepare [^{3}H]SCH K (Figure 14).

The tritiation yielded 140 mCi of crude product at 76% RCP from 0.5 Ci of water. The compound was reductively aminated with pyridazine aldehyde to generate 86 mCi after purification on a silica gel SepPak®. After completing the remaining two steps, a total of 64 mCi of [^{3}H]SCH K was generated at a specific activity of 734 mCi/mmol. ^{3}H NMR confirmed the expected regiochemistry of tritium incorporation.

Finally, the catalyst was used to prepare [^{3}H]SCH L via reaction with the pyrimidyl aminopiperidine intermediate (Figure 15).

Tritiation of the piperidinyl pyrimidinyl amine using 0.5 Ci of tritiated water yielded 117 mCi after silica gel SepPak® purification.

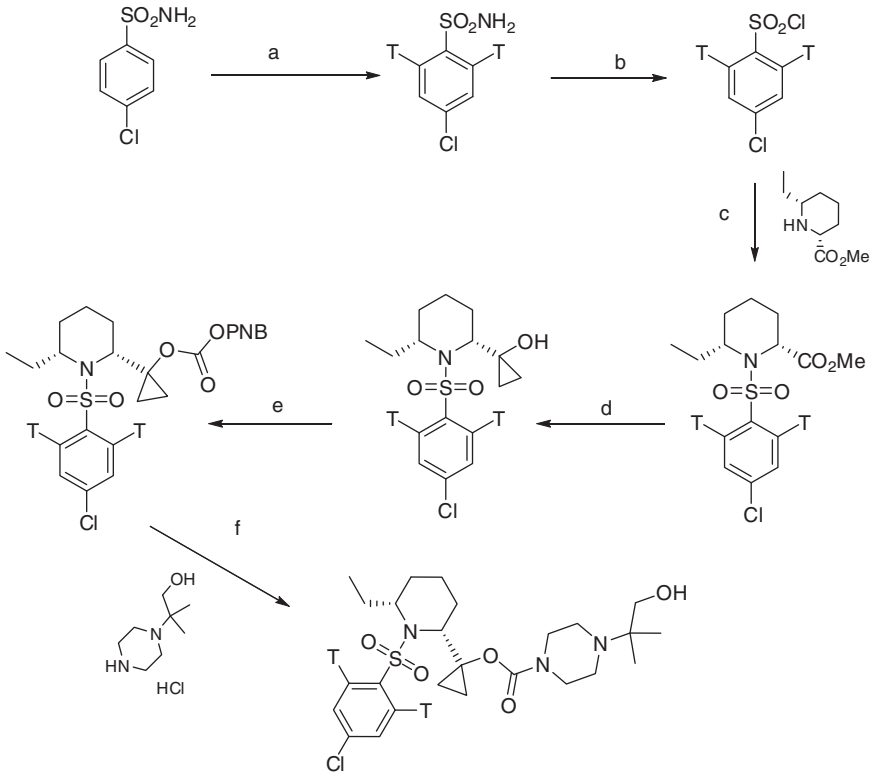

Figure 11. Synthesis of [^{3}H]SCH H via IrCODAcAc-catalysed exchange of *p*-chlorosulphonamide. Reaction Conditions: (a) IrCODAcAc, DMF, T_2O, 95°C, 16 h. (b) SO_2Cl_2, Py cat., dioxane, 90°C, 16 h. (c) Et_3N, CH_2ClCH_2Cl, 60°C, 16 h. (d) EtMgBr, $Ti(OiPr)_4$, THF, 1 h. (e) *p*-nitrophenyl chloroformate, Py, MeCN, THF, 70°C, 16 h. (f) CH_2ClCH_2Cl, Et_3N, 16 h.

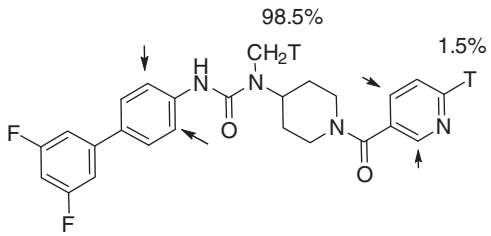

Figure 12. [^{3}H]SCH I from IrCODAcAc. Labelling conditions: SCH I (10 mg), IrCODAcAc (5 mg), THO (0.5 Ci), dioxane (100 µl), 90–95°C, 16 h.

