

## Research Article

# The syntheses of [ $^{14}\text{C}$ ] and [ $^{13}\text{C}_2, ^{15}\text{N}_3$ ]aprepitant

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## Summary

In support of a program to develop a treatment for chemotherapy-induced nausea and vomiting, two isotopically labeled forms of neurokinin-1 receptor antagonist aprepitant have been synthesized. A [ $^{14}\text{C}$ ]-labeled version was synthesized for use in metabolism studies, while a [ $^{13}\text{C}_2, ^{15}\text{N}_3$ ]-labeled version was synthesized for use in a study to determine the bioavailability of the final market image. Both syntheses utilized labeled chloroacetonitrile which was synthesized in two steps from labeled potassium cyanide. Copyright © 2004 John Wiley & Sons, Ltd.

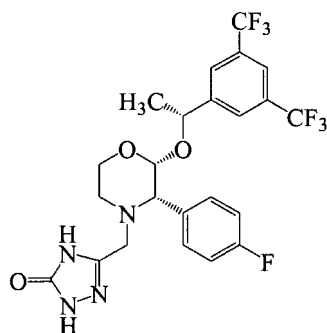
**Key Words:** substance P; hydroxyacetonitrile; chloroacetonitrile; NK1

## Introduction

Neurokinin 1 (NK1) receptor is a G-coupled protein which has the highest binding affinity for substance P among the endogenous neurokinins.<sup>1</sup> The release of substance P has been linked to inflammation and transmission of pain.<sup>2</sup> As a potential drug target, inhibition of substance P binding to the NK1 receptor has received significant attention over the last decade as a possible treatment for pain, migraines, chemotherapy-induced nausea and vomiting (CINV), and depression.<sup>3</sup> Recently, Merck's lead NK1 antagonist, aprepitant (**1**),<sup>4</sup> was approved for treatment of CINV.

During the course of development, several isotopically labeled aprepitant tracers were prepared to address a range of drug metabolism and receptor pharmacology issues. The primary tracer used for metabolism and distribution studies contained the C-14 label in the morpholine ring, and it showed aprepitant to be extensively metabolized.<sup>5</sup> Since *N*-dealkylation of the triazolone ring is a major metabolic pathway in all animal models studied, a tracer with a C-14 label in the triazolone ring was desired to study the metabolic fate of this fragment. Additionally, a stable isotope labeled form of

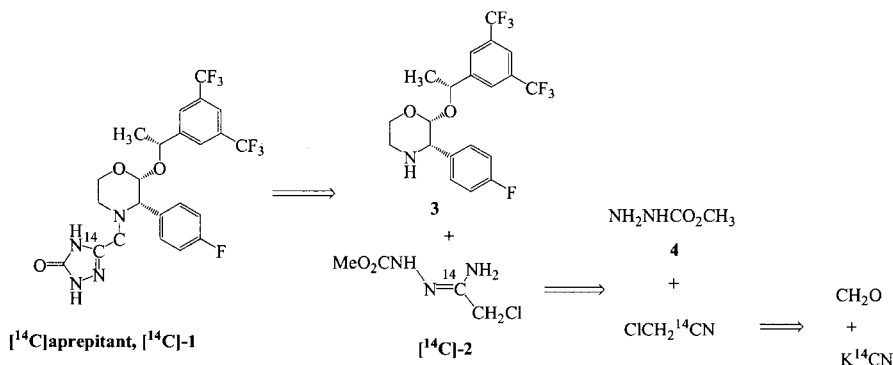
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aprepitant, **1**.

aprepitant with a minimum mass increase of 4 was required as a clinical tracer to determine the human bioavailability of the final market image (for an example of this type of application; see Reference<sup>6</sup>). Based on the synthesis of the above C-14-labeled tracer, incorporation of C-13 and N-15 could be readily accomplished to provide stable isotope labeled tracer with a mass increase of 5 amu.

