# Synthesis of *N*-methyl-*N*-(1-methylpropyl)-1-(2-chlorophenyl)-isoquinoline-3-[$^{11}$C]carboxamide ([$^{11}$C-carbonyl]PK11195) and some analogues using [$^{11}$C]carbon monoxide and 1-(2-chlorophenyl)isoquinolin-3-yl triflate

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The benzodiazepine receptor ligand, *N*-methyl-*N*-(1-methylpropyl)-1-(2-chlorophenyl)isoquinoline-3-carboxamide (PK11195), and five structurally related analogues were $^{11}$C-labelled *via* a palladium-mediated carbonylation using [$^{11}$C]carbon monoxide, 1-(2-chlorophenyl)isoquinolin-3-yl trifluoromethanesulfonate and various amines. The $^{11}$C-labelled products were obtained with decay-corrected radiochemical yields in the range of 10–55% and with high specific radioactivity (*e.g.* 200–900 GBq μmol$^{-1}$). The radiochemical purity of the final products exceeded 98%. In a typical experiment starting with 3.75 GBq [$^{11}$C]carbon monoxide, 0.57 GBq of LC-purified products were obtained within 35 min of the start of the carbonylation reaction. For confirmation of the labelling position, *N*-(1-methylethyl)-1-(2-chlorophenyl)-isoquinoline-3-($^{13}$C)carboxamide was prepared and analysed by NMR. The precursor 1-(2-chlorophenyl)isoquinolin-3-yl trifluoromethanesulfonate was synthesised in five steps starting from 2-chlorobenzophenone. The precursor *N*-methyl-*sec*-butylamine was prepared from *sec*-butylamine by the reaction with ethyl chloroformate followed by reduction with $LiAlH_4$. The non-radioactive reference compounds for the analogues were synthesised from 1-(2-chlorophenyl)isoquinoline-3-carboxylic acid and the appropriate amines.

## Introduction

The "peripheral-type" benzodiazepine receptor, also named the $\omega_3$ receptor,[1a] has been found in high concentrations in organs such as kidney, heart, adrenal cortex and testis, although its concentration in the brain is expected to be low.[1] The physiological role of the $\omega_3$ receptor is still unclear and intensive research is focused on mapping the binding site of this receptor. For this purpose different types of ligands have been developed. One important class of ligands for the $\omega_3$ receptor are benzoxazepine and benzothiazepine derivatives.[2] The first non-benzodiazepine ligand found to bind to the $\omega_3$ receptor at a nanomolar concentration level was PK11195.[3] The $^3$H-labelled PK11195 was used to investigate the subcellular localisation of the $\omega_3$ receptor in adrenal gland of rats.[4] It was also used to measure the spatial changes in glial fibrillary acidic protein messenger RNA levels in the hippocampus following transient global forebrain ischemia in rats.[5] Methyl[$^{11}$C]-labelled PK11195 is now being used as a tracer in various PET applications.[6]

Although carbon monoxide is a versatile reagent for the synthesis of carbonyl compounds,[7] [$^{11}$C]carbon monoxide has until recently[8] rarely been applied as a precursor in labeling chemistry. The main reason for this has been the problem of trapping [$^{11}$C]carbon monoxide in the reaction medium.[7] To overcome this, a method was developed that made it possible to concentrate and enclose small amounts (<50 nmol) of [$^{11}$C]-carbon monoxide in small volumes, typically 200 μL. This method has been recently applied to the synthesis of a wide range of $^{11}$C-labelled carbonyl compounds, *e.g.* $^{11}$C-labelled amides and imides using organohalides.[9] In the present report, the versatility of the method is further explored by the alternative $^{11}$C-labelling of PK11195 and the synthesis of some $^{11}$C-analogues using a palladium mediated carbonylation with [$^{11}$C]carbon monoxide and an aryl triflate.† It should be pointed out that the analogues of PK11195 presented in this paper could not be labelled with [$^{11}$C]methyl iodide. A preliminary account of this work has been reported previously[10] as a conference abstract. This paper describes the results in detail.

