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Practical Synthesis of *N*-{4-[(2-Methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl}biphenyl-2-carboxamide Monohydrochloride: an Arginine Vasopressin Antagonist

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Abstract:

A novel, reliable, and cost-effective synthetic route to *N*-{4-[(2-methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]-phenyl}biphenyl-2-carboxamide monohydrochloride (1, YM087), a potent Arginine vasopressin antagonist, has been developed. Using moisture-controlled potassium carbonate, imidazole formation from α-bromoketone furnished imidazobenzazepine, avoiding potential oxazole-ring formation. Catalytic reduction of nitro imidazobenzazepine afforded the corresponding amine in high yields. Treatment of the imidazole-containing amine directly, with a carbonyl chloride, afforded the target amide circumventing protection of the imidazole.

Introduction

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) represents a new series of dual vasopressin (AVP) V_{1A} and V_2 receptor antagonists. It is an orally active nonpeptide agent for the potential treatment of congestive heart failure (CHF), hypertension, hyponatremia, renal disease, edema, and syndrome of inappropriate antidiuretic hormone secretion (SIADH).[1] The discovery synthesis of YM087 is depicted in Scheme 1.[2] This route includes a capricious imidazole ring formation, column chromatography, and crystallization from highly flammable solvents. Low cost-performance and operational difficulties led to the investigation of a new sequence appropriate for large-scale production.

Results and Discussion

The most costly raw material, carboxylic acid **4** ($1013/kg), is used in early stages of the discovery synthesis. The overall yield from **4** to YM087 in this route is 31%; namely approximately 70% of **4** is wasted. Our strategy was to introduce **4** towards the end of the synthesis, as described in Scheme 2, thus improving the cost efficiency.

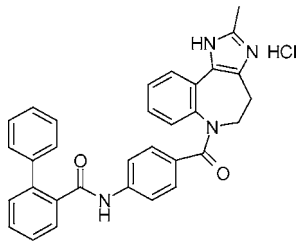

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Figure 1. **YM087 (1).**

To accomplish this, there were three key points to be addressed. These were the development of robust synthesis procedures for (1) a novel imidazobenzazepine derivative **10**, (2) a novel imidazobenzazepine derivative **9**, and (3) a selective acylation on aniline of **9**.

Synthesis of Nitro Compound 2. The primary objective for the synthesis of YM087 was the introduction of the benzazepine skeleton. On the basis of information obtained in the discovery synthesis, benzazepine derivative **12**[3] was selected as a source of the skeleton. Scheme 3 illustrates the synthetic route used to prepare nitro compound **2**. Although benzazepinone **13** was an oil and difficult to purify, crystallization of the nitro compound **2**, following acylation of **13**, provided material of sufficient quality for use in the next step.

Synthesis of a Novel Imidazobenzazepine 10. Development of the protocol for imidazole ring formation, which provides the important basic skeleton, was the most challenging step of this synthesis. In the discovery synthesis, the selectivity of the imidazole ring formation was low and column chromatography on silica afforded **8** and **14**, an awkward byproduct to separate, in 53% and 7% yield, respectively. (Scheme 4).[2]

In the new route, α-bromoketone **11** was produced in 88% yield by bromination of nitro compound **2**, with a solution of bromine in chloroform, followed by crystallization in ethanol. The following imidazole ring formation was attempted with the optimal conditions identified in the discovery synthesis studies.[2] However, the reaction did not proceed cleanly, and large quantities of oxazole **15**, an awkward byproduct to separate, was isolated. Purification

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(1) Yatsu, T.; Tomura, Y.; Tahara, A.; Wada, K.; Tsukada, J.; Uchida, W.; Tanaka, A.; Takenaka, T. *Eur. J. Pharmacol.* **1997**, *321*, 225. Tahara, A.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Takanashi, M.; Yatsu, T.; Uchida, W.; Tanaka, A. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 301. Tahara, A.; Saito, M.; Sugimoto, T.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Ishii, N.; Yatsu, T.; Uchida, W.; Tanaka, A. *Naunyn-Shmiedeberg's Arch. Pharmacol.* **1998**, *357*, 63. Tahara, A.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Ishii, N.; Yatsu, T.; Uchida, W.; Tanaka, A. *Peptides* **1998**, *19*, 691.

