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2-Substituted-4-aryl-6,7,8,9-tetrahydro-5*H*-pyrimido [4,5-*b*][1,5]oxazocin-5-one as a structurally new NK_1 antagonist

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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 NK_1 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.

Substance P (SP)[1] elicits a wide variety of biological responses, both centrally and peripherally. The binding of SP to NK_1, receptors has been implicated in the transmission of pain and stress signals, inflammation, and the contraction of smooth muscle. Therefore, NK_1 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 NK_1 antagonists.[2] In that study, we established that although compounds **1** and **2** exhibit similar and potent NK_1 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 biaryl 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 NK_1 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).

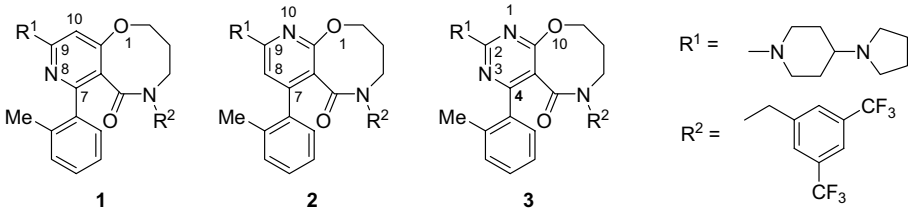

Figure 1.

Keywords: Pyrimido[4,5-*b*][1,5]oxazocin-5-one; NK_1 antagonist.
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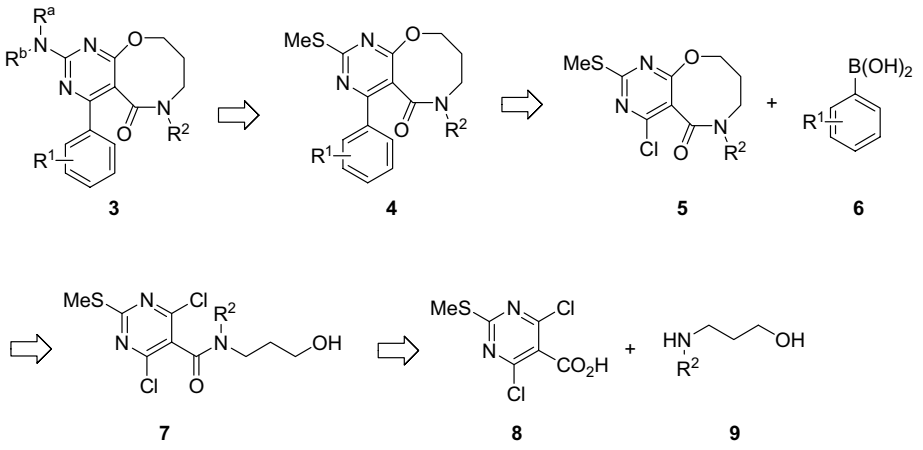


Scheme 1.

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).

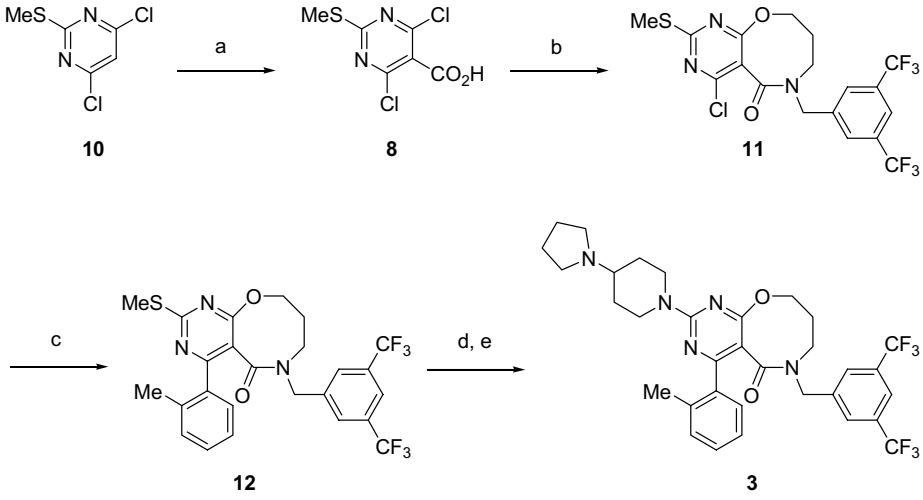
The synthesis of the desired compound **3** is shown in Scheme 2.

