HETEROCYCLES, Vol. 63, No. 5, 2004, pp. 1113 - 1122
Received, 26th January, 2004, Accepted, 23rd March, 2004, Published online, 26th March, 2004

A NEW SYNTHETIC ROUTE TO YM087, AN ARGININE VASOPRESSIN ANTAGONIST

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Abstract – A new synthesis of *N*-{4-[(2-methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl}biphenyl-2-carboxamide monohydrochloride (**1**, YM087) *via* new imidazobenzazepine intermediates is described. This method remarkably improves the overall yield of **1** compared to the original synthesis providing a more safe, reliable and cost-efficient approach to **1**.

INTRODUCTION

Since the late 1970s, the role of arginine vasopressin (AVP) has been extensively investigated. Michel *et al.*[1] identified two classes of vasopressin receptor, V_{1A} and V_2, and proved that the former mediates phospholipase C activation and causes the effects of AVP on the cardiovascular system; for example, the vasoconstrictive effect on arterial smooth muscle. Jard[2] showed that the latter mediates adenylate cyclase and plays a major role in the kidney; for example, the antidiuretic response to AVP that promotes water reabsorption. In 1994, Naitoh *et al.*[3] reported that the combined administration of vasopressin V_{1A}- and V_2-receptor antagonists confers a more beneficial effect than that produced by each antagonist alone in dogs with congestive heart failure. Okada *et al.*[4] reported that a combination of vasopressin V_{1A}- and V_2-receptor antagonists produces renal protective effects in rats with progressive renal failure. Scientists have attempted to develop non-peptide dual arginine vasopressin-receptor antagonists that can be used as a novel treatment for patients with cardiovascular pathology—in particular congestive heart failure and renal disease. Yatsu *et al.*[5] revealed that *N*-{4-[(2-methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl}biphenyl-2-carboxamide monohydrochloride (**1**, YM087; Figure 1) is an antagonist

of both receptors. A significant quantity of **1** was required during drug development and clinical trials, so studies to identify a more reliable and cost-effective synthetic route to **1** were undertaken.

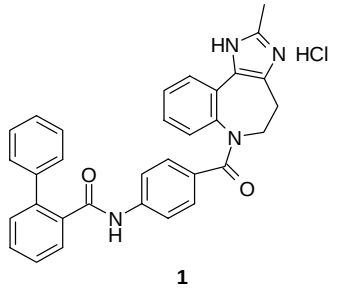
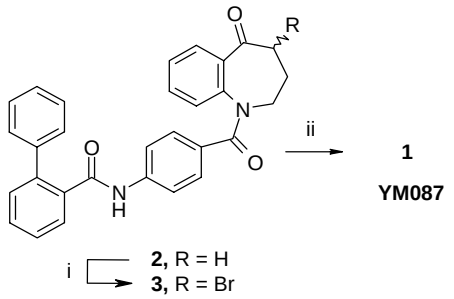


Figure 1

RESULTS AND DISCUSSION

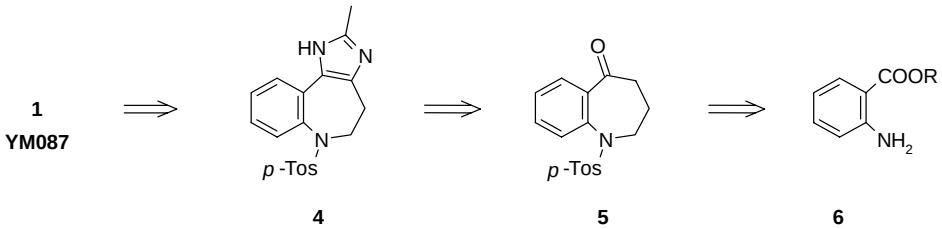
Matsuhisa *et al.*[6] reported the original synthesis of **1**. The overall yield of their route is 5% and that includes several low-yielding steps in the final stages of the synthesis; in particular, the overall yield of the last two steps is only 38% (Scheme 1), which might jeopardize the quality of the final product and result in increased production costs.



