Process Development and Large-Scale Synthesis of NK_1 Antagonist

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Received October 25, 2007; accepted November 28, 2007

A scaleable synthetic route is described to obtain 2-(4-acetylpiperadin-1-yl)-6-[3,5-bis(trifluoromethyl)-phenylmethyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (1, KRP-103) as a neurokinin ($NK)_1$ antagonist. The key step in the synthesis is the intramolecular cyclization of *N*-[3,5-bis(trifluoromethyl)phenylmethyl]-*N*-(3-hydroxypropyl)-4-chloro-6-(2-methylphenyl)-2-methylthiopyrimidine-5-carboxamide (15) which was obtained by amide formation between 4-(2-methylphenyl)-2-methylthio-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid (8) and 3-[3,5-bis(trifluoromethyl)phenylmethylamino]-1-propanol (3). Treatment of 15 with 1,8-diazabicyclo[5,4,0]undec-7-ene provided 6-[3,5-bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (6). This intermediate (6) is transformed into the candidate compound (1) by two steps; oxidation, and substitution reaction of the resultant sulfone (7) with 1-acetylpiperazine. This synthetic method is free of chromatographic purification and is amenable to large scale synthesis.

Key words KRP-103; neurokinin ($NK)_1$ antagonist; large-scale production; urinary incontinence; 2-(4-acetylpiperadin-1-yl)-6-[3,5-bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one; intramolecular cyclization

The tachykinin neuropeptides, substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), are neurotransmitters or neuromodulatory agents. Each of these structurally related neuropeptides has a preferred receptor: the NK_1 receptor for SP, the NK_2 receptor for NKA, and the NK_3 receptor for NKB. The NK_1 and NK_2 receptors are widely distributed in the central nervous system (CNS) and peripheral tissue; NK_3 may be more localized in the CNS.[1] Of these peptides, SP[2] is known to exhibit a wide variety of biological responses, both centrally and peripherally. Through binding to the NK_1 receptor, SP has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle. Therefore, NK_1 antagonists may be efficacious for the clinical treatment of a wide range of diseases. In particular, we were interested in the relationship between tachykinin and the activation of the micturition-related refluxes,[3,4] with a view to possible application in the treatment of pollakiuria and urinary incontinence. Recently, the Kyorin Discovery Chemistry group reported the design, synthesis, and evaluation of novel 2-substituted-4-aryl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]-oxazocin-5-ones.[5—7] Among these, 2-(4-acetylpiperadin-1-yl)-6-[3,5-bis(trifluoromethyl)-phenylmethyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (**1**, KRP-103) was identified as an effective NK_1 antagonist, and was promoted for development as a drug candidate for the treatment of pollakiuria and urinary incontinence.[5—7] As a continuation of this research, a large quantity of **1** was required to support the preclinical and clinical development work. Furthermore, the reduced production cost of **1** was a requested requirement in the early stage. The first synthesis of **1** by the Discovery Chemistry group is shown in Chart 1.

Condensation of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (**2**)[8] with 3-[3,5-bis(trifluoromethyl)phenylmethylamino]-1-propanol (**3**),[9] *via* acid chloride produced a condensation product (**4**), which was subjected to nucleophilic intramolecular cyclization to afford pyrimido[4,5-b][1,5]oxazocine (**5**). Suzuki coupling reaction of **5** with *o*-tolylboronic acid provided the coupled product (**6**), which was subjected to oxidation to afford a sulfone (**7**). Finally, nucleophilic displacement of **7** with 1-acetylpiperazine provided KRP-103 (**1**).[5—7] However, this method was impractical for the preparation of large quantities of material for preclinical development, because it required multiple chromatographic purifications and was not cost competitive. The formation of compound (**6**) by way of Suzuki coupling process of **5** with *o*-tolylboronic acid might be substituted for Knoevenagel condensation reaction between *o*-tolualdehyde and malonate followed by construction of 4-aryl-6-oxo-1,6-dihydropyrimidine skeleton. Herein, we describe a new practical process for the synthesis of **1**, which requires no chromatographic purification and is cost-effective to large-scale production of KRP-103 (**1**).

