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Research Article

Radiosynthesis of [^{11}C]docetaxel

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Summary

Docetaxel (Taxotere®) is an accepted chemotherapeutic agent for the treatment of breast cancer and non-small cell lung cancers. A potential means of predicting response is measuring tumor uptake of [^{11}C]docetaxel using Positron Emission Tomography (PET). The synthetic approach to introduce the ^{11}C isotope in the 2-benzoyl moiety of docetaxel unfortunately was unsuccessful. The radiosynthesis of [^{11}C]docetaxel (**6b**, Scheme 1), with the ^{11}C isotope in the BOC moiety, was however, successful using a second synthetic approach. It started with the reaction of [^{11}C]*tert*-butanol with 1,2,2,2-tetrachloroethyl chloroformate to give [^{11}C]*tert*-butyl-l,2,2,2-tetrachloroethyl carbonate in a good overall yield (62 $\pm$ 9%). In the final step, the [^{11}C]*tert*-butoxycarbonylation of the free amine of docetaxel gave [^{11}C]docetaxel **6b** in a satisfactory decay corrected yield of 10 $\pm$ 1% (from [^{11}C]CO_2). Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: docetaxel; [^{11}C]*tert*-butanol ([2-^{11}C]2-methylpropan-2-ol); *tert*-butoxycarbonylation; [^{11}C]docetaxel; positron emission tomography (PET)

Introduction

Over the past several decades, the taxane class of antimicrotubule anticancer agents is perhaps the most important class of new agents.[1,2] The direct target

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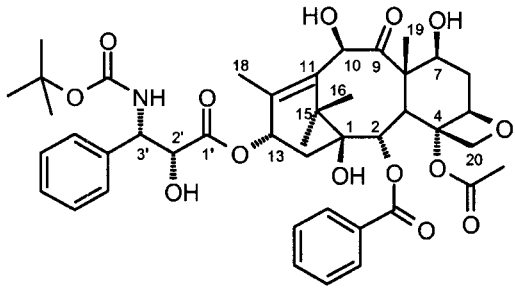


Figure 1. Docetaxel (Taxotere®), with trivial numbering of the molecule (IUPAC†)

of docetaxel (Taxotere®, Figure 1), one of the major taxanes, is the heterodimeric protein tubulin[3,4] that once polymerized ultimately leads to mitotic arrest[5,6] and thus inhibits cell proliferation. In the case of breast cancer, reported response rates after first-line docetaxel therapy in metastatic disease[7–9] or after second-line therapy[10,11] are in the order of 52–68% and 50–58%, respectively. Obviously, methods that are able to predict the response to docetaxel treatment would be very useful, as non-responders could be offered alternative therapies at a much earlier stage without suffering side effects from (ineffective) docetaxel administration. A potential means of predicting response could be measuring tumor uptake of docetaxel, labeled with a positron emitter, using Positron Emission Tomography (PET).

The present study was undertaken to label docetaxel (chemical nomenclature†) with the positron emitter carbon-11 ($t_{1/2} = 20.33$ min). There appeared to be two obvious synthetic strategies for the radiosynthesis of [^{11}C]docetaxel and both were attempted. The first synthetic approach (Figure 2(I)) was to introduce the ^{11}C isotope in the 2-benzoyl moiety of docetaxel (**6a**)† with [^{11}C]benzoyl chloride, which has been used for the synthesis of paclitaxel (Taxol®) as well.[12] The second approach was to introduce the ^{11}C isotope in the side chain (**6b**, Figure 2(II))† by a [^{11}C]*tert*-butoxycarbonylation of the free amine of docetaxel.

†(i) The chemical nomenclature for docetaxel (according to IUPAC recommendations) is: 15-[((1*R*,2*S*)-l-hydroxy-2-((1,1,-dimethylethyloxy)carbonylamino)-2-phenylethyl)carbonyloxy]-(1*S*,2*S*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-1,9,12-trihydroxy-10,14,17,17-tetramethyl-4-(methylcarbonyloxy)-11-oxo-2-(phenylcarbonyloxy)-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-ene.

(ii) Compound **6a**: 15-[((1*R*,2*S*)-l-hydroxy-2-((1,1-dimethylethyloxy)carbonylamino)-2-phenylethyl)carbonyloxy]-(1*S*,2*S*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-l,9,12-trihydroxy-10,14,17,17-tetramethyl-4-(methylcarbonyloxy)-11-oxo-2-(phenyl-[**^{11}C**]carbonyloxy)-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-ene.

(iii) Compound **6b**: 15-[((1*R*,2*S*)-l-hydroxy-2-((1,l-dimethyl-l-[**^{11}C**]ethyloxy)carbonylamino)-2-phenylethyl)-carbonyloxy]-(1*S*,2*S*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-l,9,12-trihydroxy-10,14,17,17-tetramethyl-4-(methylcarbonyloxy)-11-oxo-2-(phenylcarbonyloxy)-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-ene.

