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Synthesis of ^{3}H, $^{13}C,^{2}H_3,^{15}N$ and ^{14}C-labelled SCH 466036, a histamine 3 receptor antagonist

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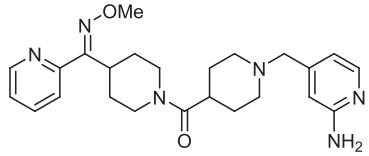
The synthesis of [^{3}H]SCH 466036, [Me-$^{3}H_3$]SCH 466036, [$^{13}C,^{2}H_3,^{15}N$]SCH 466036 and [^{14}C]SCH 466036 is described. [^{3}H]SCH 466036 was prepared in two steps via Raney Ni-catalysed exchange with tritiated water. [Me-$^{3}H_3$]SCH 466036 was prepared in a single step from [^{3}H]methyl iodide in 45% yield. [$^{13}C,^{2}H_3,^{15}N$]SCH 466036 was prepared in two steps from [^{15}N] hydroxylamine and [$^{13}C,^{2}H_3$]methyl iodide with an overall yield of 16%. [^{14}C]SCH 466036 was prepared in seven steps from [^{14}C]potassium cyanide in an overall yield of 13%.

Keywords: tritium; deuterium; carbon-14; nitrogen-15; SCH 466036; H3 antagonist

Introduction

SCH 466036, **1**, is a potent and selective histamine 3 (H3) receptor antagonist.[1–4]



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H3 antagonists have been shown to be effective in animal models of allergy, congestion, obesity and metabolic syndrome.[1–4] [^{3}H]SCH 466036 of moderate specific activity was rapidly prepared to support preliminary absorption, distribution, metabolism and excretion studies. In addition, high specific activity [^{3}H]SCH 466036 was prepared for H3 receptor-binding studies. Subsequently, stable isotope-labelled SCH 466036 was made for use as an internal standard to support the toxicology and clinical programmes, and [^{14}C]SCH 466036 was then prepared for the drug disposition group to conduct definitive pharmacokinetic and drug metabolism studies. This paper discusses the synthesis of all four isotopically labelled forms of SCH 466036.

Results and discussion

Low specific activity [^{3}H]SCH 466036, requested for pilot absorption, distribution, metabolism and excretion studies, was prepared by Raney nickel-catalysed exchange of ketone intermediate **2** with 50 Ci/mL tritiated water (Figure 1).[5]

A batch of 29 mCi of crude compound **3** was isolated from the tritiation. After silica gel chromatography, the purified intermediate **3** was heated with methoxyamine hydrochloride in pyridine to generate 39% of the desired *E* oxime **4**. After reverse-phase high performance liquid chromatography (HPLC), a batch of 5.5 mCi at 99% radiochemical purity at a specific activity of 324 mCi/mmole was obtained. ^{3}H NMR analysis (Figure 2) showed that 51% of the tritium was present in the expected 6-position in the 2-aminopyridine ring with an additional 43% present in the piperidine ring, α to the oxime, which is likely incorporated by a base-catalysed mechanism.[6,7] The remaining 6% was located in the monosubstituted ring adjacent to the pyridine nitrogen, clearly showing a much lower affinity for the Raney Ni catalyst than the 2-aminopyridine ring system.

High specific activity [^{3}H]SCH 466036, for receptor binding studies, was prepared by methylation of the free oxime **5** with [^{3}H]methyl iodide under phase-transfer conditions with the phase-transfer catalyst 'Aliquat 336' (Figure 3).

A 10-fold excess of the free oxime **5** was used in an attempt to optimize the utilization of the [^{3}H]methyl iodide and thus achieve a reasonable conversion to compound **6**. The addition of methylene chloride as an organic cosolvent facilitated the solubility of the ketone in toluene, deriving from the [^{3}H]methyl iodide solution in toluene. After purification by reverse-phase HPLC, a 45 mCi batch of [Me-$^{3}H_3$]SCH 466036 was obtained at a radiochemical purity of 98%, at specific activity of 82.9 Ci/mmole.