After completion of the two remaining steps and HPLC purification, a total batch of 63 mCi at a specific activity of mCi/mmole was generated. ^{3}H NMR showed that 90% of the label was positioned as expected. The remaining small amounts of tritium found in the pyrimidine ring may have been incorporated via a reversible 1,2 reduction analogous to that suggested by Heys in studies of $Ir[H_2(acetone)_2(Ph_3P)_2]BF_4$-catalysed exchange of benzoquinoline.[17]

Homogeneous metal-catalysed exchange with tritium gas

Our initial application of Crabtree's catalyst was its use as a reduction catalyst. We were supplied an intermediate containing a cyclohexene moiety and a reduction method using Crabtree's catalyst, which had previously been run by Medicinal Chemistry using hydrogen. The reduction was then carried with tritium gas as shown in Figure 16.

^{3}H NMR analysis indicated that in addition to the expected signals in the cyclohexane ring, showing addition across the

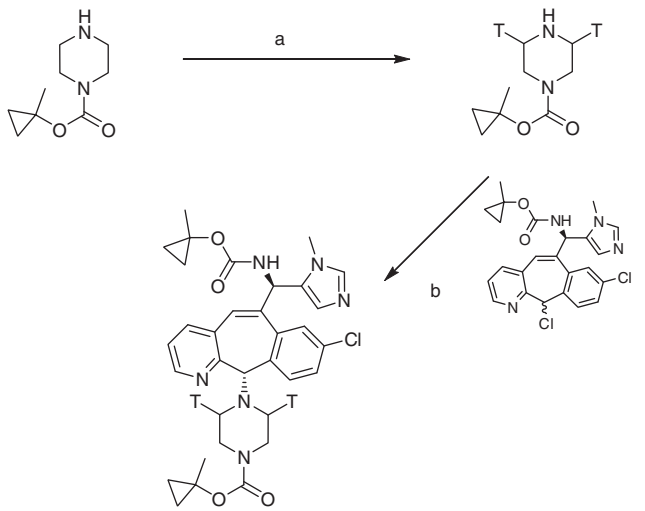

Figure 13. Synthesis of [^{3}H]SCH J with utilization of $Ru(Ph_3P)_3Cl_2$. Reaction conditions: (a) 1-methylcyclopropyl piperazine-1-carboxylate (42 mg), $Ru(Ph_3P)_3Cl_2$ (2.5 mg), dioxane (100 µl), THO (0.5 Ci), 120°C, 3 h. (b) MeCN, DIPEA, 80°C, 16 h.

1, 2-olefin and a signal in the 6-position likely caused by olefin isomerization, an additional aromatic signal equating to about 26% of the total activity was observed. It was confirmed to be located in the *ortho* position in the ring attached to the β-lactam nitrogen and thus it was concluded that the β-lactam was acting as a directing group for tritium exchange with Crabtree's catalyst. Hence, as the β-lactam is in effect a substituted acetanilide, the catalyst was next fully evaluated in a series of substituted acetanilides[18] with deuterium to determine the scope of the catalyst's activity. This was followed by tritium