Reagents: i, $CuBr_2$, $CHCl_3$, AcOEt; ii, ethanimidamide monohydrochloride, K_2CO_3, MeCN, $CHCl_3$, silica gel chromatography: $CHCl_3$/MeOH, AcOEt, HCl/AcOEt, EtOH, 38% over two steps.

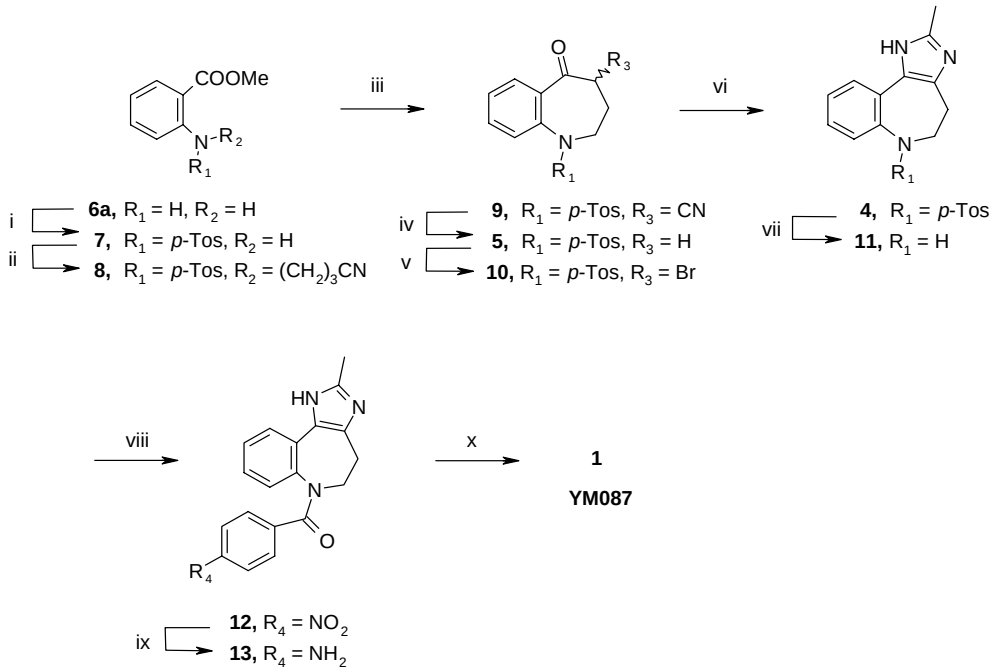
Scheme 1

Since the original synthesis includes a low-yielding imidazole-ring formation, our strategy aimed to install this structure in the early stages. A retrosynthetic analysis suggested that the *N*-substituted imidazobenzazepine (**4**) might be a key intermediate for our strategy (Scheme 2).



Scheme 2

The precursor of **4**, benzazepinone (**5**), was envisaged to be accessed by a Dieckmann cyclization of the *N*-substituted derivative of **6**. The new synthetic pathway to prepare YM087 (**1**) is outlined in Scheme 3.

