SYNTHESIS OF [^{14}C]KT3-671, 2-PROPYL-8-OXO-1-[(2'-(1H-[^{14}C] TETRAZOLE-5-YL) BIPHENYL-4-YL) METHYL]-4, 5, 6, 7-TETRAHYDRO-CYCLOHEPTIMIDAZOLE, A NOVEL POTENT NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONIST.

Naoto Ueyama, Takashi Yanagisawa* and Tsuyoshi Tomiyama
Research Laboratories, Kotobuki Pharmaceutical Co.,Ltd.
6351 Sakaki-Machi, Nagano 389-06, Japan

SUMMARY

2-Propyl-8-oxo-1-[(2'-(1H-tetrazole-5-yl) biphenyl-4-yl)methyl]-4, 5, 6, 7-tetrahydrocyclohept imidazole (KT3-671), which has been found to be a potent and selective angiotesin II receptor antagonist, was synthesized in ^{14}C-labelled form by using potassium[^{14}C]-cyanide. [^{14}C](KT3-671) **9** with a specific activity of 1.74GBq/mmol was prepared in four steps in 29.8% overall radiochemical yield from potassium[^{14}C]-cyanide.

Key words: [^{14}C]KT3-671, angiotensin-II (AII) receptor antagonist, phase-transfer agent.

INTRODUCTION

The renin-angiotensin system (RAS) plays an essential role in the regulation of blood pressure and seems to be critically involved in the development and maintenance of hypertension as well as congestive heart failure.[1] Angiotensin-II (AII) receptor antagonist, an octapeptide produced from angiotensin-I (AI) by the action of angiotensin converting enzyme (ACE) localized on the endothelium of blood vessels in the lungs, kidneys, and many other organs, is the primary effector component of the RAS. AII is a powerful vasoconstrictor that exerts its action by interaction with specific receptors which are present on cell membranes. ACE inhibitor which inhibit the conversion of AI to AII are clinically used with success. A more potentially effective approach is to block the action of AII at the AII receptor level. We have recently described, idetification of the 2-propyl-8-oxo-1-[(2'-(1H-tetrazole-5-yl) biphenyl-4-yl) methyl]-4, 5, 6, 7-tetrahydro-cycloheptimidazole (KT3-671),[2] which is a potent, long-acting and orally effective nonpeptide AII receptor antagonist and is currently undergoing clinical evaluation for the treatment of hypertension. For the purpose of pharmacokinetics and drug metabolism studies, the ^{14}C labeled forms of KT3-671were synthesized. This paper presents the synthesis of [^{14}C] KT3-671, **9**.

