JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd. Radiopharm 2006; **49**: 1141–1149.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1116

Research Article

Synthesis of 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]-[2-^{14}C]pyrimidin-4-one · 2 HCl (^{14}C-SK3530 · 2 HCl)

Hyun-Il Shin[1], Juyoung Lee[2] and Dae-Kee Kim[3,*]

[1] *Department of Chemistry, Korea RadioChemicals Center, 600 Jungja-dong, Changan-gu, Suwon, Kyungki-do 440-745, Korea*

[2] *Life Science Research Center, SK Chemicals, 600 Jungja-dong, Changan-gu, Suwon, Kyungki-do 440-745, Korea*

[3] *College of Pharmacy, Ewha Womans University, 11-1 Daehyun-dong, Seodaemun-gu, Seoul 120-750, Korea*

Summary

A new ^{14}C-labelled PDE5 inhibitor, 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]-[2-^{14}C]pyrimidin-4-one · 2 HCl (^{14}C-SK3530 · 2 HCl) (**1** · 2 HCl) was synthesized through a straightforward six-step sequence from the readily available [^{14}C-carbonyl]methyl salicylate (**2**). The overall radiochemical yield of the **1** · 2 HCl from **2** was 10.5%, and its radiochemical purity was 98.8%. Copyright © 2006 John Wiley & Sons, Ltd.

Received 23 June 2006; Revised 10 July 2006; Accepted 13 July 2006

Key Words: ^{14}C-SK3530 · 2 HCl; radiosynthesis; PDE5 inhibitor

Introduction

Male erectile dysfunction (MED), the persistent inability to achieve or maintain an erection for satisfactory sexual performance, is a common and important medical problem.[1,2] Development of the first orally effective phosphodiesterase type 5 (PDE5) inhibitor, sildenafil citrate (Viagra®; Figure 1)[3–6] spurred significant interest in the discovery of additional PDE5 inhibitors,

*Correspondence to: Dae-Kee Kim, College of Pharmacy, Ewha Womans University, 11-1 Daehyun-dong, Seodaemun-gu, Seoul 120-750, Korea. E-mail: dkkim@ewha.ac.kr

Contract/grant sponsor: Ministry of Health & Welfare, Korea; contract/grant number: 02-PJ2-PG4-PT01-0030

