Synthesis and Pharmacological Activity of the Metabolites of Pratosartan

Motoharu SONEGAWA,* Hiroaki SUZAKA, Akira TOMIYAMA, and Tsuyoshi TOMIYAMA

Kotobuki Research Laboratories, Kotobuki Seiyaku Company, Ltd.; 6351 Sakaki-Machi, Nagano 389–0697, Japan.
Received November 4, 2005; accepted February 28, 2006; published online March 2, 2006

Three hydroxylated metabolites of 2-propyl-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (Pratosartan), which is a selective angiotensin II receptor antagonist, were synthesized in confirmation of their structures and in studies of their pharmacological properties. An MTPA ester of the human main metabolite was identified with the synthesized compound by comparing ^{1}H-NMR spectra, MS spectra, and HPLC retention time. The structure of the human main metabolite was confirmed to be (*S*)-(−)-2-(1-hydroxypropyl)-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one ((*S*)-(−)-1). Also, the rat main metabolites were confirmed to be 8-hydroxylated compound (2) and 5-hydroxylated compound (3). These metabolites showed lower antagonistic activity than that of the parent compound.

Key words Pratosartan; metabolite; improved Mosher's method; absolute configuration

In the previous paper,[1] we reported the design and synthesis of Pratosartan (Chart 1), which is an orally active angiotensin II (AII) antagonist, exhibiting selective and potent antagonistic activity to AT_1 subtype. Furthermore, long duration was shown in various animal models *in vivo* experiment. Clinical trials of Pratosartan are now in progress as an antihypertensive agent.

Clarification of the possible metabolites and their therapeutic or toxic effects during the development process of new drugs is mandatory. For this purpose, we have tried to synthesize possible metabolites in human and rat to identify their structures and activities. In a pharmacokinetic study of Pratosartan, three hydroxylated metabolites were observed as major metabolites in human and rat after oral administration. These structures were characterized on the basis of MS and NMR spectra. Metabolite **1** isolated from human urine was estimated as a hydroxylated metabolite at the propyl side chain of Pratosartan. A similar hydroxlated metabolite was also reported for Losartan.[2] Metabolite **2** and **3** isolated from rat bile were estimated as 8- and 5-hydroxylated metabolites on the cycloheptane ring of Pratosartan, respectively. In this paper, we describe the synthesis of these metabolites to identify their structures and to study their pharmacological properties.

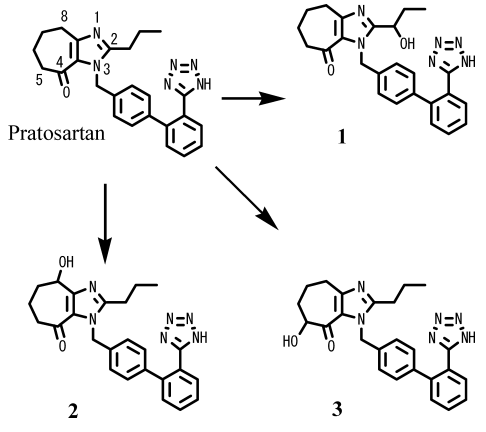

Chart 1. Structure of **1**—**3**

Chemistry

Metabolite **1** was synthesized as shown in Chart 2. Protection of 2-propyl-3*H*-cycloheptimidazol-4-one **4**[3,4] with chloromethyl methyl ether (MOMCl) gave **5**, which was treated with *N*-bromosuccinimide (NBS) to give the brominated product **6**. The bromo group was converted to an acetoxy group using sodium acetate to yield **7**. Removal of the MOM group and subsequent ester exchange of the acetate gave the corresponding alcohol **9**. Hydrogenation of **9** provided **10**, and it was alkylated with **11**[5] to afford the desired intermediate compound **12**. *N*-Alkylation of 3*H*-cycloheptimidazol-4-one in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) gave an *N*3-alkylated compound preferentially similarly to the biphasic reaction condition[6] and the regioisomer was separated easily by silica gel column chromatography. The *N*-benzylic proton of compound **12** and **20** was observed at lower field characteristically (0.4—0.5 ppm) compared to their regioisomers, which was caused by the anisotropic effect of the *C*4-carbonyl group. For the purpose of optical resolution, the racemic trityl compound **12** was converted to α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) **13** with (+)-MTPA-Cl.[7] Each diastereomer could be separated by silica gel column chromatography. Hydrolysis of the isolated single isomer **13a** gave an optically active hydroxy intermediate, and finally (+)-**1** was obtained by the successive deprotection of MTPA and trityl groups. Enantiomer (−)-**1** was obtained from **13b** in the same manner.

In order to confirm the structure, the human main metabolite was led to MTPA ester (Chart 3). The human main metabolite was protected with trityl chloride to give trityl compound **12**, and then it was converted to MTPA esters **13b** and **13c** as a single isomer with (+)-MTPA-Cl and (−)-MTPA-Cl, respectively.

The metabolite **2** was prepared as shown in Chart 4. The hydroxy group of compound **14**[8] was oxidized by manganese dioxide to give aldehyde. Alkylation of aldehyde with allyltrimethylsilane gave the corresponding alcohol,[9] which was protected using *tert*-butyldimethylchlorosilane to yield **15**. An intramolecular cyclization was accomplished by the Kulinkovich-type reaction.[10] Reaction of **15** with a $TiCl(O^iPr)_3$/^{i}PrMgCl reagent resulted in a tandem intramolecular nucleophilic acyl substitution and intramolecular car-

* To whom correspondence should be addressed. e-mail: ktb-g121@kotobuki-pharm.co.jp
© 2006 Pharmaceutical Society of Japan