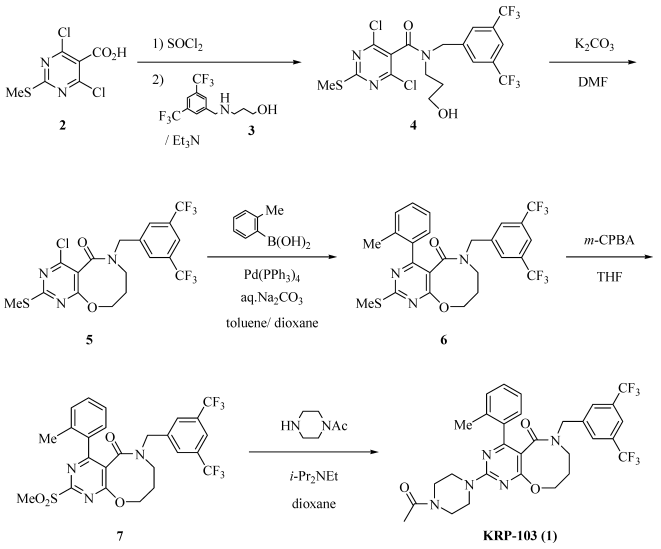

Chart 1

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Results and Discussion

A strategy was devised for the practical synthesis of **1** with regard to the process chemistry route shown in Chart 2. The intermediate (**6**) could be obtained by amide formation of a 4-arylpirimidine derivative (**8**) with **3**, followed by intramolecular cyclization. In this process, the use of expensive reagents, such as the starting material (**2**), palladium catalysts and phenyl boronic acid compounds, are avoided, which effectively reduces the target cost. The key intermediate, a 4-arylpyrimidine derivative (**8**) and β-keto ester (**9**) could be obtained from the starting *o*-tolualdehyde (**11**) *via* the cross-conjugated ester (**10**). The practical synthesis of **1** from **11** is shown in Chart 3.

A Knoevenagel reaction[10,11] of *o*-tolualdehyde (**11**) and ethyl malonate provided the condensation product (**10**) in 88% yield, which was then treated with 2-methyl-2-thiopseudourea hemisulfate (**12**) in the presence of potassium bicarbonate ($KHCO_3$) in dimethyl sulfoxide (DMSO) to give the β-keto ester (**9**) in 85% yield. During the Knoevenagel reaction, the water formed must be removed for the reaction to proceed to completion. The coupling step was performed in toluene with piperidine as the base under azeotropic conditions. The dehydrogenation of **9** was carried out under several conditions. However, dehydrogenation of **9** using some oxidants, such as MnO_2, ceric ammonium nitrate (CAN), Pd–C (>210 °C), $Mn(OAc)_3$, and $CuCl_2$, did not yield the desired compound (**13**) completely. When 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was applied to the dehydrogenation of **9** in ethyl acetate (AcOEt), **13** was obtained in 88% yield after recrystallization of the crude product from aqueous ethanol (EtOH). The saponification of **13** in aqueous sodium hydroxide under heating afforded a carboxylic acid (**8**) in 90% yield. In all of the steps, it was not necessary to use chromatographic purification, and crystallization was effective. Treatment of **8** with phosphorus oxychloride ($POCl_3$) at 80 °C provided an acid chloride (**14**), which was used for the next reaction without further purification. The reaction of **14** with **3** in the presence of triethylamine (Et_3N) gave an amide (**15**). The use of potassium carbonate (K_2CO_3) in DMF is effective in the case of intramolecular cyclization of **4**,[12] while intramolecular cyclization of **15** using this method did not proceed, and the starting material (**15**) was recovered. Therefore, other bases and solvents were examined. The best result was that where the reaction proceeded in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in DMSO to furnish compound **6** (41% yield from **8**) after recrystallization of the crude product from 2-propanol (IPA). For the initial preparation of sulfone **7** from **6** (Chart 1), the use of *m*-chloroperbenzoic acid (*m*-CPBA) is standard protocol. However, this protocol was not to be applied, because *m*-CPBA is potentially explosive and requires purification before use.[13]