[$^{13}C,^{2}H_3,^{15}$N]SCH 466036 was prepared in two steps as shown in Figure 4.

The formation of the oxime **8** was accomplished by refluxing ketone **7** with [^{15}N]hydroxylamine hydrochloride in pyridine. This led to a 50:50 mixture of the *E* and *Z* isomers, which were then

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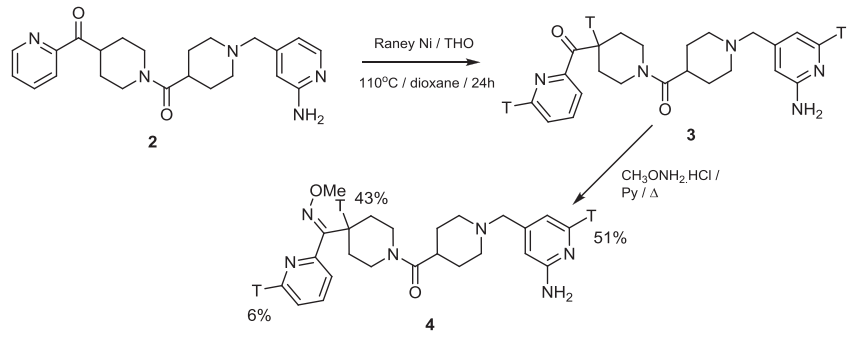

Figure 1. Synthesis of [^{3}H]SCH 466036.

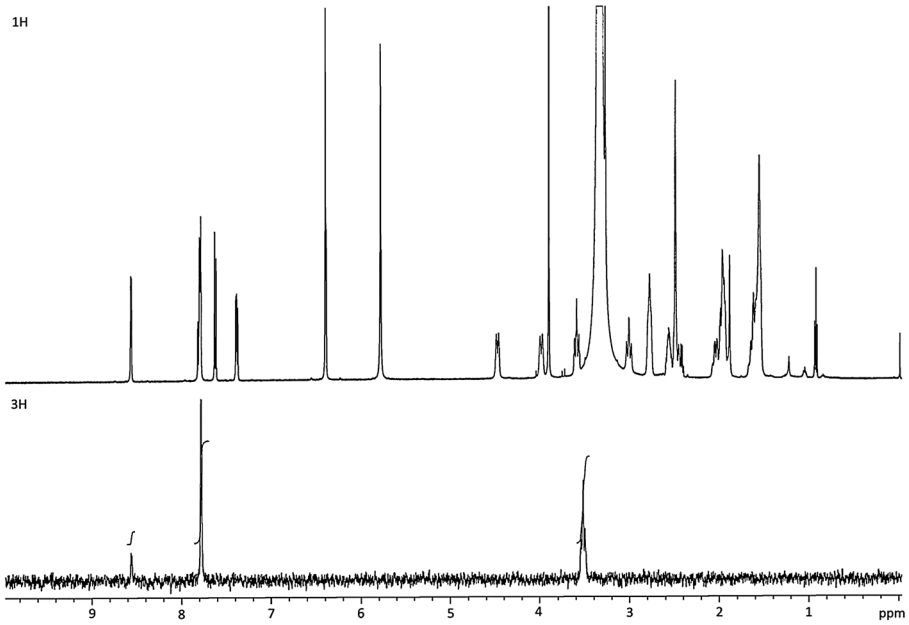

Figure 2. ^{1}H and ^{3}H NMR of [^{3}H]SCH 466036.

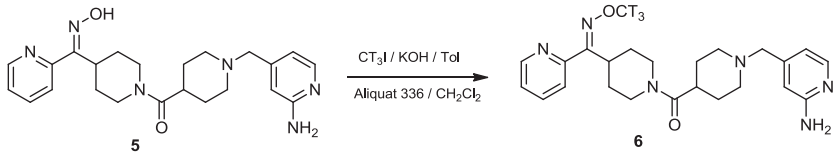

Figure 3. Synthesis of [Me-$^{3}H_3$]SCH 466036.

methylated with [^{13}C,$^{2}H_3$]methyl iodide with potassium hexamethyldisilylazide as the base. After silica gel chromatography and chiral HPLC purification of the desired *E* isomer, a batch of 114 mg of [^{13}C,$^{2}H_3$,^{15}N]SCH 466036 was isolated in overall 16% yield. Although a chiral column is not required for the separation of the oxime isomers, it provides a greatly improved separation over silica gel and a greatly improved loading over an achiral reverse-phase HPLC column.