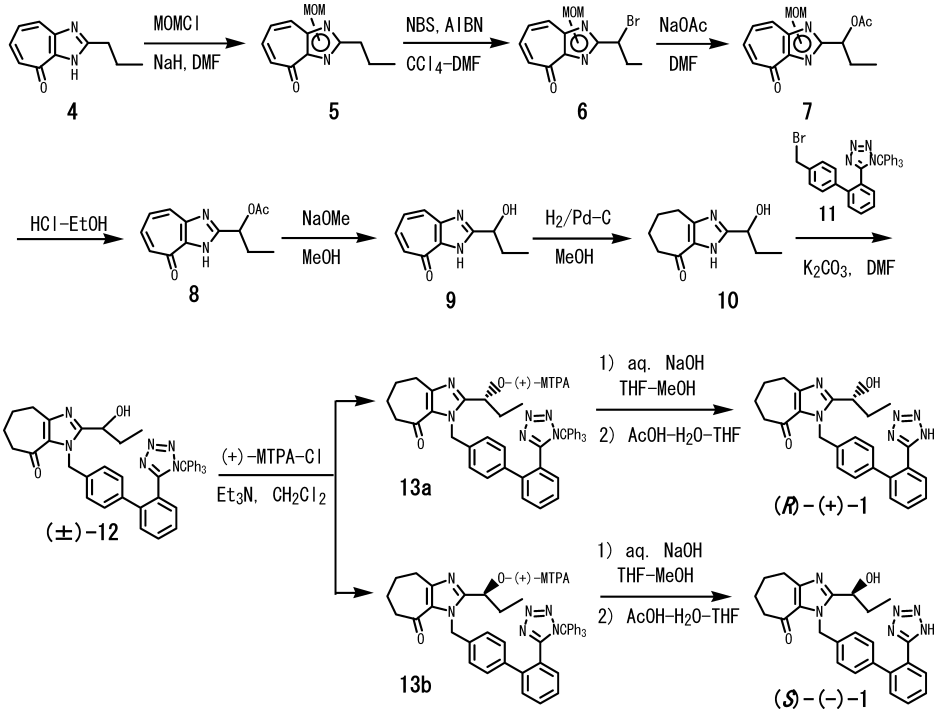

Chart 2. Preparation of (*R*)-(+)-**1** and Metabolite (*S*)-(−)-**1**

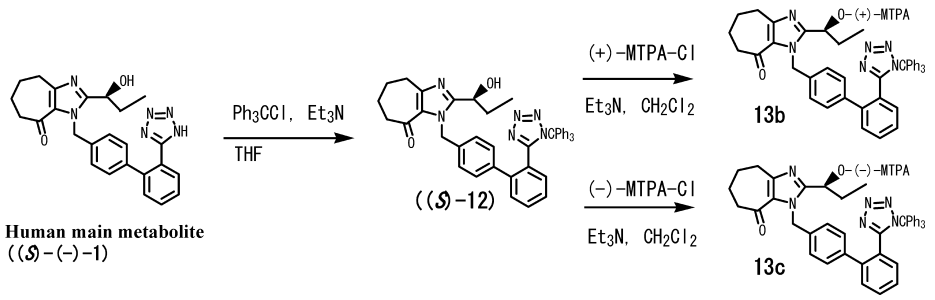

Chart 3. Preparation of **13b** and **13c**

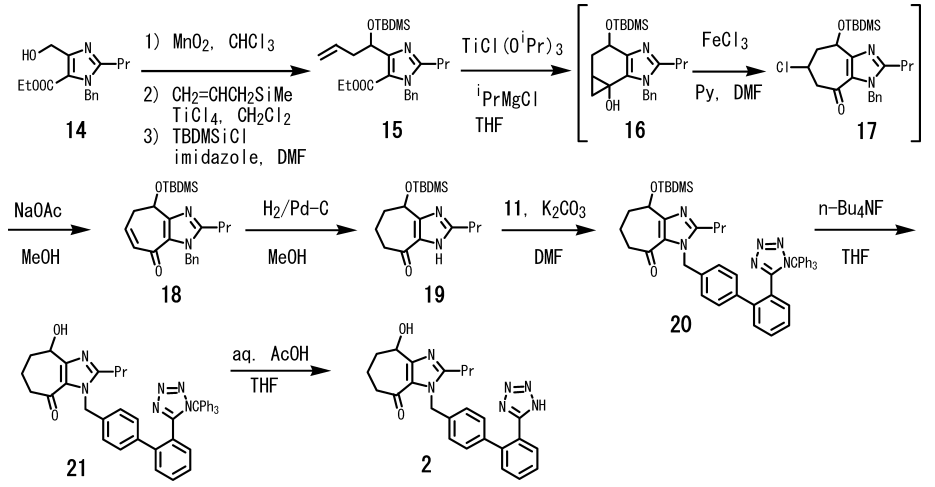

Chart 4. Preparation of Metabolite **2**

bonyl addition reaction to give **16**. Ring expansion was achieved using ferric chloride in pyridine,[11] followed by treatment with sodium acetate to yield dihydrocycloheptimidazolone **18**. Deprotection of the *N*-benzyl group and reduction of the olefin were carried out concurrently with catalytic palladium carbon under hydrogen to give **19**. Alkylation of **19** with **11** gave the corresponding biphenyl compound **20**, which was deprotected with tetrabutylammonium fluoride

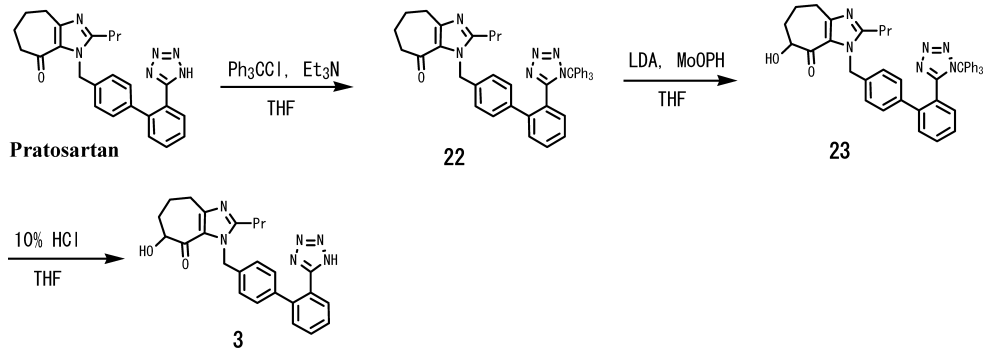

Chart 5. Preparation of Metabolite **3**

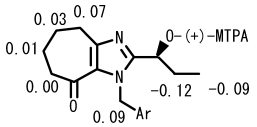

Chart 6. $\Delta\delta$ Values (ppm) Obtained by $\delta_{13a}-\delta_{13b}$

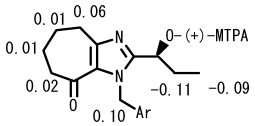

Chart 7. $\Delta\delta$ Values (ppm) Obtained by $\delta_{13c}-\delta_{13b}$

and aqueous acetic acid to give metabolite **2**.

