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Preparation of a Carbon-14 Analog of 2-[2-(4-(Dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy]ethanol[1]

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Abstract—2-[2-(4-(Dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy]ethanol (Quetiapine) labeled with ^{14}C in 11-position was synthesized in five steps from [carboxy-^{14}C]anthranilic acid. The key precursor of the target product is [11-^{14}C]dibenzothiazepin-11(10*H*)-one. The reaction is performed as one-pot process.

Keywords: Quetiapine, labeling, antipsychotic drugs

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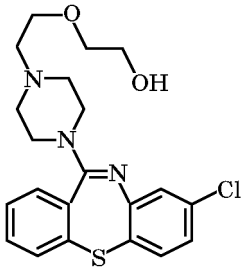
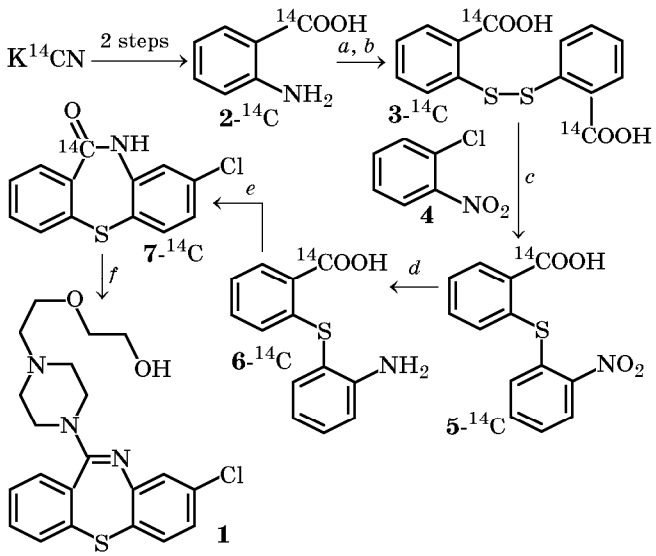
Tricyclic ring systems containing a dibenzo structure joined to a central seven-membered heteroring with a basic side chain have been a rich source of biologically active molecular entities and frequently show effects on the central nervous system [1–4]. During the last 40 years, a number of antipsychotic agents belonging to the chemical class of dibenzo epines have been introduced (e.g., Clozapine, Loxapine, Clothiapine and their analogs). Among this series of compounds, Quetiapine is one of the most widely used antipsychotic drugs, which acts as an antagonist for multiple neurotransmitter receptor sites, including serotonin ($5HT_{1A}$, $5HT_{2A}$), dopamine (D_1, D_2), histamine (H_1), and adrenaline (Alpha1, Alpha2) in the brain, as an antipsychotic agent, and as an antischizophrenic. Quetiapine has a lower affinity for D_2 receptors than dopamine, leading to an alternating D_2 blockade and contributing to the impressive tolerability profile of the substance. Quetiapine may act on depression through its antagonism of $5\text{-}HT_{2A}$ receptors and on mania through its antagonism of D_2 receptors. The compound was also found to be useful in the treatment of acute bipolar mania, either as a monotherapy or in combination with other mood stabilizers; it was useful as a monotherapy in acute bipolar depression [5–8]. However, the precise mechanism of the action of this compound is unknown [9]. Therefore, to further elucidate the mechanism of action and to support ongoing metabolism studies, there arose a need for analogs of these compounds labeled with ^{14}C in a biologically stable site. In our previous papers [10, 11], we reported a convenient method for ^{14}C labeling of Clozapine and Loxapine. Here we describe the synthesis of 2-[2-(4-[11-^{14}C]dibenzo[*b*,*f*][1,4]thiazepin-11-yl)piperazin-1-yl)ethoxy]ethanol (11-[^{14}C]Quetiapine). The key step of the synthesis is one-pot transformation of [11-^{14}C]thiazepin-11(10*H*)-one into the target product. This precursor, in turn, is prepared in four steps from [carboxy-^{14}C]anthranilic acid.



Quetiapine (**1**)

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

The synthetic pathway is shown below. After conversion of potassium [^{14}C]cyanide to [11-^{14}C]anthranilic acid **2** [12, 13], it was converted to [carboxyl-$^{14}C_2$]dithiosalicylic acid **3** via reaction with sodium nitrite in hydrochloric acid, followed by treatment of the resulting diazonium compound with a sodium disulfide solution [14]. The coupling of **3** with 1-chloro-2-nitrobenzene **4** was carried out in the presence of sodium hydroxide in water, and compound **5** was produced in 81% yield [15]. In the next step, after reduction of **5** to **6** in the presence of hydrazinium monoformate solution and zinc powder in methanol [16], the key [11-^{14}C]thiazapine-11-one was obtained in good yield by the cyclization of **6** in the presence of sulfuric acid in xylene for 15 h [17–19]. In the final step, dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one **7** was converted to [11-^{14}C]Quetiapine **1** via a one-pot synthetic procedure by using pyrophosphoryl chloride ($P_2O_3Cl_4$, a green reductive chlorination agent) in the presence of 4-hydroxyethoxyethylpiperazine (HEEP) and *N*,*N*-dimethylaniline (DMA) in toluene in almost quantitative yield [20].