[^{14}C]SCH 466036 was prepared as shown in Figure 5.

2-Cyanopyridines have classically been prepared by reaction of copper cyanide with 2-bromopyridine[8] and by reaction of pyridine-*N*-oxide with dimethyl sulfate[9] or by treatment of 1-methyloxypyridinium iodide with potassium cyanide.[10,11] The former reaction is conducted as a high temperature melt, and the product is isolated by distillation. As such, this would be a difficult reaction to replicate on the small scale that ^{14}C synthesis is normally performed. The latter reactions typically produce mixtures of the 2 and 4 isomers, although some control of the isomer ratio is possible by careful control of the reaction conditions. Selective 2-cyanation has been reported by Vorbruggen and Krolikiewicz,[12] who used trimethylsilyl chloride and a 4.5 molar excess of sodium cyanide, and by Fife and Boyer,[13,14] who reported the use of dimethylcarbamyl chloride with potassium cyanide to selectively prepare 2-cyanopyridine under mild conditions in high yields. Hence, pyridine-*N*-oxide was pretreated with dimethylcarbamyl chloride to form the 1-dimethylaminocarbonyloxy pyridinium cation that was then

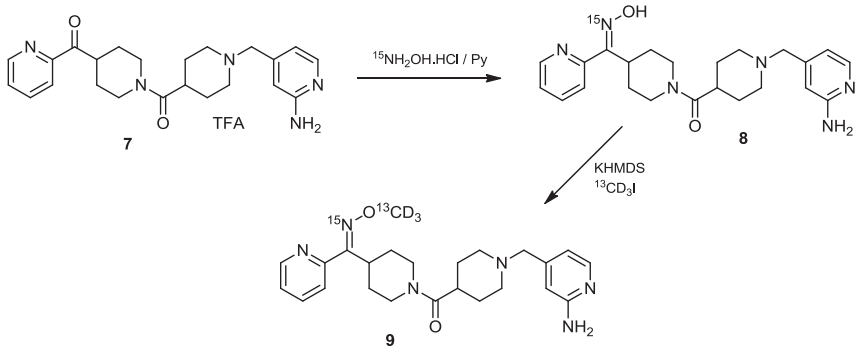

Figure 4. Synthesis of [^{13}C,$^{2}H_3$,^{15}N]SCH 466036.

treated with aqueous [^{14}C]potassium cyanide at room temperature to give compound **10**. As [^{14}C]2-cyanopyridine is volatile, the product was isolated by ether extraction and thoroughly dried over anhydrous sodium sulfate prior to concentration to a volume of about 1 mL via distillation. The ether solution containing compound **10** with 97 mCi (89% yield) was then directly reacted with the Grignard reagent[15] **11** to generate **12** in 35% yield after purification. After treatment with ethyl chloroformate to generate carboethoxy intermediate **13**, acidic hydrolysis yielded **14** as a di-hydrochloride salt in 76% yield. An attempt to directly convert **12** to **14** using 1-chloroethylchloroformate led to a 30% yield of **14**.[16] Formation of the oxime *E*/*Z* mixture was accomplished by reaction with methoxyamine hydrochloride under aqueous conditions with careful adjustment of the pH to pH 3.5–5 with sodium hydroxide. Treatment with 6 M hydrogen chloride in isopropanol and heating of the resulting slurry of the dihydrochloride salt in isopropanol led to 90% conversion to the desired *E* isomer **15**. Finally, after a standard coupling with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBt) followed by removal of the butyloxycarbonyl group with trifluoroacetic acid and HPLC purification, a 13.5 mCi batch of [^{14}C]SCH 466036 at a specific activity of 57.1 mCi/mmole was prepared in overall 13% yield from [^{14}C]potassium cyanide. The radiochemical purity as determined by reverse-phase HPLC was >99%.