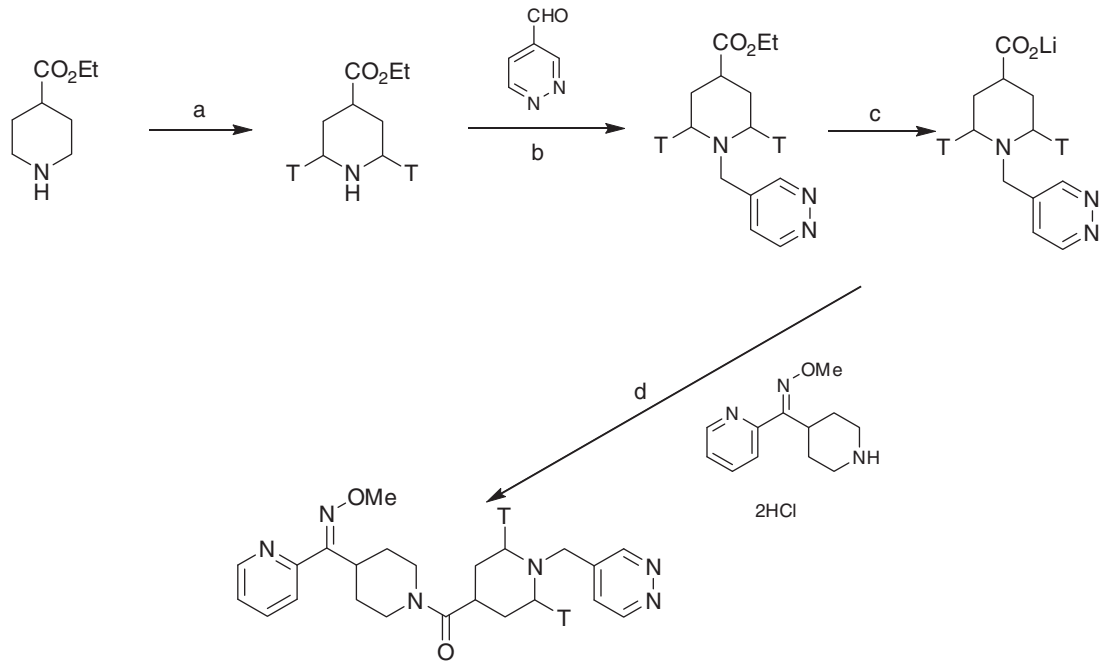

Figure 14. Synthesis of [^{3}H]SCH K with utilization of $Ru(Ph_3P)_3Cl_2$. Reaction conditions: (a) ethyl isonipecotate (30 mg), $Ru(Ph_3P)_3Cl_2$ (3 mg), dioxane (100 µl), THO (0.5 Ci), 120°C, 3 h. (b) $NaB(OAc)_3H$, CH_2Cl_2. (c) LiOH, H_2O, MeOH, THF, 16 h. (d) EDCI, HOBT, DIPEA, DMF, 72 h.

