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Preparation of Fentanyl Labeled with Carbon-14[1]

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Abstract—A convenient synthetic pathway for ^{14}C labeling of fentanyl [*N*-(1-phenethyl-4-piperidinyl)-propionanilide], a widely used narcotic analgesic agent, with good radiochemical yield was developed.

Keywords: Opioid, Fentanyl, carbon-14

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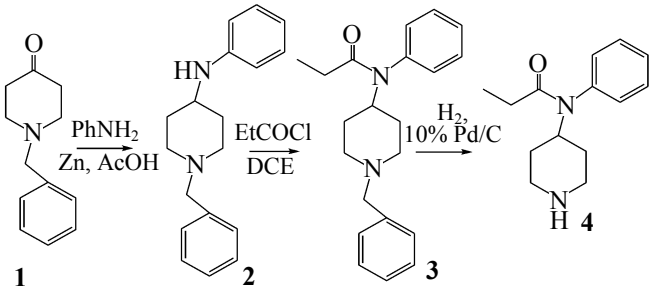
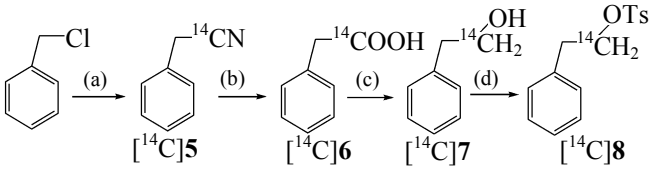
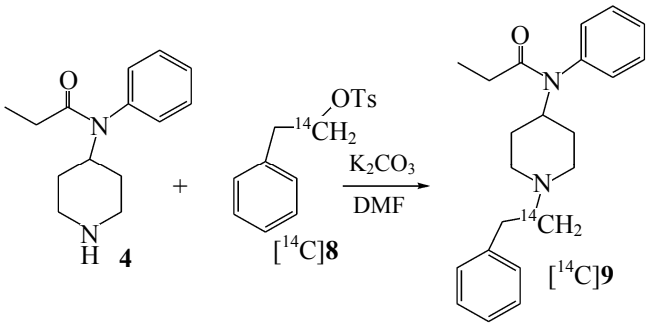
Fentanyl is a synthetic *l*-opioid receptor agonist widely used for surgical analgesia and alleviation. However, various fentanyl analogs can cause the abuse and fatalities in humans, which led to the synthesis of some stronger and safer analogs [1]. Over the last four decades, structure–activity relationship and molecular modeling studies of fentanyl analogs provided considerable insight into the key structural features and pharmacophore elements required for high-affinity binding to the *l*-receptor [2, 3]. A number of structural elements required for the analgesic activity of the fentanyl class of compounds were revealed, and novel potent fentanyl analogs were synthesized [4]. The stronger potency of fentanyl compared to that of morphine is largely due to its high lipophilicity facilitating its penetration into the central nervous system [5]. Further studies of the mechanism of action and metabolism of fentanyl require synthesis of fentanyl labeled with ^{14}C. The synthesis pathway is shown in Schemes 1–3.



Scheme 1. Scheme of the synthesis of *N*-(4-piperidinyl)-propionanilide (**4**).



Scheme 2. Scheme of the synthesis of 2-phenyl[1-^{14}C]ethyl *p*-toluenesulfonate [^{14}C]**8**. (a) K^{14}CN, EtOH, thiourea; (b) water, H_2SO_4, glacial acetic acid, reflux, 1 h; (c) dry THF, $Zn(BH_4)_2$; (d) TsCl, $BnNMe_2$, K_2CO_3.



Scheme 3. Scheme of the synthesis of [^{14}C]fentanyl.

EXPERIMENTAL

Barium [^{14}C]carbonate was converted to potassium cyanide according to the standard procedure [6]. The IR spectra were recorded on a Bruker FT-IR Vector22 instrument, and the ^1H NMR spectra, on a Varian Unity Plus 400 spectrometer (400 MHz). Radioactivity was determined with a Beckman LS6500 liquid scintillation spectrometer. The mass spectra were taken on a Finnigan TSQ-70 instrument.