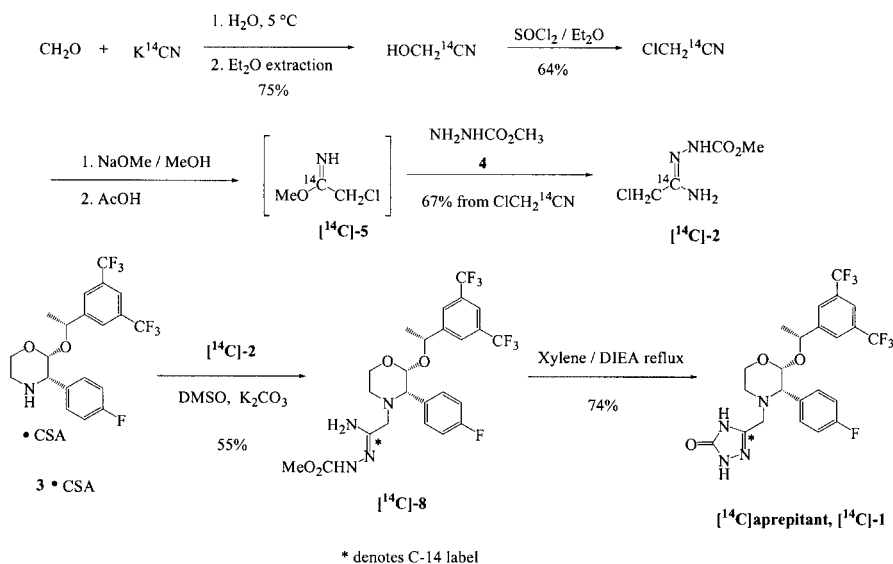
## Results and discussion

A retrosynthetic analysis for the C-14-labeled version of NK1 antagonist tracer [<sup>14</sup>C]-**1** based on the previously reported synthesis of aprepitant<sup>7</sup> led to the logical disconnection into amidrizone [<sup>14</sup>C]-**2** and amine **3** (Scheme 1). Amine **3** was available internally<sup>8</sup> while [<sup>14</sup>C]-**2** could be synthesized from [<sup>14</sup>C]chloroacetonitrile by reaction with hydrazine **4**. Previous syntheses of labeled chloroacetonitrile have relied upon the dehydration of labeled chloroacetamide which necessitated harsh reaction conditions, the inconvenient and costly preparation of [<sup>14</sup>C]chloroacetamide, and final purification by inefficient small-scale distillation.<sup>9</sup> We envisioned an alternative preparation of [<sup>14</sup>C]chloroacetonitrile from [<sup>14</sup>C]hydroxyacetonitrile which could be produced by the coupling of K<sup>14</sup>CN and paraformaldehyde.<sup>10</sup>