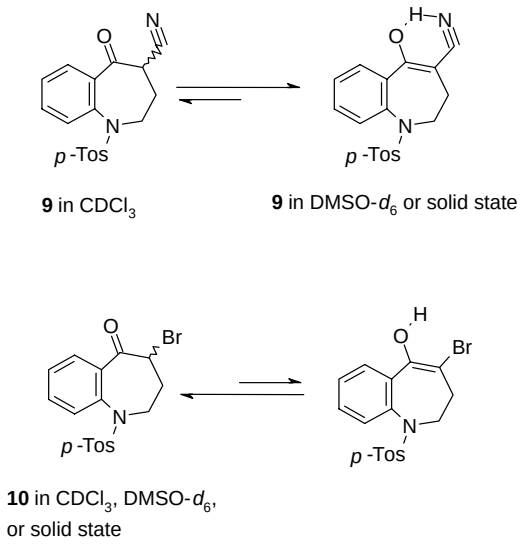


Reagents: i, *p*-TosCl, pyridine; ii, 4-chlorobutanenitrile, K_2CO_3, KI, 2-butanone; iii, *t*-BuOK, DMF; iv, AcOH, HCl; v, pyridinium hydrobromide perbromide, $CHCl_3$; vi, ethanimidamide monohydrochloride, K_2CO_3, $CHCl_3$; vii, H_2SO_4, AcOH; viii, 4-nitrobenzoyl chloride, DMF, pyridine monohydrochloride; ix, H_2, Raney nickel, MeOH; x, biphenyl-2-carboxylic acid, oxalyl chloride, DMF, CH_2Cl_2, MeCN, pyridine, HCl-AcOEt.

Scheme 3

Although methyl 2-aminobenzoate (**6a**) was tosylated using the method reported by Proctor and Thomson,[7] diluting the reaction mixture with the antisolvent, water, afforded methyl 2-{[(4-methyl-phenyl)sulfonyl]amino}benzoate (**7**) in high purity, improving the yield from 91.0% to 99.8%. The introduction of the 3-methylene unit to the benzazepine structure was performed using the procedure reported by Hirota *et al.*[8] with the exception that 2-butanone was used in place of acetone, which remarkably shortened the reaction time from 7 d to 12 h and conferred a slight improvement in the yield of methyl 2-{(3-cyanopropyl)[(4-methylphenyl)sulfonyl]amino}benzoate (**8**) from 95% to 98%. Although Hirota *et al.*[8] had effected a successful Dieckmann cyclization of **8** with sodium hydride, the handling difficulty for large-scale synthesis led us to investigate a modified method. The use of potassium *t*-butoxide instead of sodium hydride in the Dieckmann cyclization circumvented the risk of hydrogen gas evolution as well as the need for purification to remove the oil used to disperse sodium hydride. This improved the yield of 1-[(4-methylphenyl)sulfonyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-4-carbo-nitrile (**9**) from 88% in the published method[8] to 93%. The proton NMR spectrum of **9** in $CDCl_3$ showed that the hydrogen at the 4-position was in the keto form. However, the NMR spectrum in DMSO-d_6 and the IR spectrum showed the presence of an OH at the 5-position in the enol form, which is consistent with

the information reported by Hirota *et al.*[8] A comparison of the spectra of **9** and 4-bromo-1-[(4-methyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**10**) indicated that **9** was stabilized by an internal hydrogen bond forming a six-membered ring type structure in both the solid state and DMSO-d_6 solution (Scheme 4).[9, 10]



Scheme 4

9 was converted to 1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (**5**) in good yield. Bromination of **5** with pyridinium hydrobromide perbromide[11] instead of bromine improved both manipulability and the yield of **10** from 85%[12] to 89%. The reaction of **10** with ethanimidamide monohydrochloride in the presence of potassium carbonate afforded 2-methyl-6-[(4-methyl-phenyl)sulfonyl]-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine (**4**) accompanied by the oxazole by-product 2-methyl-6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-4*H*-[1,3]oxazolo[4,5-*d*][1]benzazepine, as expected.[13] The NMR spectrum of **4** in DMSO-d_6 showed a three-proton singlet at δ 2.20 and a one-proton singlet that exchanged in deuterium oxide at δ 11.61. These were attributed to a newly introduced methyl group and the amine of the imidazole ring, respectively. The presence of the proton of the imidazole amine and mass spectra distinguished **4** from the oxazole byproduct.