[1] The text was submitted by the authors in English.

4-Anilino-*N*-benzylpiperidine (2). To a mixture of *N*-benzylpiperidin-4-one **1** (0.01 mol, 1.89 g), aniline (0.01 mol), and activated zinc (0.04 mol), 90% aqueous acetic acid (0.16 mol) was added in portions. The mixture was stirred at room temperature for 24 h and at 70°C on a water bath for an additional 12 h. After the reaction completion, the mixture was diluted with methanol and filtered. The filtrate was concentrated in a vacuum and then neutralized with a 30% ammonium hydroxide solution to pH 10. The crude product was collected by filtration and recrystallized with petroleum ether to obtain the pure product in 84% yield (2.2 g). IR (KBr), ν, cm^{-1}: 3440 (N–H stretching), 3255, 3020, 2936, 2842,1615, 1526, 1490, 1372, 1318, 1255, 1087, 977, 862, 751, 690. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 1.50 (dq, 2H), 2.10 (br.d, 2H), 2.30 (br.t, 2H), 2.60 (s, 2H), 2.90 (br.d, 2H), 3.35 (m, 1H), 3.50 (br.s, 1H), 7.10–7.40 (m, Ar–H). Mass spectrum (*m*/*z*): 267 [M + 1].

***N*-(1-Benzyl-4-piperidinyl)propionanilide (3).** To a solution of **2** (8 mmol, 2.1 g) in 5 mL of 1,2-dichloroethane, propionyl chloride (24 mmol) was added dropwise, and the resulting mixture was stirred at ambient temperature for 3 h. After the reaction completion, the mixture was poured slowly to a 5% aqueous NaOH solution (5 mL) with continuous stirring. The resulting alkaline solution was extracted with dichloromethane (3 × 4 ml), and the organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified as its hydrochloride: colorless crystals, yield 2.6 g (91%). The corresponding free base was obtained by decomposition of its hydrochloride salt with a 30% NaOH solution, followed by recrystallization from petroleum ether; colorless compound **3**, yield 2.3 g (91%). IR (KBr), ν, cm^{-1}: 3430, 2941, 2822, 1659 (C=O), 1495, 1370, 1260 (C–N stretching), 1150, 1090, 705. ^{1}H NMR [$CDCl_3$, δ (ppm)]: 0.94 (t, 3H), 1.30–1.40 (m, 2H), 1.70–1.80 (m, 2H), 1.85 (q, 2H), 2.10 (m, 2H), 2.65 (m, 2H), 3.30 (t, 2H), 4.58–4.67 (m, 1H), 7.10–7.30 (m, Ar–H). Mass specrum (*m*/*z*): 323 [M + 1].

***N*-(4-Piperidinyl)propionanilide (4).** A solution of **3** (7 mmol, 2.2 g) in 5 mL of methanol–acetic acid mixture (3 : 2) was taken in a 25-mL thick-walled hydrogenation vessel containing 10 wt % Pd/C catalyst. The hydrogen gas was then fed into the vessel using a Parr apparatus at 50°C. After the hydrogen uptake ceased, the mixture was filtered through Celite. The filtrate was concentrated on a rotary evaporator, and the residue was treated with a 30% aqueous NaOH solution. The aqueous solution was extracted with ethyl acetate (2 × 4 mL), the extract was dried over anhydrous sodium sulfate, and the solvent was removed in a vacuum. The crude compound **4** thus obtained was recrystallized from petroleum ether; yield 1.5 g (93%). IR (KBr), ν, cm^{-1}: 3374, 3031, 2944, 2825, 1657, 1591, 695. ^{1}H NMR [$CDCl_3$, δ (ppm)]: 0.95 (t, 3H), 1.25 (dq, 2H), 1.56 (br.s, 1H), 1.74 (br.d, 2H), 1.91 (q, 2H), 2.11 (br.t, 2H), 3.10 (br.d, 2H), 4.66–4.79 (m, 1H), 7.13 (d, Ar–H), 7.14 (d, Ar–H), 7.37 (m, Ar–H). Mass spectrum (*m*/*z*): 233 [M + 1].