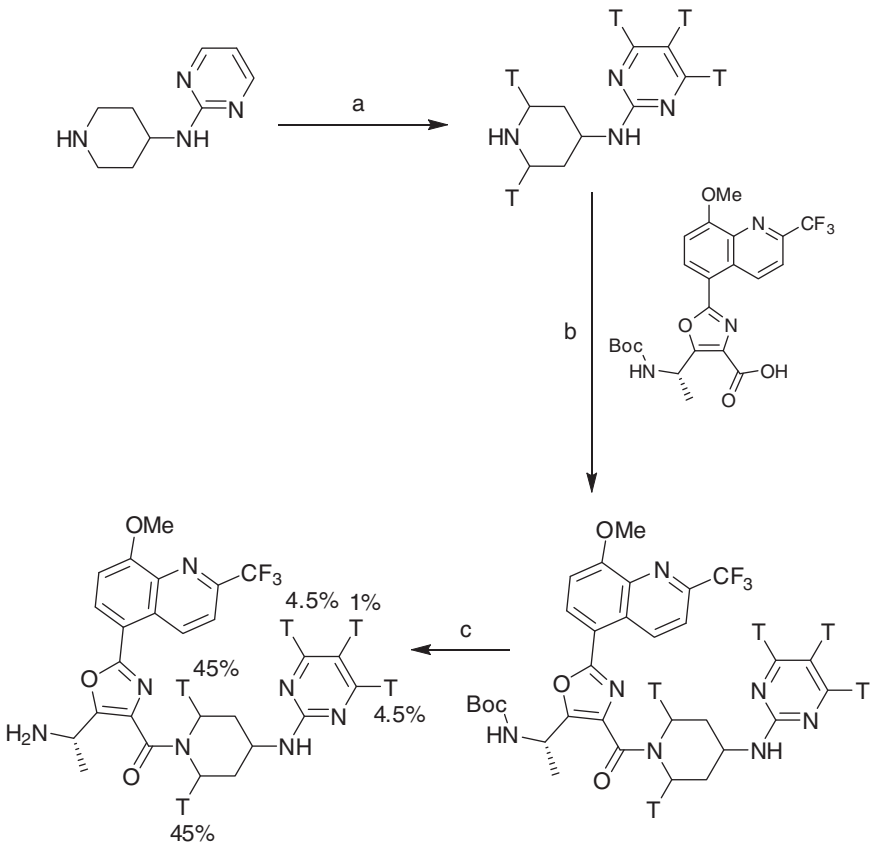

Figure 15. Synthesis of [^{3}H]-SCH L with utilization of $Ru(Ph_3P)_3Cl_2$. Reaction conditions: (a) *N*-(piperidin-4-yl)pyrimidin-2-amine (24.5 mg) $Ru(Ph_3P)_3Cl_2$ (2.4 mg), dioxane (100 µl), THO (0.5 Ci), 120°C, 3 h. (b) EDCI, HOBT, NMM, DMF, 16 h. (c) 4 M HCl in dioxane, 3 h.

exchange labelling of the β-lactam containing SCH 58235, which has been previously reported.[19]

A more recent example employed the catalyst in preparing [^{3}H]SCH N (Figure 17).

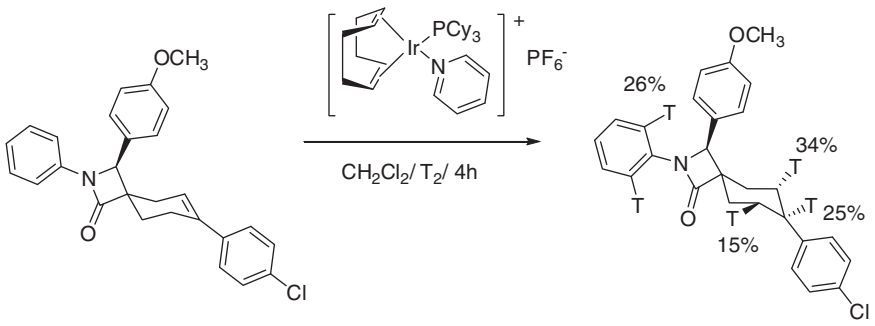

Figure 16. Preparation of [^{3}H]SCH M via tritium gas reduction with Crabtree's catalyst. Reaction conditions: SCH M (5.9 mg), Crabtree's catalyst (2 mg), methylene chloride (2 ml), T_2 (20 Ci), 4 h.

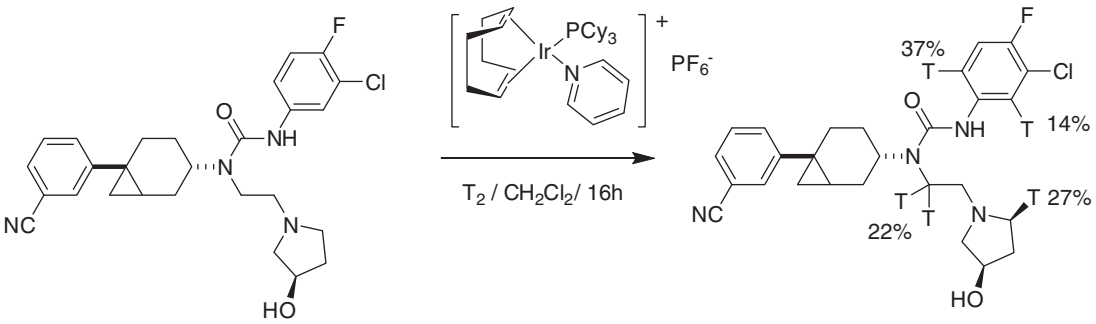

Figure 17. Synthesis of [^{3}H]SCH N via Crabtree's catalyst. Reaction conditions: SCH N (1.06 mg), Crabtree's catalyst (5.1 mg), methylene chloride (0.5 ml), T_2 (0.76 Ci), 16 h.