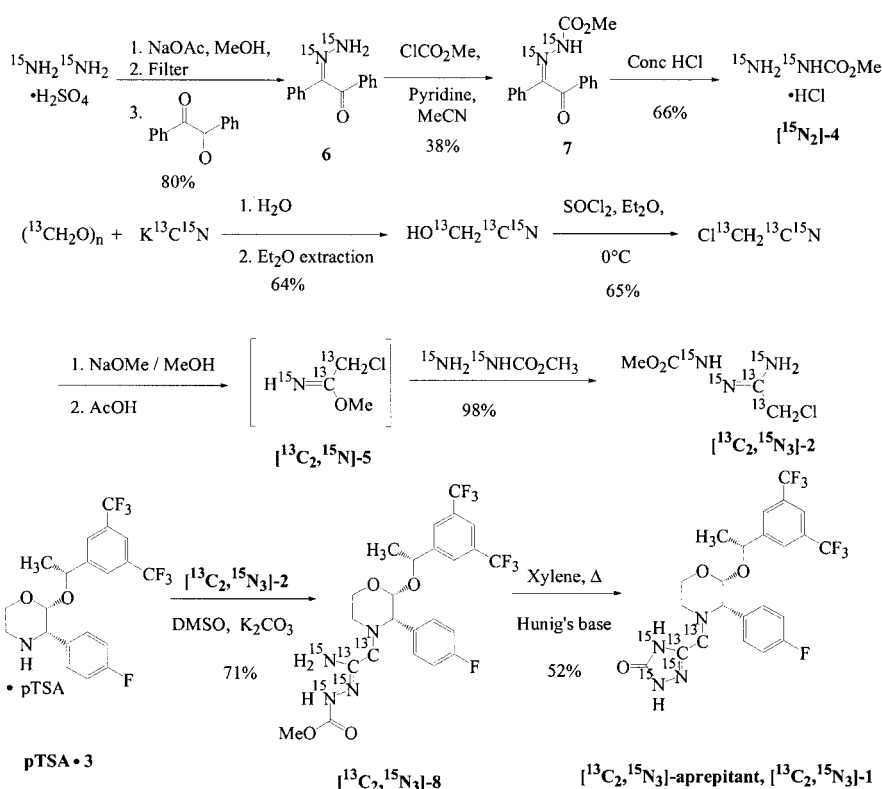
**Scheme 1. Retrosynthetic analysis of [<sup>14</sup>C]aprepitant**

The reaction of  $K^{14}CN$  and paraformaldehyde in water followed by continuous extraction for 12 h with  $Et_2O$  gave  $[^{14}C]$ hydroxyacetonitrile in 75% yield and high radiochemical purity (Scheme 2). The ethereal solution was reacted directly with  $SOCl_2$  to afford  $[^{14}C]$ chloroacetonitrile in 64% yield. Maintaining the temperature at approximately  $0^\circ C$  was critical to minimize the by-product formation. The  $[^{14}C]$ chloroacetonitrile was then treated with NaOMe in MeOH followed by hydrazinocarboxylate **4** to give amidrzone  $[^{14}C]$ -**2** in a 67% radiochemical yield. The camphorsulfonic acid salt of morpholine **3** was coupled with  $[^{14}C]$ -**2** to give a 55% yield of  $[^{14}C]$ -**8** which was cyclized in hot xylene to give  $[^{14}C]$ aprepitant in 74% radiochemical yield (8.1 mCi, 94% radiochemical purity). Purification by preparative HPLC followed by crystallization gave 4.6 mCi of  $[^{14}C]$ -**1** with 99.8% radiochemical purity.



**Scheme 2.** Synthesis of  $[^{14}C]$ aprepitant,  $[^{14}C]$ -**1**

Our approach to  $[^{13}C_2, ^{15}N_3]$ aprepitant was similar to that of the C-14 tracer except that the synthesis of  $[^{15}N_2]$ -**4** was also required. While the synthesis of  $[^{15}N_2]$ -**4** appeared trivial, attempts at mono-acylation of  $[^{15}N_2]$ hydrazine with methyl chloroformate using a variety of conditions gave substantial amounts of the bis-adduct unless a large excess of  $[^{15}N_2]$ hydrazine was utilized.<sup>11</sup> While the mono-adduct could be separated from the *bis*-adduct by column chromatography, other minor impurities were not separated and gave rise to impurities in subsequent reactions that were difficult to remove. As an alternative, a three-step procedure which provided  $[^{15}N_2]$ -**4** as a crystalline solid in high purity was used instead (Scheme 3).  $[^{15}N_2]$ Hydrazine was reacted with



**Scheme 3.** Synthesis of  $[\text{}^{13}\text{C}_2, \text{}^{15}\text{N}_3]\text{aprepitant}$

benzil<sup>12</sup> to give the corresponding hydrazone, **6**, in 80% yield. Acylation of **6** with methyl chloroformate afforded **7** in 38% yield, and **7** was hydrolyzed in concentrated HCl to give carbamate  $[\text{}^{15}\text{N}_2]\text{-4}$  as the HCl salt in 66% yield and >95% purity.

