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# [TETRAZOYL-$^{11}$C]LY202157 SYNTHESIS FOR *IN VIVO* STUDIES OF THE NMDA RECEPTOR CHANNEL COMPLEX

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## SUMMARY

[Tetrazoyl-$^{11}$C]LY202157 **8** was prepared via a three step synthesis from ethyl (3S,4aR,6S,8aR)-6-bromomethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate **4**. This bromo precursor was reacted with [$^{11}$C]hydrogen cyanide affording the corresponding [$^{11}$C]nitrile. Conversion to the tetrazole was achieved by treatment with azidotributyltin followed by hydrolysis with 6N hydrochloric acid at 200°C. After HPLC purification and analytical HPLC control, more than 370 MBq (10 mCi) of [tetrazoyl-$^{11}$C] LY202157 were obtained after an overall 60 minute synthesis time with 38% yield (EOB) and specific activity of 25.9 GBq/μmol (700 mCi/μmol). *Ex vivo* biological studies showed that the [tetrazoyl-$^{11}$C] LY202157 did not cross the brain blood barrier.

Key words : NMDA receptor, [$^{11}$C]HCN, [$^{11}$C]-1H-tetrazoyl-, PET ligand.

## INTRODUCTION

N-Methyl D-Aspartate (NMDA) receptors, a type of neuronal ionotropic receptors for L-glutamate, have a prominent role in learning and memory. They are involved in various brain pathological processes such as stroke, traumatic brain injury, epilepsy and Parkinson's- and Huntington's diseases. Although there is great interest for the *in vivo* imaging of NMDA receptors with Positron Emission Tomography (PET), suitable radioligands are not available at present.

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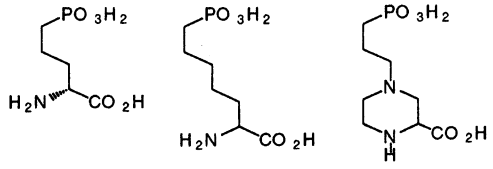
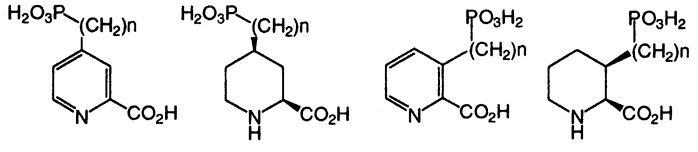
**Figure 1 : Structures of active amino acid compounds**




AP5 AP7 CPP

The study of compounds AP5 and AP7 (Fig. 1), synthesized by Watkins *et al*, suggested potential structural criteria for a NMDA receptor antagonist (1). Antagonists would require an amino acid group and an acid group separated from each other by 4 or 6 atoms. The latter can be either a carboxylic- or a phosphonic group. The cyclic analog CPP (Fig. 1), synthesized by Davies *et al* (2), has a biological activity that is 4 to 7 times that of compounds AP5 and AP7. Starting from these results Orstein *et al* (3) synthesized a series of 3- or 4-phosphonoalkyl substituted 2-pyridine- and 4-piperidine carboxylic acids (Fig. 2). After validation with binding studies using tritiated compounds, only 4-substituted piperidine II and 3-substituted piperidine IV showed high affinity and good selectivity *in vitro* for NMDA receptors (3).

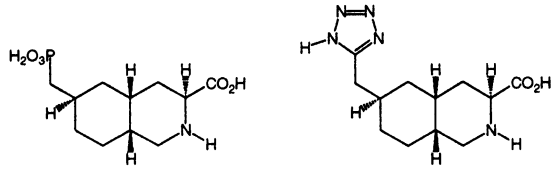
**Figure 2: Structures of phosphonoalkylpyridine and piperidine**




I (n=1-4) II (n=1-4) III (n=1-2) IV (n=1-2)

Orstein (4) replaced the phosphonic group by a tetrazoyl group increasing the *in vitro* selectivity of these molecules. More recently Orstein (5, 6) synthesized decahydroisoquinoline products with either a phosphonic acid- or a tetrazoyl group. *In vitro-* and *in vivo* biological activity were tested (5) and two molecules were retained as potential ligands for NMDA receptors (Fig. 3).

