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Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 13 (2005) 5717–5732

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 as NK_1 antagonists

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Received 11 May 2005; revised 27 May 2005; accepted 1 June 2005
Available online 29 June 2005

Abstract—A series of novel bicyclic pyrimidine derivatives was prepared as part of a search for NK_1 antagonist aimed at the treatment of urinary incontinence. Among them, **3g**, a pyrimido[4,5-*b*][1,5]oxazocine derivative, bearing a 4-acetylpiperazinyl group and a 2-methylphenyl group, was shown to have potent NK_1 antagonist activity with a K_B value of 0.105 nM and markedly increased the effective bladder capacity of guinea pigs (59.4% at 0.3 mg/kg iv and 62.8% at 3 mg/kg id). Furthermore, the effect of **3g** on bladder function appeared to differ from that of tolterodine, another classical anti-pollakiuria agent, as determined by the distention-induced rhythmic bladder contraction assay using a urethane-anesthetized guinea pig model. Compound **3g** is expected to be a promising agent for the treatment of urinary incontinence.

1. Introduction

Tachykinin, a peptide neurotransmitter that was subsequently characterized as the undecapeptide Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2,[1] binds to a series of three neurokinin receptors, NK_1, NK_2, and NK_3, which have selective affinity for substance P (SP), neurokinin A, and neurokinin B, respectively.[2] Among them, SP is known to exhibit a wide variety of biological responses[3] 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. Among them, we were interested in the relationship between tachykinin and the activation of micturition-related reflexes,[4] with a view to possible application in the treatment of pollakiuria and urinary incontinence. The disclosure by Pfizer of the first two non-peptide NK_1 antagonists, CP-96345 and CP-99994,[5] has spurred intensive research in this field. During the last few years, several other structural classes of NK_1 receptor antagonists have been reported, such as L-733060,[6] MK-869,[7] and TAK-637.[8] (Fig. 1) The areas of neurokinin antagonist development have been extensively reviewed.[9–12]

Recently, we reported the design and synthesis of pyrido[4,3-*b*]-1,5-oxazocine **1a** and pyrido[2,3-*b*]-1,5-oxazocine **2a** as potent NK_1 antagonists,[13a] which were derived from the arylpyridinecarboxamide derivative made up by incorporating the 2-[3,5-bis(trifluoromethyl)benzyloxy]-1-phenylethylamine fragment[14] into the pyridine ring. In these studies, we found that the compounds **1a** and **2a** each similarly exhibited potent NK_1 antagonist activity (in vitro), although the in vivo activity of **2a** is superior to that of **1a**. These two compounds differ structurally in (1) the position of the nitrogen atom in the pyridine ring and (2) the atropisomerism about the biaryl bond due to the difference in nature at the 8-position (**1a**, N; **2a**, CH); the rotation about the biaryl bond of **1a** would be free, whereas that of **2a** would be partially restricted on the NMR time scale.[13b,15] This property of **2a** would affect the stacking conformation that is important for NK_1 receptor recognition.[8,16,17] However, to avoid substantial analytical complications during manufacture and drug development, it is necessary to ensure either inseparable rapid

Keywords: NK_1 antagonist; Pyrimido[4,5-*b*][1,5]oxazocine; Effective bladder capacity; KRP-103.
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doi:10.1016/j.bmc.2005.06.015

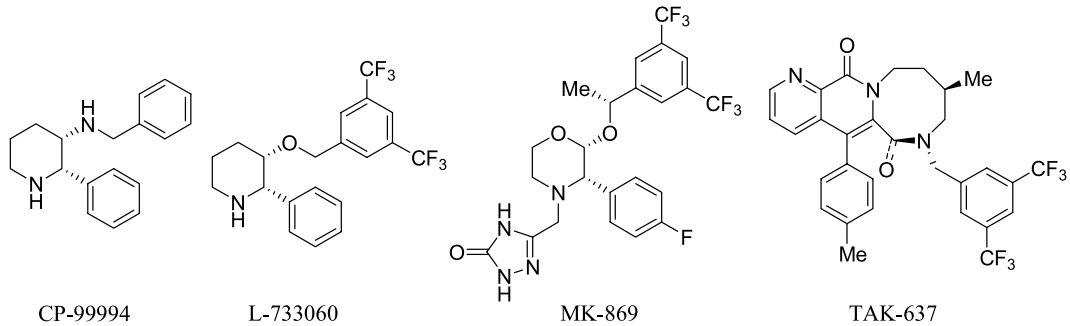


Figure 1. Chemical structures of the standard NK_1 antagonists.

