



2-Substituted-4-aryl-6,7,8,9-tetrahydro-5*H*-pyrimido [4,5-*b*][1,5]oxazocin-5-one as a structurally new NK₁ antagonist

Shigeki Seto,* Asao Tanioka, Makoto Ikeda and Shigeru Izawa

Discovery Research Laboratories, Kyorin Pharmaceutical Co., Ltd, 2399-1, Nogi, Nogi-machi, Shimotsuga-gun,
Tochigi 329-0114, Japan

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Abstract—The structurally novel pyrimido[4,5-*b*][1,5]oxazocine derivative **3**, a hybrid compound of pyrido[4,3-*b*]- and [2,3-*b*]-1,5-oxazocine (**1** and **2**, respectively), was designed and synthesized. We examined the atropisomeric property and the NK₁ antagonist activity of **3**. Compound **3** was found to possess both a feature of **1**, free rotation about the biaryl bond, and a feature of **2**, potent *in vivo* activity.

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Substance P (SP)¹ elicits a wide variety of biological responses, both centrally and peripherally. The binding of SP to NK₁ receptors has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle. Therefore, NK₁ antagonists may be clinically useful in the treatment of a wide range of diseases.

Recently, we reported the design and synthesis of the pyrido[4,3-*b*]-1,5-oxazocine **1** and the pyrido[2,3-*b*]-1,5-oxazocine **2** as potent NK₁ antagonists.² In that study, we established that although compounds **1** and **2** exhibit similar and potent NK₁ antagonist activity in vitro, the in vivo activity of **2** is superior to that of **1**. These two compounds differ structurally in the following two aspects: (1) the position of the nitrogen atom on the pyridine ring, and (2) the presence in **2** of atropisomerism about the bia-

ryl bond. Possibly because of their different structures at the 8-position (**1**, N; **2**, CH), rotation about the biaryl bond of **1** appeared to be free, whereas that of **2** was partially restricted on the NMR time scale.² This property of **2** might promote the stacking conformation that is important for NK₁ receptor recognition.³ However, in order to avoid substantial analytical complications during manufacture and drug development, it is necessary to ensure either inseparable rapid interconversion of isomers or a completely separable rigid conformation.

On the basis of these results, we became interested in the pyrimido[4,5-*b*][1,5]oxazocine **3** as a hybrid compound of **1** and **2**. Interestingly, the 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one skeleton constitutes a novel ring system that to our knowledge has not previously been described (Fig. 1).

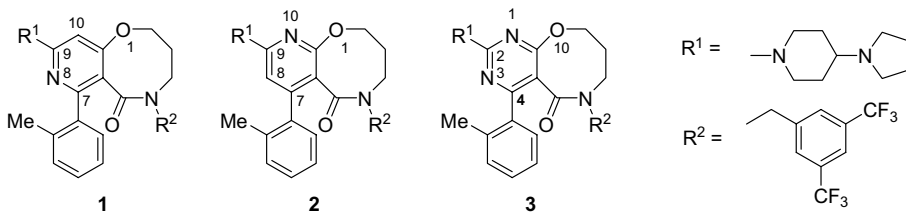
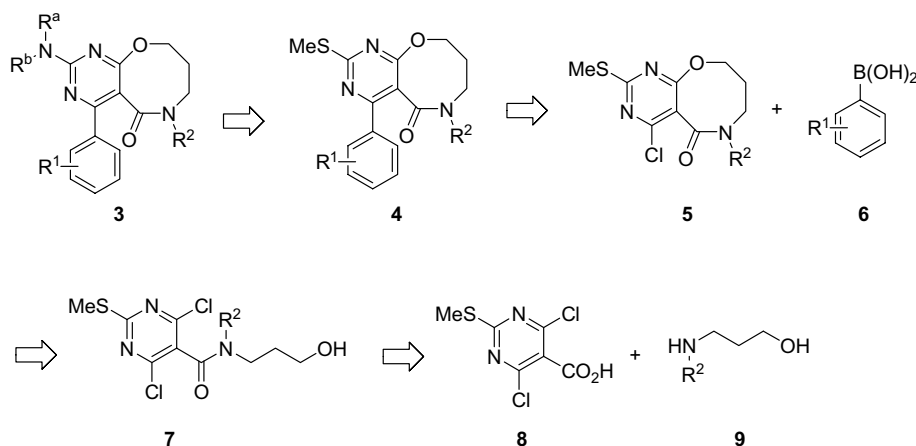


Figure 1.

Keywords: Pyrimido[4,5-*b*][1,5]oxazocin-5-one; NK₁ antagonist.

* Corresponding author. Fax: +81 280 57 1293; e-mail: shigeki.seto@mb.kyorin-pharm.co.jp



Scheme 1.

The retrosynthesis of the skeleton **3** is shown in Scheme 1. Sulfide **4** may be converted to **3** by oxidation to the corresponding sulfone and displacement with an amine nucleophile. The formation of the biaryl bond of **4** could be achieved by a Suzuki coupling reaction. The bicyclic compound **5** could be constructed from the carboxylic acid **8** by condensation with aminopropanol **9** and a subsequent cyclization reaction using nucleophilic aromatic substitution (S_NAr).