**Figure 3 : Structures of decahydroisoquinoline products**




LY235959 LY202157

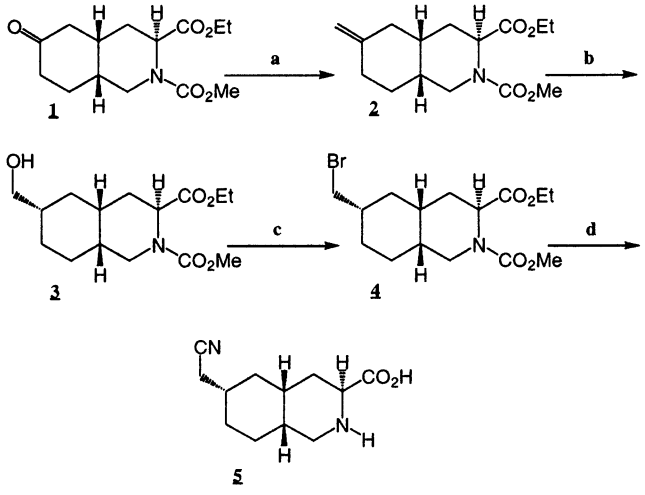
As we have developed in our laboratory a method for the labelling of the tetrazoyl moiety with carbon-11 via [$^{11}$C]hydrogen cyanide (5), we evaluated one of them: the radiolabelled analogue [tetrazoyl-$^{11}$C]LY202157 **8**, ([$^{11}$C](3S,4aR,6S,8aR)-6-(1*H*-tetrazo-5-ylmethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid).

## RESULTS AND DISCUSSION

### CHEMISTRY

The starting bromo precursor **4** was obtained as previously described by Orstein (3, 7) from the corresponding ketone **1** (Scheme 1).

**Scheme I**




a) $BrPh_3PCH_3$, $(Me_3Si)_2NNa$, THF b) $BH_3.SMe_2$, THF ; aq. $H_2O_2$, aq. NaOH, EtOH c) $Br_2$, $PPh_3$, pyridine, $CH_2Cl_2$ d) NaCN, $K_{222}$, KOH, DMF, 200°C

Ketone **1** was converted in 82% yield to the methylenyl compound **2** through a wittig reaction using methyltriphenylphosphonium bromide and sodium bis(trimethylsilyl)amide in THF. The hydroboration of alkene **2** with borane/methyl sulfide in THF at 0°C, followed by oxidation with basic hydrogen peroxide (3N aqueous NaOH, then 30% aqueous hydrogen peroxide) gave a 79% yield of the desired alcohol **3**. This hydroboration has a high diastereoselectivity providing a > 10 : 1 ratio. This ratio was determined by integration of the α-amino ester protons. This proton appeared as a triplet at δ 4.37 ppm (7); for the other enantiomer this proton appeared as two doublets at δ 4.99 and 4.82 ppm (amide rotamers) (7). Alcohol **3** was readily converted to the corresponding bromide **4** with triphenylphosphine dibromide in 87% yield.

Treatment of the bromide **4** with sodium cyanide in DMSO afforded the corresponding nitrile **5** in 70% yield. This compound was needed as a reference for the radiosynthesis of the [tetrazoyl-$^{11}$C]LY202157 **8**.

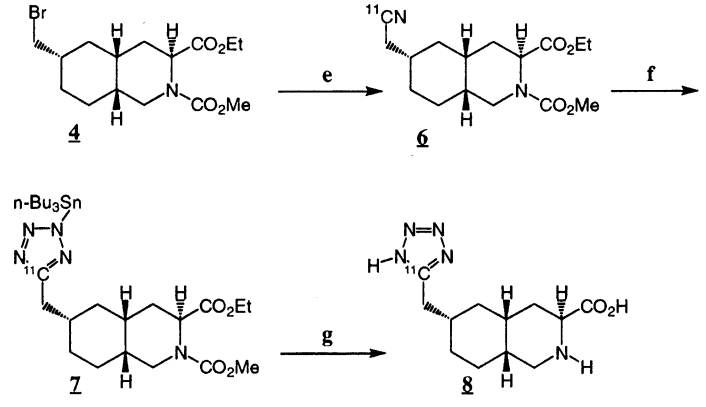
The identities of the precursor **4** and nitrile **5** were checked by comparison with 1H-NMR- and mass spectra published by Orstein (7) for these compounds.