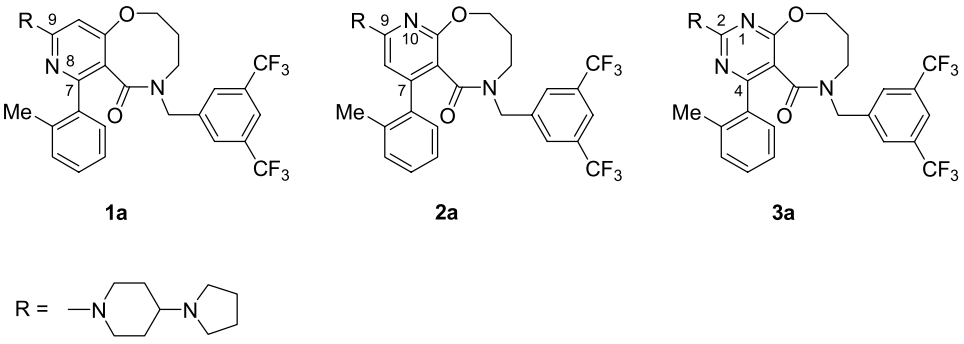


Figure 2.

interconversion of isomers or a completely separable rigid conformation.

On the basis of these results, pyrimido[4,5-*b*][1,5]oxazocine **3a** was synthesized as a hybrid compound of **1a** and **2a**.[13b] Compound **3a** was found to possess both features of **1a** and **2a**; **3a** showed potent in vivo activity similar to **2a**, and free rotation about the biaryl bond similar to **1a** (Fig. 2).

To further examine the structural requirements for activity, the compounds shown in Figure 3 were synthesized and examined for their NK_1 antagonist activity and effects on bladder function. Herein, we report the synthesis and NK_1 antagonist activity of novel pyrimido[4,5-*b*][1,5]oxazocine derivatives and its analogue, leading to the identification of a candidate drug for the treatment of urinary incontinence.

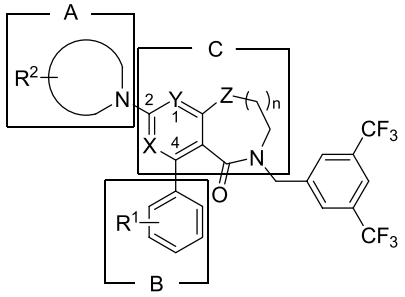
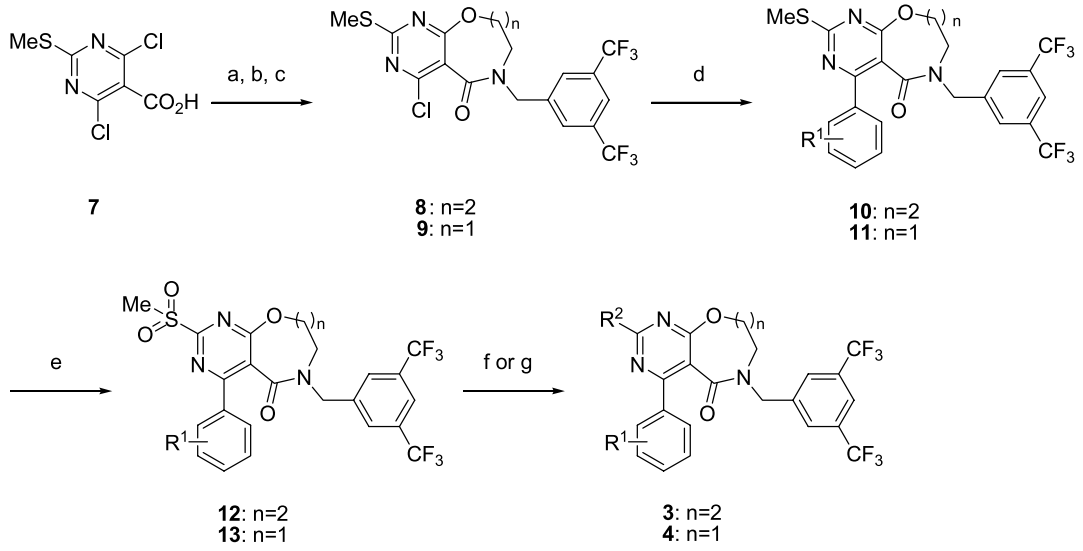


Figure 3. General formula of target compounds.