Metabolite **3** was prepared by the method shown in Chart 5. The tetrazole moiety of Pratosartan was protected using trityl chloride to give **22**, which was treated with lithium diisopropylamide and then $MoO_5 \cdot Py \cdot HMPA$ (MoOPH) to yield α-hydroxy compound **23**.[12] Finally, compound **23** was deprotected with 10% hydrochloric acid to afford metabolite **3**.

Results and Discussion

The chemical structure of the human main metabolite was confirmed by comparison of the MTPA ester **13** and it was shown to be identical with the synthetic compound **13b** on the basis of HPLC, MS and ^{1}H-NMR spectroscopy. As a result, the human main metabolite was confirmed to be (−)-**1**. On the other hand, rat main metabolites were confirmed to be **2** and **3** by direct comparison with synthetic compounds on the basis of HPLC, MS and ^{1}H-NMR spectroscopy.

The human main metabolite gave a single isomer **13b** and **13c** with (+)-MTPA-Cl and (−)-MTPA-Cl, respectively (Chart 3). Therefore, the human main metabolite was shown as an optically active compound. Accordingly, the absolute configuration of metabolite **1** was determined by the improved Mosher's method.[13,14] As shown in Chart 6, proton signals at the *N*-benzylic position and the 8-position in compound **13b** were observed at higher fields compared to those of compound **13a** ($\Delta\delta$: positive), while the signals due to 2- and 3-positions of the propyl group in **13b** were observed at lower fields compared to those of **13a** ($\Delta\delta$: negative). On the basis of this evidence, the absolute configuration of **13b** was determined to be (*S*)-**13**. Also, the identical absolute configuration was shown by comparison with **13b** and **13c** (Chart 7). From these results, the human main metabolite was determined to be (*S*)-**1**.

The synthesized metabolites were evaluated for antagonistic activity against angiotensin II-induced contraction in isolated rabbit thoracic aorta.[15] The obtained pA_2 values of these compounds are listed in Table 1 in comparison with the data of the parent compound. The human main metabolite (*S*)-**1** shows lower activity in comparison with the parent compound.

Table 1. Potencies of Pratosartan and Its Metabolites on Angiotensin II-Induced Contraction in Isolated Rabbit Thoracic Aorta

Compounds	pA_2
(*S*)-**1**	7.35
(*R*)-**1**	5.79
2	8.83
3	9.32
Pratosartan	9.75

Furthermore, the enantiomer (*R*)-**1** shows obviously lower activity. It is considered that the hydroxylation to this hydrophobic part of Pratosartan caused loss of the activity. One of the rat main metabolites, **2** shows one order lower activity in comparison with the parent compound. On the other hand, another rat main metabolite **3** shows the most potent activity among the synthesized metabolites (**1**—**3**). As a whole, these hydroxylated metabolites were found to have lower antagonistic activity in rabbit aorta than the parent compound as observed in other sartans.[4,16,17]

Conclusion

Three hydroxylated metabolites of Pratosartan were synthesized. Metabolites **1** and **3** were synthesized from the synthetic intermediate of Pratosartan, or Pratosartan itself, respectively. Metabolite **2** was synthesized from another imidazole compound by the ring expansion reaction. The human main metabolite was confirmed to be (*S*)-**1** on the basis of HPLC retention time, MS and ^{1}H-NMR spectroscopic data using the improved Mosher's method. Also, the rat main metabolites were determined to be **2** and **3**. All these metabolites showed lower antagonistic activity than that of the parent compound.

Experimental

Melting points were determined on Yamato melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30. High performance liquid chromatography (HPLC) was carried out on Hitach

655A-11 using solvents and columns (silica 60, 25 cm×4.6 mmΦ, *n*-hexane/EtOAc=95/5) with flow rate of 1.0 ml/min, and peaks were observed using an UV detector (260 nm). Specific optical rotation $[\alpha]_D^{20}$ was measured by HORIBA SEPA-200 using a cell (50 m×5 mmΦ). Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 400 MHz on a JEOL EX-400 Fourier-transform NMR spectrometer. Chemical shifts are quoted in part per million (ppm) with tetramethylsilane as an internal standard. Coupling constants (*J*) are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; dd, doublet of doublet; m, multiplet. Mass spectra (MS) were taken on a Hitachi M-80B spectrometer and ESI-MS spectra (MS (ESI)) were taken on a Finnigan TSQ 700 spectrometer. Elemental analyses were within 0.4% of theoretical values and were determined by Hitachi 026 CHN analyzer. *Rf* values and preparative TLC were done on silica gel 60F_{254} (Merck). For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used.

1(or 3)-Methoxymethyl-2-propyl-1(or 3)*H*-cycloheptimidazol-4-one (5) To a stirred solution of 2-propyl-3*H*-cycloheptimidazol-4-one (**4**) (10.0 g, 53.0 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml) was added NaH (2.98 g, 50% dispersion in mineral oil, 62.0 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h. To this mixture was added chloromethyl methyl ether (5.0 ml) at 0 °C, and then allowed to warm to room temperature, and stirred for a further 2 h. After the addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with EtOAc. The organic layer was washed with H_2O and then brine, dried over $MgSO_4$. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (3 : 1 by volume), to give title compound as thin yellow oil (7.50 g, 60.9% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, *J*=7.2 Hz), 1.82—1.99 (2H, m), 2.90 (2H, t, *J*=7.6 Hz), 3.39 (3H, s), 6.18 (2H, s), 6.96 (1H, dd, *J*=8.8, 11.2 Hz), 7.15—7.36 (2H, m), 7.72 (1H, d, *J*=11.2 Hz). MS *m*/*z*: 232 (M^+), 217, 189 (B.P.). IR (neat) cm^{-1}: 2956, 1578, 1467, 1120.

2-(1-Bromopropyl)-1(or 3)-methoxymethyl-1(or 3)*H*-cycloheptimidazol-4-one (6) A mixture of **5** (7.40 g, 31.9 mmol), *N*-bromosuccinimide (6.24 g, 35.1 mmol), 2,2′-azobis(isobutyronitrile) (0.01 g), DMF (0.1 ml) and CCl_4 (80 ml) was refluxed for 2 h. After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (3 : 1 by volume), to give title compound as thin yellow oil (8.90 g, 89.8% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, *J*=7.2 Hz), 1.82—1.99 (2H, m), 3.39 (3H, s), 4.76 (1H, t, *J*=7.6 Hz), 6.18 (2H, s), 6.96 (1H, dd, *J*=8.8, 11.2 Hz), 7.15—7.36 (2H, m), 7.72 (1H, d, *J*=11.2 Hz). MS *m*/*z*: 312 (M^++2), 300 (M^+), 297, 295, 230 (B.P.). IR (neat) cm^{-1}: 3070, 1617, 1569, 1269.