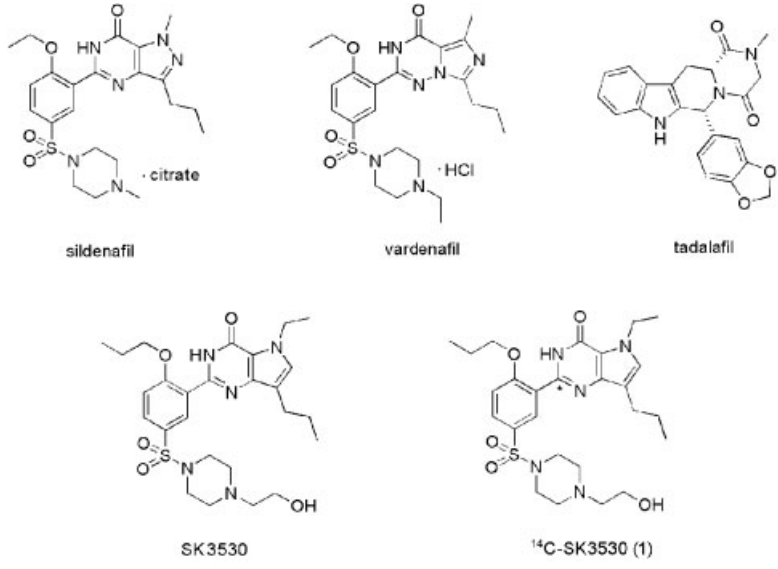


Figure 1. Structures of PDE5 inhibitors

leading to the successful launching of vardenafil (Levitra®)[7] and tadalafil (Cialis®)[8–10] in the market. Despite the clinical efficacy of these commercially available PDE5 inhibitors as a treatment for MED, there are some notable drawbacks associated with their use. Clinically significant adverse effects such as headache, facial flushing, dyspepsia and visual disturbances have been reported, and their incidence is dose-dependent.[11] Certain of these adverse effects are thought to be associated with non-specific inhibition of other PDEs.[12] Therefore, the search for more selective PDE5 inhibitors with fewer PDE-related adverse effects and greater efficacy is of primary interest. As part of our ongoing research program to develop a new more selective PDE5 inhibitor, a series of pyrrolo[3,2-*d*]pyrimidin-4-ones was synthesized.[13] Among them, 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (SK3530) was found to be a more potent and selective PDE5 inhibitor than sildenafil. SK3530 showed IC_{50} values of 0.34, 16 400, 86 500, 10.2, and 3750 nM against PDE5, PDE1, PDE3, PDE6 (rod), and PDE11A, respectively. In contrast, the IC_{50} values of sildenafil against PDE5, PDE1, PDE3, PDE6 (rod), and PDE11A were 3.50, 281, 16 200, 37, and 2730 nM, respectively.[14] In a Phase I, double-blind, placebo-controlled, ascending multiple oral dose study in healthy male volunteers, SK3530 was found to be safe and well tolerated at dose levels up to 150 mg, and no visual disturbance was reported. To facilitate the pharmacokinetic and metabolic studies of SK3530, we required the ^{14}C-labelled compound. Therefore, in this report, we describe the synthesis of 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-

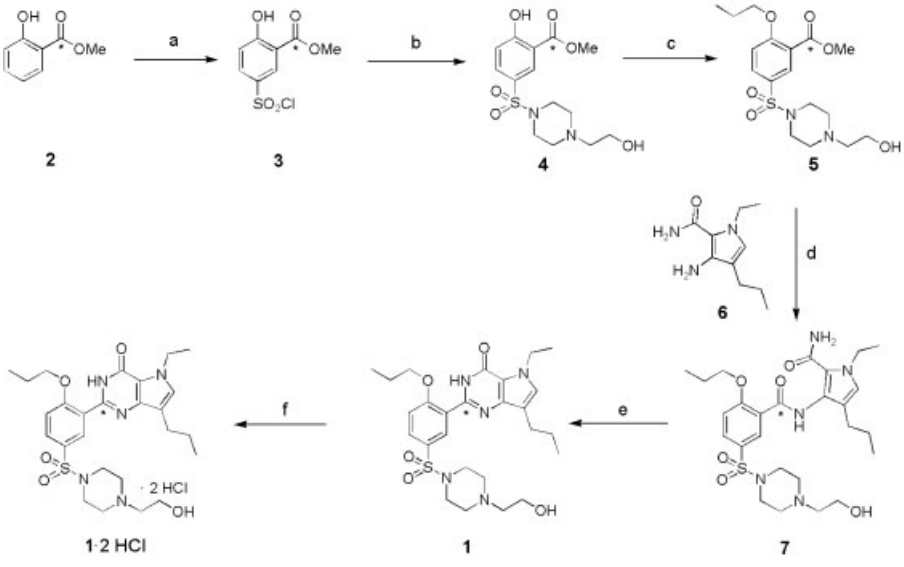
DOI: 10.1002/jlcr

7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]-[2-^{14}C]pyrimidin-4-one · 2 HCl (^{14}C-SK3530 · 2 HCl) (**1** · 2 HCl) from [^{14}C-carbonyl]methyl salicylate (**2**).

Results and discussion

The target compound **1** · 2 HCl was synthesized through a straightforward six-step sequence from the readily available [^{14}C-carbonyl]methyl salicylate (**2**)[15] as shown in Scheme 1. Chlorosulfonylation of **2** with $ClSO_3H$ and $SOCl_2$ at room temperature proceeded smoothly and selectively at the 5′-position of the phenyl ring to give 5-chlorosulfonyl-2-hydroxy-[^{14}C]benzoic acid methyl ester (**3**) in 71% yield. The chlorosulfonyl derivative **3** was readily reacted with 1-(2-hydroxyethyl)piperazine in the presence of $N(Et)_3$ in CH_2Cl_2 at room temperature for 2 h to afford 2-hydroxy-5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-[^{14}C]benzoic acid methyl ester (**4**) in 70% yield.