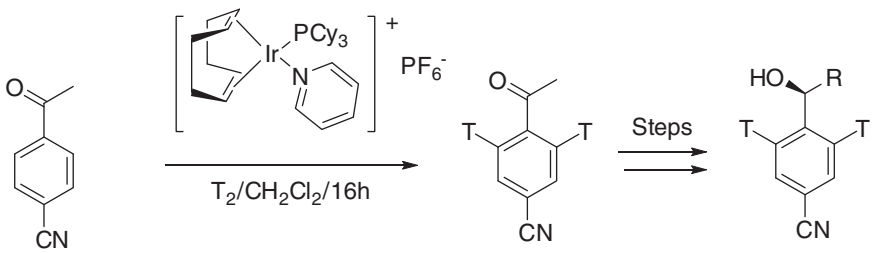

Figure 18. Synthesis of *p*-cyano[^{3}H]acetophenone via Crabtree's catalyst.

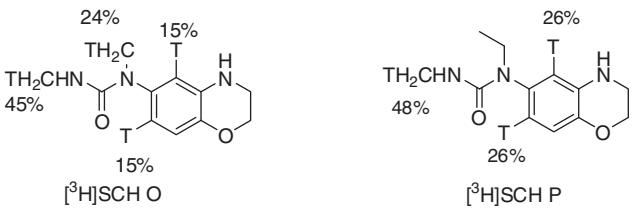

Figure 19. [^{3}H]SCH O and [^{3}H]SCH P. Labelling conditions: substrate (1 mg), Crabtree's catalyst (3.5 mg), methylene chloride (0.5 ml), T_2 (0.8 Ci), 16 h.

Owing to the presence of a nitrile, which is a catalyst poison, the reaction was run with three equivalents of catalyst relative to the substrate. A total of 109 mCi of crude product at 30% RCP product was isolated from the tritiation, which used 760 mCi of tritium gas. A 30 minute pre-reduction with deuterium gas as outlined by Heys was used in an attempt to minimize the formation of [^{3}H]cyclooctane.[15] As is typical with Crabtree reactions which are run with stoichiometric or greater amounts of catalyst, recovery of product from HPLC purification was poor, resulting in a total batch of 11 mCi @ 97.2% RCP. ^{3}H NMR

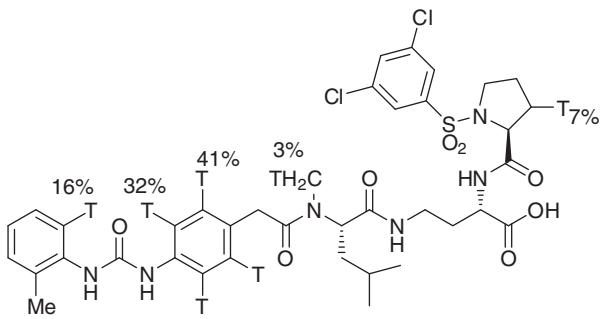

Figure 20. [^{3}H]SCH Q. Labelling conditions: SCH Q methyl ester (3.7 mg), Crabtree's catalyst (3.5 mg), methylene chloride (0.5 ml), T_2 (0.85 Ci), 16 h.

analysis showed that in addition to the expected aromatic incorporation, additional label was present in the urea ethyl substituent, and about 25% present in a single site in the pyrrolidine ring. This distribution is not unexpected as incorporation into similar sp^3 sites in *N*-methyl amides and amines has been reported by other groups, with degrees of

