Process Development and Large-Scale Synthesis of NK₁ Antagonist

Ichiro Araya,*a,b Shintaro Kanazawa,a and Hiroyuki Akita


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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-5H-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)phenylmethyl]amino]-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-5H-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-5H-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 NK₁ receptor for SP, the NK₂ receptor for NKA, and the NK₃ receptor for NKB. The NK₁ and NK₂ receptors are widely distributed in the central nervous system (CNS) and peripheral tissue; NK₃ may be more localized in the CNS. Of these peptides, SP is known to exhibit a wide variety of biological responses, both centrally and peripherally. Through binding to the NK₁ receptor, SP has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle. Therefore, NK₁ 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 reflexes, 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-5H-pyrimido[4,5-b][1,5]-oxazocin-5-ones. Among these, 2-(4-acetylpiperadin-1-yl)-6-[3,5-bis(trifluoromethyl)phenylmethyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,5]oxazocin-5-one (1, KRP-103) was identified as an effective NK₁ antagonist, and was promoted for development as a drug candidate for the treatment of pollakiuria and urinary incontinence. 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) with 3-[3,5-bis(trifluoromethyl)phenylmethyl]amino]-1-propanol (3) 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). 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).
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-arylpyrimidine 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\(^\text{10,11}^\) 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 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)\(_2\), 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\(_3\)N) gave an amide (15). The use of potassium carbonate (K\(_2\)CO\(_3\)) in DMF is effective in the case of intramolecular cyclization of 4,\(^\text{12}^\) 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.\(^\text{13}^\)
Oxidation of the methyl sulfide (6) with 30% aqueous H2O2 in the presence of sodium tungstate (Na2WO4) and acetic acid (AcOH) as a catalyst,[4,15] 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 (I). On the other hand, when magnesium bis(monoper-oxyphthalate)hexahydrate (MMPP)[6,17] was applied in CH3CN/EtOH instead of m-CPBA, the reaction proceeded to give sulfone 7 in 89% yield. Although MMPP is also poten- 
tially 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 phtha-
late 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 overall yield from the reaction of 7[5] with 1-
acetylpiperazine in the presence of sodium tungstate (Na2WO4) and acetic 
acid (AcOH) was composed of a nine-step transformation and did not re-
duce the yield of KRP-103 (I) from aqueous acetone. The present synthetic route 
was found to be 17%. A successive scale-up was conducted 
without further purification. HPLC analyses were performed on a Hitachi 
Experimental Conference on Harmonization of Technical Require-
ments for Registration of Pharmaceuticals for Human Use) guideline.[5,9] 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 Et3N 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 re-
quire any special handling and chromatographic purification. 

The overall yield of KRP-103 (I) 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 (I) was developed, which provided many significant advantages over the original process achieved by Kyorin Discovery Chemists. The intramolecular cyclization of 6-aryl-substituted-pyrimidine-5-carboxamide 15, which is synthesized from commercially available o-tolu-
aldehyde (11) in 6 steps, is the key step in the new synthesis of the intermediate 6 possessing 6,7,8,9-tetrahydro-5-
H-pyrimidino[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 pro-
files 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 Scien-
ces Inertfil ODS-3 column, detection at 210 nm). The area percentage was 
corrected for the detector response. Melting points (mp) were determined using Yaganimoto micromelting point apparatus and were uncorrected. Ele-
mental analyses are within ±0.3% of the theoretical values and were deter-
mined 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 spectrome-
ters. 1H- and 13C-NMR spectra were obtained on a Jeol EX-400 (400 MHz) spectrometer. Spectra were run in either CDCl3 or DMSO-d6 using tetram-
ethylenesilane (TMS) as an internal standard. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.
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 precipitate was filtered, washed with water (0.65 l), and dried under reduced pressure in vacuum. The precipitate was collected by filtration, washed with water (0.65 l), and saturated sodium bicarbonate (0.34 l), then dried over sodium sulfate. Concentration under reduced pressure yielded a crude material (282 g, 0.94 mol) and Et3N (41.9 g, 414 mmol) in DMSO (0.79 l) was added to a stirred suspension of 158 g (0.94 mol) of 1-acetylpiperazine (6) as a white powder (137 g, 80% yield, HPLC analysis: 99.6 area %). The 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: 1H-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-tetrahydropyrimido[4,5-b][1,5]oxazocin-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 and purified by crystallization from acetone/water (1: 2) to afford 13 as white powder (1.43 kg, 74% yield, HPLC purity: 99.3 area %). 13: mp 153—157°C. 1H-NMR data and MS data of 13 were identical with those of the previous sample (13).

**Large Scale Preparation.** Diethyl 2-(2-Methylbenzylidene)malonate (11) A mixture of 10 (2.49 kg, 10.0 mol), diethyl malonate (1.60 kg, 10.0 mol) and piperidine (255 g, 3.00 mol) in toluene (6.01 l) was refluxed for 2 h. At the end of the reaction, the resulting precipitate was collected by filtration, washed with water (2.5 l) to give a white powder (2.15 kg, 80% yield, HPLC purity: 99.3 area %). 11: 1H-NMR data and MS data of 11 were identical with those of the previous sample (11).
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$_3$N (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 IP A to give 6 as white crystals (1.79 kg, 68% yield, HPLC purity: 99.7 area %).

5-one (1, KRP-103) A mixture of the previous sample (4-(2-methylphenyl)-6,7,8,9-tetrahydro-5-one (6)) and MMPP (2.64 kg, 5.33 mol) was added to a solution of H methansulfonyl-6,7,8,9-tetrahydro-5-one (7) in AcOEt. The above solution of 7 was added dropwise 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 was added to the reaction mixture and was then stirred for 0.5 h at 15—20°C. The precipitate was filtered and washed with water (60.2 l) at 10—20°C, and the resulting mixture was then 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 acetone/water (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. 1H-NMR data and MS data of 1 were identical with those of the previous sample (1).

References and Notes