Alkylation of **4** with 1-bromopropane in anhydrous DMF in the presence of anhydrous K_2CO_3 at 65°C for 24 h produced 5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxy-[^{14}C]benzoic acid methyl ester (**5**) in 90% yield. Hydrolysis of the methyl ester group of **5** was carried out under a basic condition ($LiOH \cdot H_2O$, THF/H_2O) at room temperature for 15 h to give its carboxylic acid lithium salt in 69% yield, which was subsequently coupled with



Scheme 1. (a) $ClSO_3H$, $SOCl_2$, rt, 15 h; (b) 1-(2-hydroxyethyl)piperazine, $N(Et)_3$, CH_2Cl_2, rt, 2 h; (c) 1-bromopropane, anhydrous K_2CO_3, anhydrous DMF, 65°C, 24 h; (d) (i) $LiOH \cdot H_2O$, THF/H_2O, rt, 15 h; (ii) 6, EDC · HCl, HOBT, DMAP, pyridine, rt, 15 h; (e) *t*-BuOK, *t*-BuOH, rt, 15 h; (f) 3N HCl in THF, 0°C, 5 min, then Et_2O, 0°C, 10 min

DOI: 10.1002/jlcr

3-amino-1-ethyl-4-*n*-propyl-1*H*-pyrrole-2-carboxamide (**6**) in the presence of EDC · HCl, HOBT, and DMAP in pyridine at room temperature for 15 h to give 1-ethyl-3-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxy-[^{14}C] benzamido}-4-*n*-propyl-1*H*-pyrrole-2-carboxamide (**7**) in 71% yield. Cyclization of the 3-benzamidopyrrole-2-carboxamide **7** was efficiently affected under a basic condition (*t*-BuOK/*t*-BuOH) at room temperature for 15 h to give 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]-[2-^{14}C]pyrimidin-4-one (**1**) in 51% yield. Due to the limited aqueous solubility of **1**, it was necessary to develop a more water-soluble salt form of **1** for the *in vivo* animal experiments. Thus, a solution of **1** in CH_2Cl_2 was treated with 3 N HCl in THF at 0°C for 5 min to give its dichloride salt in 94% yield. The overall radiochemical yield of the **1** · 2 HCl from **2** in a six-step sequence was 10.5%, and its radiochemical purity was 98.8%.

Experimental

General

Reagents and solvents were purchased from Aldrich or Fluka and used without further purification. Radioactivity was measured by a Tri-carb 2100TR liquid scintillation counter (Packard) using ULTIMA FLO M (Packard) as a liquid scintillation cocktail. High performance liquid chromatography (HPLC) was performed using 1100 series (Agilent). Radiochemical purity (RCP) was determined either by an automatic TLC-linear analyzer Tracemaster 20 (EG&G Berthold) or by a HPLC radioactivity monitor LB506C-1 (EG&G Berthold) equipped with a pump, LB 5035 (EG&G Berthold) and with Flo-scint II (Packard) as the liquid scintillation cocktail. The HPLC was run on a Capcellpak C_{18} UG120 column. All reactions were monitored by TLC (silica gel 60 F_{254} plate, Merck), and ultraviolet light, automatic TLC-linear analyzer Tracemaster 20 and X-ray film (Konica) were used in TLC visualization. For column chromatography, we employed silica gel 60 (230–400 mesh; ASTM, Merck). All labelled materials were identified by chromatographic comparison with the corresponding authentic unlabelled samples. ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer; the chemical shifts are reported in parts per million (ppm) relative to TMS in $CDCl_3$ or DMSO-d_6. Electron impact mass spectra (EI-MS) were obtained on a LCQ DECA XP Plus LC-Mass spectrometer (Thermo Finnigan). Unlabeled samples prepared by the same synthetic procedure was used for mass spectra.

*[^{14}C-carbonyl]methyl salicylate (**2**).* A mixture of 2-bromoanisole (1.47 g, 7.86 mmol) and magnesium (287 mg, 11.8 mmol) in THF (40 ml) was heated at 80°C for 1 h. To the reaction mixture was added $^{14}CO_2$ generated from