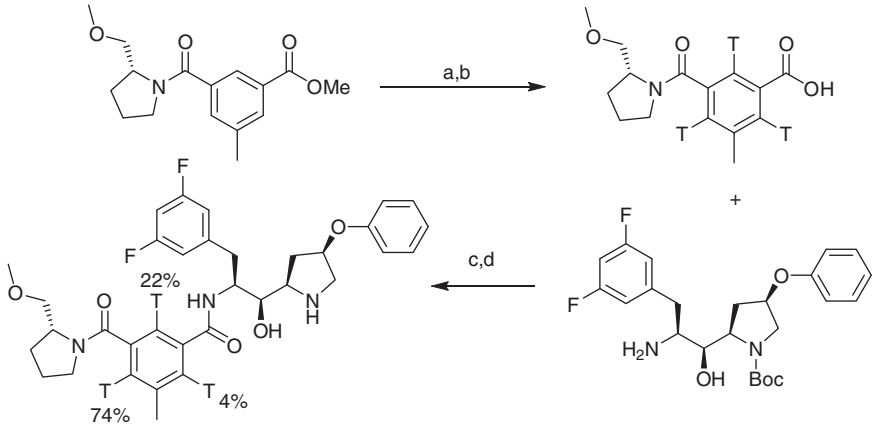

Figure 21. Synthesis of [^{3}H]SCH R with utilization of Crabtree's catalyst. Reaction conditions: (a) methyl ester (1.1 mg) Crabtree's catalyst (2.6 mg), CH_2Cl_2 (0.5 ml), T_2 (1.3 Ci), 16 h. (b) LiOH. (c) EDCI, HOBT, DIPEA, DMF. (d) 20% TFA in CH_2Cl_2.

incorporation into these positions varying extensively depending on the nature and loading of the catalyst used.[14–16]

This superstoichiometric approach was also used to prepare *p*-cyano[^{3}H]acetophenone, as an intermediate in a synthesis to be reported at a future date (Figure 18).

Using two equivalents of catalyst with 1.8 Ci of tritium gas, a total of 400 mCi of crude product at a RCP of 20% was recovered from the tritiation. Using less than one equivalent of catalyst yielded no incorporation of label.

The urea-containing structures SCH O and SCH P were also labelled using Crabtree's catalyst (Figure 19).

^{3}H NMR analysis showed an interesting selectivity difference in the tritium distribution. While the terminal methyl groups were extensively labelled in both compounds, the ethyl urea remained unlabelled in SCH O. This contrasts with the closely related SCH P, as the methyl urea was extensively labelled. Both compounds had sufficient incorporation in the *ortho* aromatic positions and proved to be adequate as tracers for *in vivo* metabolism work.

[^{3}H]SCH Q was prepared via Crabtree's catalysed exchange on the methyl ester precursor, which after purification was saponified to generate the acid (Figure 20).

The methyl ester was labelled using one equivalent of Crabtree's catalyst and 850 mCi of tritium gas, which yielded 201 mCi at a RCP of 49%. HPLC purification yielded 87 mCi, which was saponified and HPLC purified to generate a total batch of 67 mCi at a specific activity of 20.5 Ci/mmol. ^{3}H NMR analysis showed that, in addition to the urea directed tritium, the largest amount of tritium was located at positions consistent with a 6-membered cyclometallate with the carbonylmethyl functionality. The activity of carbonylmethyl as a directing group is consistent with data reported by Heys[15] on labelling polyamides with Crabtree's catalyst, and results reported by Herbert on labelling *N*, *N*-dimethylphenylacetamide with Ir (I) bidentate complexes.[20] In addition, the small amount of tritium found in the amide methyl group is not unexpected as previously discussed, and the signal from the 3-position in the pyrrolidine ring is consistent with a cyclometallate formed between the amide and the sp^3 carbon.

In a final example, Crabtree's catalyst was also used to prepare [^{3}H]SCH R via a four-step approach (Figure 21).

A modest 65 mCi yield at 72% RCP was recovered from the tritiation. After HPLC purification, the resulting intermediate was converted to a batch of 10 mCi of the final product using the Medicinal Chemistry route. The ^{3}H NMR analysis clearly showed the superiority of the dialkyl substituted amide functionality over the ester as a directing group for Crabtree's catalyst, which is consistent with the findings reported by other groups.[14]

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References

[1] D. Hesk, D. Koharski, S. Saluja, P. McNamara, C. Magatti, D. Cesarz, S. Hendershot, J. R. Jones, *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 6th International Symposium, Philadelphia 1997* (Eds.: J. R. Heys, D. G. Melillo), Wiley, Chichester, **1998**, pp. 439–443.

[2] D. Hesk, T. Duelfer, S. Hickey, D. Hochman, D. Koharski, P. McNamara, S. Saluja, *J. Label. Compd Radiopharm.* **1994**, *34*, 681–689.

[3] D. Hesk, C. Bowlen, S. Hendershot, D. Koharski, P. McNamara, D. Rettig, S. Saluja, *J. Label. Compd. Radiopharm.* **1996**, *38*, 1039–1046.