## RADIOCHEMISTRY

[Tetrazoyl-$^{11}$C]LY202157 **8** was prepared in three steps (Scheme II) from ethyl (3S,4aR,6S,8aR)-6-(1*H*-bromomethyl)-2-(methoxy-carbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate **4** and [$^{11}$C]hydrogen cyanide.

**Scheme II**




e) [$^{11}$C]HCN, $K_{222}$, KOH, DMF, 200°C f) n-$Bu_3SnN_3$ g) aqueous HCl

[$^{11}$C]Hydrogen cyanide was produced classically from [$^{11}$C]methane (8) and trapped in potassium hydroxide and kryptofix ® $K_{222}$. After evaporation to dryness of the crude radioactive material the bromo precursor **4** was reacted with hydrogen [$^{11}$C]cyanide in DMF (9). After optimisation of the PET conditions (reaction time, half life, volume), the reaction was performed at 200°C for 2 min affording the corresponding [$^{11}$C]nitrile **6**. Conversion to the tetrazole was effected, after evaporation of DMF to dryness, by treatment with azidotributyltin (10). After DMF evaporation to dryness the hydrolysis of the tin complex was performed with 6N hydrochloric acid at 200°C (11). The acidic solution of crude [tetrazoyl-$^{11}$C]LY202157 was evaporated to dryness and taken up in the mobile phase for the HPLC purification.

We optimized purification and analysis (Table I). Purification was performed by HPLC on a semi-preparative column using only a radioactivity detector. Chemical purity and radiochemical purity were checked on an analytical column using both a refractometric- and a radioactivity detector. After purification the solution of [tetrazoyl-$^{11}$C]LY202157 **8** was evaporated to dryness and taken up in physiological serum.

The first trial purification (n° 1, 2, Table I) on a CN-column showed a low specific radioactivity (12 and 20 GBq/μmol) and a low radiochemical purity (81 and 88%) when analyzed on an analytical SCX-column.

Next purification n° 3 was performed on a C18-column. The specific radioactivity, determined on an analytical SCX-HPLC column, was also low (11 GBq/μmol) for a 93% radiochemical purity with 52% of radiochemical yield.

Table I [Tetrazoyl-$^{11}$C]LY202157 **8** HPLC purification

| | Purifications | | | Analysis | | | SRA[a] | |
|---|---|---|---|---|---|---|---|---|
| n° | column | solvent | radio-chemical yield % | column | solvent | radio-chemical purity % | GBq/µmol | mCi/µmol |
| 1 | CN | $H_2O$ | - | SCX | $NaH_2PO_4$/ $H_3PO_4$ [b] | 81 [c] | 12 | 333 [c] |
| 2 | CN | $H_2O$ / MeOH [d] | - | SCX | $NaH_2PO_4$/ $H_3PO_4$ [b] | 88 [e] | 20 | 550 [e] |
| 3 | C 18 | TFA / MeOH [f] | 52 | SCX | $NaH_2PO_4$/ $H_3PO_4$ [b] | 93 | 11 | 300 |
| 4 | C 18 | $H_3PO_4$ / MeOH [g] | 62 [e] | SCX | $NaH_2PO_4$/ $H_3PO_4$ [b] | 79 [e] | 6 | 175 [e] |
| 5 | C 18 | $H_3PO_4$ / MeOH [g] | 38 [e] | SCX | $NaH_2PO_4$/ $H_3PO_4$ [b] | 95 | 26 | 700 |
| 6 | C 18 | $H_3PO_4$ / MeOH [g] | 37 | C 18 | $H_3PO_4$ /MeOH [g] | 92 | 44 | 1200 |

a : End of Bombardment b : $NaH_2PO_4$ 0.2 M / $H_3PO_4$ 0.2 M at PH = 3
c : average of 3 syntheses d : $H_2O$ / MeOH (100 /3 ) e : average of 2 syntheses
f : MeOH / TFA 0.0025M (5 / 95 ) g : MeOH / $H_3PO_4$ 0.005 M (5 / 95).