(2) Matsuhisa, A.; Taniguchi, N.; Koshio, H.; Yatsu, T.; Tanaka, A. *Chem. Pharm. Bull.* **2000**, *48* (1), 21.

(3) Hirota, T.; Fukumoto, M.; Sasaki, K.; Namba, T.; Hayakawa, S. *Heterocycles* **1986**, *24* (1), 143.

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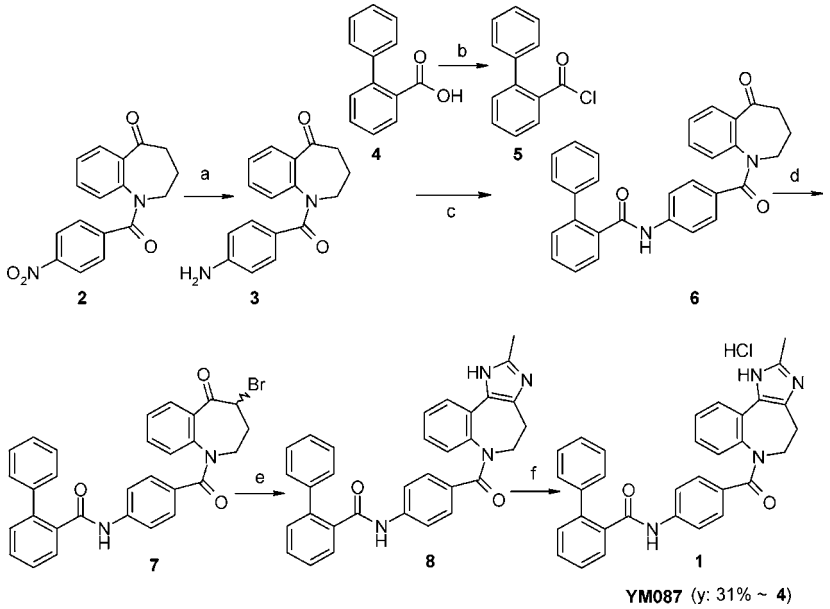
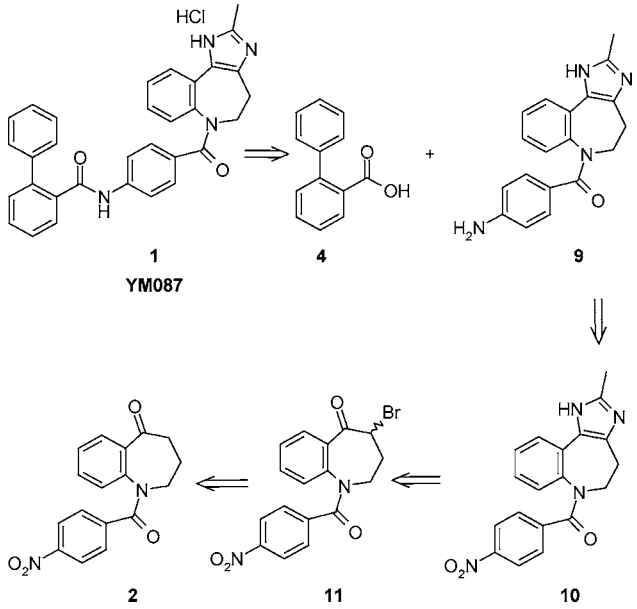
Scheme 1. **Discovery synthesis route for YM087 (1)**[a]

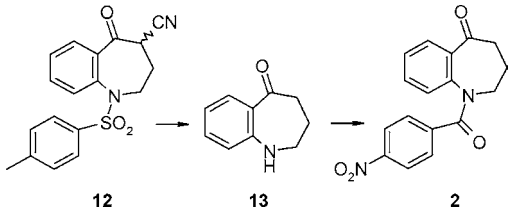


[a] (a) (i) H_2, palladium/carbon, ethanol; (ii) crystallization: dichloromethane, then *n*-hexane, 94%; (b) oxalyl chloride (excess), DMF (catalyst), dichloromethane; (c) (i) **5**, triethylamine, dichloromethane; (ii) crystallization: diethyl ether, 82% over 2 steps; (d) $CuBr_2$, chloroform, ethyl acetate; (e) (i) ethanimidamide monohydrochloride, potassium carbonate, acetonitrile; (ii) chloroform; (iii) silica gel chromatography: chloroform/methanol; (iv) crystallization: ethyl acetate, 53% over 2 steps; (f) hydrochloride in ethyl acetate, ethanol, 72%.