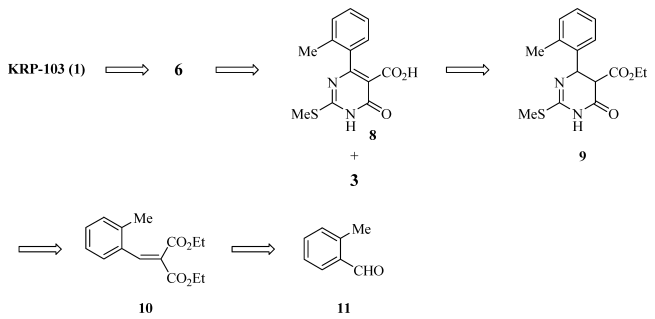

Chart 2

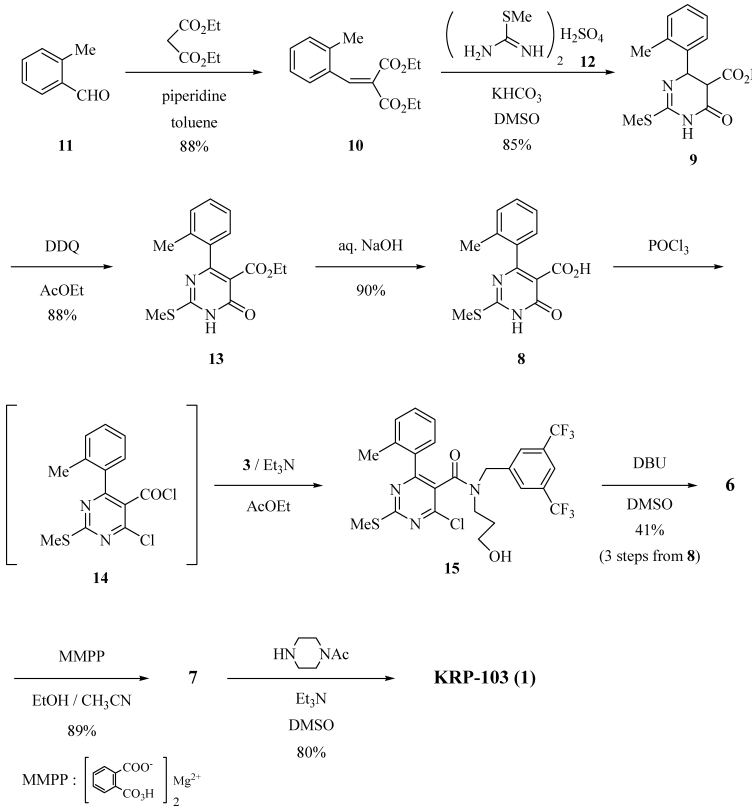

Chart 3

Oxidation of the methyl sulfide (**6**) with 30% aqueous H_2O_2 in the presence of sodium tungstate (Na_2WO_4) and acetic acid (AcOH) as a catalyst,[14,15] gave sulfone (**7**) accompanied by a small amount of by-product. Contamination by the small amount of by-product in **7** would affect the purity of KRP-103 (**1**). On the other hand, when magnesium bis(monoperoxyphthalate)hexahydrate (MMPP)[16,17] was applied in CH_3CN/EtOH instead of *m*-CPBA, the reaction proceeded to give sulfone **7** in 89% yield. Although MMPP is also potentially explosive, it's stable and low toxic compound than *m*-CPBA. Furthermore, this protocol seems to be a simple work-up, because MMPP and its resulting magnesium phthalate are easily soluble in water. Only the resulting precipitate was collected after water was added to the reaction mixture, and the resulting crude sulfone was able to be purified by crystallization to furnish pure **7** (>99% purity by HPLC). The final process in the original reaction of **7**[5] with 1-acetylpiperazine in the presence of diisopropylethylamine was carried out using 1,4-dioxane as a solvent, and the final product KRP-103 (**1**) was obtained in 65% yield. As 1,4-dioxane is defined as a class 2 solvent in the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline,[18] residual levels must be controlled. To avoid the use of 1,4-dioxane, another protocol was examined. The best result was the reaction of **7** with 1-acetylpiperazine in the presence of Et_3N in DMSO at 50—55 °C, which proceeded smoothly to furnish the final compound **1** with the desired crystal form in 80% yield after recrystallization of the crude product from aqueous acetone. The present synthetic route was composed of a nine-step transformation and did not require any special handling and chromatographic purification. The overall yield of KRP-103 (**1**) from *o*-tolualdehyde (**11**) was found to be 17%. A successive scale-up was conducted to multi-kilogram scale using a kilo-lab facility, and the overall yield of **1** was improved to 26%.

Conclusions

An efficient and safe process for the preparation of the drug candidate KRP-103 (**1**) was developed, which provided many significant advantages over the original process achieved by Kyorin Discovery Chemists. The intramolecular cyclization of 6-aryl-subsutituted-pyrimidine-5-carboxamide **15**, which is synthesized from commercially available *o*-tolualdehyde (**11**) in 6 steps, is the key step in the new synthesis of the intermediate **6** possessing 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one skeleton. The current route avoids the use of undesired chemicals like *m*-CPBA and 1,4-dioxane. All starting materials and reagents are cheap and easily available. Isolation of intermediates and product is very convenient, and the purity and impurity profiles of product and intermediates are all satisfying. The process for preparing **1** with the preferred crystal form was successfully scaled up and **1** was reliably obtained in 26% overall yield from **11** on a multi-kilogram scale in a kilo-lab facility.

Experimental

Starting materials were obtained from commercial suppliers and used without further purification. HPLC analyses were performed on a Hitachi Series L-6000 liquid chromatograph equipped with a UV detector (GL Sciences Inertsil ODS-3 column, detection at 210 nm). The area percentage was corrected for the detector response. Melting points (mp) were determined using Yanagimoto micromelting point apparatus and were uncorrected. Elemental analyses are within ±0.3% of the theoretical values and were determined using a Yanaco CHN coder MT-5. Infrared spectra were recorded with a Jasco FT/IR-5300 spectrometer. Electron impact-mass spectrometry (EI-MS) and fast atom bombardment-mass spectrometry (FAB-MS) was performed with Jeol JMS SX-102A or Jeol JMS-T100LP mass spectrometers. ^{1}H- and ^{13}C-NMR spectra were obtained on a Jeol EX-400 (400 MHz) spectrometer. Spectra were run in either $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak.