DOI: 10.1002/jlcr

reaction of $Ba^{14}CO_3$ (775 mg, 3.93 mmol, 8.21 GBq) and excess concentrated H_2SO_4, and then the mixture was stirred at −78°C for 3 h. After quenching with 1N NaOH (10 ml), the reaction mixture was washed with Et_2O (10 ml × 2) and then acidified with concentrated HCl (pH ~ 2). The aqueous layer was extracted with Et_2O (15 ml × 2) and then the combined organic layers were dried (anhydrous $MgSO_4$), filtered, and concentrated to afford [^{14}C-carbonyl]-*o*-anisic acid (567 mg, 3.73 mmol, 7.58 GBq, 92%). To a solution of [^{14}C-carbonyl]-*o*-anisic acid (567 mg, 3.73 mmol, 7.58 GBq) in CH_2Cl_2 (8 ml) at –78°C was added BBr_3 in CH_2Cl_2 (1 M solution, 11.2 ml, 11.2 mmol), and then the mixture was stirred at room temperature for 3 h. After diluting with H_2O (10 ml), the reaction mixture was extracted with Et_2O (15 ml × 2). The combined organic layers were dried (anhydrous $MgSO_4$), filtered, and concentrated to afford [^{14}C-carbonyl]salicylic acid (7.56 GBq, 99%). To a solution of [^{14}C-carbonyl]salicylic acid (7.56 GBq) in anhydrous Et_2O (15 ml) at 0°C was added excess diazomethane in Et_2O, and then the mixture was stirred at 0°C for 10 min. The reaction mixture was concentrated, dissolved with Et_2O (5 ml), filtered using a membrane filter, washed with Et_2O (3 ml), and concentrated to afford **2**[15] (566 mg, 3.72 mmol, 7.56 GBq, quantitative).

*5-Chlorosulfonyl-2-hydroxy-[^{14}C]benzoic acid methyl ester (**3**).* To a cooled solution of $SOCl_2$ (442 mg, 3.72 mmol) and $ClSO_3H$ (1.75 g, 15.0 mmol) at −10°C was added slowly [^{14}C-carbonyl]methyl salicylate (**2**) (566 mg, 3.72 mmol, 7.56 GBq), and then the mixture was stirred at room temperature for 15 h. The reaction mixture was poured slowly into H_2O (15 ml) at 0°C, and the resulting white precipitates were collected by filtration. The filtered solid was washed with H_2O (30 ml) and dried *in vacuo* (P_2O_5) for 15 h to afford **3** (644 mg, 2.57 mmol, 5.37 GBq, 71%). m.p. 76.5–77.5°C (toluene/hexanes); IR (neat) 1699 (C = O) cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 3.90 (s, 3 H, OCH_3), 6.93 (d, J = 8.7 Hz, 1 H, H-3), 7.70 (dd, J = 8.7, 2.4 Hz, 1 H, H-4), 8.03 (d, J = 2.4 Hz, 1 H, H-6).

*2-Hydroxy-5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-[^{14}C]benzoic acid methyl ester (**4**).* To a solution of **3** (644 mg, 2.57 mmol, 5.37 GBq) in CH_2Cl_2 (3.8 ml) at 0°C were added 1-(2-hydroxyethyl)piperazine (362 mg, 2.78 mmol) and $N(Et)_3$ (276 mg, 2.73 mmol), and then the mixture was stirred at room temperature for 2 h. After diluting with H_2O (3 ml), the reaction mixture was extracted with 10% MeOH in CH_2Cl_2 (4 ml × 2). The combined organic layers were dried (anhydrous $MgSO_4$), filtered, and concentrated to give a residue. To the residue was added a mixture solution of CH_2Cl_2 (1.5 ml), EtOAc (1 ml) and Et_2O (5 ml), and then the suspension was stirred at room temperature for 5 min. The resulting solid was filtered and washed with EtOAc (1 ml) and Et_2O (3 ml), and dried *in vacuo* for 30 min to afford **4** (622 mg, 1.81 mmol, 3.78 GBq,

DOI: 10.1002/jlcr

70%). m.p. 152°C (dec) (CH_2Cl_2/ Et_2O); IR (neat) 1685 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 2.30 (br s, 1 H, CH_2OH), 2.63 (t, J = 5.4 Hz, 2 H, NCH_2CH_2O), 2.70 (m, 4 H, 2 NCH_2), 3.12 (m, 4 H, 2 SO_2NCH_2), 3.64 (t, J = 5.4 Hz, 2 H, NCH_2CH_2O), 4.01 (s, 3 H, OCH_3), 7.12 (d, J = 8.7 Hz, 1 H, H-3), 7.81 (dd, J = 8.7, 2.4 Hz, 1 H, H-4), 8.26 (d, J = 2.4 Hz, 1 H, H-6), 11.26 (br s, 1 H, OH); MS (FAB) m/z 345 (MH^+).