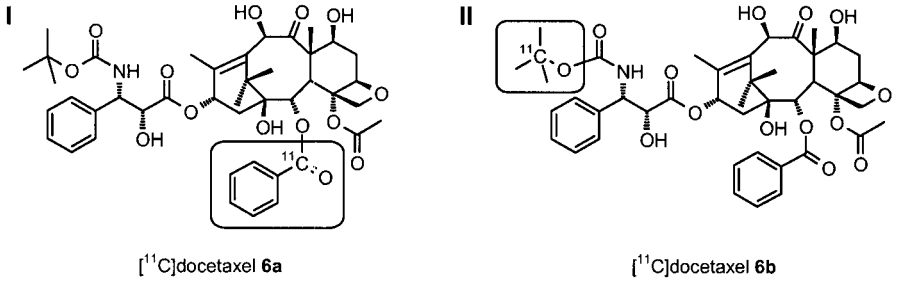


Figure 2. Different possible labeling positions of docetaxel

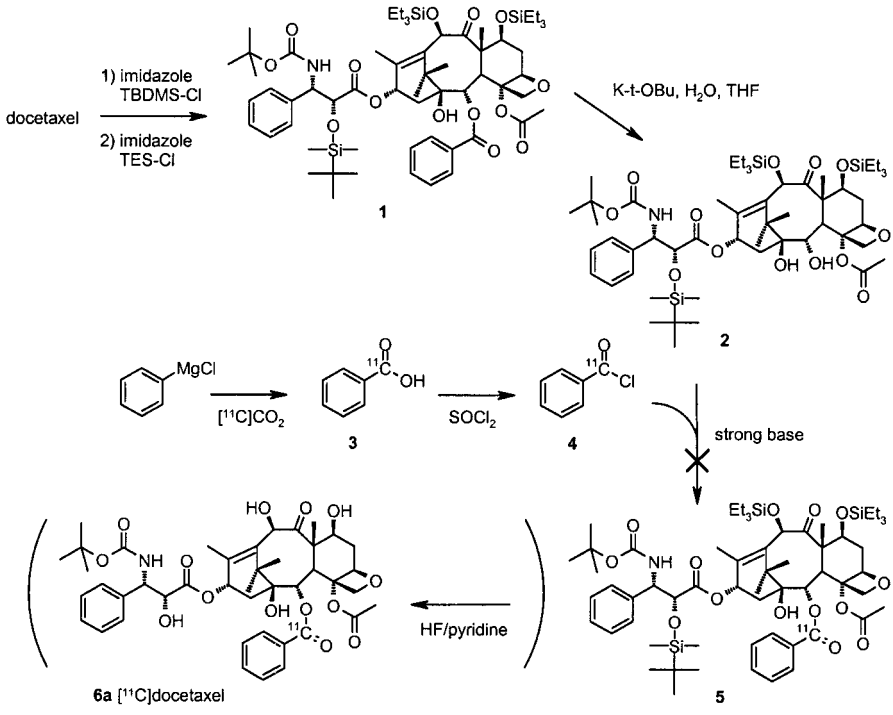
Results and discussion

Synthetic approach I: [^{11}C]docetaxel (6a)[†]

The description of several methods for the selective hydrolysis of the 2-benzoate group of paclitaxel (Taxol®) or docetaxel,[13–18] along with the expected easy access of [^{11}C]benzoic acid or [^{11}C]benzoylchloride for reacylation prompted the selection of this synthetic approach for the synthesis of [^{11}C]docetaxel **6a** (Scheme 1).

First, the most appropriate protecting groups for the 2′-,7- and 10- hydroxyl groups of docetaxel were selected. The *tert*-butyl carbamate moiety of docetaxel (side chain) was anticipated to be unstable under acidic hydrolysis and deprotection reaction conditions, so a fast and quantitative removal of the protection groups under basic conditions was a necessity. Using published methods,[14,16,18,19] the 2′-hydroxyl was protected with a *tert*-butyldimethylsilyl protecting group and both the 7- and 10-hydroxyls with triethylsilyl protecting groups in an average overall yield of $86 \pm 4\%$. The bulkiness of the former protecting group was shown to be essential for the prevention of cleavage of the entire C-13 side chain.[13,16] Next, the hydrolysis of the 2-benzoate ester of **1** was carried out. Compound **2** was obtained in a yield of about 57%, using a selective C-2 deacylation method[15,16] under 'standard' basic conditions (2 equiv. potassium *tert*-butoxide in THF, -30–0°C within ~ 3 h).

After the deprotection of **1** (Scheme 1) was achieved in an unoptimized yield of 65%, using HF/pyridine[18–20] to reassure that **5** could be deprotected similarly, a successful synthesis route for [^{11}C]benzoylchloride (**4**) was set up with some minor modifications compared to reported methods.[12,21,22] The radiochemical esterification of **4** with **2**, involving a large excess of precursor (**2**) compared to **4**, however, was unsuccessful after numerous efforts, although success of this type of reaction has been shown under standard (organic) conditions.[13,14,17] Analysis of the reaction mixtures indicated that the anion of **2** was not properly formed – recovery of unreacted [^{11}C]benzoylchloride (**4**) – with the use of small amounts of base (1.5 or 5 equiv of either Et_3N, BuLi,



Scheme 1. Synthetic approach I: [^{11}C]docetaxel 6a

LDA, $[Me_3Si]_2NLi$, DBU, phosphazene base P2-t-Bu[‡] or phosphazene base P4-t-Bu[§]) and in some cases also with larger amounts of base (10 to 100 equiv of BuLi, P2-t-Bu or P4-t-Bu). The use of large amounts of the bases Et_3N and $[Me_3Si]_2NLi$ lead to the decomposition of **4** (no conversion to the acid, however). The amounts of the moisture-sensitive bases used were very small (μl range) and although every attempt was made to exclude moisture from the system (vials, tubing, syringes, chemicals and solvents), it was unclear how much base remained intact during handling. And although the non-nucleophilic strong bases P2-t-Bu and P4-t-Bu (with pKa values of 33 and 42, respectively) are not sensitive to moisture, they probably were too bulky to reach the sterically hindered 2-hydroxyl group of **2**.

Synthetic approach II: [^{11}C]docetaxel (6b)

The side chain of docetaxel was explored as an alternative for the introduction of the ^{11}C isotope. This could be achieved at either the carbonyl or the *t*-butyl function of the BOC moiety (Figure 2(II)).[†] The former position involves a

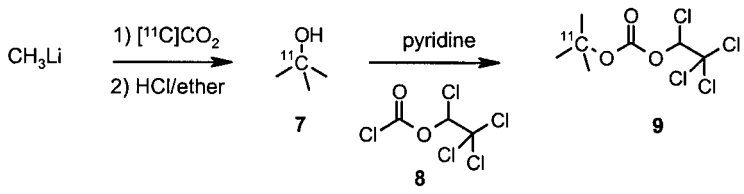
[‡] $C_{14}H_{39}N_7P_2$, Mw 367.46. For the structure see Fluka catolog.
[§] $C_{22}H_{63}N_{13}P_4$, Mw 633.73. For the structure see Fluka catolog.

reaction of the primary amine of docetaxel (**10**) with, e.g. [^{11}C]phosgene[23,24] theoretically yielding the corresponding [^{11}C]isocyanate, which in turn could react with *tert*-butanol to form [^{11}C]docetaxel. However, it is known that the synthesis of [^{11}C]phosgene is tedious and that it has been obtained in low radiochemical yields.[25] An alternative introduction of the ^{11}C isotope in the carbonyl position theoretically could be the synthesis of a [^{11}C]carbamate ester[26] of **10**, which, in principle, could be thermolyzed to yield the corresponding [^{11}C]isocyanate as well.[27,28] The radiosynthesis of the preceding [^{11}C]haloalkyl- or aryl chloroformate (RCHClO^{11}CO$_2$Cl),[29] with the ^{11}C isotope in the carbonyl function, would require the use of either [^{11}C]phosgene again or an alternative with the consequence that the ^{11}C isotope has to be introduced in an (too) early stage of the synthesis route (time limit).