The *N*-tosyl group of **4** was hydrolyzed using a mixture of sulfuric and acetic acid.[14] The NMR spectrum of 2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine (**11**) showed the N-H proton of the benzazepine ring at δ 5.84 and the disappearance of the CH_3 protons, which were observed at δ 2.30 in the NMR spectrum of **4**. The selective acylation of the benzazepine nitrogen of **11** was accomplished by reaction with 4-nitrobenzoyl chloride and pyridine monohydrochloride in dimethylformamide.[15] The NMR spectrum of 2-methyl-6-(4-nitrobenzoyl)-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine mono-hydrochloride (**12**) showed the aromatic protons of the nitrobenzoyl group to be present between δ 6.95

and 8.15, and the disappearance of the N-H proton of the benzazepine ring, which was previously observed at δ 5.84 for compound (**11**). Treatment of **12** with Raney nickel under a hydrogen atmosphere in methanol afforded {4-[(2-methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl}-amine (**13**) in good yield.[16] The NMR spectrum of **13** showed a two-proton singlet that exchanged in deuterium oxide at δ 5.42 and was therefore attributed to the N-H proton of aniline. The selective acylation of the aniline nitrogen of **13** was accomplished by reaction with biphenyl-2-carbonyl chloride and pyridine in acetonitrile to provide **1**. The NMR spectrum of **1** proved consistent with that reported by Matsuhisa *et al.*[6]

Herein, we have described a successful new synthetic route to **1** which remarkably improves the overall yield of **1** to 13% from the 5% in the original route,[6] using new imidazobenzazepine derivatives as key intermediates. This method notably doubles the overall yield of the final two steps in the original route,[6] as well as providing a more safe, reliable and cost-efficient approach to **1**, which maximizes atom economy and circumvents jeopardizing the quality of the active pharmaceutical ingredient.

EXPERIMENTAL

Reagents and solvents were used as received from commercial suppliers, unless otherwise stated. Analytical HPLC was performed on a Hitachi D-2500 system with UV detection at a wavelength of 220 or 240 nm using a YMC-pack ODS-A A-302 150 mm × 4.6 mm column and eluting with 0.2 M aqueous ammonium chloride solution-acetonitrile (1:1). ^{1}H NMR spectra were recorded on a JEOL JNM-AL400, AL500 or A500 spectrometer with chemical shifts given in ppm relative to TMS at δ = 0. MS spectra were determined on a Hitachi M-80, JEOL LX-2000, JMS-DX300 or 700T spectrometer. Mps were determined using a Yanagimoto micro-melting-point apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1600 spectrophotometer. Column chromatography was carried out on silica gel (Wako, Wakogel C-200; particle size 75-150 μm).

Methyl 2-{[(4-methylphenyl)sulfonyl]amino}benzoate (7)

4-Methylbenzenesulfonyl chloride (377 g, 1.98 mol) was added to a solution of methyl 2-aminobenzoate (**6a**) (260 g, 1.72 mol) in pyridine (520 g) at an internal temperature of 0-25˚C and the mixture was stirred at 25˚C for more than 3 h. Water was poured into the mixture at 5-25˚C and the mixture was stirred for 1 h, then cooled to 5-10˚C. The resulting crystals were isolated by filtration and dried to afford **7** (524 g, 100%) as a pale yellow powder. mp: 113˚C.[7] HPLC assay: 99.7% (area).

Methyl 2-{(3-cyanopropyl)[(4-methylphenyl)sulfonyl]amino}benzoate (8)

A mixture of *N*-tosyl benzoate (**7**) (204 g, 668 mmol), 4-chlorobutanenitrile (81.5 g, 787 mmol), potassium carbonate (183 g, 1.32 mol) and potassium iodide (32.6 g, 196 mmol) in 2-butanone (306 g) was stirred at reflux for 12 h. The mixture was then poured into water at 0-5˚C and the mixture stirred for 1 h. The resulting crystals were isolated by filtration and dried to provide **8** (243 g, 98%) as a white powder. mp: 103-104˚C.[8] HPLC assay: 99.4% (area).