1-(1(or 3)-Methoxymethyl-8-oxo-1,8-dihydro-cycloheptimidazol-2-yl)propyl Acetate (7) To a stirred solution of **6** (8.80 g, 28.3 mmol) in DMF (40 ml) was added sodium acetate (6.96 g, 84.8 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 7 h. After cooling, the reaction mixture was poured into ice-water (100 g), and extracted with EtOAc. The organic layer was washed with H_2O and then brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (1 : 1 by volume), to give title compound as thin yellow oil (7.03 g, 85.6% yield).^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, *J*=8.0 Hz), 2.10 (3H, s), 2.10—2.21 (2H, m), 3.40 (3H, s), 5.84 (1H, t, *J*=7.2 Hz), 6.00 (1H, d, *J*=10.0 Hz), 6.73 (1H, d, *J*=10.0 Hz), 6.96 (1H, d, *J*=12.4 Hz), 7.14—7.27 (2H, m), 7.74 (1H, d, *J*=11.2 Hz). MS *m*/*z*: 290 (M^+), 275, 215, 187 (B.P.). IR (neat) cm^{-1}: 2968, 2932, 1734, 1632, 1236.

1-(8-Oxo-1,8-dihydro-cycloheptimidazol-2-yl)propyl Acetate (8) To a stirred solution of **7** (6.00 g, 20.7 mmol) in EtOH (35 ml) was added saturated ethanolic HCl (5 ml) at room temperature. The reaction mixture was stirred for 0.5 h at ambient temperature. The reaction mixture was concentrated *in vacuo*, and residue was diluted with H_2O. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×100 ml). The combined extracts layer was washed with brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting EtOAc, to give title compound as thin yellow solid (4.00 g, 78.3% yield). mp: 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, *J*=7.2 Hz), 2.16 (3H, s), 2.12—2.25 (2H, m), 6.04 (1H, t, *J*=7.2 Hz), 7.07 (1H, dd, *J*=8.8, 10.8 Hz), 7.29 (1H, d, *J*=12.0 Hz), 7.44 (1H, dd, *J*=8.8, 12.0 Hz), 7.97 (1H, d, *J*=10.8 Hz). MS *m*/*z*: 246 (M^+), 203 (B.P.), 175. IR (KBr) cm^{-1}: 3034, 1743, 1617, 1563, 1515, 1236.

2-(1-Hydroxypropyl)-3*H*-cycloheptimidazol-4-one (9) To a solution of **8** (4.00 g, 16.2 mmol) in MeOH (30 ml) was added 28% NaOMe (6.3 ml, MeOH solution, 32.5 mmol). The reaction mixture was stirred for 20 min at room temperature, and concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting $CHCl_3$–EtOH (10 : 1 by volume), to give title compound as thin yellow oil (2.67 g, 80.5% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, *J*=7.2 Hz), 2.00—2.24 (2H, m), 5.09 (1H, t-like), 5.56 (1H, br s), 7.21 (1H, dd, *J*=8.8, 10.8 Hz), 7.38 (1H, d, *J*=12.0 Hz), 7.56 (1H, dd, *J*=8.8, 12.0 Hz), 7.97 (1H, d, *J*=10.8 Hz). MS *m*/*z*: 204 (M^+), 175 (B.P.), 147, 119, 92. IR (neat) cm^{-1}: 3358, 3070, 1620, 1572, 1515.

2-(1-Hydroxypropyl)-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (10) To a solution of **9** (2.00 g, 9.80 mmol) in MeOH (20 ml) was added 5% Pd on carbon (containing 50% water, 0.20 g) and the mixture was stirred at 40 °C for 14 h under an atmosphere of hydrogen (1 atm). After filtration of the catalyst, the filtrate was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting EtOAc, to give title compound as colorless oil (1.86 g, 91.2% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, *J*=7.2 Hz), 1.79—2.05 (6H, m), 2.71—2.89 (2H, m), 2.95—3.01 (2H, m), 4.82 (1H, t, *J*=4.4 Hz). MS *m*/*z*: 208 (M^+), 179 (B.P.), 147. IR (neat) cm^{-1}: 3330, 2926, 1626, 1548, 1455, 1311, 1230.

2-(1-Hydroxypropyl)-3-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (12) To a mixture of **10** (1.80 g, 8.64 mmol), 5-(4′-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole (**11**) (5.30 g, 9.51 mmol) and DMF (36 ml) was added K_2CO_3 (1.31 g, 9.51 mmol). The reaction mixture was stirred for 14 h at room temperature, and then poured into ice-water (200 g). The mixture was extracted with EtOAc, and the extract was washed with H_2O and then brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (1 : 1 by volume), to give title compound as colorless solid (3.66 g, 61.9% yield). mp: 69—71 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, *J*=7.2 Hz), 1.73—1.78 (2H, m), 1.84—1.87 (4H, m), 2.60—2.63 (2H, m), 2.97—3.00 (2H, m), 4.51 (1H, m), 5.52 (2H, s), 6.82 (2H, d, *J*=7.6 Hz), 6.93—6.95 (5H, m), 7.05 (2H, d, *J*=7.6 Hz), 7.24—7.36 (10H, m), 7.41—7.49 (3H, m), 7.85 (1H, d, *J*=7.6 Hz). MS (ESI): *m*/*z* 685 $[M+1]^+$. IR (KBr) cm^{-1}: 3450, 2950, 1638, 1449.