We perceived, however, that these haloalkyl- or aryl chloroformates could alternatively be used to introduce the ^{11}C isotope at the *t*-butyl function of the BOC moiety. The synthetic potential of haloalkyl- or aryl chloroformates via their corresponding chloroalkyl *tert*-butyl carbonates (RCHClO-CO$_2$C(CH$_3$)$_3$),[26,30] has not been explored in radiochemistry yet, and thus a method was developed here that used these carbonates for the synthesis of [^{11}C]docetaxel. In short, this method first involved the synthesis of [^{11}C]*tert*-butanol ([2-^{11}C]2-methylpropan-2-ol, **7**), which subsequently reacted with a haloalkyl- or aryl chloroformate to yield its corresponding [^{11}C]chloroalkyl *tert*-butyl carbonate. Reaction of the [^{11}C]chloroalkyl *tert*-butyl carbonate with the primary amine of docetaxel (**10**) then yielded the desired [^{11}C]docetaxel (**6b**), as discussed below.

[^{11}C]*tert*-Butanol (and also [1-^{11}C]acetate) has been described as a side product in the synthesis of [2-^{11}C]acetone.[31–33] The hypothesis that the formation of tertiary alcohols (**7**) from [^{11}C]CO$_2$ is a kinetically controlled reaction of still unhydrolyzed organolithium reagent with newly formed ketone ([2-^{11}C]acetone) during the hydrolysis step, was consistent with the observation that the quantity of **7** could be controlled by changing the amount of methyl lithium (MeLi).[33] The results of the present study showed that the formation of **7** compared to [2-^{11}C]acetone indeed was increased by using high(er) amounts of MeLi and omitting the destruction of its excess before hydrolysis of lithium diolate. Consequently, reaction of [^{11}C]CO$_2$ with 400 µl of MeLi (1.6 M solution in ether, 640 µmol) at 15°C gave **7** in a decay corrected overall yield of 85 ± 3% (n = 10, Scheme 2). Subsequent quenching of the excess of MeLi, after the formation of **7**, with 350 µl of 2 M HCl/ether (700 µmol) gave the best results with the distillation of **7**.

The subsequent selection of an appropriate haloalkyl- or aryl chloroformate to react with **7** was mainly based on the stability and (expected) reactivity of its corresponding [^{11}C]chloroalkyl *tert*-butyl carbonate. Two candidates were 1-chloroethyl *tert*-butyl carbonate, which is a stable compound that can easily

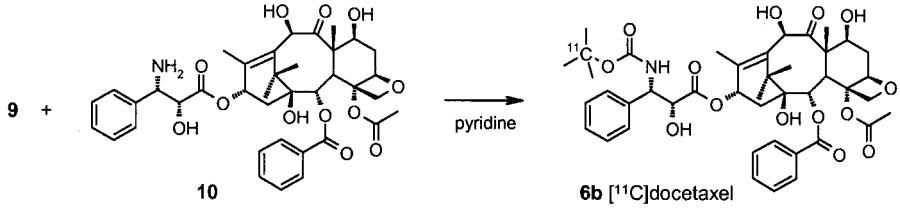


Scheme 2. Synthesis of [^{11}C]*tert*-butyl-1,2,2,2-tetrachloroethyl carbonate (9)

be distilled without significant decomposition, and 1,2,2,2-tetrachloroethyl *tert*-butyl carbonate, which is a crystalline compound that is stable for months at room temperature.[26,30] The increased electrophilicity of the carbonyl (higher reactivity) of the latter compared to 1-chloroethyl *tert*-butyl carbonate has been shown to lead to almost quantitative yields of carbamates starting from several amines.[26]

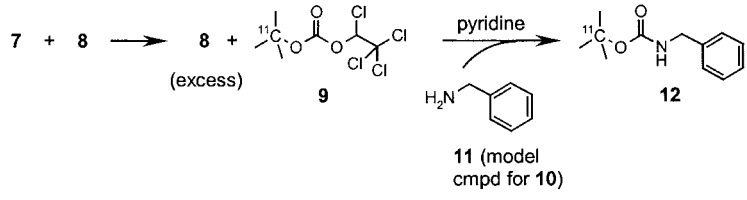
While the cold reaction of 1,2,2,2-tetrachloroethyl chloroformate (**8**) with *tert*-butanol proceeded quantitatively (98%), it was less straightforward to obtain **9** in high yields radiochemically (Scheme 2). In initial experiments, **7** was distilled first and then the solution was neutralized with pyridine in the second reaction vial. However, neutralization in the first reaction vial prior to distillation appeared more convenient, and in this way it was also possible to have **8** present in the second vial (in DCM, 0–5°C) during the distillation. Subsequently, pyridine (1 equiv) was added as a base in the second vial and the solution was kept at 45°C (3 min) to form **9** in a yield of 81 ± 11% ($n = 10$, from **7**). The use of an aqueous medium for this reaction in combination with K_2CO_3 as a base, so as to prevent the possible formation of side products (e.g. the corresponding aldehyde[26]), did not improve the yield of this reaction further.

The reaction conditions for the next reaction (**9** + **10**, Scheme 3) were explored with a model compound, instead of the primary amine of docetaxel (**10**), in order to save on the expensive precursor. Benzylamine (**11**, Table 1) was selected as the model compound to explore the optimal conditions and minimize the amount of **11** needed for the reaction with **9**. Compound **11** was added to the crude mixture of **9**, which still contained excess of **8**. This excess appeared to complicate the reaction of **11** with **9**. It seems logical that **11** will react with the excess of **8** first, and thus relatively large amounts of **11** had to be used (up to 3 mmol) for the synthesis of **12**. Entries 2 and 3 (Table 1) show that use of only 2 equivalents of **11** reduced the yield of **12** from 97% to 25%. Addition of pyridine improved the reaction significantly (entries 4 and 5), up to a yield of about 90%. A further reduction of the amount of **11** (1 equivalent) deteriorated the yield, although this was somewhat compensated by using a higher temperature. As the amount of **11** could not be reduced