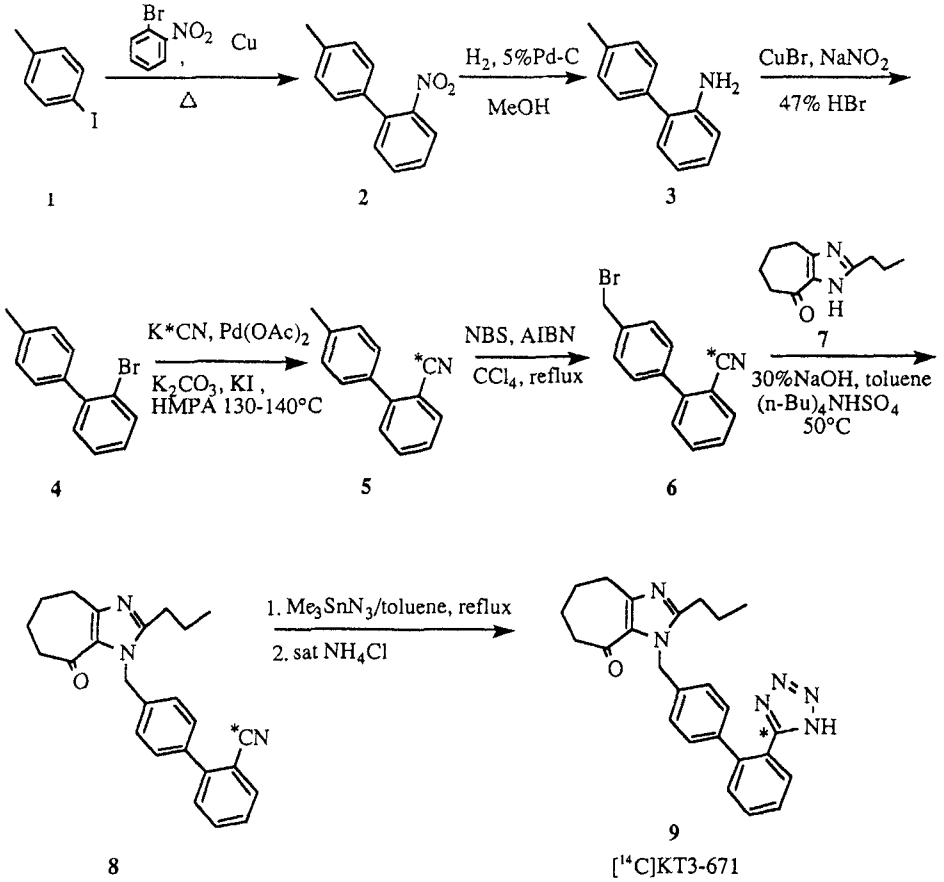
CCC 0362–4803/95/100915–05

Received 26 October 1994
Revised 25 April 1995

RESULTS AND DISCUSSION

[^{14}C] KT3-671, **9** was synthesized in seven steps (scheme1). The cross-coupling reaction[3] of 4-iodotoluene **1** with 2-bromonitrobenzene in the presence of Cu afforded the biphenyl compound **2** in a yield of 59.3%. Amination of **2** with 5% palladium-carbon (Pd-C) in CH_3OH afforded **3** in a yield of 97.1%. **3** was converted to the 4-methyl-2'-bromobiphenyl compound **4** by means of $NaNO_2$ and CuBr in the presence of 47%HBr.[4] The cyanation[5] of **4** with potassium[^{14}C]-cyanide in the presence of palladium(II)acetate $Pd(OAc)_2$ in a mixture of hexamethylphosphorictriamide (HMPA), K_2CO_3 and KI at 130-140°C for 3h afforded the key labeled compound **5** in a 50.1% yield. Conversion to the bromide **6** was carried out by free-radical bromination with N-bromosuccinimide (NBS) in refluxing carbon tetrachloride in the presence of azoisobisbutyronitrile (AIBN). The condensation of **6** with 2-propyl-4, 5, 6, 7-tetrahydro-8-oxo-cycloheptimidazole **7**[2] in the presence of tetra-*n*-butylammonium hydrogensulfate $(n\text{-Bu})_4NHSO_4$ as phase-transferagent[6] afforded **8** in a yield of 70.0%. The

Scheme 1 Synthesis of [^{14}C] KT3-671, **9**



[^{14}C]nitrile of **8**, was converted into a [^{14}C]tetrazole with trimethyltinazide $(CH_3)_3SnN_3$[7] in refluxing toluene and then reacted with saturated NH_4Cl afforded [^{14}C]KT3-671, **9** with a specific activity of 1.74GBq/mmol.

EXPERIMENTAL

Potassium[^{14}C]-cyanide(2.96 GBq, 1.85 GBq/mmol) was purchased from Amersham International plc. The reactions in the labelling synthesis were monitored by thin layer chromatography (TLC). Analytical TLC was carried out on a Merck silica gel 60 F_{254} plate (0.25 mm). Fuji Division BM-820MH silica gel was used for column chromatography. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 90MHz on a Hitachi R-90H Fourier Transform NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) were taken on a Hitachi M-80B spectrometer. These spectral data were obtained in trial experiments using unlabelled material. Radioactivity was determined with a Beckman LS-900 liquid scintillation counter using 2,5-diphenyloxazole in toluene or a mixture of toluene and Triton X-100 as a liquid scintillator. The radio high performance liquid chromatography (RHPLC) was performed on a 655A-II liquid chromatograph (Hitachi Co., Ltd.,Japan) was equipped with a 655A UV detector (Hitachi Co.) and a RS-8000 Radioanalyzer (Toso). A stainless steel column packed with octadesyl silane (TSK-gel, 80Tm, id, 4.6 x 150 mm) was used for analysis of **9**. Operating conditions: mobile phase 20mM phosphate buffer (pH 6.0)/CH_3CN=7:3 (v/v); flow rate 1.0 ml/min.; UV 250 nm; retention time for **9**, 10 min .