Experimental

Materials

[^{14}C]Potassium cyanide was purchased from Quotient Bioresearch, Fordham Cambridgeshire, UK. [^{3}H]Methyl iodide was purchased from American Radiolabeled Chemicals Inc., St. Louis, MO, USA. [^{13}C,$^{2}H_3$] Methyl iodide and [^{15}N]hydroxylamine were purchased from Cambridge Isotopes Inc., Tewksbury, MA, USA. Unlabelled intermediates **2**, **5**, **7** and **16** were obtained from Merck Process Chemistry (Union NJ, USA). All reagents and solvents were purchased from Aldrich (Milwaukee, MI, USA) and used as received unless otherwise stated. All synthetic steps were carried out under an atmosphere of argon.

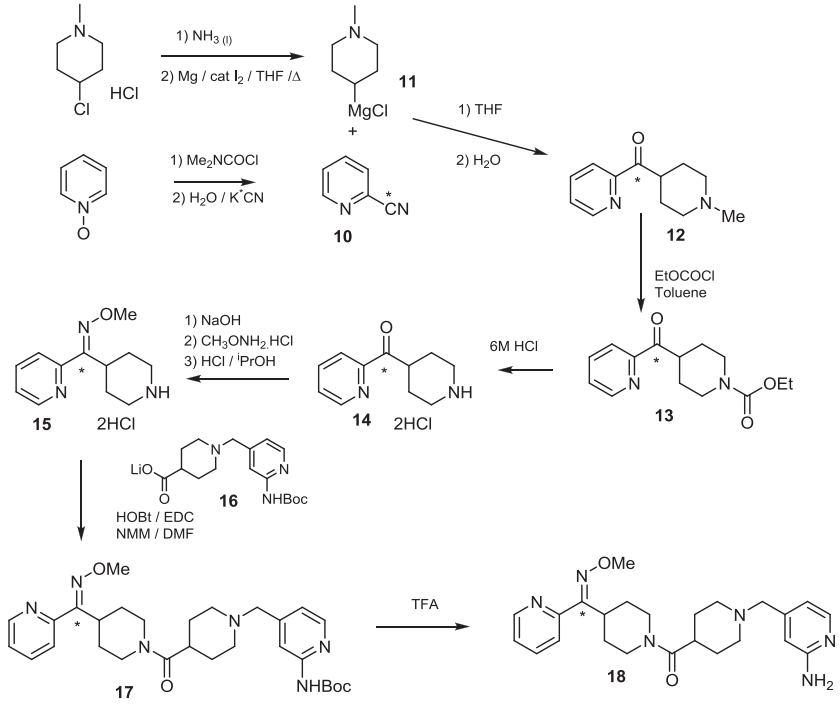

Figure 5. Synthesis of [^{14}C]SCH 466036.

Liquid scintillation counting

Radioactivity measurements were performed on a Packard 2900CA (Perkin Elmer, Downers Grove IL, USA) liquid scintillation analyser using Scintiverse BD (Perkin Elmer, Downers Grove IL, USA) as liquid scintillation cocktail.

Thin layer chromatography

Radio-thin layer chromatography (TLC) was performed with Whatman LK6DF (silica gel 60) 5 × 20 cm, 0.25 mm plates. The plates were scanned on a Bioscan 1000 linear analyser (Washington DC, USA).

System 1: Methylene chloride : methanol (90:10).
System 2: Methylene chloride : 2 M methanolic ammonia (90:10).
System 3: Ethyl acetate : hexane (50:50).
System 4: Methylene chloride : 2 M methanolic ammonia (95:5).
System 5: Methylene chloride : methanolic ammonia (98.5:1.5).