Compound **8**,[4] which was prepared from 4,6-dichloro-2-(methylthio)pyrimidine, was treated with $SOC1_2$, followed by condensation with 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-l-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 sulfide **12** with *m*CPBA and subsequent nucleophilic amination with 4-(pyrrolidinyl)piperidine afforded target compound **3**.[5]

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

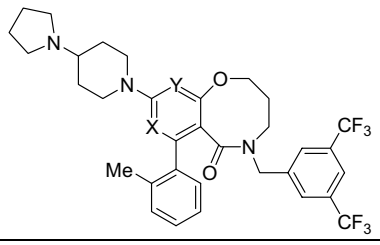
The rotation about the biaryl bond of **3** was examined. Although the NMR spectrum of **2** showed two pairs of benzylic methylene protons, presumably as a result of two-axial chirality,[2] the NMR spectrum of **3** showed one pair of benzylic methylene protons, similar to that of **1**. Consequently, 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 % $Pd(PPh_3)_4$, 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%.

Table 1. [1]H NMR properties and NK_1 antagonist activities of **1**–**3**



Compd	X	Y	[1]H NMR[a] ppm, δ (Hz) (benzylic methylene protons)	NK_1 antagonist activity[b] K_B (nM)	Effective bladder capacity increasing ratio (%) (0.3 mg/kg iv)[c]
1	N	CH	3.93, 5.34 (each 1H, d, J = 15.3 Hz)	0.339	3.97
2	CH	N	3.94, 3.95, 5.36, 5.39 (each 0.5H, d, J = 15.3 Hz)	0.210	24.2
3	N	N	3.84, 5.32 (each 1H, d, J = 15.3 Hz)	0.166	33.4
TAK-637				0.270	12.0

[a] In $CDCI_3$; d = doublet.
[b] Compounds were screened for antagonist activity on guinea pig ileum as described in the text.
[c] Effective bladder capacity was measured as the volume of saline injected into spinalized guinea pigs. The increasing effects of the test compounds were expressed as the ratio of the increase in effective bladder capacity compared with the predrug values.

groups have reported on separable amido-base atropisomerism.[3,6] However, not all the atropisomers detectable by NMR spectroscopy can be physically separated by experimental procedures.[7] We were unable to separate the atropisomers of **3** by high-performance liquid chromatography with a chiral column. To investigate the possibility of separation of the atropisomers arising from oxazocine ring inversion, the effect of temperature on the degree of coalescence of the AB pattern was examined by NMR in dimethyl sulfoxide-d_6.[7] The AB pattern for the benzylic methylene protons of **3** deteriorated to very broad peaks at 100 °C and collapsed to singlet peaks at 150 °C. In addition, each pair of oxazocine ring methylene protons showed one peak with distinct fission patterns at 150 °C. From these results, we predict that the barrier for inversion is too low to allow isolation of the enantiomers about the oxazocine ring, since rapid interconversion would occur at room temperature.[7]

We evaluated the NK_1 antagonist activity of **3** in comparison with that of a representative antagonist, TAK-637 (Table 1). The NK_1 receptor antagonist activity towards guinea pig ileum was evaluated by the previously described method[8] with slight modification. The activity was expressed as K_B values, as determined by the Schild method.[9] The effective bladder capacity was measured by injection of saline into spinalized guinea pigs according to the method previously described.[10]

Compound **3** showed potent NK_1 antagonist activity in vitro, similar to that of compounds **1**, **2**, and TAK-637. Interestingly, compound **3**, like compound **2**, showed potent in vivo activity on the effective bladder capacity of guinea pigs following iv administration.

These results indicate that the **1**–**2** hybrid compound **3**, incorporating two nitrogen atoms (*N*-1 and *N*-3; numbering for **3**) possesses features of both **1** and **2**; *N*-3 (numbering for **3**) is important for free rotation about the biaryl bond (a feature of **1**) and *N*-1 (numbering for **3**) is important for potent in vivo activity (a feature of **2**).

In conclusion, we have succeeded in the design and synthesis of the novel pyrimido[4,5-*b*][1,5]oxazocine derivative **3**, which shows potent NK_1 antagonist activity in vitro as well as potent activity on the effective bladder capacity of guinea pigs in vivo. In addition, we found that **3** had a property independent of restricted biaryl bond rotation from an NMR study, therefore, of which chemical property would be preferable as a development candidate. Further pharmacological investigations on **3** are in progress.

Acknowledgements

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5. Compound **3**: ^{1}H NMR (400 MHz, CDC1$_3$): 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 $C_{33}H_{35}F_6N_5O_2$ (M^+) 647.2695, found 647.2707. Anal. Calcd for $C_{33}H_{35}F_6N_5O_2$ 1/5H_2O: C, 60.86; H, 5.42; N, 10.75. Found: C, 60.47; H, 5.40; N, 10.47.
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