1-[(4-Methylphenyl)sulfonyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-4-carbonitrile (9)

Potassium *t*-butoxide (176 g, 1.57 mol) was added to a solution of **8** (291 g, 781 mmol) in DMF (874 mL) at an internal temperature of –10-0˚C and the mixture was stirred at 0-5 ˚C for 2 h. Water was poured into the mixture at 0-5˚C, then 30% hydrochloric acid was added dropwise at 0-20˚C and the mixture was stirred at 5˚C for 1 h. The resulting crystals were isolated by filtration to give crude **9**. A mixture of the crude **9** in methanol was stirred at reflux for 30 min, then cooled to 5˚C and stirred for 1 h. The resulting crystals were isolated by filtration and dried to afford **9** (248 g, 93%) as a white powder. mp: 153-154˚C.[17] HPLC assay: 99.7% (area). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.09 (2H, m), 2.40 (3H, s), 3.95 (2H, br s), 7.30-7.54 (8H, m), 11.0 (1H, br s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (1H, m), 2.46 (3H, s), 2.77 (1H, m), 3.49 (1H, m), 3.86 (1H, q, J = 4.0 Hz), 4.35 (1H, m), 7.34-7.88 (8H, m). IR (KBr): 3,122, 2,221 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23; S, 9.42. Found: C, 63.30; H, 4.64; N, 8.15; S, 9.43. MS *m*/*z*: 339 (M^+ –1).

1-[(4-Methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (5)

9 (248 g, 729 mmol) was added to a mixture of acetic acid (470 g) and concentrated hydrochloric acid (576 g), and the mixture stirred at an internal temperature of 80˚C for 11 h. The mixture was cooled, then water was added dropwise at 0-20 ˚C. The mixture was stirred at 5˚C for 1 h, and the resulting crystals were isolated by filtration and dried to provide **5**. 30% aqueous sodium hydroxide solution and ethyl acetate were added to the filtrate and the mixture was stirred. The organic and aqueous layers were separated and the organic layer was washed with water, then concentrated. The resulting residue was dissolved in pyridine (179 g), 4-methylbenzenesulfonyl chloride (95.2 g, 499 mmol) was added to the solution at an internal temperature of 10-20˚C and the mixture was stirred for more than 1 h. Water was added at 10-20 ˚C and the mixture was cooled to 5˚C. The resulting crystals were isolated by filtration and dried to afford **5**. The combined mass of **5** was 224 g (97%). mp: 125-126˚C.[7] HPLC assay: 99.1% (area).

4-Bromo-1-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (10)

Pyridinium hydrobromide perbromide (198 g, 619 mmol) was added to a solution of **5** (195 g, 618 mmol) in chloroform (1800 mL) and the mixture stirred at an internal temperature of 15-30˚C for 1 h. The mixture was washed with water and 5% aqueous sodium bicarbonate solution, then concentrated. The resulting residue was dissolved in ethanol at reflux, then cooled to 0˚C and stirred for 1 h. The resulting crystals were isolated by filtration and dried to give **10** (216 g, 89%) as a slightly yellowish-white powder. mp: 128-130˚C.[12] HPLC assay: 96.0% (area). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (1H, m), 2.40 (3H, s), 2.53 (1H, m), 3.74 (1H, m), 4.13 (1H, dt, J = 4.8, 14.4 Hz), 4.93 (1H, dd, J = 4.4, 7.8 Hz), 7.30-7.62 (8H, m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (1H, m), 2.42 (3H, s), 2.66 (1H, m), 3.70 (1H, m), 4.36 (1H, dt, J = 4.4, 14.8 Hz), 4.58 (1H, dd, J = 4.4, 7.6 Hz), 7.25-7.59 (8H, m). IR (KBr): 1697 cm^{-1}. MS *m*/*z*: 394 (M^+ +1).