High performance liquid chromatography

A Waters 2695 Alliance System with a Waters 996 Photodiode array detector (Milford MA, USA) was used. Radiochemical purity was determined by a Radiomatic C150 radio flow detector (Perkin Elmer, Downers Grove IL, USA) with Flo-Scint III liquid scintillation cocktail (Perkin Elmer, Downers Grove IL, USA). The following systems were used:

System 1: Agilent Zorbax Extend C18, 50 × 4.6 mm, 1.8 μ 266 nm, 0.05 M pH 10 triethylammonium acetate : acetonitrile (72:28) for 6 min followed by a step gradient to acetonitrile, 1 mL/min.
System 2: Agilent Zorbax Extend C18, 150 × 3 mm, 5 μ 254 nm, 0.05 M pH 9 triethylammonium acetate : acetonitrile (70:30) for 15 min followed by a step gradient to acetonitrile, 0.5 mL/min.
System 3: YMC Pro C18 150 × 4.6 mm, 5 μ, 275 nm, 0.05 M pH 4 triethyl ammonium acetate (85:15) acetonitrile for 15 min followed by a step gradient to acetonitrile, 1 mL/min.
System 4: Waters Xterra C18 150 × 3 mm, 5 μ, 230 nm, 0.02 M sodium tetraborate : acetonitrile (85:15), 0.5 mL/min.

Specific activity measurements

The chemical concentrations of [^{3}H] and [^{14}C]SCH 466036 were determined using an ultraviolet-based HPLC assay (systems 1 and 2) using an authentic standard of SCH 466036 for [^{3}H]SCH 466036 and a reference standard of SCH 466036 for [Me-$^3H_3$]SCH 466036 and [^{14}C] SCH 466036. These data were used in conjunction with the radiochemical concentration to calculate the specific activity values.

Mass spectrometry

Mass spectra were acquired on the JEOL MStation magnetic sector mass spectrometer (JEOL USA, Inc., Peabody, MA, USA) operating in the positive-ion electrospray ionization or fast atom bombardment (FAB) ionization mode.

Synthesis of [^{3}H]SCH 466036

*[^{3}H](1-((2Aminopyridin-4-yl)methyl)piperidin-4-yl)(4-picolinoylpiperidin-1-yl)methanone (**3**)*

A 40 mg of Raney Ni slurry in acetone was weighed into a thick-walled glass tritiation ampoule, and the acetone was removed under a stream of nitrogen. Compound **2** (20 mg) was then added followed by dioxane (100 μL) and tritiated water (50 Ci/mL, 500 mCi, 10 μL). The tube was capped with a rubber septum, frozen in liquid nitrogen, evacuated and sealed in a flame. The reaction was heated for 24 h at 110 °C, before being cooled to room temperature and opened. The ampoule contents were partitioned between 1 M potassium hydroxide solution (2 mL) and methylene chloride (5 mL). The methylene chloride layer was removed, and the aqueous layer further extracted with methylene chloride (3 × 5 mL). The combined extracts were washed with water (2 mL) and evaporated to dryness. A total of 29 mCi of **3** at a radiochemical purity of 79% (TLC system 2) was isolated. The crude product was purified by chromatography on silica gel using a methylene chloride : methanol gradient (0–10%). Fractions containing the purified product were pooled and evaporated to dryness to yield 19 mCi of **3**, which was used directly in the next step.

*[^{3}H](E)-(1-((2-Aminopyridin-4-yl)methyl)piperidin-4-yl)(4-((methoxyimino)(pyridin-2-yl)methyl)piperidin-1-yl)methanone [^{3}H] SCH 466036 (**4**)*