2-Phenyl[1-^{14}C]acetic acid [^{14}C]6. A solution of benzyl chloride (2.0 g, 15.8 mmol) in EtOH (4 mL) was added dropwise over a period of 45 min to a solution of potassium [^{14}C]cyanide (500 mg, 7.4 mmol, 697 MBq) in water (1.5 mL), and the mixture was refluxed for 6 h. Thiourea (42 mg, 5.55 mmol) and EtOH (2 mL) were added, and the mixture was refluxed for a further 1 h. The solution was concentrated under reduced pressure and partitioned between Et_2O and water. The organic phase was washed with water, dried, and evaporated to obtain crude benzyl cyanide [^{14}C]**5** as a yellow oil. Water (4 mL), concentrated H_2SO_4 (4 mL) and glacial acetic acid (4 mL) were added to this product, and the mixture was refluxed for 1 h. Then, the mixture was diluted with water (50 mL) and extracted with Et_2O (3 × 10 mL). The organic extract was dried and evaporated to give 2-phenyl[1-^{14}C]acetic acid [^{14}C]**6** as beige crystals [7] (625 mg, 4.5 mmol, 425 MBq, 61%). ^{1}H NMR [$CDCl_3$, δ (ppm)]: 7.24–7.39 (m, 5H, ArH); 3.63 (s, 2H). Mass spectrum (*m*/*z*): 139 [M + 1].

2-Phenyl[1-^{14}C]ethanol [^{14}C]7. To 500 mg (340 MBq) of [1-^{14}C]**6**, 1.5 mL of dry THF and then 3.0 mL of a 0.66 M solution of $Zn(BH_4)_2$ (2 mmol) in 2 mL of THF were added. The contents were refluxed and then cooled to room temperature, and the excess hydride was quenched with 0.25 mL of dilute H_2SO_4 (2 N). Then, the reaction mixture was saturated with anhydrous K_2CO_3, and the organic layer was separated. The residue was extracted with 2 × 2 mL of THF. The combined organic extracts were dried over anhydrous K_2CO_3 and then concentrated under reduced pressure to yield 412 mg (320 MBq, 94%) of 2-phenyl-[1-^{14}C]ethanol [^{14}C]**7**. Mass spectrum (*m*/*z*): 125 [M + 1].

2-Phenylethyl *p*-toluenesulfonate [^{14}C]8. TsCl (858 mg, 4.5 mmol) was added over a period of 1 h (6 portions at 10-min intervals) to a stirred suspension

of alcohol [^{14}C]**7** (366 mg, 284 MBq, 3 mmol), $BnNMe_2$ (405 mg, 3 mmol), and K_2CO_3 (1.2 g, 9 mmol) in water (2 mL) at 20–25°C. A 1 M aqueous KOH solution (1.5 mL) was continuously added using a microfeeder to the reaction mixture so as to maintain pH 10 (monitored with a pH meter). The mixture was stirred at the same temperature for an additional 1 h. To decompose excess TsCl, *N*,*N*-dimethylethylenediamine (100 mg) was added to the mixture, and the mixture was stirred for 10 min. Water was added, and the solution was extracted with EtOAc (2 × 4 mL). The organic phase was washed with water and concentrated NaCl solution, dried (Na_2SO_4), and concentrated. The obtained crude tosylate was sufficiently pure (yield 90%, 421.2 mg, 255.6 MBq) [8]. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 2.43 (s, 3H), 2.96 (t, 2H, *J* 7.1 Hz), 4.22 (t, 2H, *J* 7.1 Hz), 7.13 (m, 2H), 7.18–7.34 (m, 5H), 7.63 (m, 2H). IR (KBr), ν, cm^{-1}: 2955, 1596, 1458, 1366, 1277, 1108, 968. Mass spectrum (*m*/*z*): 279 [M + 1].