## Results and discussion

The $^{11}$C-labelled 1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)isoquinoline-3-carboxamide **7a** and five analogues **7b**–**f** were synthesised in a 200 μL micro-autoclave using tetrakis(triphenylphosphine)palladium(0), the triflate **6**, amines, lithium bromide and [$^{11}$C]carbon monoxide at a conc. of around $10^{-4}$ M (see Scheme 2). In the syntheses, the [$^{11}$C]-carbon monoxide and the reaction mixture were transferred into the micro-autoclave at ambient temperature and then placed in a heated oil bath for 5 min. The micro-autoclave reached the set temperature within 5 min as determined by independent measurement. The conversion of [$^{11}$C]carbon monoxide to products (trapping efficiency) was up to 97% (Table 1) and the decay-corrected radiochemical yields of LC-purified products, calculated from [$^{11}$C]carbon monoxide, were 10 to 55% (Table 1). The specific radioactivity of LC-purified products, using irradiation of 10 μA h, was 248 to 976 GBq μmol$^{-1}$ (Table 1) as determined by LC-MS. The radiochemical purity exceeded 98%. In a typical experiment starting with 3.35 GBq of [$^{11}$C]carbon monoxide, 0.57 GBq of purified product was obtained within 35 min from the start of the carbonylation reaction. The identities of the $^{11}$C-labelled products were confirmed by LC-MS. Preliminary identification

† The IUPAC name for triflate is trifluoromethanesulfonate.

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**Table 1** Radiochemical yields and specific radioactivity for the $^{11}$C-labelled PK11195 and some analogues

| Entry | Amine | Product | Amount of amine/μmol | Trapping efficiency (%)[a] | RCY[b,c] | Specific Radioactivity/ GBq μmol$^{-1}$ |
|---|---|---|---|---|---|---|
| 1 | *N*-Methyl-*sec*-butylamine | **7a** | 120 | 95 ± 1 | 55 ± 1 (3) | 393 |
| 2 | *sec*-Butylamine | **7b** | 143 | 97 ± 2 | 45 ± 1 (3) | 431 |
| 3 | Isopropylamine | **7c** | 175 | 97 ± 2 | 47 ± 2 (3) | 248 |
| 4 | *N*,*N*-Dipropylamine | **7d** | 142 | 93 ± 2 | 35 ± 1 (2) | 336 |
| 5 | *N*,*N*-Diallylamine | **7e** | 160 | 80 ± 5 | 26 ± 1 (2) | 535 |
| 6 | Aniline | **7f** | 164 | 91 ± 2 | 10 ± 1 (2) | 976 |

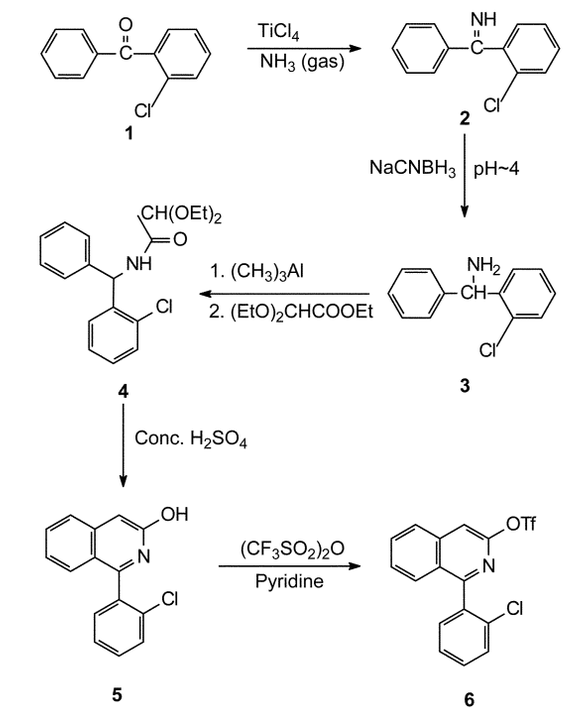
[a] Decay-corrected, the fraction of radioactivity left in the crude product after purging with nitrogen. [b] RCY= radiochemical yield; decay-corrected, calculated from the amount of radioactivity in the crude product before purg ing with nitrogen, and the radioactivity of the LC purified product. [c] Values in parentheses shows the number of runs.

was performed using analytical LC with co-injection of non-radioactive materials. The labelling position for compound **7c** was confirmed by comparison of the $^{13}$C NMR spectra of the $^{13}$C-substituted product with that of the non-radioactive reference compound **12a**. The $^{13}$C-compound was prepared using ($^{13}$C)carbon monoxide, triflate and amine under the similar conditions to those used for the preparation of $^{11}$C-compounds. The $^{13}$C NMR analysis of the product gave only one peak (from carbonyl carbon at 163.95 ppm) which matched the carbonyl peak in the $^{13}$C NMR spectrum of the reference compound **12a**.