The remaining steps in the synthesis of  $[\text{}^{13}\text{C}_2, \text{}^{15}\text{N}_3]\text{aprepitant}$  were accomplished as previously described for  $[\text{}^{14}\text{C}]\text{aprepitant}$ . Since both  $[\text{}^{13}\text{C}_2, \text{}^{15}\text{N}]\text{-hydroxyacetonitrile}$  and  $[\text{}^{13}\text{C}_2, \text{}^{15}\text{N}]\text{chloroacetonitrile}$  are volatile, the quantity of compound present in the ethereal solutions was determined by  $^1\text{H}$  NMR using naphthalene as an internal standard. Purification of the final compound was effected by preparative HPLC followed by crystallization to give 569 mg of  $[\text{}^{13}\text{C}_2, \text{}^{15}\text{N}_3]\text{aprepitant}$  with 99.7% UV purity (238 nm).

In summary, we have reported the syntheses of  $[\text{}^{14}\text{C}]$  and  $[\text{}^{13}\text{C}_2, \text{}^{15}\text{N}_3]\text{aprepitant}$  which served as important tracers for obtaining detailed late-stage drug metabolism information. Both syntheses benefitted from the use of an improved synthesis of labeled chloroacetonitrile from readily available labeled precursors.

## Experimental

### General

[ $^{15}\text{N}_2$ ]hydrazine hydrogen sulfate, potassium [ $^{13}\text{C}$ ,  $^{15}\text{N}$ ]cyanide, and [ $^{13}\text{C}$ ] paraformaldehyde were obtained from Cambridge Isotope Laboratories, and **3** was obtained from Merck Process Research. Anhydrous solvents were obtained from Aldrich and were dried over 4 Å molecular sieves for at least 24 h prior to use. Analytical HPLC was performed using a Shimadzu HPLC system with LC-10ATVP pumps, a SPD-10AVP UV detector, a CTO-10ASVP column oven heated to 30°C, and a SCL-10A controller.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Varian U-400 spectrometer and were referenced to the residual solvent peak (7.26 and 77.00 ppm for  $\text{CDCl}_3$ , 3.30 and 49.2 ppm for  $\text{CD}_3\text{OD}$ , and 2.49 and 39.5 ppm for  $^2\text{H}_6$ -DMSO). LC/MS analyses were performed on an HP MSD-100 using a XDB-C8 column, with 5–95% gradient over 15 min with MeCN–2 mM ammonium formate buffer (pH = 3.5) and electrospray ionization. The reaction products were identified by HPLC comparison with the commercially available materials or Merck Process Chemistry intermediates when available using either method A (40/60 to 60/40 MeCN/0.1% aqueous  $\text{HClO}_4$  gradient elution over 30 min, Zorbax RX C-8); method B (35/65 to 80/20 MeCN/0.1%  $\text{H}_3\text{PO}_4$  over 20 min, YMC ODS-AQ); method C (20% MeCN–0.1%  $\text{H}_3\text{PO}_4$  for 30 min, Zorbax RX C-8); method D (0–5% MeCN–0.1% phosphoric acid over 30 min, Phenomenex Aqua C-18); or method E (45% MeCN/0.1% aqueous  $\text{HClO}_4$  for 30 min, Zorbax RX C-8). All HPLC analyses were conducted using a flow rate of 1 ml/min on 4.6 mm  $\times$  250 mm columns heated to 30°C and concluded with a 10 min wash of 100% MeCN. Preparative HPLC conditions are described separately.