4-Methyl-2'-nitorobiphenyl. 2

To a stirred mixture of 1-bromo-2-nitrobenzene (20g, 0.1mol) and 4-iodotoluene **1** (21g, 0.1mol) in an oil bath at 180-190°C under an argon atmosphere was added copper powder (31g, 0.5mol) in portions over 1h. When one-third of the copper had been added, the reaction started with the temperature increasing spontaneously to 240°C. The mixture was allowed to air cool to 210°C and was held at 210°C during the addition of the remaining copper and then for an additional an hour. After cooling the mixture to room tempertaure, benzene was added and filtered, the resulting filtrate was concentrated *in vacuo*. The resulting product was purified by silica gel column chromatography [benzene:*n*-hexane (1:2)] to give 12.6g (59.3%) of **2.**

^{1}H-NMR ($CDCl_3$) δ : 2.41(3H, s, CH_3) 7.26-8.25(8H, m, aromatic). MS(m/z) : 213(M^+).

4-Methyl-2'-aminobiphenyl. 3

A mixture of **2** (12g, 56mmol), 5% Pd-C (0.6g), and 100ml of MeOH was stirred at room temperature under hydrogen gas for 6h. The mixture was filtered through Celite and the resulting

mixture was concentrated *in vacuo* to give 9.9g (97.1%) of **3**.
^{1}H-NMR ($CDCl_3$) δ : 2.43(3H, s, CH_3), 6.90-8.25(10H, m, aromatic). MS(m/z) : 183(M^+).

4-Methyl-2'-bromobiphenyl. 4

A suspension of 4-Methyl-2'-aminobiphenyl **3** (9g, 49mmol) in 10ml of H_2O was heated to reflux and 30ml of 47%HBr was added. The mixture was maintained at reflux for 20min then cooled to 0°C. A solution of $NaNO_2$ (3.4g, 49mmol) in 5ml of H_2O was added with rapid stirring while maintaining the temperature at 0°C. The resulting diazonium solution was stirred at 0°C for 15min and then added dropwise to a rapidly stirring mixture of CuBr (7.7g, 54mmol) in 20ml of 47% HBr. After the suspension was stirred at room temperature for 20min, the resulting suspension was filtered and the filtrates was extracted with Et_2O (30mlx3). The combined organic phases were washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel column chromatography [*n*-hexane] to give 5.1g (42.4%) of **4.**
^{1}H-NMR ($CDCl_3$) δ : 2.42(3H, s, CH_3), 7.10-8.05(8H, m, aromatic). MS(m/z) : 247(M^+).

4-Methyl-2'-[^{14}C]cyanobiphenyl. 5

A suspension of **4** (168mg, 0.68mmol), K*CN (40mg, 0.62mmol, 1.13GBq), KI (9.2mg, 0.05mmol), K_2CO_3 (6.9mg, 0.05mmol), $Pd(OAc)_2$ (35mg, 0.16mmol), and 10ml of hexamethylphosphorictriamide (HMPA) was heated at 130-140°C for 3h under argon atomosphere. The mixture was allowed to cool to room temperature and diluted with benzene and filtered. The organic phases were separated and residure was washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* . The resulting product was purified by silica gel column chromatography [*n*-hexane] to give 59.1mg (50.1%) of **5.**
mp = 49-50°C; IR (KBr) cm^{-1} =2200 (CN); ^{1}H-NMR ($CDCl_3$) δ : 2.42(3H, s, -CH_3), 7.10-8.05(8H, m). MS(m/z) : 193(M^+).

4-Bromomethyl-2'-[^{14}C]cyanobiphenyl. 6

A solution of **5** (59.1mg, 0.31mmol), N-bromosuccinimide (NBS)(61mg, 0.34mmol), azoisobisbutyronitrile (AIBN) (1.5mg, 0.01mmol) and 1.5ml of CCl_4 was refluxed for 3h. After cooling to room temperature, the resulting suspension was filtered and the residure was washed with 2ml of CCl_4 concentrated *in vacuo* to give 92.8mg of **6** as crude product.
^{1}H-NMR ($CDCl_3$) δ : 4.56(2H, s, -CH_2-), 7.48-8.01(8H, m, aromatic). MS(m/z) : 272(M^+).