[^{14}C]Fentanyl [^{14}C]9. A 10-mL two-necked round-bottomed flask was charged with 2.5 mL of acetonitrile and 20 mmol of anhydrous K_2CO_3, and tetrabutylammonium bromide (10 mol %) and compound **4** (2.0 mmol) were added. Then, compound [^{14}C]**8** (390 mg, 237 MBq, 2.5 mmol) was added slowly with stirring, and the reaction mixture was refluxed with stirring until the reaction was complete (monitored by TLC). The reaction mixture was then filtered to remove solid residues. The filtrate was concentrated in a vacuum to obtain a dark colored solid residue. The residue was purified by crystallization to give the pure compound. Colorless crystalline solid, yield 50% (420 mg, 118 MBq). IR (KBr), ν, cm^{-1}: 2941, 2822, 1657, 1592, 1493, 1381, 1264, 1122, 1052, 732, 700, 604. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 1.02 (t, 3H), 1.42 (dq, 2H), 1.80 (br.d, 2H), 1.91 (q, 2H), 2.14 (br.t, 2H), 2.52 (m, 2H), 2.72 (m, 2H), 2.99 (br.d, 2H), 4.67 (m, 1H), 7.05 (dd, Ar–H), 7.08–7.09 (m, Ar–H), 7.19 (dd, Ar–H), 7.36–7.39 (m, Ar–H). Mass spectrum (*m*/*z*): 339.5 [M + 1].

RESULTS AND DISCUSSION

A procedure for preparing [^{14}C]fentanyl containing the label in the aniline ring was reported previously; the overall radiochemical yield was as low as 18% [9]. In this case, the label is introduced into sites resistant to metabolic extraction. In our procedure, the label was introduced into the position adjacent to the piperidine nitrogen atom. The synthesis starts with the reaction of potassium [^{14}C]cyanide with benzyl chloride to obtain benzyl [^{14}C]cyanide. Its acid hydrolysis yields 2-phenyl[1-^{14}C]acetic acid, which, in turn, is reduced with $Zn(BH_4)_2$ to obtain 2-phenyl[1-^{14}C]ethanol. This product is converted to tosylate by the reaction with TsCl. Finally, the condensation of the radioactive and nonradioactive fragments is performed. This procedure is novel, and the overall radiochemical yield based on potassium [^{14}C]cyanide was 26%.

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REFERENCES

1. Higashikawa, Y. and Suzuki, S., *Forens. Toxicol.*, 2008, vol. 26, no. 1, pp. 1–5.
2. Helsley, G.C., Lunsford, C.D., Welstead, W.J., Jr., et al., *J. Med. Chem.*, 1969, vol. 12, no. 4, pp. 583–586.
3. Van Bever, W.F.M., Niemegeers, C.J.E., and Janssen, P.A.J., *J. Med. Chem.*, 1974, vol. 17, pp. 1047–1050.
4. Vuckovic, S.M., Ivanovic, M.D., Prostran, M.S., et al., *Jpn. J. Pharmacol.*, 1998, vol. 78, no. 4, pp. 523–527.
5. Ivanovic, M.D., Vuckovic, S., Ristovic, Z., et al., *Iugoslav. Physiol. Pharmacol. Acta*, 1995, vol. 31, pp. 195–199.
6. Perry, C.W., Burger, W., and Delaney, C.M., *J. Label. Compd. Radiopharm.*, 2005, vol. 16, no. 4, pp. 645–649.
7. Corrie, J.E.T. and Munasinghe, V.R.N., *J. Label. Compd. Radiopharm.*, 2005, vol. 48, pp. 231–233.
8. Morita, J.I., Nakatsuji, H., Misaki, T., and Tanabe, Y., *Green Chem.*, 2005, vol. 7, pp. 711–715.
9. Bagley, J.R. and Wilhelm, J.A., *J. Label. Compd. Radiopharm.*, 1992, vol. 31, no. 11, pp. 945–950.