### Benzil [ $^{15}\text{N}_2$ ]hydrazone (**[ $^{15}\text{N}_2$ ]-6**)

The procedure of Nenitzescu was modified as follows.<sup>12</sup> A solution of 15.5 g (117 mmol) of [ $^{15}\text{N}_2$ ]hydrazine sulfate and 39.6 g (483 mmol) of NaOAc in 100 ml of water was heated for 30 min at 60°C under  $\text{N}_2$ . The solution was diluted with 80 ml of MeOH and was cooled to room temperature (rt). The resulting precipitate was removed by filtration, and 20.0 g (95.2 mmol) of benzil was added to the solution. The resulting slurry was heated at 60°C for 2 h with vigorous stirring. The solution was cooled to rt, and the precipitate removed by filtration to give 17.2 g (80%) of [ $^{15}\text{N}_2$ ]-**6** as a yellow solid. LC/MS (M/Z (abundance)): 227.1 (100), 228.1 (15), 249.1 (13).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.95 (m, 2H), 7.53 (m, 3H), 7.47 (m, 3H), 7.35 (m, 2H).

*N*-(1-[ $^{15}\text{N}$ ]-1-aza-3-oxo-2,3-diphenylprop-1-enyl)[ $^{15}\text{N}$ ]methoxycarboxamide ([ $^{15}\text{N}_2$ ]-7)

A solution of 15.5 g (68.5 mmol) of hydrazone [ $^{15}\text{N}_2$ ]-6 in 400 ml of MeCN and 19 ml (240 mmol) of pyridine was stirred rapidly at rt as 21 ml (270 mmol) of methylchloroformate was added in 2 ml aliquots over 1 h. The reaction mixture was stirred overnight at rt, and the precipitate was removed by filtration. The solution was concentrated to dryness at reduced pressure to give 23.1 g of a yellow solid which was purified by flash column chromatography on neutral alumina (100% hexane to 25% EtOAc in hexane). Product containing fractions were combined to give 7.40 g (26.1 mmol, 38%) of [ $^{15}\text{N}_2$ ]-7 as a yellow solid. LC/MS (M/Z (abundance)): 285.1 (100), 286.1 (18), 307 (15).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (t,  $J=80$  Hz, 1H), 8.16 (d,  $J=7.2$  Hz, 1H), 7.86 (d,  $J=7.1$  Hz, 1H), 7.60 (m, 2H), 7.45 (m, 3H), 7.33 (m, 3H), 3.81 (s, 3H).

*Methyl* [ $^{15}\text{N}_2$ ]hydrazinocarbamate hydrochloride ([ $^{15}\text{N}_2$ ]-4)

A biphasic solution of 3.33 g (11.7 mmol) of [ $^{15}\text{N}_2$ ]-7 in 30 ml of  $\text{CH}_2\text{Cl}_2$  and 15 ml of conc. HCl was stirred and heated at  $70^\circ\text{C}$  under  $\text{N}_2$ , and the reaction followed by TLC (4:1 Hex:EtOAc) during which time a white precipitate formed. After 3 h, the solid was removed by filtration through a glass frit to give 998 mg (7.77 mmol, 66%) of [ $^{15}\text{N}_2$ ]-4, as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$  3.66 (s).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$  156.2 (br), 53.0.

[ $^{13}\text{C}_2$ ,  $^{15}\text{N}$ ]Hydroxyacetonitrile

A solution of 4.33 g (64.6 mmol) of  $\text{K}^{13}\text{C}^{15}\text{N}$  in 15 ml of water was cooled and stirred at  $0^\circ\text{C}$  as 1.96 g (42 mmol) of [ $^{13}\text{C}$ ]paraformaldehyde was added. The solution was stirred for 35 min at which time the pH was adjusted to 2.5 with conc.  $\text{H}_2\text{SO}_4$ . The solution was transferred to a liquid-liquid continuous extraction apparatus and was extracted with 120 ml  $\text{Et}_2\text{O}$  for 48 h. Midway through the extraction an additional 50 ml of ether was added.  $^1\text{H}$  NMR analysis of the ethereal solution using naphthalene as an internal standard showed a total of 2.50 g (64%) of [ $^{13}\text{C}_2$ ,  $^{15}\text{N}$ ]hydroxyacetonitrile to be present in 30.4 g (ca. 43 ml) of ether.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.78 (br s, 1H), 4.24 (ddd,  $J=151.2$ , 6.1, 1.1 Hz, 2H) spectrum also shows two 6 line multiplets at 7.44 (4.5H), 7.80 (4.5H) for naphthalene and peaks at 3.44 (q,  $J=7.0$  Hz, 3.4H) and 1.17 (t, 50H,  $J=7.0$  Hz) for diethyl ether.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  118.0 (dd,  $J=60$ , 16 Hz), 48.2 (d,  $J=58$  Hz); the spectrum also contains  $\text{H}^{13}\text{C}^{15}\text{N}$  at 109.1 (d,  $J=18$  Hz) and diethyl ether at 65.7, 15.1.