*5-[4-(2-Hydroxyethyl)piperazin-1-ylsulfonyl]-2-n-propoxy-[^{14}C]benzoic acid methyl ester (**5**).* To a stirred solution of **4** (622 mg, 1.81 mmol, 3.78 GBq) in anhydrous DMF (3.5 ml) at room temperature were added anhydrous K_2CO_3 (375 mg, 2.71 mmol) and 1-bromopropane (288 mg, 2.34 mmol), and then the mixture was heated at 65°C for 24 h. The reaction mixture was filtered and washed with EtOAc (5 ml × 3), and then the combined organic layers were concentrated to give a residue. To the residue was added H_2O (5 ml), and then the mixture was extracted with EtOAc (5 ml × 3). The combined organic layers were washed with H_2O (7 ml), dried (anhydrous $MgSO_4$), and concentrated to afford **5** (627 mg, 1.62 mmol, 3.42 GBq, 90%) as a solid. m.p. 88–89°C (EtOAc/hexanes); IR (neat) 3242 (OH), 1741 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$/ TMS) δ 1.09 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.84–1.95 (m, 2 H, $OCH_2CH_2CH_3$), 2.23 (br s, 1 H, OH), 2.54 (t, J = 5. 4 Hz, 2 H, NCH_2CH_2O), 2.60 (m, 4 H, 2 NCH_2), 3.04 (m, 4 H, 2 SO_2NCH_2), 3.58 (t, J = 5.4 Hz, 2 H, NCH_2CH_2O), 3.91 (s, 3 H, OCH_3), 4.08 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.07 (d, J = 9.0 Hz, 1 H, H-3), 7.82 (dd, J = 9.0, 2.4 Hz, 1 H, H-4), 8.15 (d, J = 2.4 Hz, 1 H, H-6); MS (FAB) m/z 387 (MH^+).

*1-Ethyl-3-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-n-propoxy-[^{14}C]-benzamido}-4-n-propyl-1H-pyrrole-2-carboxamide (**7**).* To a solution of **5** (627 mg, 1.62 mmol, 3.42 GBq) in THF/H_2O (2.5 ml/0.62 ml) at room temperature was added $LiOH \cdot H_2O$ (82 mg, 1.95 mmol), and then the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated and dried *in vacuo* for 30 min to give a residue. The residue was dissolved in THF (5 ml), and the solution was stirred at room temperature for 2 h. The resulting precipitates were filtered, washed with THF (3 ml × 2), and dried *in vacuo* (P_2O_5) for 3 h to afford the corresponding lithium salt (421 mg, 1.11 mmol, 2.32 GBq, 69%). A mixture of the lithium salt (421 mg, 1.11 mmol, 2.32 GBq), 3-amino-1-ethyl-4-*n*-propyl-1*H*-pyrrole-2-carboxamide (**6**) (181 mg, 0.93 mmol), EDC · HCl (213 mg, 1.11 mmol), HOBT (126 mg, 0.93 mmol), and DMAP (6 mg, 0.049 mmol) in pyridine (2.8 ml) was stirred at room temperature for 15 h, and then the reaction mixture was concentrated to give a residue. To the residue was added H_2O (5 ml), and then the aqueous layer was extracted with CH_2Cl_2 (5 ml × 2). The combined organic layers were washed with H_2O (5 ml), dried (anhydrous $MgSO_4$), concentrated, and dried

DOI: 10.1002/jlcr

in vacuo for 5 h to afford **7** (423 mg, 0.770 mmol, 1.65 GBq, 71%) as a solid. m.p. 128–129°C (CH_2Cl_2/Et_2O); IR (neat) 3359 (NH), 1653 (C = O) cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.92 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.09 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.41 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 1.48–1.60 (m, 2 H, $CH_2CH_2CH_3$), 1.90–2.02 (m, 2 H, $OCH_2CH_2CH_3$), 2.33 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.56 (t, J = 5.4 Hz, 2 H, NCH_2CH_2O), 2.62 (dd, J = 4.8, 4.5 Hz, 4 H, 2 NCH_2), 3.09 (br dd, J = 4.8, 4.5 Hz, 4 H, 2 SO_2NCH_2), 3.59 (t, J = 5.4 Hz, 2 H, NCH_2CH_2O), 4.27 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (q, J = 7.2 Hz, 2 H, NCH_2CH_3), 6.61 (s, 1 H, H-2), 7.18 (d, J = 8.7 Hz, 1 H, H-3′), 7.90 (dd, J = 8.7, 2.4 Hz, 1 H, H-4′), 8.65 (d, J = 2.4 Hz, 1 H, H-6′), 9.16 (br s, 1 H, NH); MS (FAB) m/z 550 (MH^+).