To a solution of 19 mCi of **3** in pyridine (0.5 mL) was added methoxyamine hydrochloride (8.8 mg). The reaction was heated at 90 °C overnight and then assayed in HPLC system 2, which showed 80% conversion to a (1:1) mixture of *E* and *Z* oxime isomers. The reaction was evaporated to dryness, diluted with water (2 mL) and adjusted to >pH 10 with concentrated ammonia. The resulting suspension was extracted with methylene chloride (3 × 5 mL). The combined extracts were washed with water (2 mL), dried over anhydrous sodium sulfate and evaporated to dryness. The product was purified by reverse-phase HPLC using a 250 × 9.4 mm Extend C18 column with a mobile phase of 0.05 M pH 9 triethylammonium acetate : acetonitrile (70:30) at a flow of 4 mL/min and 254 nm. Fractions containing the purified product were pooled, evaporated to dryness and dissolved in 20 mL ethanol. A total of 5.6 mCi of [^{3}H]SCH 466036 **4** was isolated at a radiochemical purity of 99.8% and 99.0% (HPLC system 1 and TLC system 2) and a specific activity of 372 mCi/mmol. ^{3}H NMR: (426 MHz) d_6-DMSO, δ8.56(d) 6%, δ7.78(d) 51%, δ3.56(m) 43%.

Synthesis of [Me-$^3H_3$]SCH 466036

*(E)-(1-((2-Aminopyridin-4-yl)methyl)piperidin-4-yl)(4-(([Me-$^3H_3$] methoxyimino)(pyridin-2-yl)methyl)piperidin-1-yl)methanone (**6**)*

Compound **5** (4.05 mg, 0.988 μmol) was suspended in potassium hydroxide solution (0.1 M, 250 μL), water (250 μL) and methylene chloride (300 μL). A stock solution of Aliquat 336 (670 mg) in toluene (10 mL) was prepared and 60 μL, 0.996 μmol of this was added to the reaction. A toluene solution of 85 Ci/mmol [^{3}H]methyl iodide (100 mCi, 500 μL) was added, and the resulting two-phase mixture was vigorously stirred overnight. The reaction was diluted with the addition of water (2 mL) and ethyl acetate (2 mL). The ethyl acetate layer was removed, and the aqueous layer extracted with ethyl acetate (3 × 3 mL). The combined ethyl acetate fractions were washed with water (1 mL), dried over anhydrous sodium sulphate and evaporated to dryness to yield 64 mCi of crude product at 77% radiochemical purity in HPLC system 1. The product was purified as described for **4** to yield 46 mCi at a radiochemical purity of 99.0% and 98.4% (HPLC system 1 and TLC system 2) and a specific activity of 82.9 Ci/mmol.

Synthesis of [^{13}C,$^2H_3$,^{15}N]SCH 466036

*(E)-(1-((2-Aminopyridin-4-yl)methyl)piperidin-4-yl)(4-((hydroxy[^{15}N] imino)(pyridin-2-yl)methyl)piperidin-1-yl)methanone (**8**)*

Compound **7** (1.0 g, 2.45 mmol) and [^{15}N]hydroxylamine hydrochloride (1.04 g, 14.72 mmol) were dissolved in pyridine (12 mL). The reaction was heated at 80 °C for 5 h at which point the reaction was complete (TLC system 1). The solution was evaporated to dryness, dissolved in toluene and re-evaporated to dryness. The crude product was initially purified by chromatography on silica gel using a gradient of methylene chloride and methanol (0–50%). Fractions containing the purified

product were pooled and evaporated to dryness to yield the purified product **8**, 1 g. The batch was further purified on a Chiralpak AD column, 50 cm × 5 cm, ID, with a mobile phase of hexane : isopropanol : diethylamine (75:25:0.5) at a flow of 40 mL/min and detection at 254 nm. Fractions containing the purified product were pooled and evaporated to dryness to yield 440 mg (43%) of compound **8**.