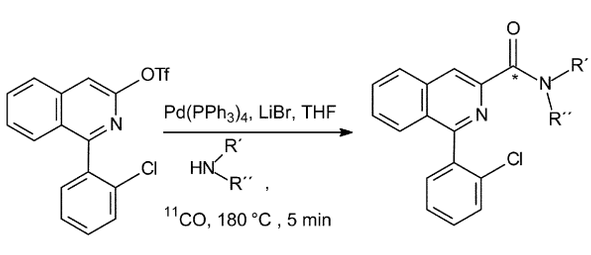
In initial experiments, the hydrochloride salt of the amine **10** was used. The tetrahydrofuran (THF) solution of the free base was prepared by treatment with 2,2,6,6-tetramethylpiperidine (TMP) followed by separation of the TMP–hydrochloride. Under these conditions, both the trapping efficiency (52%) and the radiochemical yield (27%) were low. One reason for this was the relatively low concentration of the amine (0.23 μM). Another reason could be the residual TMP which could affect the reaction rate and result in side-products. By using the free amine at higher concentrations (0.48 μM), the possible negative effect of TMP was avoided. In this case both the trapping efficiency (95%) and the radiochemical yield (55%) were improved.

The lead compound PK11195 has previously been labelled with $^{11}$C in the *N*-methyl group using [$^{11}$C]methyl iodide.[11] The carbonylation method may have advantages over the former method for the following reasons. (i) Due to minimal isotopic dilution[9a] in the precursor production, the specific radioactivity of the product is high (*e.g.* 393 GBq μmol$^{-1}$ for **7a**) compared to the corresponding values described elsewhere[11] for the same compound $^{11}$C-labelled at the methyl position (20–96 GBq μmol$^{-1}$. (ii) The approach allows the possibility of readily preparing a broad range of $^{11}$C-labelled analogues of PK11195 by simply employing different amines including structures that are difficult to $^{11}$C-label using previously available strategies. (iii) The labelled target compounds are easily separated from labelled side products and precursors by preparative LC. (iv) From a biological point of view, labelling a carbonyl group can be advantageous in cases where there are differences in metabolic stability.

The triflate **6** was prepared according to Scheme 1. A one-pot, reductive amination[12] of ketone **1** in the presence of $TiCl_4$, $NH_3$ (g) and $NaCNBH_3$ gave amine **3** *via* imine **2**. The reduction of imine **2** was pH dependent and an optimum was found at around pH = 4. The pH was adjusted by the addition of methanolic HCl. The amide **4** was obtained from amine **3** by the reaction with ethyl diethoxyacetate. Reactions between amines and esters are usually sluggish and for this reason the amine was activated by conversion to the aluminium amide by treatment with trimethylaluminium.[13] The aluminium amide reacted with ethyl diethoxyacetate at ambient temperature to form **4**. Cyclisation of **4** in the presence of conc. $H_2SO_4$ at ambient temperature[14] gave alcohol **5**. Finally, alcohol **5** was treated with trifluoromethanesulfonic anhydride at ambient




**Scheme 1**



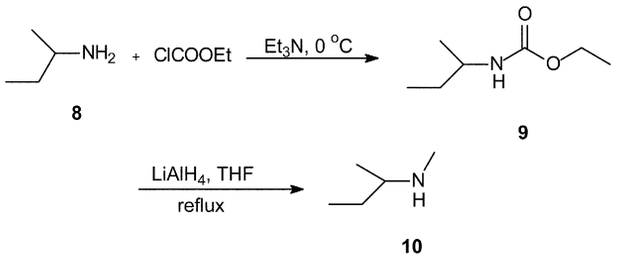

R′= *sec*-butyl and R′′ = methyl (**7a**); R′= *sec*-butyl and R′′ = H (**7b**); R′= isopropyl and R′′=H (**7c**); R′= propyl and R′′= propyl (**7d**); R′= allyl and R′′= allyl (**7e**); R′= phenyl and R′′ = H (**7f**) * = $^{11}$C