2-Methyl-6-[(4-methylphenyl)sulfonyl]-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine (4)

Ethanimidamide monohydrochloride (14.5 g, 153 mmol) and potassium carbonate (21.2 g, 153 mmol) were added to a solution of **10** (12.1 g, 30.7 mmol) in chloroform (480 mL), and the resulting mixture stirred at reflux for 4 d, using Dean-Stark apparatus to remove water by azeotropic distillation. The mixture was washed with water, then concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with $CHCl_3$/AcOEt (2:1), then recrystallized in ethanol to provide **4** (5.71 g, 53%) as a slightly brownish-white powder and the oxazole, 2-methyl-6-[(4-methylphenyl)-sulfonyl]-5,6-dihydro-4*H*-[1,3]oxazolo[4,5-*d*][1]benzazepine (3.04 g, 28%) as a slightly yellowish-white powder. ***Imidazole (4)***: mp: 111-112˚C. HPLC assay: 99.6% (area). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (3H, s), 2.30 (3H, s), 2.99 (2H, br s), 3.33 (2H, s), 7.12-7.41 (7H, m), 8.00 (1H, br s), 11.61 (1H, br s). Anal. Calcd for $C_{19}H_{19}N_3O_2S{\cdot}0.5C_2H_6O{\cdot}0.5H_2O$: C, 62.32; H, 6.01; N, 10.90; S, 8.32. Found: C, 62.32; H, 5.92; N, 10.86; S, 8.39. MS *m*/*z*: 354 (M^+ +1). ***Oxazole***: mp: 109-110˚C. HPLC assay: 98.2% (area). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (3H, s), 2.38 (3H, s), 2.82 (1H, m), 3.20 (2H, m), 4.60 (1H, m), 7.02 (2H, d, J = 10.0 Hz), 7.27-7.35 (4H, m), 7.64 (2H, m). Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.19; H, 5.08; N, 7.81; S, 9.03. MS *m*/*z*: 355 (M^+ +1).

2-Methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine (11)

Imidazole (**4**) (3.00 g, 8.49 mmol) was heated in a mixture of acetic acid (9.3 mL) and concentrated sulfuric acid (6.0 mL) at 70˚C for 51 h. The mixture was cooled, then water was added dropwise at 10-35 ˚C. Ethyl acetate was added to the mixture, and the organic and aqueous layers were separated. The aqueous layer was basified with 25% sodium hydroxide solution, and ethyl acetate was added to the mixture. The organic layer was separated, then concentrated. The resulting residue was dissolved in ethyl acetate at reflux, then cooled to 0˚C and stirred for 30 min. The resulting crystals were isolated by

filtration and dried to provide **11** (1.04 g, 61%) as a slightly brownish-white powder. mp: 178-180˚C. HPLC assay: 99.0% (area). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.25 (3H, s), 2.81 (2H, t, J = 5.0 Hz), 3.16 (2H, q, J = 5.0 Hz), 5.84 (1H, br s), 6.68-6.87 (3H, m), 7.85 (1H, br s) 11.6 (1H, br s). Anal. Calcd for $C_{12}H_{13}N_3$·0.15H_2O: C, 71.37; H, 6.64; N, 20.81. Found: C, 71.64; H, 6.52; N, 20.53. MS *m/z*: 200 (M^+ +1).

2-Methyl-6-(4-nitrobenzoyl)-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzazepine monohydrochloride (12)

Pyridine monohydrochloride (1.74 g, 15.1 mmol) was added to a solution of **11** (1.00 g, 5.02 mmol) in DMF (20 mL) at 25˚C. The mixture was cooled, then 4-nitrobenzoyl chloride (1.02 g, 5.50 mmol) was added at 0˚C. The mixture was warmed to 25˚C and stirred for 3 h. The mixture was cooled to 0˚C and the resulting crystals were isolated by filtration and dried to afford **12** (1.40 g, 73%) as a slightly brownish-white powder. mp: >250˚C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.70 (3H, s), 3.10 (2H, m), 3.31 (1H, m), 3.37 (2H, br s), 4.97 (1H, m), 6.95 (1H, d, J = 7.6 Hz), 7.07 (1H, t, J = 7.6 Hz), 7.11-7.41 (3H, m), 8.04 (2H, d, J = 8.8 Hz), 8.15 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{19}H_{16}N_4O_3$·HCl: C, 59.30; H, 4.45; N, 14.56; Cl, 9.21. Found: C, 59.04; H, 4.47; N, 14.75; Cl, 9.21. MS *m/z*: 349 (M^+ +1).