Scheme 2. **New synthesis route for YM087 (1)**



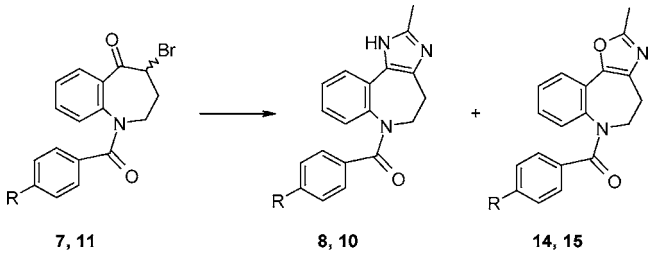
Scheme 3. **Synthesis route for nitro compound (2)**



by column chromatography on silica afforded target imidazole **10** and byproduct **15** in 38% and 21% yield, respectively.

A further series of experiments were performed in order to suppress the undesired side reaction. It was discovered that the reaction is seriously affected by the moisture content

Scheme 4. **Target and byproduct of imidazole ring formation from 7 or 11**



7, 8, 14 R = -CONH-(2-C_6H_5)C_6H_4
10, 11, 15 R = -NO_2

of the hygroscopic potassium carbonate powder, although not by stirring speed, particle size of potassium carbonate,[4] and batch-to-batch variability of potassium carbonate or ethanimidamide monohydrochloride.

Table 1 shows the effect of the water content of the potassium carbonate on the reaction. The yield of byproduct **15** was inversely proportional to the water content and was controlled below 20% in the reactions with 10 to 15% moist potassium carbonate.[5]

The possible reaction mechanism in the higher water content systems is described in Scheme 5. Assuming the formation of stable internal hydrogen bonds in the enol form **17**, in the lower water content systems,[6] we can explain the results shown in Table 1 as follows: (1) In the lower water

(4) The particle size of potassium carbonate examined was less than 105 μm, and the variation in this range showed no difference in the reaction.

(5) Moist potassium carbonate containing various amounts of water was prepared by exposing to the humidity in the ambient air. Up to 16%, which is the same water-content level with 1.5 hydrate, of water absorption to potassium carbonate, was observed in the experiments.

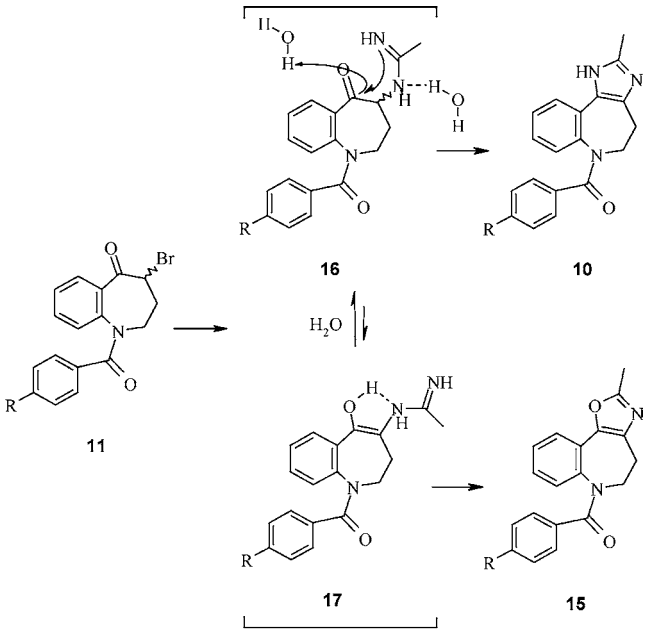
(6) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed.; Wiley & Sons: New York, 1985; pp 66−68.

Table 1. **Effect of water content in K_2CO_3 on imidazole ring formation**

H_2O content[a] (w/w %)	ratio (**10**:**15**)[b]	reaction time[c] (h)
0	38:51	97
2.5	62:27	64
5	66:23	63
10	71:17	45
15	79:8	21

[a] Amount of water in K_2CO_3.[5] [b] Monitored by HPLC. [c] The time that residual starting material was not observed or not more than 1% by HPLC.