**Scheme 2**

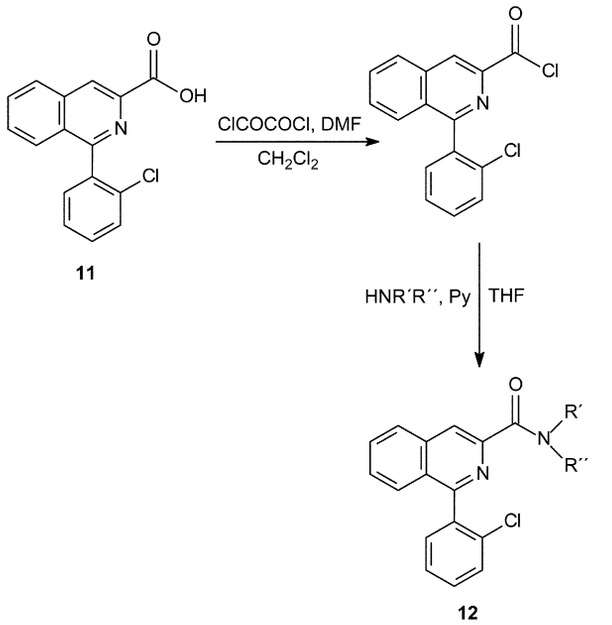
temperature[15] to give triflate **6**. Triflate **6** was then used to prepare labelled compounds **7a**–**f** (Scheme 2).

Amine **10** was prepared from commercially available *sec*-butylamine **8** by a reaction with ethyl chloroformate followed by reduction with $LiAlH_4$ (Scheme 3).[16] After work-up, the amine **10** was obtained as the hydrochloride salt. The free base was liberated with KOH, extracted with diethyl ether and then carefully distilled.

The reference materials for the lead compound PK11195 and one of the analogues **7b** are commercially available. The refer-




**Scheme 3**




R´= isopropyl and R´´ = H (**12a**), R´ = R´´ = propyl (**12b**), R´= R´´ = allyl (**12c**), R´= phenyl and R´´ = H (**12d**)

**Scheme 4**

ence compounds for the other four analogues were synthesised from different amines and carboxylic acid **11** (Scheme 4). The acid 1-(2-chlorophenyl)isoquinoline-3-carboxylic acid was synthesised in three steps starting with *o*-chlorobenzoyl chloride and glycine. *o*-Chlorobenzoyl chloride was reacted with glycine in a basic medium[17] to give 2-chlorohippuric acid (2-chlorobenzamidoacetic acid) which was then treated with benzaldehyde in the presence of sodium acetate and acetic anhydride to form 2-(2-chlorophenyl)-4-benzylidene-5(4*H*)-oxazolone. This oxazolone was aromatized to 1-(2-chlorophenyl)isoquinoline-3-carboxylic acid **11** in the presence of a Lewis acid ($AlCl_3$) and HCl.[18] Finally the carboxylic acid was converted to an amide by reacting with oxalyl chloride followed by the appropriate amines.[19]

All of the compounds (labelled and unlabelled), except for **3**, **7a** and **10**, presented in this paper are novel. The syntheses of unlabelled compounds **3**[20] and **10**[16b] have been reported previously but were prepared by different methods. Compound **3** was reported[20a] to be an oil ($bp_{20\ Torr}$ 186–188 °C) whereas we obtained it as a white solid (mp 42 °C). The labelled compound **7a** was reported previously to be $^{11}$C-labelled at the *N*-methyl position. The report presented here describes the $^{11}$C-labelling of this compound at the carbonyl position.

## Experimental

### General

[$^{11}$C]Carbon dioxide was prepared using the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. The $^{14}$N(p,α)$^{11}$C reaction was performed in a gas target chamber containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA, Oxygen 4.8) bombarded with 17 MeV protons to give [$^{11}$C]carbon dioxide. [$^{11}$C]Carbon monoxide was produced from [$^{11}$C]carbon dioxide by a process described previously.[21]

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector in series with a $\beta^+$-flow detector. The following mobile phases were used: 0.05 M ammonium formate, pH 3.5 (A) and acetonitrile–$H_2O$, 50 : 7 (B). For analytical LC, a Jones Chromatography Genesis $C_{18}$ (4 μm, 250 × 4.6 mm id) column was used with a flow of 1.5 mL $min^{-1}$. For semi-preparative LC, a Jones Chromatography Genesis $C_{18}$ (4 μm, 250 × 10 mm id) column was used with a flow of 4 mL $min^{-1}$. Synthia, an automated synthesis system,[22] was used for LC injection and fraction collection. Data collection and LC control were performed using a Beckman System Gold chromatography software package.