[ $^{13}\text{C}_2$ ,  $^{15}\text{N}$ ]Chloroacetonitrile

A solution of ca. 1.39 g (23.1 mmol) [ $^{13}\text{C}_2$ ,  $^{15}\text{N}$ ]hydroxyacetonitrile in 33 ml of  $\text{Et}_2\text{O}$  and 4.1 ml (79 mmol) of pyridine was stirred and cooled at  $0^\circ\text{C}$  as 4.0 ml

(55 mmol) of  $\text{SOCl}_2$  was added over 45 min. After complete addition, the reaction was stirred at  $0^\circ\text{C}$  for 1 h and at rt for 3 h, and 10 ml of a solution of saturated aq. NaCl was added. The aqueous layer was removed and the organic layer was extracted with 5 ml of saturated aq. NaCl. The organic layer was dried ( $\text{MgSO}_4$ ) and filtered to give 23.7 g of an ethereal solution.  $^1\text{H}$  NMR analysis using naphthalene as an internal standard showed the yield to be 1.20 g (14.9 mmol, 65%) of  $[\text{C}_2, \text{N}]$ chloroacetonitrile.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.03 (ddd,  $J=80, 7.8, 1.7$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  114.3 (dd,  $J=66, 18$  Hz), 24.5 (dd,  $J=66, 2.5$  Hz). The spectrum also shows peaks for naphthalene at 133.4, 127.8, 125.8, diethyl ether at 65.8 and 15.2, and a  $[\text{C}_2, \text{N}]$  containing by-product at 113 (dd) and 48.2 (d).

*N-((1Z)-2- $[\text{C}_2, \text{N}]$ amino-1- $[\text{C}_2, \text{N}]$ aza-3-chloro- $[\text{C}_2, \text{N}]$ prop-1-enyl)-methoxycarboxamide ( $[\text{C}_2, \text{N}_3]$ -2)*

A solution of ca. 680 mg (8.51 mmol) of  $\text{ClCH}_2\text{C}^{13}\text{N}$  in 64 ml of ether was cooled to  $0^\circ\text{C}$  as 17 ml of a 0.33 M solution (5.64 mmol) of NaOMe in MeOH was added. The solution was warmed to rt and stirred for 1 h, and 0.50 ml of HOAc (8.74 mmol) and 984 mg (7.6 mmol) of methyl  $[\text{N}_2]$ hydrazinocarbamate hydrochloride were added sequentially. The reaction was stirred under  $\text{N}_2$  overnight, and the solvent was removed under a stream of  $\text{N}_2$  to give 1.43 g of  $[\text{C}_2, \text{N}_3]$ -2 as a brown oil.  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO, 400 MHz)  $\delta$  4.05 (d,  $J=76$  Hz, 2H), 3.58 (d,  $J=4.3$  Hz, 3H).