Scheme 5. **Possible reaction mechanism of 10 and 15 in the systems with higher water content**



10, 11, 15, 16, 17 R = $-NO_2$

content systems, the equilibrium between the keto and enol form would lie towards the enol due to stabilization by internal hydrogen bonds. This might retard the internal nucleophilic attack on the carbonyl carbon in keto form **16** by the terminal amine, which would result in oxazole **15** being isolated as the major product. (2) In the higher water content systems, water could reduce the enol **17** concentration by hydrogen bonding with the α-amine, making this group less available for internal hydrogen bonding, so imidazole **10** was obtained as a main product.

Reaction with 15% moist potassium carbonate afforded the target imidazole, following crystallization in ethyl acetate, in good yield and purity, namely 98% area by HPLC assay, 67% yield. This novel approach for imidazole ring formation allowed manufacture of the key intermediate **10** on a large scale, avoiding column chromatography as a result of the consistent control of the unwanted side reaction.

Synthesis of a Novel Imidazobenzazepine 9. For the reduction of imidazobenzazepine **10**, reduction by tin chloride[7] and catalytic hydrogenation over palladium/carbon[8] and Raney nickel[9] were investigated (Table 2).

Table 2. **Reduction of nitro compound 10**

condition	batch scale[a] (mL/g)	yield %	purity %[b]
$SnCl_2$	1600	25	99<
Pd−C	89	93	99<
Ra−Ni	59	94	99<

[a] Maximum volume in a batch per amount of product **9**. [b] HPLC assay (area %) of **9**.

Reduction of **10** by $SnCl_2 \cdot 2H_2O$ in ethanol appeared to reach completion, although amine **9** was isolated in only 25% yield. It was proposed that this low yield was due to the capture of **9** in resulting insoluble materials.

Catalytic hydrogenations over palladium/carbon or Raney nickel in methanol or a mixture of methanol and DMF, respectively, also proceeded to completion. However, a high quality novel key intermediate **9** was obtained in good yield in each case, after the removal of the catalyst followed by recrystallization in a mixture of methanol and water. There were no significant operational problems in these catalytic hydrogenations; hence an efficient, practical large-scale production method for a novel key intermediate **9** was identified.

Synthesis of YM087 (1). A selective acylation on the aniline of **9** was the last key objective in the synthesis of YM087. There are two potential reaction sites for acylation of amine **9**, namely the nitrogen of imidazole and aniline. As we had expected, based on the unstable property of acyl imidazoles,[10] the reaction of amine **9** with **5** occurred without the need to protect the imidazole, and YM087 was obtained in good yield. This one step acylation is ideal for large-scale productions, shortening the manufacturing period, reducing the production cost, and eliminating useless chemical elements.

Conclusion

We have developed a practical, efficient, comparatively safe, and inexpensive sequence for large-scale production of YM087 in a controlled and reproducible manner. This straightforward process provides a 2-fold increase in the yield of YM087 over the discovery synthesis with respect to **4**, the most costly raw material. All of the intermediates and the final target are isolated cleanly in high yield without chromatographic purification and crystallization from highly flammable solvents. The key features of this procedure are (1) a reliable imidazole formation from α-bromoketones by controlling the amount of water in potassium carbonate, thus preventing unwanted side reactions; (2) an efficient catalytic reduction of nitro imidazole compounds avoiding expansion of batch size; and (3) a selective acylation of amines in the presence of unprotected imidazoles.

Experimental Section

Reagents and solvents were used as received from commercial suppliers, unless otherwise stated. All equipment

(7) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25* (8), 839.
(8) Bakke, J. M.; Riha, J. *J. Heterocycl. Chem.* **1999**, *36*, 1143.
(9) Dewar, M. J. S.; King, F. E. *J. Chem. Soc.* **1945**, 114.
(10) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley & Sons: New York, 1991; pp 385−397.

were inspected visually for cleanliness and integrity before use. Chlorinated solvents were used in some experimental procedures because of the low solubility of the materials.

Analytical HPLC was performed on a Hitachi D-2500 system with UV detection at a wavelength of 240 nm using a YMC-pack ODS-A A-302 150 mm × 4.6 mm column and elution with 0.2 M ammonium chloride aqueous solution−acetonitrile 2:3 to 2:1 or 0.02 M K_2HPO_4 aqueous solution adjusted at pH 6.0−acetonitrile 2:3 to 2:1. ^{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 $\delta = 0$. Mass spectra were determined on a Hitachi M-80, JEOL JMS-DX300, or 700T spectrometer. Melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected. All the potassium carbonate used in this article was powder potassium carbonate purchased from commercial suppliers, and its particle size was less than 105 μm. The particle size was determined using a Tsutsui−Rikagaku−Kikai M-2 type electromagnetic vibration sieve. The water content of potassium carbonate was determined by a test for loss on ignition, described in JIS (Japan Industrial Standard) K 0067.