All quantitative radioactivity measurements were performed using an ion chamber (Veenstra Instrumenten bv, VDC-202). For rough estimations of radioactivity during production, a portable dose-rate meter was used (Långenäs eltekniska AB).

In the analysis of **7**, the unlabelled reference substance was used in the LC runs. The identities of synthesised materials were determined using $^1$H and $^{13}$C NMR, GC-MS and LC-MS. NMR spectra were recorded on a Varian Gemini-200 (200 MHz), a Varian XL 300 (300 MHz) and a Varian Unity-400 (400 MHz) NMR spectrometers. Tetramethylsilane or chloroform-$d_1$ was used as the internal standard. LC-MS was performed using a Fisons VG Platform mass spectrometer with electrospray ionisation. A Beckman 126 pump, a CMA 240 autosampler and a Beckman Ultrasphere ODS $C_{18}$ (5 μm, 100 × 4.6 mm id) column were used for LC-MS separation. Mobile phases were A and B. GC-MS was performed with a Finnigan GCQ mass spectrometer coupled to a Finnigan Q-GC. Melting points were determined using a Büchi melting point apparatus.

2-Chlorobenzophenone, titanium tetrachloride, sodium cyanoborohydride, trimethylaluminium, ethyl diethoxyacetate, trifluoromethanesulfonic anhydride, pyridine, THF, *sec*-butylamine, ethyl chloroformate, triethylamine, lithium-aluminium hydride, lithium chloride, lithium bromide, conc. sulfuric acid and tetrakis(triphenylphosphine)palladium(0) were obtained from Aldrich. Ammonia was obtained from Skoghalsverken AB, Sweden. The reference substances PK11195 and *N*-sec-butyl-1-(2-chlorophenyl)isoquinoline-3-carboxamide (*nor*-PK11195) were obtained from Sigma RBI.

THF was distilled from sodium–benzophenone under nitrogen. Pyridine was distilled from $CaH_2$ under nitrogen.

### Synthesis of precursor

**α-(2-Chlorophenyl)phenylmethylamine 3.** Titanium tetrachloride (8.0 mL, 13.8 g, 0.073 mol) was added to a solution of 2-chlorobenzophenone (10.8 g, 0.05 mol) in dry toluene (300 mL). The reddish-brown solution was cooled to 0–5 °C and purged with $NH_3$ (g) for 20 min. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was carefully quenched with a methanolic solution of $NaCNBH_3$ (9.0 g, 0.15 mol in 100 mL of methanol). The mixture was acidified (pH ~ 4) with methanolic HCl and stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure, water (300 mL) and ether (300 mL) were added and made basic (pH ~ 12) with solid KOH. The white precipitate was filtered off and the organic layer was separated, acidified (pH ~ 2) with conc. HCl and extracted with water. The water extract was made basic (pH ~ 12) with solid KOH, saturated with NaCl and extracted with diethyl ether (2 × 200 mL). The ether extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a white solid (6.4 g, 59%), mp 42 °C (lit. oil, $bp_{20\ Torr}$ 186–188 °C).

$\delta_H$ (200 MHz, $CDCl_3$): 7.6 (1H, dd), 7.1–7.5 (8H, m), 5.7 (1H, s), 1.8 (2H, br s). $\delta_C$ (50 MHZ, $CDCl_3$): 144.0, 142.0, 133.0, 129.5, 128.2, 128.1, 127.9, 127.0, 126.9, 126.8, 55.1. GC-MS: *m*/*z* 217, 201, 180, 165, 140, 106, 77.

***N*-[α-(2-Chlorophenyl)phenylmethyl]-2,2-diethoxyacetamide 4.** A solution of the amine **3** (0.88 g, 4 mmol) in dry $CH_2Cl_2$ (15 mL) was carefully treated with trimethylaluminium (2.0 mL of a 2 M solution in hexane) and the mixture was stirred at room temperature for 15 min under argon. Ethyl diethoxyacetate (0.8 mL, 0.7 g, 4 mmol) was added and the reaction mixture was stirred under argon at 25 °C for 20 h. The reaction was carefully quenched with 1 M HCl and extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a colourless oil. Yield 66% (calculated from the integral values of the proton spectrum).