Diethyl 2-(2-Methylbenzylidene)malonate (10) A mixture of *o*-tolualdehyde **11** (150 g, 1.25 mol), diethyl malonate (210 g, 1.25 mol) and piperidine (31.9 g, 375 mmol) in toluene (750 ml) was refluxed for 2.5 h using Dean–Stark apparatus. During the reflux, piperidine (10.6 g, 125 mmol) was added to the mixture at 0.5 h and 1 h. After cooling, the reaction mixture was concentrated under reduced pressure. The crude product was purified by distillation to give **10** (140 °C/120 Pa) as a pale yellow oil (289 g, 88% yield, HPLC purity: 95.8 area %). **10**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.17 (3H, t, J=7.1 Hz), 1.34 (3H, t, J=7.1 Hz), 2.38 (3H, s), 4.22 (2H, q, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 7.15 (1H, t, J=7.8 Hz), 7.21 (1H, d, J=7.6 Hz), 7.27 (1H, dt, J=1.2, 7.6 Hz), 7.33 (1H, d, J=7.8 Hz), 7.97 (1H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 13.7, 14.0, 19.7, 61.2, 61.4, 125.8, 127.6, 127.8, 129.8, 130.2, 132.6, 137.4, 141.5, 163.9, 166.1. IR (KBr) cm^{-1}: 1729, 1257, 1212, 1067. EI-MS *m*/*z*: 217, 262 (M^+). *Anal*. Calcd for $C_{15}H_{18}O_4$ (MW: 262.30): C, 68.68; H, 6.92. Found: C, 68.84; H, 6.90.

Ethyl 4-(2-Methylphenyl)-2-methylthio-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate (9) Potassium bicarbonate (439 g, 4.38 mol) was added to a stirred suspension of **10** (287 g, 1.09 mol) and 2-methyl-2-thiopseudourea hemisulfate (**12**: 622 g, 2.19 mol) in DMSO (2.18 l). The reaction mixture was allowed to warm to 50 °C and was stirred for 2.5 h. After cooling to 20 °C, the reaction mixture was poured into water (1.09 l) and the resulting mixture was stirred for 0.5 h at 16—20 °C. The precipitate was collected by filtration and purified by recrystallization from IPA/water (4 : 1) to give **9** as a white powder (285 g, 85% yield, HPLC purity: 99.4 area %). **9**: mp 135—137 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.15 (3H, t, J=7.3 Hz), 2.42 (3H, s), 2.44 (3H, s), 3.66 (1H, d, J=8.3 Hz), 4.15 (2H, q, J=7.3 Hz), 5.43 (1H, d, J=8.3 Hz), 7.07—7.10 (1H, m), 7.16—7.21 (3H, m), 8.13 (1H, br). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 13.1, 13.8, 19.3, 52.6, 59.1, 61.8, 126.0, 126.2, 127.8, 131.0, 135.8, 137.2, 152.2, 166.1, 167.6. IR (KBr) cm^{-1}: 3115, 1749, 1715, 1605, 1143, 766. EI-MS *m*/*z*: 233, 306 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S$ (MW: 306.38): C, 58.80; H, 5.92; N, 9.14. Found: C, 58.36; H, 5.84; N, 9.05.

Ethyl 4-(2-Methylphenyl)-2-methylthio-6-oxo-1,6-dihydropyrimidine-5-carboxylate (13) DDQ (239 g, 1.02 mol) was added to a stirred suspension of **9** (284 g, 0.93 mol) in AcOEt (1.42 l), and the reaction mixture was stirred for 2.5 h at 23—46 °C. After cooling to 25 °C, the insoluble portion was removed by filtration, and washed with AcOEt (0.28 l). The combined filtrate was washed with 2.4% aqueous sodium bicarbonate solution (1.42 l), then water (0.5 l×2), and was concentrated under reduced pressure. The residue was crystallized from 50% aqueous EtOH to give **13** as colorless crystals (249 g, 88% yield, HPLC purity: 99.9 area %). **13**: mp 136—139 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.84 (3H, t, J=6.8 Hz), 2.24 (3H, s), 2.58 (3H, s), 4.02 (2H, q, J=6.8 Hz), 7.14 (1H, d, J=7.3 Hz), 7.18—7.24 (2H, m), 7.28—7.37 (1H, m), 12.40 (1H, br). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 13.3, 13.5, 19.5, 61.2, 125.3 (2C), 127.6 (2C), 129.0, 130.1, 135.4, 137.9, 164.1, 165.6, 166.3. IR (KBr) cm^{-1}: 2925, 1645, 1537, 1199, 1071, 551. EI-MS *m*/*z*: 231, 304 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_3S$ (MW: 304.36): C, 59.19; H, 5.30; N, 9.20. Found: C, 59.41; H, 5.34; N, 9.19.