1,2,3,4-Tetrahydro-5*H*-1-benzazepin-5-one (13). 1-[(4-Methylphenyl)sulfonyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-4-carbonitrile **12**[3] (180 g, 529 mmol) was heated in a mixture of acetic acid (830 mL, 14.5 mol) and concentrated hydrochloric acid (830 mL, 7.97 mol) at reflux for 10 h. The mixture was cooled, poured into water, and filtered to remove insoluble materials. To the filtrate, 33% sodium hydroxide aqueous solution and ethyl acetate were added. The organic and aqueous layers were separated, and the organic layer was washed with water then concentrated to give **13** (36.6 g, 43%) as an oily product.[11] HPLC assay: 88.5% (area). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (m, 2H), 2.84 (t, 2H), 3.26 (t, 2H), 4.62 (br s, 1H), 6.74−6.85 (m, 2H), 7.22−7.28 (m, 1H), 7.73 (d, 1H).

1-(4-Nitrobenzoyl)-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (2). Triethylamine (29.4 g, 291 mmol) and 4-nitrobenzoyl chloride (43.1 g, 232 mmol) were added to a solution of benzazepinone **13** (31.2 g, 194 mmol) in dichloromethane (310 mL), and the mixture was stirred at 25 °C for 2 h. The mixture was washed with saturated sodium bicarbonate aqueous solution, water, 1 M hydrochloric acid, and brine then concentrated. The resulting residue was dissolved in chloroform (90 mL), methanol (620 mL) was added, and the mixture was stirred at 25 °C for 20 h. The resulting crystals were filtered off and dried to give **2** as slightly brown crystals (45.0 g, 75%). HPLC assay: 99.9% (area). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (m, 2H), 2.90 (m, 3H), 4.10 (m, 1H), 6.70 (m, 1H), 7.20−7.55 (m, 4H), 7.85 (d, 1H), 8.05 (d, 2H). MS *m*/*z*: 311 ($M^+ + 1$).

4-Bromo-1-(4-nitrobenzoyl)-1,2,3,4-tetrahydro-5*H*-1-benzazepin-5-one (11). Bromine (7.88 g, 49.3 mmol) was added to a solution of nitro compound **2** (15.3 g, 49.3 mmol) in chloroform (125 mL) at an internal temperature of 5 to 30 °C over 1 h. The mixture was washed with water and 10% sodium bicarbonate aqueous solution then concentrated. Ethanol was added to the resulting residue and the mixture was heated at reflux, then cooled to 15 to 30 °C. The resulting crystals were filtered off and dried to give **11** (16.9 g, 88%). Mp: 134.0−137.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (m, 1H), 2.71 (m, 1H), 3.57 (m, 1H), 4.93 (m, 2H), 6.69 (s, 1H), 7.23−7.35 (m, 4H), 7.74 (s, 1H), 8.03 (d, 2H). Anal. Calcd for $C_{17}H_{13}N_2O_4Br$: C, 52.46; H, 3.37; N, 7.20; Br, 20.53. Found: C, 52.14; H, 3.33; N, 7.11; Br, 20.78. MS *m*/*z*: 390 ($M^+ + 1$).

2-Methyl-6-(4-nitrobenzoyl)-1,4,5,6-tetrahydroimidazo-[4,5-*d*][1]benzazepine (10). Ethanimidamide monohydrochloride (15.2 g, 161 mmol) and potassium carbonate (26.1 g, 161 mmol)[12] were added to a solution of α-bromoketone **11** (12.5 g, 32.1 mmol) in chloroform (440 mL), and the mixture was heated at reflux for 18 h. The mixture was cooled to 25 °C, washed with water, and then concentrated. Ethyl acetate was added to the resulting residue, and the mixture was heated at reflux and then cooled to 0−5 °C. The resulting crystals were filtered off and dried to give **10** as yellowish brown crystals (7.50 g, 67%). Mp > 250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (s, 3H), 2.98 (d, 1H), 3.12 (t, 1H), 3.46 (m, 1H), 5.10 (d, 1H), 6.60 (d, 1H), 6.86 (t, 1H), 7.25 (m, 4H), 7.95 (d, 2H), 8.24 (br s, $^1/_2$H),[13] 9.10 (br s, $^1/_2$H). [13] Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.49; H, 4.64; N, 16.03. MS *m*/*z*: 349 ($M^+ + 1$).