$\delta_H$ (200 MHz, $CDCl_3$): 7.1–7.4 (9H, m), 6.6 (1H, d), 5.2 (1H, s), 4.8 (1H, s), 3.5–3.8 (4H, m), 1.1–1.2 (6H, m). $\delta_C$ (50 MHz, $CDCl_3$): 167, 140, 138, 133, 131, 128.8, 128.7, 126, 127.4, 127, 126.9, 98, 63, 54, 15. GC-MS: *m*/*z* 348, 312, 266, 256, 238, 216, 201, 165, 138, 103, 77, 75, 57.

**1-(2-Chlorophenyl)isoquinolin-3-ol 5.** A solution of amide **4** (0.93 g in 15 mL of $CH_2Cl_2$) was added slowly with ice cold conc. $H_2SO_4$ (15 mL) and the mixture was stirred overnight at ambient temperature. The reaction mixture was poured onto ice and carefully neutralised with 20% $NH_3$ solution. The product was extracted with $CH_2Cl_2$ (2 × 150 mL), dried over $MgSO_4$ and concentrated to give the crude product. The crude product was purified by flash chromatography using pentane–diethyl ether (1 : 1) as the eluent ($R_f$ = 0.4) to give the product as a bright yellow solid (0.42 g, 60%), mp 223 °C.

$\delta_H$ (300 MHz, DMSO): 10.8 (1H, br s), 7.8 (1H, d), 7.4–7.6 (5H, m), 7.2–7.3 (2H, m), 7.0 (1H, s). $\delta_C$ (75 MHz, DMSO): 159.5, 139.9, 137.5, 132.0, 131.3, 130.3, 129.3, 127.1, 126.4, 125.7, 124.0, 122.0, 100.3. GC-MS: *m*/*z* 255, 227, 192, 165, 137, 113, 95, 81, 63.

**1-(2-Chlorophenyl)isoquinolin-3-yl trifluoromethanesulfonate 6.** A suspension of **5** (0.37 g) in dry pyridine (10 mL) was cooled to 0 °C and carefully treated with trifluoromethanesulfonic anhydride (0.4 mL, 0.68 g, 2.3 mmol). The mixture was allowed to warm to room temperature and stirred over night. The solvent was removed under reduced pressure and the residue was partitioned between water and diethyl ether. The ether extract was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography using hexane–diethyl ether (1 : 1) as the eluent ($R_f$=0.6) to afford the product as a yellow solid (0.40 g, 71%), mp 72 °C.

$\delta_H$ (200 MHz, $CDCl_3$): 7.95–7.99 (1H, d), 7.71–7.81 (2H, m), 7.66 (1H, s), 7.44–7.63 (5H, m). $\delta_C$ (50 MHz, $CDCl_3$): 158.9, 151.0, 138.9, 136.2, 133.2, 131.6, 131.3, 130.5, 129.8, 128.3, 127.6, 127.2, 126.8, 110.8, 109–128 (q, $-CF_3$). GC-MS: *m*/*z* 387, 359, 254, 236, 228, 226, 202, 191, 164.

***N*-Methyl-*sec*-butylamine 10.** A solution of *sec*-butylamine (1.0 g, 13.7 mmol) in dry diethyl ether (15 mL) was cooled to 0 °C and treated with triethylamine (1.9 mL, 1.41 g, 14 mmol). Ethyl chloroformate (1.3 mL, 1.49 g, 13.7 mmol) was added dropwise and the mixture was stirred at room temperature for 1 h under nitrogen. Water (20 mL) was added and the product was extracted with diethyl ether (3 × 15 mL). The ether extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the carbamate **9** as a colourless oil (1.73 g, 87%). A solution of carbamate **9** (1.0 g, 6.9 mmol) in dry THF (10 mL) was treated carefully with $LiAlH_4$ (10 mL of a 1 M solution in THF) and the mixture was refluxed for 4 h under argon. The excess hydride was decomposed by slow addition of water (15 mL). The precipitate was filtered off and the filtrate was made acidic (pH ~ 2) with conc. HCl. The solvent was removed under reduced pressure and the residue was dissolved in water and extracted with diethyl ether. The aqueous extract was concentrated under reduced pressure (assisted with the addition of ethanol) to give the amine as the hydrochloride salt (0.72 g, 85%), mp 120 °C (lit. 120–122 °C).