Scheme 3. Synthetic approach II: [^{11}C]docetaxel 6b

Table 1. Model reaction of a primary amine with 9



Entry	8 (μmol)	9 SPE[a]	11 (μmol)	eq[b]	py μl	Temp (°C)	min	Yield 12 (%[c])	n
1	170	No	2748	(16)	–	65	(5)	98 ± 2	2
2	170	No	824	(5)	–	65	(5)	97 ± 5	2
3	170	No	320	(2)	–	65	(5)	25 ± 2	2
4	170	No	320	(2)	50	65	(4)	83 ± 15	2
5	170	No	320	(2)	150	65	(4)	91	1
6	170	No	165	(1)	150	70	(4)	25	1
7	170	No	165	(1)	150	100	(4)	64 ± 15[d]	5
8	130	No	137	(1)	150	100	(5)	4 ± 5[e]	2
9	100	No	100	(1)	150	100	(4)	–	4
10	170	No	82	(0.5)	150	110	(4)	43 ± 3	2
11	170	Yes	458	(2.7)	150	95	(3)	99 ± 0	3
12	180	Yes	137	(0.75)	150	95	(3)	96	1
13	180	Yes	90	(0.5)	150	95	(3)	87 ± 15	4
14	180	Yes	55	(0.3)	150	95	(3)	97	1
15	180	Yes	45	(0.25)	150	95	(3)	94 ± 1	2
16	180	Yes	27	(0.15)	150	95	(3)	92	1
17	180	Yes	18	(0.10)	150	95	(3)	14 ± 12	3

[a] Solid phase extraction (SPE) purification of **9** (Sep-Pak tC18 Plus).
[b] Equivalents of **11** compared to **8**.
[c] Calculated starting from **9** (vial **2**).
[d] Also tried in 150 μl Et_3N instead of pyridine or pyridine in combination with either 80 μmol phenylpiperazine or 2,2,4,4 tetramethylpiperidine, without improved results.
[e] **9** was not (properly) formed.

further, the next optimization step was to use less 1,2,2,2-tetrachloroethyl chloroformate (**8**) in the prior reaction. From entries 8 and 9 it is clear, however, that at least 170 μmol of **8** was needed for a proper synthesis of **9** (and thus for the synthesis of **12**) and that it was not possible to further reduce the excess of **8**. A solution to this problem was found in a solid-phase

Table 2. Optimizing reaction conditions for the synthesis of 6b (Scheme 3)

Entry	**10**[a] (μmol)	eq[b]	Temp (°C) min	Yield **6b** (%[c])	Overall yield **6b** (%[d])	*n*	Remarks
1	48	(0.27)	80 (3)	2	0.6	1	No reaction
2	55	(0.30)	50 (3)	4	2	1	No reaction
3	105	(0.59)	70 (3)	5 ± 2	2 ± 2	2	Decomposition
4	105	(0.59)	45 (6)	19 ± 3	10 ± 1	5	

[a] Mixtures containing **9** were purified on Sep-Pak tC18 Plus prior to reaction with **10**.
[b] Calculated starting from **9** (vial ***2***).
[c] Decay corrected from **9** (vial **2**).
[d] Decay corrected from [^{11}C]CO_2.

extraction of the crude mixture containing **9** and **8**, prior to the reaction with **11**. The mixture was diluted with water (hydrolysis of the excess of **8**) and loaded onto a Sep-Pak tC18 Plus. Subsequently, **9** was eluted with THF and collected in a vial for the reaction with **11**. With this method **9** could be synthesized in high yields, and compound **12** could be obtained in good yields as well, with a reduced amount of **11** (0.15 equivalents, entries 7,11–17).

These optimized conditions (Table 1, entry 16) were then used for the reaction with the primary amine of docetaxel (**10**) and **9**. Neither 0.27 equiv (48 μmol, 35 mg) nor 0.30 equiv (55 μmol, 40 mg) of **10**, however, yielded any product **6b** (entries 1 and 2, Table 2) despite the proper formation of **9**. The required amount of **10** appeared to be 0.59 equiv (105 μmol, entry 4). Furthermore, at high temperatures (70°C, entry 3) decomposition of the starting material (**9**) occurred. HPLC analysis showed that prolonged reaction times (longer than 6 min) had no beneficial effect on the yield of **6b** (due to decay). Finally, using 0.59 equiv of **10** (105 μmol, 75 mg) at a temperature of 45°C for 6 min (entry 4) gave optimal decay corrected overall yields of **6b** (10 ± 1%).

Experimental

Materials and methods

Docetaxel was a gift from Aventis Pharma B.V. (Hoevelaken, the Netherlands). Unless otherwise stated, all other chemical reagents were purchased from Aldrich (Aldrich Chemie, Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands). Solvents were purified and dried by standard procedures before use. Thin-layer chromatography (TLC) was carried out using aluminum sheets ($20 \times 20\,cm^2$) with silica gel F_{254} from Merck. Spots were visualized under UV (254 nm). For monitoring radiochemical reactions, TLC plates were scanned using a Molecular Dynamics Storm 820 (Storm scanner control version 5.01) phosphorimager and quantified using the software package ImageQuant

(v5.2). Preparative column chromatography was performed on silica gel (230–400 mesh ASTM). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-200 or an MSL 400 spectrometer. Chemical shifts (δ) were determined relative to the solvent and converted to the tetramethylsilane scale using δ = 3.35 ppm for CD_3OD and 7.26 ppm for $CDCl_3$. The assignment was confirmed using ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY NMR spectra (for numbering see Figure 1). [^{11}C]Carbon dioxide was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using an IBA 18/9 cyclon.[31] Abbreviations: tetrahydrofuran (THF), pyridine (py), dichloromethane (DCM), ethyl acetate (EtOAc), *N*,*N*-dimethylformamide (DMF), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), lithium diisopropylamide (LDA) and methyl lithium (MeLi).

Synthethic approach I: [^{11}C]docetaxel (6a)

2′-(tert-butyldimethylsilyl)-docetaxel. Docetaxel (55 mg, 68.2 μmol) was dissolved in DMF (600 μl). To the mixture were added imidazole (23 mg, 0.34 mmol, 5 eq.) and *tert*-butyldimethylsilylchloride (51 mg, 0.34 mmol, 5 eq.) and the solution was stirred at 60°C for 2 h. After cooling down, again 5 equivalents of both imidazole and *tert*-butyldiethylsilylchloride were added. The mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and extracted with water (2 × 30 ml) and brine (1 × 30 ml). The organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/hexane = 1/2). Yield 62 mg (66.8 μmol, 98%), R_f 0.87 (EtOAc); ^{1}H NMR (200 MHz, $CDCI_3$) δ 8.05 (d, 2 H, J = 7.02 Hz, $benzoyl_{ortho}$), 7.53 (t, 2 H, J = 7.11 Hz, $benzoyl_{para}$), 7.43 (q, 2 H, J = 7.61 Hz, $benzoyl_{meta}$), 7.38–7.19 (m, 5 H, phenyl), 6.26 (t, 1 H, J = 8.6 Hz, H-13), 5.63 (d, lH, J = 7.08 Hz, H-2), 5.47 (d, 1 H, J = 9.51 Hz, H-3′), 5.20 (s, 1 H, H-10), 4.92 (d, 1 H, J = 7.88 Hz, H-5), 4.46 (m, 1 H, H-2′), 4.30–4.18 (m, 3 H, H-7, H-20), 3.88 (d, 1 H, J = 7.07 Hz, H-3), 2.49 (s, 3 H, $COCH_3$), 2.48–2.10 (m, 3 H, 1 × H-6, H-14), 1.85 (s, 4 H, 1 × H-6, H-18), 1.70 (s, 3 H, H-19), 1.24 (s, 9 H, $OC(CH_3)_3$), 1.19 (s, 3 H, H-l6), 1.15 (s, 3 H, H-l7), 0.68 (s, 9 H, $SiC(CH_3)_3$), −0.19 (s, 3 H, $SiCH_3$), −0.37 (s, 3 H, $SiCH_3$) ppm.