{**4-[(2-Methyl-4,5-dihydroimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl**}**amine (9).** Nitro compound **10** (6 g, 17.2 mmol) was hydrogenated over Raney nickel at 25 °C under hydrogen atmosphere for 1 h in the mixture of methanol (60 mL) and DMF (20 mL). The catalyst was removed by filtration and washed with methanol. Water was poured into the filtrate, and the resulting crystals were filtered off and dried to give **9**. The filtrate was concentrated, and methanol and water were added to the resulting residue. The mixture was heated at reflux and then cooled to 25 °C. The resulting crystals were filtered off and dried to afford **9**. The combined mass of **9** was 5.59 g (94%). Mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6):[14] δ 2.31 (s, 3H), 2.77−3.12 (m, 3H), 4.98 (d, 1H), 5.42 (s, 2H), 6.22 (d, 2H), 6.66 (m, 3H), 6.86 (t, 1H), 7.14 (t, 1H), 8.10 (d, 1H), 11.88 (s, 1H). Anal. Calcd for $C_{19}H_{18}N_4O\cdot{}^3/_2H_2O$: 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).** To a solution of biphenyl-2-carboxylic acid **4** (3.66 g, 18.5 mmol) in dichloromethane (74 mL) DMF (0.11 g, 1.50 mmol) and oxalyl chloride (4.62 g, 36.4 mmol) were added at −15 °C, and the mixture was warmed slowly to 25 °C and stirred for over 2 h. After completion of the reaction, the mixture was

(11) The experiments showed no evidence of HCN gas, and this suggested that the reaction consisted of the hydrolysis and decarboxylation of the nitrile. For example, see: Coan, S. B.; Becker, E. I. *Org. Synth.* **1955**, *35*, 32.

(12) 15% moist potassium carbonate (5.0 mol per mol of α-bromoketone **11**) was used.

(13) The data indicated that tautomers of compound **10** (−N=C−NH− or −NH−C=N−) existed in the ratio of 1 to 1 in $CDCl_3$.

(14) The data indicated that tautomers of compound **9** (−N=C−NH− or −NH−C=N−) existed in the ratio of 3 to 1 in DMSO-d_6.

concentrated. The resulting residue was diluted with dichloromethane and concentrated. This process was repeated 3 times to give biphenyl-2-carbonyl chloride **5** as an oily product. Acetonitrile (50 mL) was added to **5**, and the mixture was poured into a suspension of amine **9** (5.32 g, 15.4 mmol) and pyridine (3.8 mL, 47.2 mmol) in acetonitrile (100 mL) at 0 °C. The mixture was warmed slowly to 25 °C, then heated at reflux for over 30 min, and cooled. A solution of hydrogen chloride in ethyl acetate was added to the mixture at an internal temperature of 5 to 30 °C, and the mixture was stirred at 25 °C for 30 min. The resulting crystals were filtered off and dried to give **1** (6.20 g, 74%). Mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.68 (s, 3H), 2.99 (t, 1H, J = 11.6 Hz), 3.09−3.20 (m, 2H), 4.99 (d, 1H, J = 11.6 Hz), 6.86 (d, 1H, J = 7.3 Hz), 6.93 (d, 2H, J = 7.3 Hz), 7.14 (t, 1H, J = 7.3 Hz), 7.25−7.58 (m, 12H), 8.09 (d, 1H, J = 7.3 Hz), 10.31 (s, 1H), 14.73 (br s, 2H). Anal. Calcd for $C_{32}H_{26}N_4O_2 \cdot HCl \cdot {}^1/_2H_2O$: C, 70.65; H, 5.19; N, 10.30; Cl, 6.52. Found: C, 70.84; H, 5.10; N, 10.40; Cl, 6.47. MS m/z: 499 ($M^+ + 1$).

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Note Added after ASAP. Errors were introduced in the data in the last paragraph during processing of galley corrections, and the tables were numbered out of sequence in the version published on the Web 11/1/2003. The corrected version, published 11/6/2003, and the print version are correct.

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