Purifications (n° 4, 5) were performed with a new mobile phase on a C18-column. The specific radioactivity, determined on an analytical SCX-HPLC column, depended on the collected part of the radioactive peak : 6 and 26 GBq/µmol for a 79 and 95% radiochemical purity. These apparent low specific radioactivities were due to an inactive impurity collected with the radioactive product.
Purification n° 6, performed on a C18 column and analyzed on a C18 column, gave a good result : good radiochemical purity (92%), good specific radioactivity (44 GBq/µmol) but low yield (37%).
Finally, the pure radioactive product **8** might be obtained using a C 18 column (Table I) by the collection of the middle of the radioactive peak. This method gave high specific radioactivity but low quantity of radioactive product.
However, usually more than 370 MBq (10 mCi) of [tetrazoyl-$^{11}$C]LY202157 were obtained after an overall synthesis time of 60 minutes (formulation included) with 38% yield (EOB) and a specific activity of 26 GBq/µmol (700 mCi/µmol).

## BIODISTRIBUTION STUDIES

Adult male Sprague Dawley rats were injected in the tail vein with 3.33 to 4.44 MBq (90 to 120 µCi) of [tetrazoyl-$^{11}$C]LY202157 **8** with 26 MBq/µmol (700 mCi/µmol) in physiological saline . A series of 3 rats were sacrificed 10, 20, 30, 45, 60 minutes post injection (p.i). Radioactivity in different brain areas, peripheral organs, blood and

plasma was measured using a γ well counter. The tissue distribution time course (Table II and III) of [tetrazoyl-$^{11}$C]LY202157 8 is expressed in percent of injected dose per gram of wet tissue (% ID/g).

TABLE II : Brain tissue distribution in % ID/g

| Time min | brainstem | cerebellum | colliculi | thalamus | hippocampus | striatum | front. cortex | post. cortex |
|---|---|---|---|---|---|---|---|---|
| 10 | 0.031 | 0.019 | 0.014 | 0.014 | 0.017 | 0.006 | 0.013 | 0.014 |
| 20 | 0.009 | 0.007 | 0.009 | 0.013 | 0.011 | 0.013 | 0.003 | 0.005 |
| 30 | 0.005 | 0.008 | 0.007 | 0.013 | 0.006 | 0.002 | 0.003 | 0.006 |
| 45 | 0.003 | 0.007 | 0.006 | 0.004 | 0.004 | 0.002 | 0.005 | 0.003 |
| 60 | 0.006 | 0.003 | 0.010 | 0.006 | 0.001 | 0.004 | 0.002 | 0.005 |

Brain uptake was rapid and homogeneous in all structures. Radioactivity concentrations were low (< 0.1 % ID/g 10 min p.i) and decreased continuously (< 0.005 % ID/g 45 min). In peripheral organs the highest concentration was found in the kidney (> 10 % ID/g 10 min p.i). Liver, heart and blood showed lower concentration (> 0.5 % ID/g 10 min). Rapid radioactivity clearance was observed (<0.7 % ID/g 45 min).

TABLE III : Tissue distribution in % ID/g

| Time (min) | liver | kidney | heart | blood |
|---|---|---|---|---|
| 10 | 0.573 | 10.604 | 0.172 | 0.333 |
| 20 | 0.741 | 8.597 | 0.092 | 0.164 |
| 30 | 0.712 | 9.942 | 0.061 | 0.112 |
| 45 | 0.667 | 4.793 | 0.009 | 0.001 |

## CONCLUSION

We have developed a procedure that provides [tetrazoyl-$^{11}$C]LY202157 **8** with a high radiochemical purity and a high specific radioactivity. The radiochemical yield is sufficient to perform biological studies on rodents. However, this new labelled compound had a very poor brain extraction and consequently a very low regional distribution. In conclusion, the [tetrazoyl-$^{11}$C]LY202157 is not a suitable candidate for further development as an *in vivo* PET ligand.

## EXPERIMENTAL

THF was distilled from sodium and benzophenone. DMF was distilled under reduced pressure from barium oxide. The solvents were stored under argon. Other chemicals and solvents were purchased from Aldrich with the best reagent grade available and were used without purification. Ketone **1** and LY202157 were gifts from Lilly Research Laboratories. $^1$H-NMR spectra were recorded on a Bruker AMX 300 and chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Mass spectra were measured on a Nermag R10-10 by DCI using ammonia as ionisation gas at 70eV. Flash chromatography was performed on silica (Merck, 200-400 µm). Analytical TLC was conducted on Merck silica (Kieselgel 60 F254, 5 x 10 cm).