*(E)-(1-((2-Aminopyridin-4-yl)methyl)piperidin-4-yl)(4-(([^{13}C,$^{2}H_3$]methoxy[^{15}N]imino)(pyridin-2-yl)methyl)piperidin-1-yl)methanon [^{13}C,$^{2}H_3$,^{15}N]SCH 466036 (**9**)*

Compound **8** (296 mg, 0.7 mmol) was dissolved in freshly distilled dimethylformamide (DMF) (3.8 mL) and cooled to −10 °C. Potassium hexamethyldisilazide solution (0.5 M, 1.4 mL, 0.7 mmol) was added dropwise over 5 min, and the solution was stirred at this temperature for 30 min. A stock solution of [^{13}C,$^{2}H_3$]methyl iodide (0.2 mL) was prepared in freshly distilled tetrahydrofuran (THF) (2 mL), and 0.46 mL (0.74 mmol) of this solution was added dropwise over 5 min to the reaction. The reaction was stirred for 1 h at this temperature and then quenched by the addition of brine (8 mL). The product was extracted with methylene chloride (2 × 10 mL) and 10% ethanol in methylene chloride (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified on silica gel and by HPLC on a ChiralPak AD column using the same conditions described for compound **8** to yield a total of 200 mg of compound **9**. The batch was finally recrystallized from methanol : water to yield a total of 114 mg (37% yield of **9**). Purity (HPLC system 2): 99.3%. FAB-MS/MS: *m/z* 442. High resolution MS: *m/z* 442.2864 confirms the composition of $C_{23}^{13}CH_{30}^{2}H_3O_2N_5^{15}N$.

Synthesis of [^{14}C]SCH 466036

*[^{14}C]2-cyanopyridine (**10**)*

In a flame-dried 10-mL flask, pyridine-*N*-oxide (180.3 mg, 1.896 mmol) was added and heated to 70 °C until a complete melt was achieved. *N*, *N*-dimethylcarbamyl chloride (190 μL, 2.1 mmol) was added dropwise at this temperature, and a precipitate formed. Heating was continued for a further 2 h, and then the reaction was cooled to room temperature. The activated pyridine was dissolved in water (0.8 mL), and this solution was added dropwise to a 0 °C solution of [^{14}C]potassium cyanide (123.5 mg, 100 mCi, 1.896 mmol). The reaction was stirred at this temperature for 5 min and then at room temperature overnight. Analysis by TLC system 3 showed complete reaction. Potassium carbonate solution (1 M, 200 μL) was added to the reaction, and the product was extracted with ether (3 × 7 mL). The combined ether extracts were washed with water (1 mL), dried over anhydrous sodium sulfate, filtered and concentrated by distillation using a short path condenser to a volume of about 1 mL and used directly in the next step. Yield = 97 mCi.

*(1-Methylpiperidin-4-yl)(pyridin-2-yl)[^{14}C]methanone (**12**)*

The ether solution of [^{14}C]2-cyanopyridine (97 mCi) was cooled to 0 °C, and a THF solution of (1-methylpiperidin-4-yl)magnesium chloride[15] **11** (2.5 M, 1.5 mL, 3.84 mmol) was added dropwise. The reaction was stirred at 0 °C for 90 min and then was quenched by the addition of concentrated hydrochloric acid (HCl) (420 μL), crushed ice and ethyl acetate (4 mL). Stirring was continued for a further 20 min at 0 °C and at room temperature for 2 h at which point analysis by TLC system 4 showed complete reaction. The ether layer was removed, and the aqueous fraction was basified with concentrated ammonia to pH 11 and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and evaporated to an oil. The crude product was purified by chromatography on silica gel using a gradient of methylene chloride : methanol (0–5% methanol) to yield **12** (39 mCi) as a yellow oil after concentration, which was used directly in the next step.

*Piperidin-4-yl(pyridin-2-yl)[^{14}C]methanone dihydrochloride (**14**)*

A solution of **12** (39 mCi, 0.64 mmol) in anhydrous toluene (2 mL) was heated to 70 °C. Ethyl chloroformate (190 μL, 1.99 mmol) was added dropwise, and the reaction heated for 2 h at this temperature. Analysis by TLC system 5 showed complete reaction. The reaction was cooled to room temperature, and potassium bicarbonate solution (1 M, 220 μL) added. The organic layer was removed, and the residual aqueous layer extracted with toluene (5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to yield **13** (29.5 mCi) as an oil. HCl (6 M, 5.5 mL) was added, and the reaction heated overnight at 110 °C. After cooling to room temperature, the reaction was concentrated to a volume of around 1 mL and used directly in the next step.