1-[8-Oxo-1-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6,7,8-hexahydrocycloheptimidazol-2-yl]propyl α-Methoxy-(α-trifluoromethyl)phenylacetate (13a, b) A solution of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.00 g, 3.96 mmol) in CH_2Cl_2 (10 ml) was added dropwise to **12** (2.71 g, 3.96 mmol) and triethylamine (0.55 ml, 3.96 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 14 h, and then poured into ice-water (100 g). The mixture was extracted with CH_2Cl_2 and the extract was washed with brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (8 : 1 by volume), to give **13a** as colorless solid (1.51 g, 42.4% yield), and then eluting *n*-hexane–EtOAc (6 : 1 by volume), to give **13b** as colorless solid (1.32 g, 37.0% yield). **13a**: mp: 78—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.53 (3H, t, *J*=7.2 Hz), 1.50—1.59 (1H, m), 1.85—2.00 (5H, m), 2.70 (2H, m), 3.03 (2H, m), 3.51 (3H, s), 5.33 (1H, d, *J*=16.0 Hz), 5.61—5.65 (1H, m), 6.14 (1H, d, *J*=16.0 Hz), 6.92 (2H, d, *J*=8.0 Hz), 6.93—7.00 (5H, m), 7.09 (2H, d, *J*=8.0 Hz), 7.22—7.55 (18H, m), 7.86 (1H, d, *J*=7.6 Hz). MS (ESI): *m*/*z*: 901 $[M+1]^+$. IR (KBr) cm^{-1}: 2962, 1743, 1644, 1449, 1233, 1167. **13b**: mp: 80—81 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.61 (3H, t, *J*=7.2 Hz), 1.66 (1H, m), 1.80—2.00 (5H, m), 2.70 (2H, m), 2.96 (2H, m), 3.52 (3H, s), 5.23 (1H, d, *J*=16.0 Hz), 5.65—5.68 (1H, m), 6.04 (1H, d, *J*=16.0 Hz), 6.88 (2H, d, *J*=8.0 Hz), 6.95—6.98 (5H, m), 7.08 (2H, d, *J*=8.0 Hz), 7.25—7.54 (18H, m), 7.85 (1H, dd, *J*=2.0, 7.6 Hz). MS (ESI): *m*/*z* 901 $[M+1]^+$. IR (KBr) cm^{-1}: 2920, 1740, 1647, 1449, 1257, 1117.

(*S*)-(−)-2-(1-Hydroxypropyl)-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one ((*S*)-(−)-1) To a stirred solution of **13b** (0.90 g, 1.00 mmol) in tetrahydrofuran (THF) (6 ml) was added MeOH (6 ml) and 3 M aqueous NaOH (9 ml) and stirred for 14 h at room temperature. The reaction mixture was concentrated *in vacuo*, and added water (10 ml). The mixture was extracted with chloroform (2×20 ml). The combined extracts layer was washed with brine, dried over $MgSO_4$. The organic layer was concentrated *in vacuo*. The residue was dissolved with THF (1.2 ml). To this solution was added acetic acid (3 ml) and H_2O (1.2 ml). The reaction mixture was stirred for 14 h at room temperature, and then concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting $CHCl_3$–MeOH (10 : 1 by volume), to give title compound as colorless solid (0.38 g, 86.0% yield). mp: 93—94 °C. $[\alpha]_D^{20}$ = −2.8° (*c*=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, *J*=7.2 Hz), 1.80—1.90 (6H, m), 2.65 (2H, m), 2.83 (2H, m), 4.58 (1H, t, *J*=6.8 Hz), 5.34 (1H, d, *J*=16.8 Hz), 5.89 (1H, d, *J*=16.8 Hz), 6.89 (2H, d, *J*=8.0 Hz), 7.00 (2H, d, *J*=8.0 Hz), 7.34 (1H, s), 7.35 (1H, d, *J*=8.0 Hz), 7.45 (1H, t, *J*=8.0 Hz),

7.54 (1H, t, J=8.0 Hz), 7.91 (1H, d, J=8.0 Hz). MS (ESI): m/z 443 $[M+1]^+$. *Anal.* Calcd for $C_{25}H_{26}N_6O_2$: C, 67.86; H, 5.92; N, 18.99. Found: C, 67.80; H, 6.03; N, 18.93. IR (KBr) cm^{-1}: 3358, 2926, 1638, 1533, 1464, 756.

(*R*)-(+)-2-(1-Hydroxypropyl)-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one ((*R*)-(+)-1) The title compound was prepared using a procedure similar to that described (*S*)-(−)-**1** from the corresponding ester **13a** as colorless solid. mp: 93—95 °C. $[\alpha]_D^{20}=-2.8°$ (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7.2 Hz), 1.78—1.94 (6H, m), 2.64 (2H, t, J=6.4 Hz), 2.83 (2H, m), 4.58 (1H, t, J=6.8 Hz), 5.40 (1H, d, J=16.4 Hz), 5.83 (1H, d, J=16.4 Hz), 6.93 (2H, d, J=8.0 Hz), 7.09 (2H, d, J=8.0 Hz), 7.36 (1H, s), 7.42 (1H, d, J=8.0 Hz), 7.50 (1H, t, J=8.0 Hz), 7.57 (1H, t, J=8.0 Hz), 7.99 (1H, d, J=8.0 Hz). MS (ESI): m/z 443 $[M+1]^+$. *Anal.* Calcd for $C_{25}H_{26}N_6O_2$: C, 67.86; H, 5.92; N, 18.99. Found: C, 67.93; H, 6.00; N, 18.80. IR (KBr) cm^{-1}: 3358, 2926, 1638, 1533, 1464, 756.

1-[8-Oxo-1-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6,7,8-hexahydrocycloheptimidazol-2-yl]propyl α-Methoxy-(α-trifluoromethyl)phenylacetate (13c, b) To a stirred solution of the human main metabolite (11.7 mg 26 μmol) in CH_2Cl_2 1 ml was added trityl chloride (8.1 mg 29 μmol) and triethyl amine (5 μl, 36 μmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, purified by preparative TLC (EtOAc/*n*-hexane=1 : 1), to give the trityl compound **12** (17.7 mg) *Rf* 0.44 (EtOAc/*n*-hexane=1 : 1). To a stirred solution of **12** (7.4 mg 11 μmol) in CH_2Cl_2 0.25 ml was added (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (40 μl, 214 μmol) and triethyl amine (40 μl, 287 μmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was purified directly by preparative TLC (EtOAc/*n*-hexane=1 : 3), to give **13c** (10.6 mg) as colorless amorphous. *Rf* 0.74 (EtOAc/*n*-hexane=1 : 3). ^{1}H-NMR ($CDCl_3$) δ: 0.51 (3H, t, J=7.2 Hz), 1.49—1.60 (2H, m), 1.83—2.00 (4H, m), 2.70 (2H, m), 3.02 (2H, m), 3.50 (3H, s), 5.33 (1H, d, J=16.0 Hz), 5.61—5.65 (1H, m), 6.15 (1H, d, J=16.0 Hz), 6.92 (2H, d, J=8.0 Hz), 6.93—6.99 (5H, m), 7.09 (2H, d, J=8.0 Hz), 7.24—7.60 (18H, m), 7.86 (1H, d, J=7.6 Hz). MS (ESI): m/z: 901 $[M+1]^+$. IR (KBr) cm^{-1}: 2960, 1745, 1644, 1448, 1230, 1166. Compound **13b** was obtained with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl-chloride in same manner as colorless amorphous. ^{1}H-NMR, MS and IR data was identified with that of **13b** already obtained.