2′-(tert-butyldimethylsilyl)-7,10-di-(triethylsilyl)-docetaxel (1). 2′-(*tert*-butyldimethylsilyl)-docetaxel (62 mg, 66.8 μmol) was dissolved in DMF (500 μl). To the mixture were added imidazole (50 mg, 0.74 mmol) and triethylsilylchloride (105 μ1, 0.63 mmol) and the solution was stirred overnight at room temperature. The mixture was diluted with EtOAc and extracted with water (2 × 30 ml) and brine (1 × 30 ml). The organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/hexane = 1/4). Yield 65 mg (56.5 μmol, 83%), R_f 0.42 (EtOAc/hexane = 1/4); ^{1}H NMR (400 MHz, $CDC1_3$) δ 8.04 (d, 2 H, J = 7.00 Hz, $benzoyl_{ortho}$), 7.52 (t, 2 H, J = 7.10 Hz, $benzoyl_{para}$), 7.38 (q, 2 H, J = 6.89 Hz, $benzoyl_{meta}$), 7.31–7.20 (m,

5 H, phenyl), 6.18 (t, 1 H, $J = 8.6$ Hz, H-13), 5.61 (d, 1 H, $J = 6.99$ Hz, H-2), 5.35–5.26 (m, 1 H, H-3′), 5.10 (s, 1 H, H-10), 4.87 (d, 1 H, $J = 8.21$ Hz, H-5), 4.46 (m, 1 H, H-2′), 4.33 (m, 1 H, H-7), 4.18 (q, 2 H, $J = 16.34$ Hz, H-20), 3.81 (d, 1 H, $J = 6.97$ Hz, H-3), 2.49 (s, 3 H, $COCH_3$), 2.48–1.85 (m, 3 H, 1 × H-6, H-14), 1.78 (s, 4 H, 1 × H-6, H-18), 1.61 (s, 3 H, H-19), 1.26 (s, 9 H, $OC(CH_3)_3$), 1.16 (s, 3 H, H-16), 0.90 (t, 12 H, $J = 8.05$ Hz, H-17, $SiCH_2CH_3$), 0.68 (s, 9 H, $SiC(CH_3)_3$), 0.52 (q, 12 H, = 8.01 Hz, $SiCH_2CH_3$), −0.19 (s, 3 H, $SiCH_3$), −0.38 (s, 3 H, $SiCH_3$) ppm; ^{13}C NMR (100-MHz, $CDC1_3$) δ 200.87 (C-9), 171.38 (C-1′), 170.20 ($COCH_3$), 167.09 (COC_6H_5), 155.13 (NHCO), 139.41 (phenyl), 138.53 (C-12), 135.83 (C-11), 133.52 ($benzoyl_{para}$), 130.18 ($benzoyl_{ortho}$), 129.29 (benzoyl), 128.66 ($benzoyl_{meta}$), 128.53 ($phenyl_{ortho}$), 127.64 ($phenyl_{para}$), 126.42 ($phenyl_{meta}$), 84.28 (C-5), 81.00 (C-4), 79.89 ($OC(CH_3)_3$), 79.13 (C-1), 76.58 (C-20), 75.70 (C-2′), 75.11 (C-2), 74.01 (C-10), 72.79 (C-7), 71.34 (C-13), 57.73 (C-8), 56.21 (C-3′), 46.45 (C-3), 43.26 (C-15), 37.23 (C-6), 35.75 (C-14), 28.13 ($OC(CH_3)_3$), 26.64 (C-16), 25.45 ($SiC(CH_3)_3$), 22.97 ($COCH_3$), 21.08 (C-17), 18.16 ($SiC(CH_3)_3$), 14.20 (C-18), 10.14 (C-19), 6.73, 6.47 ($SiCH_2CH_3$), 5.17, 4.27 ($SiCH_2CH_3$), −5.39, −5.97 ($SiCH_3$) ppm.

2′-(tert-butyldimethylsilyl)-2-debenzoyl-7,10-di-(triethylsilyl)-docetaxel (2). 1 (65 mg, 57.4 μmol) was dissolved in THF (1 ml). The mixture was cooled (ice/salt bath) and K-*t*-OBu (13 mg, 115 μmol, 2 eq.) and H_2O (1.2 μl, 1.2 eq.) were added. The mixture was stirred at −30°C (cold room) for 1 h. Then it was allowed to reach 0°C in 3.5 h, and was stirred at 0°C for 0.5 h. The mixture was quenched with a saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc (2 × 50 ml) and the combined organic layers were washed with H_2O (2 × 50 ml) and brine (1 × 75 ml), dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (EtOAc/hexane = 1/2). Yield 34.2 mg (32.7 μmol, 57%), R_f 0.21 (EtOAc/hexane = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.17 (m, 5 H, phenyl), 6.17 (t, 1 H, $J = 10$ Hz, H-13), 5.46 (d, 1 H, $J = 9.14$ Hz, NH), 5.21 (d, 1 H, $J = 8.63$ Hz, H-3′), 5.09 (s, 1 H, H-10), 4.94 (d, 1 H, $J = 9.39$ Hz, H-5), 4.62 (q, 2 H, $J = 12.69$ Hz, H-20), 4.44 (bs, 1 H, H-2′), 4.34 (dd, 1 H, $J = 10.15$ Hz, H-7), 3.93–3.88 (m, 1 H, H-2), 3.50–3.47 (m, 1 H, H-3), 2.56–2.47 (m, 1 H, H-6), 2.39 (s, 3 H, $COCH_3$), 2.20–2.06 (m, 1 H, H-14), 1.98–1.88 (m, 1 H, H-6), 1.79 (s, 4 H, H-14, H-18), 1.64 (s, 3 H, H-19), 1.42 (s, 9 H, $OC(CH_3)_3$), 1.21 (s, 3 H, H-16), 1.11 (s, 3 H, H-17), 1.01–0.94 (m, 18 H, $SiCH_2CH_3$), 0.74 (s, 9 H, $SiC(CH_3)_3$), 0.68–0.52 (m, 12 H, $SiCH_2CH_3$), −0.11 (s, 3 H, $SiCH_3$), −0.34 (s, 3 H, $SiCH_3$) ppm; ^{13}C NMR (100.1 MHz, $CDC1_3$) δ 205.87 (C-9), 171.64 (C-l′), 169.56 ($COCH_3$), 155.27 (NHCO), 138.82 (phenyl), 137.94 (C-11), 134.08 (C-12), 128.49, 127.67, 126.47 (phenyl), 83.65 (C-5), 82.57 (C-4), 80.01 ($OC(CH_3)_3$), 78.28 (C-1), 78.12 (C-20), 76.47 (C-10, C-2′), 74.82 (C-2), 72.79 (C-7), 72.15 (C-13), 58.34 (C-8),