$\delta_H$ (300 MHz, $CDCl_3$): 9.2 (2H, br s) 3.0 (1H, m), 2.5 (3H, t), 1.9 (1H, m), 1.7 (1H, m), 1.3 (3H, d), 0.9 (3H, t). $\delta_C$ (75 MHz, $CDCl_3$): 56.7, 29.6, 25.6, 15.2, 9.8.

## Synthesis of reference compounds

**General procedure.** 1-(2-Chlorophenyl)isoquinoline-3-carboxylic acid **11** (300 mg, 1.06 mmol) was suspended in dry $CH_2Cl_2$ (10 mL) and oxalyl chloride (185 μL, 2.12 mmol) was added followed by 2 drops of DMF. The mixture was stirred at 25 °C for 2 h. The solvent was removed under reduced pressure and traces of oxalyl chloride were removed by the addition and subsequent evaporation of toluene (2 × 3 mL). The residue was dissolved in dry THF (10 mL) and added to an ice cold solution of the amine (1.5 mmol) and pyridine (86 μL, 1.06 mmol) in THF (10 mL). The mixture was stirred at 25 °C for another 2 h, concentrated under reduced pressure and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic extract was washed with water (2 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by flash chromatography using ethyl acetate–pentane (1 : 1) as the eluent. The compound **12d** was purified by recrystallization from absolute ethanol.

*N-(1-Methylethyl)-1-(2-chlorophenyl)isoquinoline-3-carboxamide 12a.* Yield 75%, mp 148 °C. $\delta_H$ (400 MHz, $CDCl_3$): 8.6 (1H, s), 8.1 (2H, m), 7.6 (2H, m), 7.5 (2H, m), 7.4 (3H, m), 4.3 (1H, m), 1.2 (6H, m). $\delta_C$ (100 MHz, $CDCl_3$): 163.8, 157.3, 142.9, 137.8, 136.6, 133.4, 131.5, 130.7, 130.1, 129.8, 128.8, 128.5, 128.2, 127.2, 126.8, 120.2, 41.4, 22.86, 22.84. GC-MS: *m*/*z* 324, 309, 281, 266, 241, 239, 220, 203, 176, 150, 139, 120, 102, 88, 87, 58.

*N*,*N*-Dipropyl-1-(*2-chlorophenyl)isoquinoline-3-carboxamide 12b.* Yield 55%, mp 104 °C. $\delta_H$ (400 MHz, $CDCl_3$): 8.0 (1H, s), 7.9 (1H, d), 7.7 (1H, t), 7.6–7.5 (3H, m), 7.4–7.3 (3H, m), 3.5–3.4 (3H, m), 3.3 (1H, m), 1.7 (2H, m), 1.6 (1H, m), 0.9 (3H, t), 0.6 (3H, t). $\delta_C$ (100 MHz, $CDCl_3$): 169.0, 157.4, 148.2, 138.1, 136.6, 133.3, 131.3, 130.6, 130.0, 129.7, 128.3, 127.8, 127.2, 127.1, 126.8, 120.9, 51.0, 48.3, 22.3, 21.02, 11.7, 11.1. GC-MS: *m*/*z* 366, 337, 309, 281, 266, 242, 239, 203, 176, 128, 101, 58.

*N*,*N*-Diallyl-1-(*2-chlorophenyl)isoquinoline-3-carboxamide 12c.* Yield 50%, mp 120 °C. $\delta_H$ (400 MHz, $CDCl_3$): 8.1 (1H, s), 7.9 (1H, d), 7.7 (1H, t), 7.6 (1H, d), 7.5 (2H, m), 7.4 (3H, m), 5.9 (2H, m), 5.2 (2H, m), 5.0 (2H, m), 4.1 (3H, m), 4.0 (1H, m). $\delta_C$ (100 MHz, $CDCl_3$): 169.1, 157.5, 147.3, 137.8, 136.5, 134.1, 133.3, 133.0, 131.3, 130.7, 130.0, 129.7, 128.5, 127.8, 127.4, 127.2, 126.8, 121.3, 117.8, 117.7, 51.0, 47.8. GC-MS: *m*/*z* 362, 334, 327, 321, 293, 284, 267, 266, 253, 239, 204, 176, 151, 128, 97, 68.