4-(2-Methylphenyl)-2-methylthio-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (8) A suspension of **13** (248 g, 814 mmol) in 1 M aqueous sodium hydroxide (3.26 l) was heated at 80—85 °C for 2.5 h. After cooling to 10 °C, the reaction mixture was adjusted to pH 2 with 2 M HCl, and the resulting mixture was stirred for 1 h at 10—15 °C. The precipitate was collected by filtration, washed with water (0.99 l), and then air-dried for 0.5 h. The obtained crude product (273 g) was suspended in IPA (1.73 l), and the mixture was refluxed for 1 h. After cooling to 10 °C, the mixture was stirred for 1 h at 7—10 °C. The precipitate was collected by filtration to give **8** as a white powder (216 g, 90% yield, HPLC purity: 99.9 area %). **8**: mp 231—233 °C (dec.). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 2.22 (3H, s), 2.49 (3H, s), 7.19—7.36 (4H, m), 13.39 (1H, br). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 12.9, 19.3, 125.3, 127.7, 128.8, 130.0, 135.1 (3C), 137.0, 162.1, 163.2, 165.3. IR (KBr) cm^{-1}: 2937, 1720, 1605, 1456, 1005, 775. EI-MS *m*/*z*: 231,

276 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_3S$ (MW: 276.31): C, 56.51; H, 4.38; N, 10.14. Found: C, 56.50; H, 4.34; N, 10.10.

***N*-[3,5-Bis(trifluoromethyl)phenylmethyl]-*N*-(3-hydroxypropyl)-4-chloro-6-(2-methylphenyl)-2-methylthiopyrimidine-5-carboxamide (15)** A mixture of **8** (215 g, 780 mmol) and phosphorus oxychloride (478 g, 3.11 mmol) was heated at 75—80 °C for 1 h. After cooling to 20 °C, the reaction mixture was poured into cooling-water (1.51 l) at 0—18 °C, and the resulting mixture was stirred for 0.5 h at 18—22 °C. The precipitate was collected by filtration, washed with water (0.65 l). The obtained precipitate was dissolved in AcOEt (2.59 l), and was successively washed with water (0.86 l×2), 10% aqueous sodium bicarbonate (0.65 l) and 10% aqueous sodium chloride (0.43 l), to give a solution of 4-chloro-6-(2-methylphenyl)-2-methylthiopyrimidine-5-carbonyl chloride (**14**) in AcOEt. The above solution was added dropwise to a solution of **3** (282 g, 0.94 mol) and Et_3N (158 g, 1.56 mol) in AcOEt (0.43 l) at 4—10 °C, and then the reaction mixture was stirred for 0.5 h at 7—10 °C. The reaction mixture was washed with water (0.65 l), 0.5 M HCl (0.65 l), 10% aqueous sodium bicarbonate (0.65 l) and saturated sodium chloride (0.43 l), then dried over sodium sulfate. Concentration under reduced pressure yielded a crude material **15** as colorless crystals (498 g). This compound was used for the next step without further purification. **15**: mp 148—150 °C (50% aqueous IPA); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.44—1.48 (1H, m), 1.60—1.67 (1H, m), 2.29 (3H, s), 2.59 (3H, s), 2.88—3.18 (1H, m), 3.20—3.26 (1H, m), 3.51 (2H, q, J=5.6 Hz), 4.48 (1H, d, J=15.1 Hz), 4.78 (1H, d, J=15.1 Hz), 7.04 (1H, t, J=7.6 Hz), 7.19—7.31 (3H, m), 7.59 (2H, s), 7.77 (1H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.2, 19.6, 27.3, 43.8, 47.2, 64.1, 109.2, 109.3, 122.0 (quintet, J=4 Hz), 123.1 (q, J=273 Hz), 125.0, 126.6, 128.6, 128.6, 129.1, 130.4, 132.1 (q, J=33 Hz), 135.7, 137.8, 138.9, 166.6, 167.3, 171.2, 172.9. IR (KBr) cm^{-1}: 3474, 1618, 1544, 1277, 1133, 765. FAB-MS (positive) *m/z*: 578 $[M+H]^+$. *Anal.* Calcd for $C_{25}H_{22}ClF_6N_3O_2S$ (MW: 577.97): C, 51.95; H, 3.84; N, 7.27. Found: C, 51.95; H, 3.82; N, 7.17.