5-Ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-n-propoxyphenyl}-7-n-propyl-3,5-dihydro-4H-pyrrolo[3,2-d]-[2-^{14}C]pyrimidin-4-one (**1**). To a solution of **7** (423 mg, 0.770 mmol, 1.65 GBq) in *t*-BuOH (3 ml) at room temperature was added *t*-BuOK (104 mg, 0.927 mmol), and then the mixture was stirred at room temperature for 15 h and concentrated to ~1.5 ml. After diluting with H_2O (5 ml), the reaction mixture was adjusted to pH 7 ~ 8 with 1 N HCl and extracted with CH_2Cl_2 (5 ml × 3). The combined organic layers were dried (anhydrous $MgSO_4$), filtered, and concentrated to afford a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 20/1) to give a residue. The residue was solidified with EtOAc/Et_2O (2 ml/8 ml), filtered, and dried *in vacuo* to give a crude product. The crude product was then crystallized from EtOAc, filtered, washed with EtOAc/Et_2O (1/1, 2 ml × 2), and dried *in vacuo* for 30 min to afford **1** (215 mg, 0.404 mmol, 844 MBq, 51%). m.p. 159.5–160.5°C (EtOAc/Et_2O); IR (neat) 3519 (OH), 3330 (NH), 1684 (C = O) cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 1.00 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.19 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.48 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 1.68–1.81 (m, 2 H, $CH_2CH_2CH_3$), 1.99–2.11 (m, 2 H, $OCH_2CH_2CH_3$), 2.30 (br s, 1 H, OH), 2.55 (t, J = 5.4 Hz, 2 H, CH_2CH_2OH), 2.61 (dd, J = 5.1, 4.5 Hz, 4 H, 2 NCH_2), 2.72 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.12 (br dd, J = 5.1, 4.5 Hz, 4 H, 2 SO_2NCH_2), 3.57 (t, J = 5.4 Hz, 2 H, CH_2CH_2OH), 4.25 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.46 (q, J = 7.2 Hz, 2 H, NCH_2CH_3), 6.97 (s, 1 H, H-2), 7.15 (d, J = 8.7 Hz, 1 H, H-3′), 7.81 (dd, J = 8.7, 2.4 Hz, 1 H, H-4′), 8.89 (d, J = 2.4 Hz, 1 H, H-6′), 10.70 (br s, 1 H, NH); MS (FAB) m/z 532 (MH^+).

5-Ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-n-propoxyphenyl}-7-n-propyl-3,5-dihydro-4H-pyrrolo[3,2-d]-[2-^{14}C]pyrimidin-4-one·2 HCl (^{14}C-SK3530·2 HCl) (**1**·2 HCl). To a solution of **1** (215 mg, 0.404 mmol, 844 MBq) in CH_2Cl_2 (1 ml) at 0°C was added 3 N HCl in THF (0.4 ml, 1.2 mmol), and then the mixture was stirred at 0°C for 5 min. To the reaction mixture was added Et_2O (3 ml), and then the suspension was stirred at 0°C for