56.79 (C-3′), 46.63 (C-3), 42.80 (C-15), 37.45 (C-6), 35.68 (C-14), 28.24 ($OC(CH_3)_3$), 26.04 (C-16), 25.48 ($SiC(CH_3)_3$), 23.07 ($COCH_3$), 20.73 (C-17), 18.12 ($SiC(CH_3)_3$), 13.64 (C-18), 10.70 (C-19), 6.94, 6.87 ($SiCH_2CH_3$), 6.08, 5.28 ($SiCH_2CH_3$), −5.35, −5.97 ($SiCH_3$) ppm.

Docetaxel. **1** (14 mg, 12.2 μmol) was dissolved in dry cold THF (500 μl, 5°C) in a Teflon flask. HF/pyridine (420 μl) was added and the solution was stirred at room temperature for 2 h, and subsequently at 40°C for 30 min. The solution was diluted with EtOAc (30 ml). The organic layer was washed successively with 5% $NaHCO_3$ (2 × 10 ml), 5% HC1 (2 × 10 ml), water (10 ml) and brine (15 ml). The organic phase was dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (EtOAc/hexane = 1/1). Yield 6.4 mg (7.9 μmol, 65%), R_f 0.08 (EtOAc/hexane = 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09(d, 2 H, J = 6.99 Hz, benzoyl$_{ortho}$), 7.61 (t, 2 H, J = 7.10 Hz, benzoyl$_{para}$), 7.50 (t, 2 H, J = 6.89 Hz, benzoyl$_{meta}$), 7.33–7.23 (m, 5 H, phenyl), 6.21 (t, 1 H, J = 8.40 Hz, H-13), 5.65 (d, 1 H, J = 6.99 Hz, H-2), 5.28–5.24 (m, 1 H, H-3′), 5.18 (s, 1 H, H-10), 4.94 (d, 1 H, J = 8.21 Hz, H-5), 4.61 (d, 1 H, H-2′), 4.33–4.14 (m, 1 H, H-7), 4.33–4.14 (m, 2 H, H-20), 3.92 (d, 1 H, J = 6.89 Hz, H-3), 2.64–2.53 (m, 1 H, H-6), 2.36 (s, 3 H, $COCH_3$), 2.27 (m, 2 H, H-14), 1.88–1.79 (m, 1 H, H-6), 1.84 (s, 3 H, H-18), 1.76 (s, 3 H, H-19), 1.34 (s, 9 H, $OC(CH_3)_3$), 1.25 (s, 3 H, H-16), 1.14 (s, 3 H, H-17) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.36 (C-9), 170.26 (C-1′), 169.20 ($COCH_3$), 167.02 (COC_6H_5), 141.21 (phenyl), 138.40 (C-12), 135.95 (C-11), 133.69 (benzoyl$_{para}$), 130.16 (benzoyl$_{ortho}$), 129.15 (benzoyl), 128.83 (benzoyl$_{meta}$), 128.70 (phenyl$_{ortho}$), 127.07 (phenyl$_{para}$), 126.75 (phenyl$_{meta}$), 84.08 (C-5), 81.07 (C-4), 80.22 ($OC(CH_3)_3$), 78.82 (C-1), 76.70 (C-20), 74.79 (C-2), 74.54 (C-10), 73.65 (C-2′), 72.46 (C-13), 72.02 (C-7), 57.64 (C-8), 57.10 (C-3′), 46.46 (C-3), 43.07 (C-15), 37.06 (C-6), 35.74 (C-14), 28.19 ($OC(CH_3)_3$), 26.44 (C-16), 22.70 ($COCH_3$), 22.56 (C-17), 14.36 (C-18), 9.84 (C-19) ppm.

Radiosynthesis of [α-^{11}C]benzoylchloride (4). [α-^{11}C]benzoylchloride was prepared according to published methods with minor modifications.[21,22] Briefly, at the end-of-bombardment (EOB), the [^{11}C]CO_2 was transferred from the target with a helium flow of 1000 ml/min and trapped in a stainless-steel coil cooled in liquid nitrogen. The cooling bath was removed and the [^{11}C]CO_2 was transferred to the silicone septum sealed reaction vial via a helium sweep gas (10–15 ml/min). The reaction vial was purged with helium and charged with 75 μl of 2 M phenylmagnesiumchloride (Aldrich), diluted with 225 μl of dry THF. The amount of [^{11}C]CO_2 trapped usually was >95%. After obtaining maximum radioactivity in the vial (~4 min), the sweep gas was switched off and the vial was heated at 55°C for 2 min and then cooled to 21°C. The mixture was treated with 150 μl of 1 M HCl/ether and $SOC1_2$ (0.3 mmol in

THF) and heated at 65°C for 3 min. The excess of chemicals and solvent was removed by keeping the vial at 68°C and purging with helium (50 ml/min above the solution). During this process some of the activity was lost (trapped on the ascarite column, ~30%). THF was added to the reaction vial (500 µl) and subsequently [^{11}C]benzoylchloride (**4**) was distilled for 5 min using helium sweep gas (~20 ml/min) from the vial (90°C) to a vacuumized second vial containing solvent at −70°C. Finally, the vacuum and the sweep gas were removed.