*N-[3-(2-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}(3S,2R)-3-(4-fluorophenyl)morpholin-4-yl)-(1Z)-2- $[\text{C}_2, \text{N}]$ amino-1- $[\text{C}_2, \text{N}]$ azaprop-1-enyl]-methoxy-carbox $[\text{C}_2, \text{N}]$ amide ( $[\text{C}_2, \text{N}_3]$ -8)*

A slurry of 1.15 g (6.7 mmol) of chloroamidrizone  $[\text{C}_2, \text{N}_3]$ -2, 1.72 g (2.82 mmol) of *p*-toluenesulfonic acid salt **3**, and 2.14 g (15.4 mmol) of  $\text{K}_2\text{CO}_3$  in 7 ml of DMSO was stirred at rt for 2 h at which time HPLC analysis (method A) showed the reaction to be complete. The reaction mixture was diluted with 100 ml of water and extracted with EtOAc ( $4 \times 20$  ml). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated to dryness to give 4.7 g of a brown oil. The oil was purified by flash column chromatography on silica gel (20:1:2  $\text{PhCH}_3$ :EtOAc:MeOH), and product containing fractions were combined and concentrated to give 2.7 g of a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (s, 1H), 7.35 (m, 2H), 7.16 (s, 2H), 7.04 (t,  $J=8.6$  Hz, 2H), 4.89 (q,  $J=6.5$  Hz, 1H), 4.34 (d,  $J=2.8$  Hz, 1H), 4.24 (td,  $J=11.7, 2.1$  Hz, 1H), 3.77 (s, 3H), 3.66 (dd,  $J=1.9, 11.2$  Hz, 1H), 3.50 (m, 1H), 3.47 (s, 1H), 2.97 (d,  $J=11.7$  Hz, 1H), 2.92 (d,  $J=17, 136$  Hz, 1H), 2.51 (t,  $J=11.8$  Hz, 1H), 1.47 (d,  $J=6.6$  Hz, 3H).

*[<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N<sub>3</sub>]aprepitant ([<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N<sub>3</sub>]-1)*

A solution of 2.37 g (4.20 mmol) of [<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N<sub>3</sub>]-8 in 50 ml of xylene and 15 ml of diisopropylethylamine was purged with N<sub>2</sub> and heated at 150°C for 3 h. HPLC analysis (method A) showed the reaction to be complete. The solvents were then removed at reduced pressure to afford 2.471 g of an orange oil. The compound was taken up in PhCH<sub>3</sub> and purified by flash column chromatography on silica gel (10:1:1 PhCH<sub>3</sub>:MeOH:EtOAc). Product containing fractions were combined and concentrated to give 1.34 g of an off white solid, and HPLC analysis (method A) showed the compound to be 89% pure by UV analysis at 220 nm. The solid was dissolved in 5 ml of MeOH and 2 ml of 0.1% H<sub>3</sub>PO<sub>4</sub> and was purified in four portions by preparative HPLC (Zorbax RX C-8, 50:50 MeCN:0.1% aq. H<sub>3</sub>PO<sub>4</sub>, 20 ml/min). The fractions were analyzed by HPLC (method A) and pure fractions were pooled. The combined fractions were concentrated at reduced pressure until H<sub>2</sub>O began condensing, neutralized to pH > 8 with Na<sub>2</sub>CO<sub>3</sub>, and extracted with EtOAc (5 × 50 ml). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated, at reduced pressure to give 839 mg of a white solid. The solid was dissolved in 5 ml of MeOH and was heated at 30°C as 3 ml of water was added over 1 h by syringe pump. The slurry was heated at 50°C and was then cooled to rt. The solid was removed by filtration through a glass frit and was washed with 2 ml of water. The solid was dried under vacuum for 3 h to give 569 mg of [<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N<sub>3</sub>]aprepitant. HPLC analysis (method B) showed the UV purity (220 nm) to be 99.6%. LC/MS (M/Z (abundance)): 534.1 (0.63) 535.0 (100), 536 (22.1), 537 (3.3), 538 (0.1). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.71 (s, 1H), 7.52 (t, *J* = 6.5 Hz, 2H), 7.32 (s, 2H), 7.05 (t, *J* = 8.9 Hz, 2H), 4.95 (q, *J* = 6.6 Hz, 1H), 4.35 (d, *J* = 2.8 Hz, 1H), 4.28 (td, *J* = 11.7, 2.4 Hz, 1H), 3.66 (dq, *J* = 11.4, 1.9 Hz, 1H), 3.56 (dm, *J* = 140 Hz, 1H), 3.49 (t, *J* = 2.4 Hz, 1H), 2.87 (d, *J* = 11.9 Hz, 1H), 2.85 (ddm, *J* = 135, 14.2 Hz, 1H), 2.49 (tt, *J* = 11.5, 2.7 Hz, 1H), 1.44 (d, *J* = 6.7 Hz, 3H).