3-Benzyl-5-[1-(*tert*-butyldimethylsilanyloxy)but-3-enyl]-2-propyl-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (15) To a solution of 3-benzyl-5-hydroxymethyl-2-propyl-3*H*-imidazole-4-carboxylic acid ethyl ester (**14**) (6.05 g, 20.0 mmol) in $CHCl_3$ (60 ml) was added manganese(IV) oxide (52.2 g, 600 mmol). The reaction mixture was stirred at room temperature for 1.5 h. and was filtrated. The filtrate was concentrated *in vacuo*, and the residue was diluted with CH_2Cl_2 (80 ml). To the solution was added allyltrimetylsilane (3.5 ml, 22.0 mmol). Titanium(IV) chloride (2.2 ml, 20.1 mmol) was added dropwise to this solution at −78 °C. Stirring was continued for 7 h at −78 °C to ambient temperature. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The extract was washed with brine, and dried over $MgSO_4$, and concentrated *in vacuo*. The reside was dissolved with DMF (40 ml). To this solution was added imidazole (2.72 g, 40.0 mmol) and *tert*-butyldimethylsilyl chloride (4.22 g, 28.0 mmol) at room temperature and stirred for 2 h. H_2O was added to the reaction mixture and the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (4 : 1 by volume), to give title compound as colorless oil (7.62 g, 83.4% yield). ^{1}H-NMR ($CDCl_3$) δ: −0.04 (3H, s), −0.01 (3H, s), 0.84 (9H, s), 0.89 (3H, t, J=7.2 Hz), 1.27 (3H, t, J=7.2 Hz), 1.65 (2H, m), 2.46—2.50 (1H, m), 2.65 (2H, t, J=7.6 Hz), 2.67—2.70 (1H, m), 4.22 (2H, q, J=7.2 Hz), 4.98—5.07 (2H, m), 5.40—5.43 (1H, m), 5.51 (2H, q, J=16.6 Hz), 5.80—5.87 (1H, m), 6.90 (2H, d, J=7.4 Hz), 7.21—7.30 (3H, m). MS m/z: 399 (M^+-57), 267, 91 (B.P.). IR (neat) cm^{-1}: 1698, 1461, 1383, 1278, 1248.

3-Benzyl-8-(*tert*-butyldimethylsilanyloxy)-2-propyl-7,8-dihydro-3*H*-cycloheptimidazol-4-one (18) To a mixture of **15** (10.35 g, 22.7 mmol), chlorotriisopropoxytitanium(IV) (45.4 ml, 1 M in *n*-hexane, 45.4 mmol) and THF (450 ml) was added isopropylmagnesium chloride (90.8 ml, 2 M in THF, 182 mmol) at −60 °C. The reaction mixture was allowed to warm to room temperature slowly and stirred for 20 h. After the addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was dissolved with DMF (100 ml). To the stirred solution was added pyridine (4.1 ml, 51.0 mmol) and ferric(III) chloride (8.10 g, 49.9 mmol) at room temperature and stirred for 1 h. The reaction mixture was poured into a 1 N hydrochloric acid and extracted with EtOAc. The organic layer was washed with H_2O and the brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was dissolved in MeOH (110 ml). To the solution was added sodium acetate (18.6 g, 227 mmol) and refluxed for 1 h. The reaction mixture was concentrated *in vacuo*. To the residue was added H_2O and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (4 : 1 by volume), to give title compound as colorless oil (0.91 g, 10.0% yield). ^{1}H-NMR ($CDCl_3$) δ: −0.05 (3H, s), 0.12 (3H, s), 0.83 (9H, s), 0.94 (3H, t, J=7.2 Hz), 1.74 (2H, m), 2.61 (2H, t, J=7.2 Hz), 2.73—2.78 (1H, m), 2.83—2.89 (1H, m), 4.89—5.00 (1H, m), 5.63 (2H, s), 6.10—6.14 (1H, m), 6.38—6.44 (1H, m), 6.97—7.00 (2H, m), 7.22—7.30 (3H, m). MS m/z: 353 (M^+-57), 285, 91 (B.P.). IR (neat) cm^{-1}: 1641, 1602, 1458, 1398, 1383, 1251.

8-(*tert*-Butyldimethylsilanyloxy)-2-propyl-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (19) To a solution of **18** (0.91 g, 2.22 mmol) in MeOH (9.1 ml) was added 5% Pd on carbon (containing 50% water, 0.10 g) and the mixture was stirred for 48 h under an atmosphere of hydrogen (1 atm) at room temperature. After filtration of the catalyst, the filtrate was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting EtOAc, to give title compound as colorless solid (0.53 g, 74.0% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.19 (3H, s), 0.88 (9H, s), 0.98 (3H, t, J=7.2 Hz), 1.72—1.82 (4H, m), 2.12—2.18 (1H, m), 2.29—2.32 (1H, m), 2.57—2.87 (4H, m), 4.95—4.97 (1H, m), 9.62 (1H, br s). MS m/z: 307 (M^+-15), 265 (M^+-57), 191, 149, 75 (B.P.). mp: 142—144 °C. IR (KBr) cm^{-1}: 3250, 2920, 1737, 1617, 1548, 1521, 1461, 1392, 1242.