2′-(tert-butyldimethylsilyl)-7,10-di-(triethylsilyl)-[^{11}C]docetaxel (5). [α-^{11}C] benzoylchloride (**4**) was prepared and distilled as described above. In general, the second vial contained precursor 2′-(*tert*-butyldimethylsilyl)-2-debenzoyl-7,10-di-(triethylsilyl)-docetaxel (**2**, 4 mg, 3.8 µmol) in 400 µl dioxane that was treated with a base 1–3 min (r.t) prior to distillation of **4** into this vial. After distillation, the mixture was heated at 45–50°C for 3–6 min. The base used was either Et_3N (10 or 100 equiv), BuLi (1, 5, 10 or 50 equiv), LDA (1.5 or 5 equiv), $[Me_3Si]_2NLi$ (1.5, 5 or 10 equiv), DBU (1.5 or 5 equiv), phosphazene base P2-t-Bu[‡] (1.5, 5,10 or 15 equiv) or phosphazene base P4-t-Bu[§] (10 equiv).

Synthetic approach II: [^{11}C]docetaxel (6b)

The primary amine of docetaxel (10). Docetaxel (290 mg, 0.36 mmol) was dissolved in 25 ml of concentrated formic acid, and the solution was stirred for 4 h at room temperature. The mixture was concentrated and coevaporated with toluene (4 ×). The residue obtained was extracted with a $NaHCO_3$ solution (5% w/v, 2 × 40 ml) and EtOAc (3 × 25 ml). The organic layer was dried and concentrated, and a white powder was obtained. This was purified by column chromatography (EtOAc/MeOH = 95/5). Yield 230 mg (0.33 µmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 8.04 (d, 2 H, J = 8.80 Hz, $benzoyl_{ortho}$), 7.70 (t, 1 H, J = 7.20 Hz, $benzoyl_{para}$), 7.59 (t, 2 H, J = 7.20 Hz, $benzoyl_{meta}$), 7.55–7.48 (m, 4 H, $phenyl_{ortho+meta}$), 7.43–7.38 (m, 1 H, $phenyl_{para}$), 6.08 (t, 1 H, J = 7.20 Hz, H-13), 5.60 (d, 1 H, J = 5.60 Hz, H-2), 5.23 (s, 1 H, H-10), 4.96 (m, 1 H, H-5), 4.59 (s, 2 H, H-2′, H-3′), 4.19–4.22 (m, 1 H, H-7), 4.14 (s, 2 H, H-20), 3.80 (d, 1 H, J = 7.20 Hz, H-3), 2.48–2.39 (m, 1 H, H-6), 2.20 (s, 3 H, H-21), 2.01–1.90 (m, 1 H, H-14), 1.88 (s, 3 H, H-18), 1.87–1.78 (m, 1 H, H-6), 1.77–1.69 (m, 1 H, H-14), 1.68 (s, 3 H, H-19), 1.12 (s, 3 H, H-16), 1.09 (s, 3 H, H-17) ppm; ^{13}C NMR (100 MHz, MeOD) δ 210.18 (C-9), 171.57 (C-1′), 170.71 ($COCH_3$), 166.58 (COC_2H_5), 137.81 (C-12), 137.13 (C-11), 133.71 ($benzoyl_{para}$), 133.59 (phenyl), 130.42 (benzoyl), 130.07 ($benzoyl_{ortho}$, $phenyl_{para}$), 129.51 ($phenyl_{ortho}$), 128.70 ($benzoyl_{meta}$), 128.13 ($phenyl_{meta}$), 84.90 (C-5), 81.30 (C-4), 78.15 (C-1), 76.56 (C-20), 75.35 (C-2), 74.59 (C-10), 73.47 (C-2′), 71.66 (C-7), 71.53 (C-13), 57.98 (C-3′), 57.87 (C-8),

46.87 (C-3), 43.43 (C-15), 36.47 (C-6), 35.75 (C-14), 25.97 (C-16), 22.22 (C-21), 20.58 (C-17), 13.46 (C-18), 9.51 (C-19) ppm.

Radiosynthesis of [^{11}C]tert-butanol ([2-^{11}C]2-methylpropan-2-ol, 7). A reaction vial was purged with helium and charged with 400 µl MeLi (1.6 M in ether). The [^{11}C]CO_2 was transferred to the vial (15°C). After obtaining maximum radioactivity in the vial (~3 min), the sweep gas was switched off and the mixture was treated with 350 µl of 2 M HCl/ether and 65 µl of pyridine. The product was analyzed by HPLC (Kromasil 100 RP C-18 column 250 × 4.6 mm; CH_3CN/H_2O 20/80, 1 ml/min, 254 nm). The retention time was 5.8 min and the overall decay corrected radiochemical yield was 85 ± 3% ($n = 10$).

Radiosynthesis of [^{11}C]tert-butyl-1,2,2,2-tetrachloroethyl carbonate (9). [^{11}C]*tert*-butanol (**7**) was distilled (He-flow 15 ml/min) from the reaction vial (100°C) to a second vial (10°C) containing 0.20 mmol (30 µl) of 1,2,2,2-tetrachloroethyl chloroformate (**8**) in 200 µl of DCM. After completion of the distillation (5–6 min) the sweep gas was removed, and 0.27 mmol (22 µl) of pyridine (in 100 µl THF) was added. The mixture was heated at 60°C (3 min) and then cooled to 20°C. The product was analyzed by HPLC (Partisil 10 µm Silica column 250 × 4.6 mm; hexane/EtOAc 80/20; 0.7 ml/min, 254 nm). The retention time was 9.3 min and the decay corrected radiochemical yield was 81 ± 11% ($n = 10$, from **7**) and (62 ± 9% (from [^{11}C]CO_2).

Radiosynthesis of [^{11}C]docetaxel (6b). The mixture containing [^{11}C]*tert*-butyl-1,2,2,2-tetrachloroethyl carbonate (**9**) was diluted with water (18 ml), and loaded onto a Sep-Pak tC18 Plus. Compound **9** was eluted with THF (700 µl) and collected in another reaction vial and the solution was cooled (10°C). Subsequently, 75 mg (0.11 mmol) of the primary amine of docetaxel (***10***, in 225 µl THF) and pyridine (150 µl) were added. The mixture was heated at 45°C (6 min) and then cooled to ambient temperature. The product was analyzed by HPLC, using either a Kromasil 100 RP C-18 column (250 × 4.6 mm; CH_3CN/H_2O 20/80, 1 ml/min, 221 nm with a retention time of 12.6 min) or using a LiChrosphere 100 RP C-8 column (150 × 4.6 mm; $MeOH/H_2O$ 65/35, 1 ml/min, 221 nm with a retention time of 12.3 min). The decay corrected radiochemical yield was 19 ± 3% ($n = 5$, from **9**); and 10 ± 1% ($n = 5$, from [^{11}C]CO_2).