6-[3,5-Bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (6) A mixture of crude **15** (498 g) and DBU (142 g, 936 mmol) in DMSO (1.51 l) was heated at 55—60 °C for 1 h. After cooling to 10 °C, water (3.02 l) was added at 3—10 °C, and the resulting mixture was stirred for 0.5 h at 8—10 °C. The resulting precipitate was collected by filtration, and purified by crystallization twice from 75% aqueous IPA to give **6** as colorless crystals (173 g, 41% yield from **8**, HPLC purity: 99.9 area %). **6**: mp 144—147 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.97—2.06 (1H, m), 2.16—2.21 (1H, m), 2.24 (3H, s), 2.56 (3H, s), 3.34 (1H, dd, J=4.4, 15.6 Hz), 3.72—3.80 (1H, m), 3.87 (1H, d, J=14.6 Hz), 4.37—4.48 (2H, m), 5.31 (1H, d, J=15.1 Hz), 6.92 (1H, d, J=7.3 Hz), 7.04 (1H, t, J=7.3 Hz), 7.23 (2H, t, J=7.8 Hz), 7.57 (2H, s), 7.82 (1H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.2, 19.6, 27.3, 43.8, 47.2, 64.1, 109.2, 109.3, 122.0 (quintet, J=4 Hz), 123.1 (q, J=273 Hz), 125.0, 126.6, 128.6, 128.6, 129.1, 130.4, 132.1 (q, J=33 Hz), 135.7, 137.8, 138.9, 166.6, 167.3, 171.2, 172.9. IR (KBr) cm^{-1}: 1634, 1538, 1516, 1281, 1191, 1124, 683. FAB-MS (positive) *m/z*: 542 $[M+H]^+$. *Anal.* Calcd for $C_{25}H_{21}F_6N_3O_2S$ (MW: 541.51): C, 55.45; H, 3.91; N, 7.76. Found: C, 55.34; H, 3.90; N, 7.67.

6-[3,5-Bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-2-methansulfonyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (7) MMPP (294 g, 475 mmol) was added to a solution of **6** (172 g, 317 mmol) in acetonitrile (0.69 l) and EtOH (0.34 l) at 16—29 °C (exothermic reaction), and the reaction mixture was stirred for 4 h at 18—24 °C. Water (2.06 l) was added to the reaction mixture and was then stirred for 1 h at 21—24 °C. The precipitate was filtered, washed with water (0.52 l), and purified by crystallization from a mixed solvent of AcOEt/IPA/water (1 : 3 : 0.8) to give **7** as a white powder (161 g, 89% yield, HPLC analysis: 99.8 area %). **7**: mp 212—213 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 2.05—2.13 (1H, m), 2.23 (3H, s), 2.26—2.31 (1H, m), 3.34 (3H, s), 3.44 (1H, dd, J=5.4, 15.6 Hz), 3.68—3.76 (1H, m), 3.91 (1H, d, J=14.6 Hz), 4.48—4.59 (2H, m), 5.30 (1H, d, J=14.6 Hz), 6.88 (1H, d, J=7.3 Hz), 7.02 (1H, t, J=7.3 Hz), 7.24—7.32 (2H, m), 7.58 (2H, s), 7.85 (1H, s). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 19.2, 27.0, 38.9, 44.0, 46.7, 65.6, 117.2, 121.4 (quintet, J=4 Hz), 123.2 (q, J=273 Hz), 124.4, 127.0, 129.0, 129.4, 129.4, 129.8, 130.2 (q, J=33 Hz), 135.5, 136.8, 139.9, 163.7, 165.3, 167.6, 171.3. IR (KBr) cm^{-1}: 1642, 1546, 1527, 1279, 1182, 1130, 760. FAB-MS (positive) *m/z*: 574 $[M+H]^+$. *Anal.* Calcd for $C_{25}H_{21}F_6N_3O_4S$ (MW: 573.51): C, 52.36; H, 3.69; N, 7.33. Found: C, 52.34; H, 3.60; N, 7.28.