[4] D. Hesk, K. Voronin, P. McNamara, P. Royster, D. Koharski, S. Hendershot, S. Saluja, V. Truong, T. M. Chan, *J. Label. Compd. Radiopharm.* **2007**, *50*, 131–137.

[5] J. L. Garnett, M. A. Long, *Isotopes in the Physical and Biomedical Sciences*, Vol. 1, Part A (Eds.: J. R. Jones, E. Buncel), Elsevier, Amsterdam, **1987**, 86–121.

[6] E Alexakis, J. R. Jones, W. J. S. Lockley, *Tetrahedron Lett.* **2006**, *47*, 5025–5028.

[7] S. C. Schou, *J. Label. Compd. Radiopharm.* **2009**, *52*, 376–382.

[8] E. A. Evans, H. C. Shepherd, J. C. Turner, D. C. Warrell, *J. Label. Compd. Radiopharm.* **1974**, *10*, 569–587.

[9] a) W. J. S. Lockley, *Tetrahedron Lett.* **1982**, *23*, 3819–3822; b) W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1984**, *21*, 45–57; c) W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1985**, *22*, 623–630; d) D. Hesk, J. R. Jones, W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1990**, *28*, 1427–1436; e) D. J. Wilkinson, W. J. S. Lockley, *J. Label. Compd. Radiopharm.* **1985**, *22*, 883–892; f) W. J. S. Lockley, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **1984**, *21*, 363–373; g) W. J. S. Lockley, D. Hesk, J. R. Jones, *J. Pharm. Sci.* **1991**, *80*, 887–890; h) D. Hesk, J. R. Jones, W. J. S. Lockley, D. J. Wilkinson, *J. Label. Compd. Radiopharm.* **1990**, *28*, 1309–1320.

[10] D. Hesk, P. McNamara, D. Koharski, K. Voronin, V. Truong, in *Synthesis and Applications of Isotopically Labelled Compounds*,

Proceedings of the 10th International Symposium, Chicago June 14th– 18th 2009, *J. Label. Compd. Radiopharm*. **2010**, *53*, 239–243.

[11] R. N. Garman, M. J. Hickey, L. P. Kingston, B. McAuley, J. R. Jones, W. J. S. Lockley, A. N. Mather, D. J. Wilkinson, *J. Label. Compd. Radiopharm*. **2005**, *48*, 75–84.

[12] C. F. Lavey, D. Hesk, S. Borges, D. Koharski, P. McNamara, in *Synthesis and Applications of Isotopically Labelled Compounds*, *Proceedings of the 10th International Symposium, Chicago June 14th– 18th 2009*, *J. Label. Compd. Radiopharm*. **2010**, *53*, 368–371.

[13] O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* **1991**, 3, 234.

[14] W. Chen, K. T. Garnes, S. H. Levinson, D. Saunders, S. G. Senderoff, A. Y. L. Shu, A. J. Villani, J. R. Heys, *J. Label. Compd. Radiopharm*. **1997**, *39*, 291–298.

[15] A. Y. L. Shu, D. Saunders, S. H. Levinson, S. W. Landvatter, A. Mahoney, S. G. Senderoff, J. F. Mack, J. R. Heys, *J. Label. Compd. Radiopharm*. **1999**, *42*, 797–809.

[16] R. Salter, M. Chappelle, A. Morgan, Th. Moenius, P. Ackermann, M. Studer, F. Spindler, in *Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the 7th International Symposium, Dresden 2000*, (Eds.: U. Pleiss, R. Voges), Wiley, Chichester, **2001**, pp. 63–67.

[17] J. R. Heys, *Chem. Commun*. **1992**, 680–681.

[18] D. Hesk, P. R. Das, B. Evans, *J. Label. Compd. Radiopharm*. **1995**, *36*, 497–502.

[19] D. Hesk, G. Bignan, J. Lee, J, Yang, K. Voronin, C. Magatti, P. McNamara, D. Koharski, S. Hendershot, S. Saluja, S. Wang, *J. Label. Compd. Radiopharm*. **2002**, *45*, 145–155.

[20] J. M. Herbert, A. D. Kohler, A. McNeill, *J. Label. Compd. Radiopharm*. **2005**, *48*, 285–294.