*N*-Phenyl-1-(*2-chlorophenyl)isoquinoline-3-carboxamide 12d.* Yield 40%, mp 159 °C. $\delta_H$ (400 MHz, $CDCl_3$): 10.1 (1H, br s), 8.7 (1H, s), 8.1 (1H, d), 7.7–7.8 (4H, m), 7.6 (2H, m), 7.5 (3H, m), 7.3–7.4 (2H, m), 7.1 (1H, t). $\delta_C$ (100 MHz, $CDCl_3$): 162.6, 157.5, 142.6, 137.9, 137.6, 136.8, 133.5, 131.5, 131.1, 130.3, 130.0, 129.3, 129.0, 128.7, 128.5, 127.5, 126.9, 124.3, 120.8, 119.9. GC-MS: *m*/*z* 358, 329, 281, 265, 256, 239, 225, 203, 176, 152, 135, 88, 73.

## Synthesis of *N*-methyl-*N*-(1-methylpropyl)-1-(2-chlorophenyl)-isoquinoline-3-[$^{11}$C]carboxamide and analogues

**General procedure.** The triflate **6** (6.2 mg, 16.0 μmol), tetrakis(triphenylphosphine)palladium (4.6 mg, 4.2 μmol) and

LiBr (2.0 mg, 23 μmol) were placed in a vial (1 mL). The vial was flushed with nitrogen and the contents were dissolved in THF (250 μL). The mixture was shaken until the solution was homogeneous. Amine (143 μmol) was added and the resulting mixture was transferred under pressure (35 MPa) to the micro-autoclave (200 μl), pre-charged with [$^{11}$C]carbon monoxide in helium. The micro-autoclave was heated at 180 °C for 5 min. The crude product was transferred to a pre-evacuated, septum-fitted vial (5 mL). The micro-autoclave was washed with THF (200 μL) which was emptied into the same collection vial. The radioactivity was measured before and after the vial was purged with nitrogen. The solvent volume was reduced to less than 0.2 mL by heating at 50 °C and purging with nitrogen. Acetonitrile–water (1 : 1, 2 mL) was added and the resulting solution was injected onto the semi-preparative LC. Solvent A–B (50 : 50), linear gradient to 0 : 100 within 8 min, flow 4 mL min$^{-1}$, $t_R$= 12.5, 12.6, 11.9, 12.8, 11.8 and 13.5 min for products **7a**, **7b**, **7c**, **7d**, **7e** and **7f** respectively. The identity and radiochemical purity of the collected fractions were assessed by analytical LC: solvent A–B (70 : 30), linear gradient to 0 : 100 within 10 min, flow 1.5 mL min$^{-1}$, wavelength 254 nm, $t_R$ = 9.3, 11.3, 10.5, 11.8, 11.1 and 12.6 min for products **7a**, **7b**, **7c**, **7d**, **7e** and **7f** respectively. LC-MS: *m*/*z* 353, 339, 325, 367, 363 and 359 ($M^+$ + 1) for products **7a**, **7b**, **7c**, **7d**, **7e** and **7f** respectively.

**Synthesis of *N*-(1-methylethyl)1-(2-chlorophenyl)-isoquinoline-3-($^{13}$C)carboxamide ($^{13}$C-7c).** Tetrakis(triphenylphosphine)palladium (9.6 mg, 8.8 μmol), triflate **6** (15.5 mg, 40 μmol) and LiBr (4.3 mg, 49.4 μmol) were put in a vial (1 mL). The vial was flushed with nitrogen and the contents were dissolved in THF (250 μL). Isopropylamine (20 μL, 234 μmol) was added and the resulting homogeneous mixture and ($^{13}$C)carbon monoxide were transferred under pressure (35 MPa) to the micro-autoclave (200 μL). The micro-autoclave was heated (180 °C) for 10 min. The crude product was transferred to a pre-evacuated, septum-fitted vial (5 mL). The solvent was evaporated by purging with nitrogen at 50 °C. A sufficient quantity of the corresponding $^{11}$C-labelled compound was added to the crude product and purified by semipreparative LC using the same chromatographic method as described for the $^{11}$C-labelled compound. The radioactive fraction was collected and evaporated under reduced pressure to yield the title compound (4.0 mg, 32% calculated from **6**). $\delta_C$ (100 MHz, $CDCl_3$): 163.95 (carbonyl carbon).

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