Conclusions

Methods that are able to predict response to docetaxel treatment would be very useful to select the non-responders from the responders. Then, alternative therapies could be offered at a much earlier stage. The radiosynthesis of [^{11}C]docetaxel **6b** was developed using a two-pot procedure. The synthesis

started with [^{11}C]*tert*-butanol, that in turn was reacted with 1,2,2,2-tetrachloroethyl chloroformate to give [^{11}C]*tert*-butyl-1,2,2,2-tetrachloroethyl carbonate. Finally, the [^{11}C]*tert*-butoxycarbonylation of the free amine of docetaxel gave [^{11}C]docetaxel **6b**. Research concerning the purification of **6b** via a semipreparative HPLC system, as well as its formulation is in progress. The pharmacokinetics of a tracer dose of docetaxel may be studied afterwards. The main objective will then be to assess whether uptake of [^{11}C]docetaxel by breast cancer tumor deposits has prognostic value for response to therapeutic doses.

References

1. Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. *J Am Chem Soc* 1971; **93**: 2325–2327.
2. Mangatal L, Adeline MT, Guenard D, Guerittevoegelein F, Potier P. *Tetrahedron* 1989; **45**: 4177–4190.
3. Gueritte F. *Curr Pharm Des* 2001; **7**: 1229–1249.
4. Manfredi JJ, Horwitz SB. *Pharmacol Ther* 1984; **25**: 83–125.
5. Jordan MA, Wilson L. *Curr Opin Cell Biol* 1998; **10**: 123–130.
6. Laidlaw J, Raventos-Suarez C, Fairchild CR, Peterson RW, Menendez AT. *Proc AACR* 2000; **41**: 216.
7. Trudeau ME, Eisenhauer EA, Higgins BP, Letendre F, Lofters WS, Norris BD, Vandenberg TA, Delorme F, Muldal AM. *J Clin Oncol* 1996; **14**: 422–428.
8. Hudis CA, Seidman AD, Crown JP, Balmaceda C, Freilich R, Gilewski TA, Hakes TB, Currie V, Lebwohl DE, Baselga J, Raptis G, Gollub M, Robles M, Bruno R, Norton L. *J Clin Oncol* 1996; **14**: 58–65.
9. Chevallier B, Fumoleau P, Kerbrat P, Dieras V, Roche H, Krakowski I, Azli N, Bayssas M, Lentz MA, Van Glabbeke M. *J Clin Oncol* 1995; **13**: 314–322.
10. Ravdin PM, Burris HA, III, Cook G, Eisenberg P, Kane M, Bierman WA, Mortimer J, Genevois E, Bellet RE. *J Clin Oncol* 1995; **13**: 2879–2885.
11. Valero V, Holmes FA, Walters RS, Theriault RL, Esparza L, Fraschini G, Fonseca GA, Bellet RE, Buzdar AU, Hortobagyi GN. *J Clin Oncol* 1995; **13**: 2886–2894.
12. Ravert HT, Klecker RW, Collins JM, Mathews WB, Pomper MG, Wahl RL, Dannals RF. *J Label Compd Radiopharm* 2002; **45**: 471–477.
13. Chaudhary AG, Gharpure MM, Rimoldi JM, Chordia MD, Gunatilaka AAL, Kingston DGI. *J Am Chem Soc* 1994; **116**: 4097–4098.
14. Kingston DGI, Chaudhary AG, Chordia MD, Gharpure M, Gunatilaka AAL, Higgs PI, Rimoldi JM, Samala L, Jagtap PC, Giannakakou P, Jiang YQ, Lin CM, Hamel E, Long BH, Fairchild CR, Johnston KA. *J Med Chem* 1998; **41**: 3715–3726.
15. Datta A, Jayasinghe LR, Georg GI. *J Org Chem* 1994; **59**: 4689–4690.
16. Georg GI, Ali SM, Boge TC, Datta A, Falborg L, Himes RH. *Tetrahadron Lett* 1994; **35**: 8931–8934.

17. Pulicani JP, Bezard D, Bourzat JD, Bouchard H, Zucco M, Deprez D, Commercon A. *Tetrehedron Lett* 1994; **35**: 9717–9720.
18. Gunatilaka AAL, Ramdayal FD, Sarragiotto MH, Kingston DGI, Sackett DL, Hamel E. *J Org Chem* 1999; **64**: 2694–2703.
19. Chordia MD, Kingston DGI. *J Org Chem* 1996; **61**: 799–801.
20. Jagtap PG, Kingston DGI. *Tetrahedron Lett* 1999; **40**: 189–192.
21. Mathews WB, Burns HD, Dannals RF, Ravert HT, Naylor EM. *J Label Compd Radiopharm* 1995; **36**: 729–737.
22. McCarron JA, Turton DR, Pike VW, Poole KG. *J Label Compd Radiopharm* 1996; **38**: 941–953.
23. Crouzel C, Hinnen F, Maitre E. *Appl Radiat Isot* 1995; **46**: 167–170.
24. Brown GD, Henderson D, Steel C, Luthra S, Price PM, Brady F. *Nucl Med Biol* 2001; **28**: 991–998.
25. Schirbel A, Holschbach MH, Coenen HH. *J Label Compd Radiopharm* 1999; **42**:537-551.
26. Barcelo G, Senet J-P, Sennyey G. *Synthesis* 1986; **8**: 627–632.
27. Kurita K, Matsumura T, Iwakura Y. *J Org Chem* 1976; **41**: 2070–2071.
28. Sasse A, Kiec-Kononowicz K, Stark H, Motyl M, Reidemeister S, Ganellin CR, Ligneau X, Schwartz JC, Schunack W. *J Med Chem* 1999; **42**: 593–600.
29. Nowakowski J. *J Prakt Chem* 1992; **334**: 187–189.
30. Barcelo G, Senet J-PG, Sennyey G. *J Org Chem* 1985; **50**: 3951–3953.
31. van der Meij M, Carruthers NI, Herscheid JDM, Jablonowski JA, Leysen JE, Windhorst AD. *J Label Compd Radiopharm* 2003; **46**: 1075–1085.
32. Soloviev D, Matarrese M, Moresco RM, Todde S, Bonasera TA, Sudati F, Simonelli P, Magni F, Colombo D, Carpinelli A, Kienle MG, Fazio F. *Neurochem Int* 2001; **38**: 169–180.
33. Studenov AR, Berridge MS, Soloviev DV, Matarrese M, Todde S. *Nucl Med Biol* 1999; **26**: 431–435.