8-(*tert*-Butyldimethylsilanyloxy)-2-propyl-3-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (20) To a mixture of **19** (0.53 g, 1.64 mmol), **11** (1.10 g, 1.97 mmol) and DMF (4.2 ml) was added K_2CO_3 (0.46 g, 3.33 mmol). The reaction mixture was stirred for 14 h at room temperature, and then poured into H_2O. The mixture was extracted with EtOAc, and the extract was washed with H_2O and then brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (1 : 1 by volume), to give title compound as colorless solid (0.60 g, 45.7% yield). ^{1}H-NMR ($CDCl_3$) δ: −0.05 (3H, s), 0.15 (3H, s), 0.85 (9H, s), 0.87 (3H, t, J=7.2 Hz), 1.65—1.72 (3H, m), 1.99—2.05 (1H, m), 2.10—2.17 (2H, m), 2.47—2.52 (3H, m), 3.08—3.14 (1H, m), 5.07—5.09 (1H, m), 5.39 (1H, d, J=16.0 Hz), 5.52 (1H, d, J=16.0 Hz), 6.74 (2H, d, J=8.4 Hz), 6.93 (6H, d, J=7.2 Hz), 7.05 (2H, d, J=8.4 Hz), 7.22—7.36 (10H, m), 7.42—7.50 (2H, m), 7.89 (1H, d, J=7.6 Hz). MS (ESI) m/z: 800 $[M+1]^+$. IR (KBr) cm^{-1}: 2920, 1641, 1461, 1383, 1251.

8-Hydroxy-2-propyl-3-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (21) To a stirred solution of **20** (1.80 g, 2.25 mmol) in THF (9 ml) was added tetrabutylammonium fluoride (4.5 ml, 1 M in THF, 4.50 mmol) at room temperature. The reaction mixture was allowed to warm to 50 °C and stirred for 3 h. After the addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (4 : 1 by volume), to give title compound as colorless oil (1.34 g, 87.0% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.2 Hz), 1.39—1.41 (1H, m), 1.69 (2H, m), 1.83—1.97 (3H, m), 2.32—2.35 (1H, m), 2.50 (2H, t, J=7.2 Hz), 2.62—2.66 (2H, m), 4.90—4.93 (1H, m), 5.46 (2H, dd, J=4.8, 16.0 Hz), 6.78 (2H, d, J=8.4 Hz), 6.92—6.95 (6H, m), 7.07 (2H, d, J=7.6 Hz), 7.24—7.36 (10H, m), 7.42—7.50 (2H, m), 7.89 (1H, m). MS (ESI) m/z: 685 $[M+1]^+$. IR (neat) cm^{-1}: 2998, 2950, 1641, 1464, 1215.

8-Hydroxy-2-propyl-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (2) To a stirred solution of **21** (1.34 g, 1.96 mmol) in THF (5 ml) was added acetic acid (3 ml) and H_2O (1 ml). The reaction mixture was stirred for 17 h at room temperature, and then concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting $CHCl_3$–MeOH (10 : 1 by volume), to give title compound as colorless solid (0.74 g, 85.3% yield). mp: 192—194 °C. ^{1}H-NMR (CD_3OD) δ: 0.97 (3H, t, J=7.2 Hz), 1.66 (2H, m), 1.87—1.95 (1H, m), 2.17—2.20 (3H, m), 2.62—2.73 (3H, m), 2.83—2.95 (1H, m), 4.97—5.01 (1H, m), 5.97 (2H, s), 6.99 (2H, d, J=8.4 Hz), 7.11 (2H, d, J=8.4 Hz), 7.56—7.60 (2H, m). 7.67—7.79 (2H, m). MS (ESI) m/z: 443 $[M+1]^+$. *Anal.* Calcd for $C_{25}H_{26}N_6O_2$: C, 67.86; H, 5.92; N, 18.99. Found: C, 68.04; H, 6.14; N, 19.08. IR (KBr) cm^{-1}: 3400, 1641, 1464, 1215.

2-Propyl-3-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (22) To a suspension of 2-

propyl-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (Pratosartan) (2.00 g, 4.69 mmol) and THF (20 ml) was added trityl chloride (1.57 g, 5.63 mmol) and triethyl amine (0.78 ml) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and to the residue saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc (2×50 ml). The combined extracts layer was washed with H_2O and then brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–EtOAc (1 : 1 by volume), to give title compound as colorless powder (3.03 g, 96.6% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.6 Hz), 1.63—1.72 (4H, m), 1.80—1.93 (4H, m), 2.48 (2H, t, J=7.8 Hz), 2.62 (2H, t, J=6.0 Hz), 3.00 (2H, t, J=6.4 Hz), 5.45 (2H, s), 6.78 (2H, d, J=8.4 Hz), 6.93 (6H, d, J=8.4 Hz), 7.06 (2H, d, J=8.4 Hz), 7.23—7.36 (10H, m), 7.42—7.50 (2H, m), 7.88 (1H, d, J=8.0 Hz). MS (ESI) *m*/*z*: 669 $[M+1]^+$. IR (KBr) cm^{-1}: 2908, 1634, 1464, 744, 696.

5-Hydroxy-2-propyl-3-[2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazol-4-one (23) A solution of **22** (0.67 g, 1.00 mmol) in THF (5 ml) was added dropwise to lithium diisopropylamide (1.7 ml, 0.9 M in pentane/THF, 1.5 mmol) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C. To this mixture was added MoOPH (0.65 g. 1.50 mmol) and then allowed to warm at −25 °C. The reaction mixture was stirred for 30 min at −25 °C. To this reaction mixture was added saturated aqueous Na_2SO_3 (50 ml) and the allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×50 ml). The combined extracts layer was washed with H_2O and then brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting *n*-hexane–AcOEt (1 : 1 by volume), to give title compound as colorless powder (0.38 g, 55.5% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.2 Hz), 1.48—1.75 (3H, m), 1.76—2.00 (1H, m), 2.00—2.23 (1H, m), 2.30—2.45 (1H, m), 2.51 (2H, t, J=7.8 Hz), 2.85—3.15 (2H, m), 4.12 (1H, d, J=2.1 Hz), 4.20—4.35 (1H, m), 5.35 (1H, d, J=16.0 Hz), 5.58 (1H, d, J=16.0 Hz), 6.77 (2H, d, J=8.0 Hz), 6.93 (6H, d, J=7.2 Hz), 7.08 (2H, d, J=8.0 Hz), 7.22—7.40 (10H, m), 7.42—7.50 (2H, m), 7.90 (1H, d, J=7.2 Hz). MS (ESI) *m*/*z*: 685 $[M+1]^+$. IR (KBr) cm^{-1}: 3450, 2930, 1630, 744, 699.