*(E)-Piperidin-4-yl(pyridin-2-yl)[^{14}C]methanone O-methyl oxime (**15**)*

The 1-mL solution of **14** generated in the previous step (29.5 mCi and 0.52 mmol) was diluted with water (2 mL) and basified to pH 10 with 25% sodium hydroxide solution. Methoxyamine hydrochloride solution (30 wt.%, 80 μL, 1.04 mmol) was added, and the pH was adjusted with 25% sodium hydroxide solution to a range of pH 3.5–5. The reaction was then heated at 55 °C for 5 h at which point monitoring by HPLC system 4 showed complete conversion to a (1:1) mixture of *E* and *Z* isomers of 15. The reaction was cooled to room temperature, basified with 25% sodium hydroxide solution to pH 13 and extracted with methylene chloride (3 × 6 mL). The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered and evaporated to an oil. The oil was then dissolved in toluene (280 μL), and a solution of HCl in isopropanol (5–6 M, 280 μL) was added. The solution was heated to 65 °C at which point a slurry was formed. After cooling to room temperature, the solid was washed with isopropanol (3 × 1 mL) with the isopropanol removed by a medium porosity filter stick. An additional 700 μL of isopropanol was added, and the slurry was heated at 80 °C overnight. Analysis by HPLC system 2 showed that a (90:8) ratio of *E* to *Z* oxime had formed. The isopropanol was removed by filter stick, and the solid dried under vacuum to yield 108 mg, 25 mCi of **15**.

(E)-tert-Butyl (4-((4-(4-((methoxyimino)(pyridin-2-yl)[^{14}C]methyl) piperidine-1-carbonyl)piperidin-1-yl)methyl)pyridin-2-yl) carbamate (**17**)

Compound **17** (125.7 mg, 0.37 mmol) and **15** (25 mCi, 108 mg and 0.37 mmol) were dissolved in DMF (650 μL), and *N*-methyl morpholine (190 mL, 1.7 mmol), EDC (106.4 mg, 0.56 mmol) and HOBt (75 mg, 0.56 mmol) were added. The reaction was stirred overnight at room temperature and was shown to be complete by TLC system 1. The DMF was removed by evaporation, and the resulting oil partitioned between methylene chloride (10 mL) and water (4 mL). The methylene chloride layer was removed, and the aqueous layer extracted with a further 10 mL of methylene chloride. The combined methylene chloride layers were washed with sodium bicarbonate solution (0.3 M, 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to yield **17** (18 mCi) as an oil, which was used directly in the next step.

*(E)-(1-((2-Aminopyridin-4-yl)[^{14}C]methyl)piperidin-4-yl)(4-((methoxyimino)(pyridin-2-yl)methyl)piperidin-1-yl)methanone [^{14}C]SCH 466036 (**18**)*

Trifluoroacetic acid (500 μL) was added to a solution of **17** (18 mCi, 0.327 mmol) in methylene chloride (1.8 mL), and the reaction stirred overnight at room temperature. Analysis by TLC system 1 showed complete reaction. Water (2 mL) was added, and the reaction basified to pH 10 with 25% sodium hydroxide solution. The methylene chloride layer was removed, and the aqueous layer extracted with methylene chloride (3 × 7 mL). The combined methylene chloride layers were washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to an oil. The crude product was purified by chromatography on silica gel using a methylene chloride : 2 M methanolic ammonia gradient (0–5% methanolic ammonia). Fractions containing the purified product were pooled and evaporated to dryness to yield 16 mCi of **18**,

which contained 5% of the undesired *Z* oxime isomer. The batch was further purified by reverse-phase HPLC as described for **3** to yield a total of 13.5 mCi at a radiochemical purity of 99.1% and 99.6% (HPLC systems 2 and 3) and a specific activity of 57.1 mCi/mmol.

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Conflict of Interest

The authors did not report any conflict of interest.

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