2-(4-Acetylpiperadin-1-yl)-6-[3,5-bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (1, KRP-103) A mixture of **7** (158 g, 276 mmol), 1-acetylpiperazine (50.0 g, 386 mmol) and Et_3N (41.9 g, 414 mmol) in DMSO (0.79 l) was stirred for 3.5 h at 50—55 °C. After cooling to 25 °C, the reaction mixture was poured into cooling water (2.37 l) at 15—25 °C, and the resulting mixture was then stirred for 0.5 h at 15—20 °C. The precipitate was filtered and washed with water (0.32 l). The obtained precipitate (280 g) was dissolved in AcOEt (1.58 l), washed with 10% aqueous sodium chloride (0.40 l), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by crystallization from AcOEt/hexane (1 : 2), and further purified by recrystallization from acetone/water (1 : 2) to afford **1** as a white powder (137 g, 80% yield, HPLC analysis: 99.6 area %). **1**: mp 186—187 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.95—2.02 (1H, m), 2.11—2.18 (1H, m), 2.14 (3H, s), 2.25 (3H, s), 3.30 (1H, dd, J=5.1, 15.4 Hz), 3.50 (2H, t, J=5.1 Hz), 3.63—3.67 (2H, m), 3.77—3.93 (6H, m), 4.32—4.41 (2H, m), 5.32 (1H, d, J=15.1 Hz), 6.95 (1H, d, J=7.1 Hz), 7.04—7.08 (1H, m), 7.21—7.25 (2H, m), 7.57 (2H, s), 7.81 (1H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 19.6, 21.5, 27.3, 41.2, 43.6, 43.7, 43.8, 46.1, 47.1, 63.8, 103.2, 121.8 (t, J=4 Hz), 123.1 (q, J=273 Hz), 125.0, 126.5, 128.5, 128.5, 128.7, 130.3, 132.0 (q, J=33 Hz), 135.5, 139.1, 139.4, 160.1, 167.8, 168.2, 169.2, 172.5. IR (KBr) cm^{-1}: 1631, 1565, 1286. FAB-MS (positive) *m/z*: 622 $[M+H]^+$. *Anal.* Calcd for $C_{30}H_{29}F_6N_5O_3$: C, 57.97; H, 4.70; N, 11.27. Found: C, 58.08; H, 4.72; N, 11.34.

Large Scale Preparation. Diethyl 2-(2-Methylbenzylidene)malonate (10) A mixture of *o*-tolualdehyde **11** (1.12 kg, 10.0 mol), diethyl malonate (1.60 kg, 10.0 mol) and piperidine (255 g, 3.00 mol) in toluene (6.0 l) was refluxed for 3 h, using Dean–Stark apparatus. During the reflux, piperidine (85.2 g, 1.00 mol) was added to the mixture at 0.5 h and 1 h. After cooling, the reaction mixture was concentrated under reduced pressure. The crude product was purified by distillation to give **10** (160—163 °C/267 Pa) as a yellow oil (2.35 kg, 90% yield, HPLC purity: 94.8 area %). **10**: ^{1}H-NMR data and MS data of **10** were identical with those of the previous sample (**10**).

Ethyl 4-(2-Methylphenyl)-2-methylthio-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate (9) Potassium bicarbonate (3.51 kg, 35.1 mol) was added to a stirred suspension of **10** (2.30 kg, 8.76 mol) and **12** (4.89 kg, 17.5 mol) in DMSO (17.5 l). The reaction mixture was allowed to warm to 50—55 °C and was stirred for 3 h. After cooling to 25 °C, the reaction mixture was poured into cooling water (87.6 l) at 12—19 °C, and the resulting mixture was stirred for 1 h at 17—19 °C. The precipitate was collected by filtration and purified by crystallization from IPA/water (4 : 1) to give **9** as a white powder (2.15 kg, 80% yield, HPLC purity: 99.3 area %). **9**: mp 135—137 °C. ^{1}H-NMR data and MS data of **9** were identical with those of the previous sample (**9**).

Ethyl 4-(2-Methylphenyl)-2-methylthio-6-oxo-1,6-dihydropyrimidine-5-carboxylate (13) DDQ (1.80 kg, 7.93 mol) was added to a stirred suspension of **9** (2.15 kg, 7.00 mol) in AcOEt (13.0 l), and the reaction mixture was stirred for 2.5 h at 20—52 °C. After cooling to 23 °C, the insoluble portion was removed by filtration, and washed with AcOEt (2.2 l). The combined filtrate was concentrated under reduced pressure. The obtained residue was triturated with 8% aqueous sodium bicarbonate (20.0 l), then the resulting precipitate was collected by filtration, washed water (3.0 l) to give a crude material (wet, 2.50 kg). The crude material was crystallized from 50% aqueous EtOH to give **13** as pale brown crystals (1.93 kg, 90% yield, HPLC purity: 99.9 area %). **13**: mp 136—139 °C. ^{1}H-NMR data and MS data of **13** were identical with those of the previous sample (**13**).