The synthesis of the desired compound **3** is shown in Scheme 2.

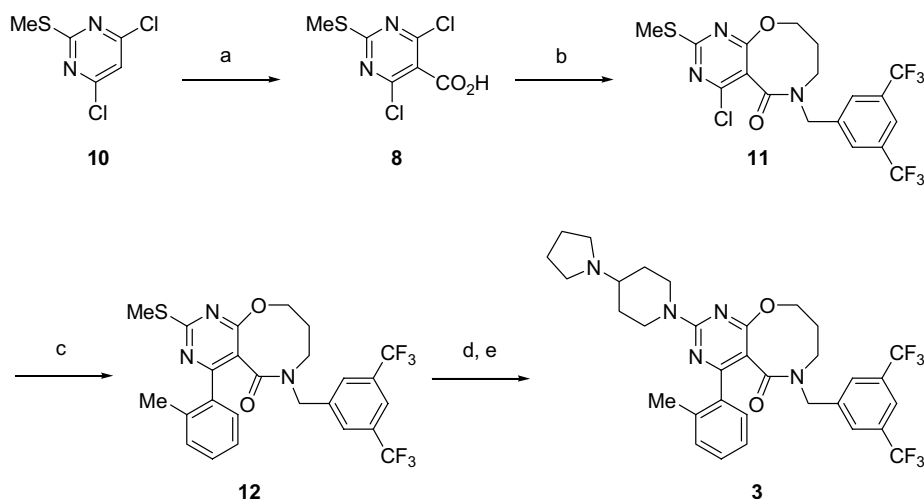
Compound **8**,⁴ which was prepared from 4,6-dichloro-2-(methylthio)pyrimidine, was treated with SOCl_2 , followed by condensation with 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol^{3a} and intramolecular cyclization using potassium carbonate to afford the bicyclic compound **11**. Suzuki coupling reactions of **11** with 2-methylphenylboronic acids afforded the corresponding biaryl compounds **12** in good yield. Oxidation of sul-

fide **12** with *m*CPBA and subsequent nucleophilic amination with 4-(pyrrolidinyl)piperidine afforded target compound **3**.⁵

The characteristic ^1H NMR properties of compounds **1**, **2**, and **3** are summarized in Table 1.

The rotation about the biaryl bond of **3** was examined. Although the NMR spectrum of **2** showed two pairs of benzylic methylene protons, presumably as a result of two-axial chirality,² the NMR spectrum of **3** showed one pair of benzylic methylene protons, similar to that of **1**. Consequently, rotation about the biaryl bond of **3** appears to be free on the NMR timescale at room temperature.

The interconversion about oxazocine ring of **3** was examined. Compound **3** showed a distinct AB pattern for the benzylic and ring methylene protons that might indicate a slow interconversion about the oxazocine ring on the NMR timescale at room temperature.³ Several



Scheme 2. Reagents and conditions: (a) (1) LDA, THF, -78°C , 5 h; (2) CO_2 , 1 h; (3) HCl, rt, 1 h, 58%; (b) (1) SOCl_2 , DMF, reflux, 2 h; (2) 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol, THF, 0°C , 1 h then rt, 3 h; (3) K_2CO_3 , DMF, 80°C , 1 h, 63%; (c) 2-methylphenylboronic acid, 10 mol % $\text{Pd}(\text{PPh}_3)_4$, 2 M Na_2CO_3 , toluene, dioxane; reflux, 6 h, 95%; (d) *m*CPBA, THF, 0°C , 0.5 h then rt, 3 h, 99%; (e) 4-(pyrrolidinyl)piperidine, 1,4-dioxane, diisopropylethylamine, reflux, 5 h, 64%.

Cc1ccc2c(c1)c3c(c2)c(=O)n4ccccc4c3=O

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5. Compound **3**: ^1H NMR (400 MHz, CDCl_3): δ 1.45–1.58 (2H, m), 1.75–1.87 (4H, m), 1.87–2.05 (4H, m), 2.05–2.18 (2H, m), 2.18–2.37 (1H, m), 2.25 (3H, s), 2.57–2.69 (3H, m), 2.90–3.01 (2H, m), 3.23–3.32 (1H, m), 3.76–3.89 (1H, m), 3.84 (1H, d, $J = 15.3$ Hz), 4.27–4.41 (2H, m), 4.67–4.80 (1H, m), 5.32 (1H, d, $J = 15.3$ Hz), 6.92–6.98 (1H, m), 7.02–7.08 (1H, m), 7.18–7.25 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HUMS (EI): calcd for $\text{C}_{33}\text{H}_{35}\text{F}_6\text{N}_5\text{O}_2 (\text{M}^+)$ 647.2695, found 647.2707. Anal. Calcd for $\text{C}_{33}\text{H}_{35}\text{F}_6\text{N}_5\text{O}_2 \cdot 1/5\text{H}_2\text{O}$: C, 60.86; H, 5.42; N, 10.75. Found: C, 60.47; H, 5.40; N, 10.47.
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