Scheme of the synthesis of **1**. (*a*) $NaNO_2$, HCl_{aq}; (*b*) Na_2S_2; (*c*) $NaOH_{aq}$; (*d*) hydrazinium monoformate, Zn, MeOH; (*e*) H_2SO_4, xylene; (*f*) $P_2O_3Cl_4$, HEEP, DMA, toluene.

Barium [^{14}C]carbonate was converted to potassium [^{14}C]cyanide using the standard procedure [14]. The IR spectra were recorded on a Bruker FT-IR Vector 22 instrument, and the ^{1}H NMR spectra, on a Varian Unity Plus 400 spectrometer (400 MHz). A Waters HPLC system (Waters, Milford, MA, the United States) was used for chromatographic determination of Quetiapine fumarate. It consisted of a 1525 Binary HPLC pump and a 2487 Dual λ absorbance detector set at 230 nm. Samples were injected with a Rheodyne 7725(i) (Cotati, CA, the United States) injection valve equipped with a 20-μL sample loop. Waters Breeze chromatographic software was used for data acquisition and processing. A Welcrom C_{18} column (4.6 × 250 mm, 5 μm) was used for separation. The isocratic mobile phase consisted of 10 mM phosphate buffer (pH 3) and acetonitrile (50 : 50 v/v). It was fed at a flow rate of 1.0 mL min^{-1} at ambient temperature (25°C). The radioactivity was determined with a Beckman LS6500 liquid scintillation spectrometer. The mass spectra were taken with a Finnigan TSQ-70 instrument.

[Carboxyl-$^{14}C_2$]dithiosalicylic acid, 3. [Carboxyl-^{14}C]anthranilic acid **2** with a specific activity of 200 MBq mmol^{-1} was prepared according to our previous report [15]. To an aqueous solution of [carboxyl-^{14}C]anthranilic acid (685 mg, 1000 MBq, 5 mmol) in water (5 mL) and concentrated hydrochloric acid (1 mL) at 5°C, a solution of sodium nitrite (345 mg) in water (2.5 mL) was added at such a rate as to keep the temperature below 5°C. The resulting solution of the diazonium derivative was slowly added to the alkaline sodium disulfide solution, keeping the temperature below 5°C. Then, the mixture was allowed to warm up to room temperature. After the evolution of nitrogen ceased, a solution of concentrated hydrochloric acid (0.9 mL) was added. Then, the resulting precipitate of [carboxyl-^{14}C]dithiosalicylic acid **3** was filtered off and washed with water. After that, the precipitate was dissolved in a solution of anhydrous sodium carbonate (300 mg) in water (10 mL) by heating, and the mixture was filtered while hot. Finally, the [carboxyl-^{14}C]dithiosalicylic acid **3** was reprecipitated by adding concentrated hydrochloric acid. The resulting product was filtered off, washed with cooled water and ether, and dried under vacuum to give **3** (655 mg, 850 MBq, 2.14 mmol) in 86% yield. IR (KBr): 3100, 2600, 1675, 1250, 1450 cm^{-1}.

Preparation of Na_2S_2. Powdered sulfur (170 g) was added to a solution of sodium sulfide ($Na_2S\cdot 9H_2O$) (1.3 g) in boiling water (1.5 mL). After dissolving the sulfur powder on heating with stirring, a solution of NaOH (200 mg) in water (0.5 mL) was added, and the resulting mixture was cooled to room temperature and finally in an ice–salt bath.

[Carboxyl-$^{14}C_2$]-2-(2-nitrophenylthio)benzoic acid,

5. 1-Chloro-2-nitrobenzene (675 mg) was added to a solution of dithiosalicylic acid **3** (625 mg, 811.06 MBq, 2.04 mmol) and NaOH (325 mg) in water (2.5 ml), and the mixture was refluxed at 100–105°C for 5 h. After the extraction of the reaction mixture with ethyl acetate (2 × 5 mL), the aqueous layer was neutralized with a hydrochloric acid solution and then extracted with ethyl acetate (2 × 5 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give [carboxyl-$^{14}C_2$]-2-(2-nitrophenylthio)benzoic acid **5** (1010 mg, 728.25 MBq, 3.67 mmol) in 89.8% yield. IR (KBr): 3320, 1679, 1573, 1523, 1448, 1341, 1259, 1146, 1102, 850, 750 cm^{-1}. ^{1}H NMR (DMSO-d_6, TMS), δ, ppm: 10.5 (br.s), 8.0 (d.d, 1H), 7.5 (t, 1H), 7.2 (m, 2H), 7.1 (d.d, 3H), 6.9 (t, 1H).