DOI: 10.1002/jlcr

10 min. The resulting solid was filtered, washed with Et_2O (2 ml × 3), and dried (P_2O_5) *in vacuo* for 15 h to afford **1** · 2 HCl (^{14}C-SK3530 · 2 HCl) (230 mg, 0.380 mmol, 795 MBq, 2.09 GBq/mmol, 94%). IR (neat) 3336 (OH), 1715 (C = O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.98 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.38 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 1.59–1.71 (m, 2 H, $CH_2CH_2CH_3$), 1.71–1.83 (m, 2 H, $OCH_2CH_2CH_3$), 2.62 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.97 (m, 2 H, CH_2CH_2OH), 3.18 (m, 4 H, 2 SO_2NCH_2), 3.55 (m, 2 H, CH_2CH_2OH), 3.77 (m, 4 H, 2 NCH_2), 4.17 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.40 (q, J = 7.2 Hz, 2 H, NCH_2CH_3), 6.31 (br s, 3 H, OH and 2 H^+), 7.35 (s, 1 H, H-2), 7.44 (d, J = 8.7 Hz, 1 H, H-3′), 7.89 (dd, J = 8.7, 2.4 Hz, 1 H, H-4′), 8.07 (d, J = 2.4 Hz, 1H, H-6'), 10.84 (br s, 1 H, NH); MS (FAB) m/z 532 (MH^+). The purity of **1** · 2 HCl was determined by HPLC using the following eluent system: A; 20 mM KH_2PO_4:CH_3CN = 8:2 (pH 7.0), B; 20 mM KH_2PO_4:CH_3CN = 3:7 (pH 7.0). Gradient: 0 min → 25 min; A/B = 100/0 → 0/100, 25 → 29 min; A/B = 0/100 → 0/100, 29 → 30 min; A/B = 0/100 → 100/0, 30 min → 35 min; 100/0 → 100/0, Flow rate; 1 ml/min, Detector; UV 294 nm, Temperature; 25°C, Retention time; UV = 14.25 min, RI = 14.35 min, Purity; UV = 99.4%, RI = 98.8%.

Conclusion

We have recently developed 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (SK3530) as a new class of PDE5 inhibitor that is more potent and selective than sildenafil. To facilitate the pharmacokinetic and metabolic studies of SK3530, we required the ^{14}C-labelled compound. In this report, we described the synthesis of 5-ethyl-2-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulfonyl]-2-*n*-propoxyphenyl}-7-*n*-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]-[2-^{14}C]pyrimidin-4-one · 2 HCl (^{14}C-SK3530 · 2 HCl) (**1** · 2 HCl) from [^{14}C-carbonyl]methyl salicylate (**2**). The compound **1** · 2 HCl was synthesized through a straightforward six-step sequence from the readily available **2**. The overall radiochemical yield of the **1** · 2 HCl from **2** was 10.5%, and its radiochemical purity was 98.8%.

Acknowledgements

This work was supported by a grant (02-PJ2-PG4-PT01-0030) from Ministry of Health & Welfare, Korea.

References

1. Lue TF. *N Engl J Med* 2000; **342**: 1802–1818.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. *J Urol* 1994; **151**: 54–56.
3. Brook G. *Drugs Today* 2000; **36**: 125–134.

DOI: 10.1002/jlcr

4. Martel AM, Graul A, Rabasseda X, Castaner R. *Drugs Future* 1997; **22**: 138–143.
5. Terrett NK, Bell AS, Brown D, Ellis P. *Bioorg Med Chem Lett* 1996; **6**: 1819–1824.
6. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, Osterloh IH, Gingell C. *Int J Urol Res* 1996; **8**: 47–52.
7. Sorbera LA, Martin L, Rabasseda J, Castaner J. *Drugs Future* 2001; **26**: 141–144.
8. Sorbera LA, Martin L, Leeson PA, Castaner J. *Drugs Future* 2001; **26**: 15–19.
9. Daugan A, Grondin P, Ruault C, Gouville ACLM, Coste H, Kirilovsky J, Hyafil F, Labaudiniere R. *J Med Chem* 2003; **46**: 4525–4532.
10. Daugan A, Grondin P, Ruault C, Gouville ACLM, Coste H, Linget JM, Kirilovsky J, Hyafil F, Labaudiniere R. *J Med Chem* 2003; **46**: 4533–4542.
11. Sui Z. *Expert Opin Ther Pat* 2003; **13**: 1373–1388.
12. Beavo JA. *Physiol Rev* 1995; **75**: 725–748.
13. Kim DK, Lee JY, Ryu DH, Lee NK, Lee SH, Kim NH, Kim JS, Ryu JH, Choi JY, Im GJ, Choi WS, Kim TK. EP 1257553 B1, 2004.
14. Gbekor E, Bethell S, Fawcett L, Mount N, Phillips S. *J Urol* 2002; **167**: 967.
15. Nobuyoshi H, Shinji K. *J Label Compd Radiopharm* 1986; **23**: 853–856.

DOI: 10.1002/jlcr