5-Hydroxy-2-propyl-3-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-5,6,7,8-tetrahydro-3*H*-cycloheptimidazo-4-one (3) To a solution of **23** (0.15 g, 0.22 mmol) in THF (2.5 ml) was added 10% HCl (1.5 ml) at room temperature and stirred for 14 h. The reaction mixture was neutralized with 10% aqueous NaOH and extracted with $CHCl_3$ (3×20 ml). The combined extracts layer was washed with H_2O and then brine, dried over Na_2SO_4. The organic layer was concentrated *in vacuo*. The residue was subjected to chromatography over silica gel eluting $CHCl_3$–EtOH (1 : 3 by volume), to give title compound as colorless powder (0.60 g, 62.2% yield). mp: 74—76 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, t, J=7.2 Hz), 1.50—1.75 (4H, m), 1.85—2.15 (2H, m), 2.45—2.55 (3H, m), 2.87 (2H, t, J=6.2 Hz), 4.29 (1H, dd, J=4.0, 10.4 Hz), 5.49 (1H, d, J=16.8 Hz), 5.64 (1H, d, J=16.8 Hz), 6.93 (2H, d, J=8.0 Hz), 7.04 (2H, d, J=8.0 Hz), 7.48 (1H, d, J=7.8 Hz), 7.51 (1H, d, J=8.0 Hz), 7.58—7.65 (2H, m). MS (ESI): *m*/*z* 443 $[M+1]^+$. *Anal.* Calcd for $C_{25}H_{26}N_6O_2$: C, 67.86; H, 5.92; N, 18.99. Found: C, 67.67; H, 6.04; N, 18.95. IR (KBr) cm^{-1}: 3400, 2926, 1630, 1467, 1377, 756.

Effects on AII Contractile Responses in Isolated Rabbit Aorta Thoracic aorta was isolated from male New Zealand white rabbits (2.7—3.2 kg, Tokyo Laboratory Animals Science Inc., Tokyo, Japan). The aorta was cleaned off connective tissue and adherent fat and cut into 3 mm ring segments. Opened ring preparations were used in the present study. The vascular endothelium was removed by gently rubbing the intimal surface of the blood vessel with cotton wool. Preparations were mounted vertically in organ baths containing 10 ml of Krebs-Ringer solution (NaCl, 120.3; KCl, 4.8; $MgSO_4 \cdot 7H_2O$, 1.3; KH_2PO_4, 1.2; $CaCl_2 \cdot 2H_2O$, 1.2; $NaHCO_3$, 24.2 and glucose, 5.5 mM) maintained at 37 °C and bubbled with a 95% O_2+5% CO_2 gas. Under the resting tension of 1.5 g, isometric tension changes were recorded on a polygraph (Nihon Kohden, Tokyo, Japan) through a force displacement transducer (T-7-30-240; Orientec, Tokyo, Japan). After a 1.5 h equilibration period, the cumulative concentration–response curve for AII was constructed by the method of stepwise addition of the agonist. Then, AII was washed out repeatedly for 1 h. Tissues were incubated with various concentrations of compounds for 20 min and the concentration–response curve for AII was again obtained. Responses were expressed as a percentage of the maximum response in the first concentration–response curve for AII. To measure the potency of the antagonist, the pA_2 values were determined from Schild plots using the least squares method. The effects of test compound on the contractile responses of rabbit aorta induced by KCl, norepinephrine and serotonin were also examined.

Acknowledgements We thank Professor S. Ikegami, Teikyo University, for his generous and helpful discussions. We also thank Dr. Akira Ohno for his technical assistance; Miss Noriko Koide for *in vitro* testing.

References

1) Yanagisawa T., Ueyama N., Kawai T., Sonegawa M., Baba H., Mochizuki S., Kosakai K., Tomiyama T., *Bioorg. Med. Chem. Lett.*, **3**, 1559—1564 (1993).
2) Stearns R. A., Miller R. R., Doss G. A., Chakravarty P. K., Rosegay A., Gatto G. J., Chiu S.-H. L., *Drug Metab. Dispos.*, **20**, 281—287 (1992).
3) Sonegawa M., Iwai Y., Tomiyama H., Tomiyama T., *Chem. Pharm. Bull.*, **54**, 703—705 (2006).
4) Nakazawa J., Sato Y., Soma N., *Sankyou Kenkyusyo Nenpo*, **21**, 47—56 (1969).
5) 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., Wells G. J., Wexler R. R., Wong P. C., Yoo S.-E., Timmermans P. B. M. W. M., *J. Med. Chem.*, **34**, 2525—2547 (1991).
6) Sonegawa M., Yokota M., Tomiyama H., Tomiyama T., *Chem. Pharm. Bull.*, **54**, 706—710 (2006).
7) Dale J. A., Mosher H. S., *J. Am. Chem. Soc.*, **95**, 512—519 (1973).
8) Yanagisawa H., Amemiya Y., Kanazaki T., Fujimoto K., Shimoji Y., Fujimoto Y., Sada T., Mizuno M., Koike H., *Bioorg. Med. Chem. Lett.*, **4**, 177—182 (1994).
9) Hosomi A., Sakurai H., *Tetrahedron Lett.*, **17**, 1295—1298 (1976).
10) Hikichi S., Hareau G. P.-J., Sato F., *Tetrahedron Lett.*, **38**, 8299—8302 (1997).
11) Ito Y., Fujii S., Nakatsuka M., Kawamoto F., Saegusa T., *Org. Syn.*, **59**, 113—121 (1979).
12) Vedejs E., Engler D. A., Telschow J. E., *J. Org. Chem.*, **43**, 188—195 (1978).
13) Ohtani I., Kusumi T., Kashman Y., Kakisawa H., *J. Am. Chem. Soc.*, **113**, 4092—4096 (1991).
14) Mori M., Saitoh F., Uesaka N., Shibasaki M., *Chem. Lett.*, **1993**, 213—216 (1993).
15) Wong P. C., Price W. A., Chiu A. T., Duncia J. V., Carini D. J., Wexler R. R., Johnson A. L., Timmermans P. B. M. W. M., *J. Pharmacol. Exp. Ther.*, **255**, 211—217 (1990).
16) Waldmeier F., Flesch G., Müller P., Winkler T., Kriemler H.-P., Bühlmayer P., Gasparo M. De, *Xenobiotica*, **27**, 59—71 (1997).
17) Chando T. J., Everett D. W., Kahle A. D., Starrett A. M., Vachharajani N., Shyu W. C., Kripalani K. J., Barbhaiya R. H., *Drug Metab. Dispos.*, **26**, 408—417 (1998).