For radiopurification a CN- or a C18-column (9.4 x 250 mm, 80 Å) was used with a Waters system (Waters 510 pump) and radioactivity GM detector. HPLC analyses were performed using a Waters system (Waters 510 pump) with a Waters refractometry detector (Waters 410) and a radioactivity GM detector. The compounds were analyzed either on a Zorbax ® 300-SCX column (4.6 x 25 mm, 5 µm, 300 Å) or on a Zorbax ® C18-column (4.6 x 25 mm, 5 µm, 80 Å). Radioactivity was measured using a Capintec CRC-127R dose calibrator. [$^{11}$C]methane was produced with a cyclotron using the $^{14}$N(p,α)$^{11}$C reaction and converted to [$^{11}$C]HCN (8).

### Ethyl-(3S,4aR,8aR)-6-methylenyl-2-(methoxycarbonyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate 2

Sodium bis-(trimethylsilyl)amide (4.8 g, 24.7 mmol) in 20 ml THF was added to a 0°C stirred suspension of 9 g (24.7 mmol) of methyl triphenylphosphonium bromide in 30 ml THF. After 15 min, the suspension was added via a teflon cannula to a 0°C ketone **1** solution (5 g, 17.6 mmol) in 20 ml of THF. The reaction mixture, maintained at 0°C, was stirred for 150 min. After workup (water / ether, 3 x 50 ml) a brown oily residue was obtained. This residue was dissolved in 50 ml of ethyl acetate / heptane (25 / 75), stirred for 1 hour, then filtered. The filtrate was concentrated *in vacuo* to dryness. Chromatography of the residue (200 g silica, heptane / ethyl acetate: 80 / 20) gave 4.1 g (82%) of **3**.
$^1$H NMR (DMSO-d$^6$, 27°C) : 4.9 (d, J=12 Hz, 1H) ; 4.8 (s, 1H) ; 4.7 (s, 1H) ; 4.2 (q, J=6 Hz, 2H) ; 3.8 (dd, J=12 Hz, 24 Hz, 1H) ; 3.6 (d, J=7Hz, 1H) ; 3.2 (dd, J=12 Hz, 30 Hz, 1H) ; 2.4 (t, J=12 Hz, 3H) ; 2.1 (m, 2H) ; 1.8 (m, 4H) ; 1.3 (t, J=6 Hz, 3H). M.S. (DCI-$NH_3$) : (M+1) = 282 : 100% ; (M+18) = 299 : 56%.
TLC (kieselgel 60) : Rf = 0.27 (heptane / ethyl acetate : 80 / 20).

**Ethyl (3S,4aR,6S,8aR)-6-(hydroxymethyl)-2-(methoxycarbonyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8,8a-decahydroisoquinoline-3-carboxylate 3**

A 0°C stirred solution of 4 g (14.2 mmol) of **2** in 10 ml of THF was treated dropwise with 5 ml of a borane methyl sulfide (0.72 g, 9.5 mmol) THF solution. After 2.5 hr at 0°C, the reaction mixture was stirred for 2 hr at room temperature. Then it was cooled to 0°C and successively 2.5 ml of ethanol, 19.6 ml of sodium hydroxide 3N (58.9 mmol) and 19.6 ml of 30% hydrogen peroxide (192 mmol) were added. After 20 min at 0°C, the reaction mixture was warmed to room temperature and stirred for an additional 2 hr. Workup (ether 3 x 50 ml) afforded a colorless oily residue. Purification by chromatography on silica gel (200 g, heptane / ethyl acetate : 80 / 20) gave 3.4 g (79%) of colorless oil **3**.
$^1$H NMR (DMSO-d$^6$, 79°C) : 4.4 (t, J=5 Hz, 1H) ; 4.2 (q, J=6 Hz, 2H) ; 3.7 (s, 3H) ; 3.5 (d, j=7 Hz, 2H) ; 3.4 (m, 2H) ; 2.1 (m, 1H) ; 2-1.5 (m, 8H) ; 1.3 (t, j=6 Hz, 3H) ; 1.2 (m, 2H). M.S. (DCI-$NH_3$) : (M+1) = 300 : 100% ; (M+18) = 318.
TLC (kieselgel 60) : Rf = 0.3 (heptane / ethyl acetate : 40 / 60).