4-(2-Methylphenyl)-2-methylthio-6-oxo-1,6-dihydropyrimidine-5-carboxylic Acid (8) A suspension of **13** (1.93 kg, 6.33 mol) in 1 M aqueous sodium hydroxide (25.3 l) was heated at 80—83 °C for 1.5 h. After cooling to 8 °C, the reaction mixture was adjusted to pH 2 with 2 M HCl, and the resulting mixture was stirred for 1 h at 10—13 °C. The precipitate was collected by filtration, washed with water (7.73 l), and then air-dried for 0.5 h. The obtained crude product (wet, 2.77 kg) was suspended in IPA (13.5 l), and the mixture was refluxed for 1 h. After cooling to 10 °C, the mixture was stirred for 1 h at 6—10 °C. The precipitate was collected by filtration to give **8** as a white powder (1.69 kg, 97% yield, HPLC purity: 99.6 area %). **8**: mp 232—233 °C (dec.). ^{1}H-NMR data and MS data of **8** were identical with those of the previous sample (**8**).

6-[3,5-Bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (6) A mixture of **8** (1.34 kg, 4.85 mol) and phosphorus oxychloride (2.97 kg, 19.4 mol) was heated at 75—82 °C for 1 h. After cooling to 25 °C, the reaction mixture was poured into ice-cold water (9.38 l) (exothermic reaction), and the resulting mixture was stirred for 0.5 h at 18—24 °C. The precipitate was collected by filtration, washed with water (4.02 l). The obtained precipitate (wet, 2.50 kg) was dissolved in AcOEt (16.1 l), and was successively washed with water (5.36 l×2), 10% aqueous sodium bicarbon-

ate (4.02 l) and 28% aqueous sodium chloride (2.68 l), to give a solution of **14** in AcOEt. The above solution of **14** was added dropwise to a solution of **3** (1.75 kg, 5.82 mol) and Et_3N (0.98 kg, 9.70 mol) in AcOEt (2.68 l) at 4—10 °C, and then the reaction mixture was stirred for 0.5 h at 8—10 °C. The reaction mixture was washed with water (4.02 l), 0.5 M HCl (4.02 l), 10% aqueous sodium bicarbonate (4.02 l) and saturated aqueous sodium chloride (2.68 l), then dried over sodium sulfate. Concentration under reduced pressure yielded a crude amide **15**. To a solution of **15** in DMSO (9.38 l), DBU (886 g, 5.82 mol) was added and the reaction mixture was heated at 55—60 °C for 1 h. After cooling to 30 °C, the reaction mixture was added to cooling water (18.8 l) at 6—18 °C, and the resulting mixture was stirred for 0.5 h at 8—10 °C. The resulting precipitate was collected by filtration, washed with water (6.7 l) to give a crude material (wet, 8.33 kg). The crude material was crystallized from IPA to give **6** as white crystals (1.79 kg, 68% yield, HPLC purity: 99.1 area %). **6**: mp 146—148 °C. ^{1}H-NMR data and MS data of **6** were identical with those of the previous sample (**6**).

6-[3,5-Bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-2-methansulfonyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (7) MMPP (2.64 kg, 5.33 mol) was added to a solution of **6** (1.54 kg, 2.84 mol) in acetonitrile (6.12 l) and EtOH (3.06 l) at 18 °C, and the reaction mixture was stirred for 4 h at 18—50 °C (exothermic reaction). Water (18.4 l) was added to the reaction mixture and was then stirred for 1 h at 20 °C. The precipitate was filtered, washed with water (8.0 l) to give a crude material (wet, 2.96 kg). The crude material was subjected to crystallization from a mixed solvent of AcOEt/IPA/water (1 : 3 : 0.8) to give **7** as a white powder (1.31 kg, 80% yield, HPLC purity: 99.7 area %). **7**: mp 210—212 °C. ^{1}H-NMR data and MS data of **7** were identical with those of the previous sample (**7**).

2-(4-Acethylpiperadin-1-yl)-6-[3,5-bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-b][1,5]oxazocin-5-one (1, KRP-103) A mixture of the **7** (4.02 kg, 6.99 mol), 1-acetylpiperazine (1.30 kg, 10.2 mol) and Et_3N (1.08 kg, 10.7 mol) in DMSO (20.1 l) was stirred for 3.5 h at 50—56 °C. The reaction mixture was poured into cooling water (60.2 l) at 10—20 °C, and the resulting mixture was then stirred for 0.5 h at 15—20 °C. The precipitate was filtered and washed with water (12.0 l). The obtained precipitate (wet, 15.0 kg) was dissolved in AcOEt (40.1 l), washed with 10% aqueous sodium chloride (10.0 l), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by crystallization from AcOEt/hexane (1 : 2), and further purified by recrystallization from acetone/water (1 : 2) to afford **1** as white powder (3.29 kg, 76%, HPLC purity: 99.7 area %). **1**: mp 187—188 °C. ^{1}H-NMR data and MS data of **1** were identical with those of the previous sample (**1**). IR(KBr) cm^{-1}: 1631, 1565, 1286. *Anal.* Calcd for $C_{30}H_{29}F_6N_5O_3$: C, 57.97; H, 4.70; N, 11.27. Found: C, 58.01; H, 4.53; N, 11.20.

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