{4-[(2-Methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl}amine (13)

Nitro compound (**12**) (1.30 g, 3.38 mmol) was hydrogenated by stirring with Raney nickel (0.4 g) at 25˚C under a hydrogen atmosphere in methanol (26 mL) for 1 h. The catalyst was removed by filtration and the filtrate was concentrated. Water was added to the resulting residue and the mixture was basified with saturated sodium bicarbonate solution and stirred at 25˚C for 1 h. The resulting crystals were isolated by filtration and dried to give **13** (1.01 g, 94%) as a grayish-white solid. mp: >250˚C. ^{1}H NMR (400 MHz, DMSO-d_6)[18]: δ 2.31 (3H, s), 2.77-3.12 (3H, m), 4.98 (1H, d, J = 12.2 Hz), 5.42 (2H, s), 6.22 (2H, d, J = 8.8 Hz), 6.66 (3H, m), 6.86 (1H, t, J = 7.8 Hz), 7.14 (1H, t, J = 7.8 Hz), 8.10 (1H, d, J = 7.8 Hz), 11.88 (1H, s). Anal. Calcd for $C_{19}H_{18}N_4O$·1.5H_2O: C, 66.07; H, 6.13; N, 16.22. Found: C, 65.98; H, 6.08; N, 16.19. MS *m/z*: 319 (M^+ +1).

***N*-{4-[(2-Methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl}biphenyl-2-carboxamide monohydrochloride (1, YM087)**

DMF (22 mg, 0.30 mmol) and oxalyl chloride (942 mg, 7.42 mmol) were added to a solution of biphenyl-2-carboxylic acid (746 mg, 3.76 mmol) in dichloromethane (15 mL) at –15˚C, and the mixture was warmed slowly to 25˚C and stirred for more than 2 h, then concentrated. The resulting residue was diluted with dichloromethane and concentrated. This process was repeated three times to give

biphenyl-2-carbonyl chloride as an oily product. Acetonitrile (10 mL) was added to the oil, and the mixture was poured into a suspension of amine (**13**) (1.00 g, 3.14 mmol) and pyridine (0.76 mL, 9.44 mmol) in acetonitrile (20 mL) at 0˚C. The mixture was warmed slowly to 25˚C, then heated at reflux for more than 30 min and cooled. A solution of hydrogen chloride in ethyl acetate was added to the mixture at an internal temperature of 5-30˚C and the mixture was stirred at 25˚C for 30 min. The resulting crystals were isolated by filtration and dried to give **1** (1.24 g, 74%) as a slightly grayish-white powder. mp >250˚C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.68 (3H, s), 2.99 (1H, t, J = 11.6 Hz), 3.09-3.20 (2H, m), 4.99 (1H, d, J = 11.6 Hz), 6.86 (1H, d, J = 7.3 Hz), 6.93 (2H, d, J = 7.3 Hz), 7.14 (1H, t, J = 7.3 Hz), 7.25-7.58 (12H, m), 8.09 (1H, d, J = 7.3 Hz), 10.31 (1H, s), 14.73 (2H, br s). Anal. Calcd for $C_{32}H_{26}N_4O_2{\cdot}HCl{\cdot}0.5H_2O$: C, 70.65; H, 5.19; N, 10.30; Cl, 6.52. Found: C, 70.68; H, 5.16; N, 10.33; Cl, 6.41. MS *m/z*: 499 (M^+ +1).

ACKNOWLEDGEMENTS

We are grateful to Hidenori Iwamoto (Goei Shoji Co. Ltd., Tokyo) for helpful advice and to the staff of the Chemistry laboratory (Yamanouchi Pharmaceutical Co. Ltd., Tsukuba) for technical assistance. We are also grateful to the Analysis and Metabolism laboratories (Yamanouchi Pharmaceutical Co. Ltd., Tsukuba) for elemental analysis and spectral measurements.

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