*[<sup>14</sup>C]Hydroxyacetonitrile*

The previously described route for [<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N]hydroxyacetonitrile was followed using 114 mg (1.75 mmol, 57 mCi/mmol) of K<sup>14</sup>CN, 4 ml of water, and 56 mg (1.87 mmol) of paraformaldehyde. Liquid–liquid continuous extraction for 12 h gave 77 ml of an ethereal solution that contained 86 mCi of the desired product. <sup>1</sup>H NMR and HPLC (method C) analysis showed the compound to be of > 95% radiochemical purity.

*[<sup>14</sup>C]Chloroacetonitrile*

The previously described route for [<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N]chloroacetonitrile was followed using 63 mCi (1.1 mmol, 57 mCi/mmol) of [<sup>14</sup>C]hydroxyacetonitrile in 51 ml of



Et<sub>2</sub>O, 140 mg (1.7 mmol) of pyridine, and 223 mg (1.9 mmol) of SOCl<sub>2</sub> to give 52 mCi in 23 ml of ether. HPLC analysis (method C) showed the product to have a purity of 82% with 18% [<sup>14</sup>C]hydroxyacetonitrile present.

*N-((1Z)-2-amino-1-aza-3-chloro-[3-<sup>14</sup>C]prop-1-enyl)methoxycarbox-amide ([<sup>14</sup>C]-2)*

The previously described route for [<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N<sub>3</sub>]-**2** was followed using 24.3 mCi (0.43 mmol, 82% purity, 57 mCi/mmol) of ClCH<sub>2</sub> <sup>14</sup>CN, 98.3 mg (1.3 mmol) of ClCH<sub>2</sub>CN, 7 ml of MeOH, 89 mg (1.66 mmol) NaOMe, 100 mg (1.66 mmol) of HOAc, and 137 mg (1.52 mmol) of methyl hydrazinocarbamate hydrochloride to give 20 mCi of a methanol solution which contained 63% [<sup>14</sup>C]-**2**, 16% [<sup>14</sup>C]hydroxyacetonitrile, and 10% chloroacetonitrile by HPLC analysis (method D).

*[<sup>14</sup>C]aprepitant, ([<sup>14</sup>C]-1)*

The previously described route for [<sup>13</sup>C<sub>2</sub>,<sup>15</sup>N<sub>3</sub>]-**1** was followed using 20 mCi (1.83 mmol, 11 mCi/mmol, 63% radiochemical purity) of chloroamidrizonc [<sup>14</sup>C]-**2**, 1.4 g (2.0 mmol) of (*R*)-camphorsulfonic acid salt **3**, and 632 mg (5.6 mmol) of K<sub>2</sub>CO<sub>3</sub> in 15 ml of DMSO. Product isolation was performed as described previously to give 11 mCi of [<sup>14</sup>C]-**8**. The crude reaction extract was then refluxed in 30 ml Xylene overnight to give 10 mCi [<sup>14</sup>C]-**1**. Prep-HPLC (Zorbax RX C-8, 45% MeCN–0.1% phosphoric acid, 20 ml/min) gave 5.1 mCi of [<sup>14</sup>C]-**1** which was crystallized from 2.5 ml MeOH and 1 ml of H<sub>2</sub>O as previously described to give 190 mg (4.6 mCi, 23% yield) of [<sup>14</sup>C]aprepitant with a radiochemical purity of 99.8% (method E) and a specific activity of 13 mCi/mmol.

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