**Ethyl (3S,4aR,6S,8aR)-6-(bromomethyl)-2-(methoxycarbonyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate 4**

To a suspension of dibromotriphenylphosphine, prepared from 2.7 g (10.4 mmol) of triphenylphosphine and 0.53 ml (10.4 mmol) of bromine in 30 ml of dichloromethane, was added a solution of 2.3 g (76.8 mmol) of alcohol **3** and 1.7 ml (20.7 mmol) of pyridine in 20 ml of dichloromethane. The reaction mixture was stirred at 0°C for 15 min, warmed to room temperature and stirred for 75 min. Workup was performed with 10% sodium hydrogencarbonate (40 ml), dichloromethane (2 x 50 ml) and diethyl ether (50 ml). The yellow residue was suspended in 30 ml of 50% heptane / diethyl ether and stirred at room temperature. After filtration the filtrate was concentrated *in vacuo* to give a yellow oily residue. Chromatography on silica gel (200 g, heptane / ethyl acetate : 60 / 40) gave 2.6 g (87%) of a colorless oil **4**.
$^1$H NMR (DMSO-d$^6$, 79°C) : 4.4 (t, J=5 Hz, 1H) ; 4.2 (q, J=6 Hz, 2H) ; 3.7 (s, 3H) ; 3.5 (dd, J=3 Hz, 10 Hz, 2H) ; 3.4 (dd, J=2 Hz, 10 Hz, 2H) ; 2.2 (m, 1H) ; 2-1.5 (m, 8H) ; 1.4 (m, 2H) ; 1.3 (t, J=6Hz, 3H). M.S. (DCI-$NH_3$) : (M+1) = 362 : 100% ; (M+18) = 379 : 19%.
TLC (kieselgel 60) : Rf = 0.33 (heptane / ethyl acetate : 70 / 30).

**Ethyl (3S,4aR,6S,8aR)-6-(cyanomethyl)-2-(methoxycarbonyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate 5**

A solution of 135 mg (2.8 mmol) of sodium cyanide and 500 mg (1.4 mmol) of bromo compound **4** in 5 ml of DMSO was stirred and heated at 75°C for 2 hr. Then the reaction mixture was cooled to room temperature and workup was performed with water brine / dichloromethane : 50 /50 (3 x 20 ml) and ether (20 ml) to give a

yellow oily residue. Chromatography on silica gel (100 g, heptane / ethyl acetate ; 60 / 40) gave 300 mg (70%) of a colorless oil **5**.
M.S. (DCI-$NH_3$) : (M+1) = 309 : 100% ; (M+18) = 326 : 76%.

**[tetrazoyl-$^{11}$C]-(3S,4aR,6S,8aR)-6-(1H-tetrazol-5-ylmethyl))-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid : [$^{11}$C]LY202157 8**

Experiments were performed after 45 min irradiation of a nitrogen / hydrogen (95 / 5, v / v) target with a 25 µA beam of 20 MeV protons. The irradiation produced 37 GBq (1 Ci) of [$^{11}$C]methane on average (end of bombardment). [$^{11}$C]hydrogen cyanide was produced classically (8) and trapped in 100 µl of potassium hydroxide (0.05N) with 0.7 to 1.2 mg (2 to 3 µmol) of kryptofix® $K_{222}$ with 95% efficiency in a conical vial (2 ml) at room temperature. The radioactive solution was concentrated to dryness at 200°C under helium stream. Then 5.4 to 7.2 mg (15 to 20 µmol) of bromo precursor **4** in 200 µl of DMF were added to the vial and the sealed vial was heated for 2 min at 200°C. After solvent evaporation of the crude radioactive material under a helium stream at 200°C, 50 µl (179 µmol) of azidotributyltin in 50 µl of DMF were added, heated to 200°C for 5 min in a sealed vial and then concentrated under a stream of helium at 200°C. Decomplexation was performed at 200°C for 4 min in the presence of hydrochloric acid (6N, 200 µl) in a sealed vial and then evaporated to dryness under a stream of helium at 200°C. The labelled compound was taken up in mobile phase solvent (MeOH / $H_3PO_4$ 0.005M ; 5 / 95) and purified by HPLC on a reversed phase C18 column. After formulation, an average of 370 MBq (10 mCi) of [$^{11}$C]LY202157 were produced at 60 min with 38% yield with a specific radioactivity of 26 MBq/µmol (700 mCi/µmol) on average (EOB). The radioactive purity and the chemical purity were determined by HPLC on an analytical C 18 column.

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