[Carboxyl-^{14}C]-2-(2-aminophenylthio)benzoic acid, 6. A suspension of [carboxyl-^{14}C]-2-(2-nitrophenylthio)benzoic acid **5** (1000 mg, 721.04 MBq, 3.63 mmol) and zinc dust (475 mg) in methanol (3 mL) was stirred in a nitrogen atmosphere with hydrazinium monoformate (1.5 mL) at room temperature. After the reaction completion (monitored by TLC), the reaction mixture was filtered through Celite. The filtered mixture was evaporated, and the residue was dissolved in chloroform and washed with a concentrated aqueous NaCl solution to remove excess hydrazinium monoformate. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give compound **6** (820 mg, 663.45 MBq, 3.34 mmol) in 92% yield.

Preparation of hydrazinium monoformate solution. Hydrazinium monoformate was prepared by slowly neutralizing equimolar amounts of hydrazine hydrate and 85% formic acid in an ice water bath with stirring.

[11-^{14}C]-10*H*-Dibenzo[*b*,*f*][1,4]thiazepin-11-one, 7. A solution of [carboxyl-^{14}C]-2-(2-aminophenylthio)-benzoic acid **6** (800 mg, 647.25 MBq, 3.26 mmol) in xylene (10 mL) with the addition of sulfuric acid (0.1 mL) was refluxed at 145–150°C for 6 h. Then the mixture was cooled to room temperature, after which the resulting solid was filtered off and washed with methanol. The solid was dried under reduced pressure to give [11-^{14}C]thiazepin-11-one **7** (675 mg, 588.95 MBq, 2.97 mmol) in 91% yield. IR (KBr): 3171, 1649, 1477, 1376 cm^{-1}. ^{1}H NMR (DMSO-d_6, TMS), δ, ppm: 7.10–7.20 (m, 1H), 7.20–7.25 (d, 1H), 7.30–7.40 (t, 1H), 7.40–7.60 (m, 4H), 7.60–7.70 (d, 1H), 10.70 (d, 1H). MS (70 eV): *m*/*z* = 230 (*M* + 1).

2-[2-(4-([11-^{14}C]Dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, 1. Pyrophosphoryl chloride (0.28 mL) was added to a solution of dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one **7** (675 mg, 588.95 MBq, 2.97 mmol) and *N*,*N*-dimethylaniline (400 mg) in dry toluene (4 mL). After stirring the resulting suspension at 20–25°C for 30 min, the reaction mixture was refluxed at 110–112°C for 4.5 h. After slowly cooling the reaction mixture to 25°C, 4-hydroxyethoxyethylpiperazine (2.1 g, 4 equivalents) was added to the resulting iminochloride intermediate. After refluxing the reaction mixture at 105–107°C for 21 h, a NaOH solution (7 mL, 5%) was added to the reaction mixture over a period of 15 min at room temperature. The mixture was stirred for an additional 30 min, after which the organic and aqueous phases were separated. The organic phase was washed with water (15 mL), the layers were separated, and water (5 mL) was added to the organic phase. The product was converted to its water-soluble HCl salt by adding concentrated HCl to pH between 2 and 3. The aqueous phase was separated, 10 mL of dichloromethane was added, and the mixture was alkalized to pH 10–11 with a 25% NaOH solution (10 mL). The dichloromethane phase was separated, dried over sodium sulfate, filtered, and the dichloromethane was distilled off under reduced pressure to obtain [11-^{14}C]Quetiapine **1** as free base (1.125 g, 583 MBq, 2.94 mmol) in 99% yield. HPLC (conditions see above) R_t 2.50 min. IR (KBr): 3318, 2869, 1600, 1413 cm^{-1}. ^{1}H NMR ($CDCl_3$, TMS), δ, ppm: 2.45–2.55 (m, 2H), 2.45–2.70 (m, 2H), 3.60–3.70 (m, 6H), 3.70–3.80 (m, 6H), 6.85 (d, 1H, *J* = 8.0 Hz), 7.10 (m, 1H), 7.20 (d, 1H, *J* = 7.6 Hz), 7.25–7.40 (m, 4H), 7.55 (m, 1H). MS (70 eV): *m*/*z* = 386 (*M* + 1).

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