2-Propyl-8-oxo-1-[(2'-[^{14}C]cyanobiphenyl-4-yl)methyl]-4,5,6,7-tetrahydoro-cyclohept imidazole. 8

A suspension of imidazole 7[3] (119mg, 0.58mmol), compound **6** (92.8ml), tetra-*n*-butylammonium hydrogensulfate (*n*-Bu_4NHSO_4)(49mg,0.04mmol), 30%NaOH (3ml) in 15ml of toluene was heated at 50°C for 6h under an argon atmosphere. After cooling the reaction mixture, the solution was extracted with AcOEt (3ml x 3). The organic solvents were combined, washed with brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The resulting product was purified by silica gel column chromatography [ethyl acetate:*n*-hexane(1:1)] to give 83.2mg (70.0%) of **8** as colorless oil.
^{1}H-NMR ($CDCl_3$) δ : 0.86(3H, t, $CH_2CH_2C\underline{H}_3$), 1.38-2.10(6H, m), 2.30-2.79(4H, m), 2.96(2H, t, -$C\underline{H}_2CH_2CH_3$), 5.43(2H, s, -$C\underline{H}_2C_6H_4$), 6.84-7.80(8H, m, aromatic). MS(m/z) : 383(M^+).

2-Propyl-8-oxo-1-[(2'-(1H-[^{14}C]tetrazole-5yl)biphenyl-4yl)methyl-4,5,6,7-tetrahydoro-cycloheptimidazole. ([^{14}C]KT3-671), 9

A solution of **8** (83.2mg, 0.22 mmol) and trimethyltinazide ($(CH_3)_3SnN_3$ (0.16g, 0.76 mmol) in 5 ml of toluene was refluxed for 72h. The mixture was cooled to room temperature, filtered and the solvent was evaporated *in vacuo*. The residue was dissolved in saturated NH_4Cl (2 ml), and the mixture was stirred for 0.5h. The solvent was evaporated *in vacuo* and the purified by column chromatography on silica gel [chloroform:methyl alcohol(30:1)] to give 80.0mg (85.0%, 0.33GBq) of **9** as a white solid. The purity was 99% on RHPLC. mp = 134-136°C. IR (KBr) cm^{-1} = 2998,2950,1640.
^{1}H-NMR ($CDCl_3$) δ : 0.84(3H, t, -$CH_2CH_2C\underline{H}_3$), 1.40-2.10(6H, m), 2.30-2.79(4H, m), 2.98 (2H, t, -$C\underline{H}_2CH_2CH_3$), 5.45(2H, s, -$C\underline{H}_2C_6H_4$), 6.90-7.90(9H, m). MS (m/z): 426(M^+).

REFERENCES

1. Ferrario C. M., -J. Cardiovasc. Pharmacol. 15: (suppl.3) (1990).
2. Yanagisawa T., Ueyama N., Kawai T., Sonegawa M., Baba H., Mochizuki S., Kosakai K., and Tomiyama T., -Bioorg & Med. Chem. Letters. 3: 1559 (1993).
3. Carini D. J., Duncia J. V., Johnson A. L., Chiu A. T., Price W. A., Wong P. C., and Timmermans P. B. M. W. -J. Med. Chem. 33: 1330 (1990).
4. Harrington P. J., Hegedus L. S., -J. Org. Chem. 49: 2657 (1984).
5. Takagi K., Okamoto T., Sakakibara Y., Ohno A., Oka S., Hayama N., -Bull. Chem. Soc. Jpn. 48: 3298 (1975).
6. Dakka J., Sasson Y., -J. Chem. Soc. Chem. Commun. 1421 (1987).
7. Carini D. J., Duncia J. V., Aldrich P. E., Chiu A. T., Johnson A. L., Pierce M. E., Price W. A., Santella III J. B., and Timmermans P. B. M. W. -J. Med. Chem. 34: 2525 (1991).