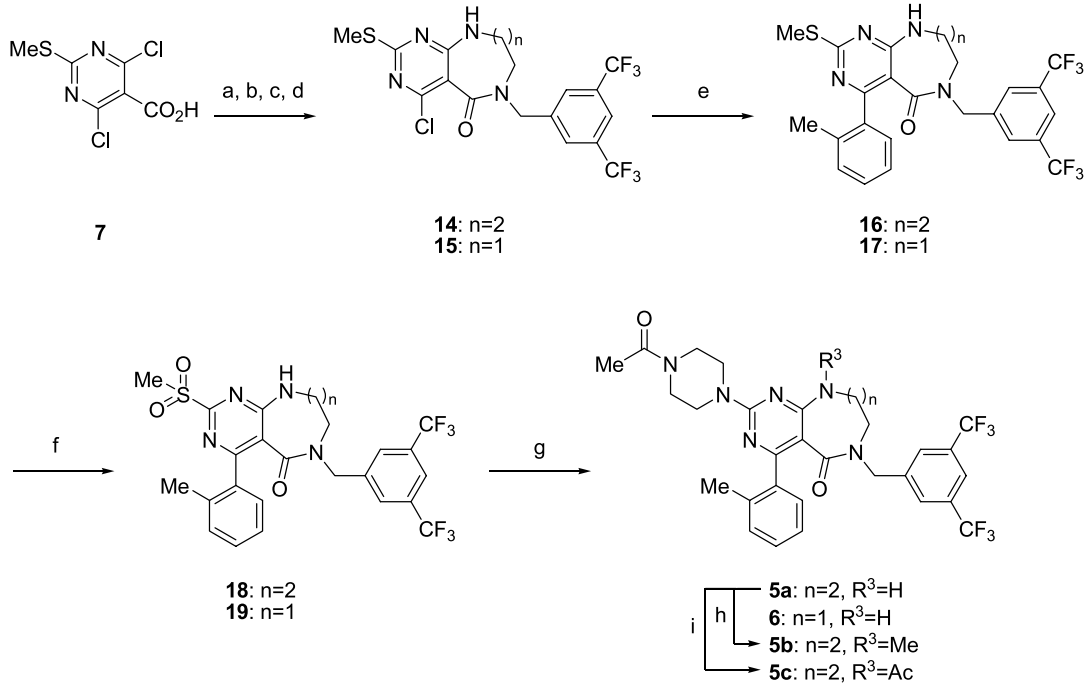
2. Chemistry

As shown in Scheme 1, we synthesized pyrimido[4,5-*b*]-[1,5]oxazocine derivatives **3** and pyrimido[5,4-*f*][1,4] oxazepine derivatives **4** following the procedure for synthesizing **3a** reported in our earlier paper.[13b] Compound **7**,[18] 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[8] and cyclization using potassium carbonate to afford the bicyclic compound **8**. Suzuki coupling reaction of **8** with various substituted phenylboronic acids afforded the corresponding biaryl compounds **10** in good yield. Oxidation of sulfide **10** with *m*CPBA afforded sulfone **12**. The synthesis of compound **3** was achieved by nucleophilic amination of **12** with the corresponding amine nucleophiles. When *N*-protected diamine was used as a nucleophile, subsequent deprotection with hydrogen chloride and condensation with acetic anhydride or methylsulfonyl chloride were accomplished. The synthesis of **4**, which contains the oxazepine ring, was carried out in a manner similar to that of **3**.

The synthesis of pyrimido[4,5-*b*][1,5]diazocine derivatives **5** and pyrimido[4,5-*e*][1,4]diazepine derivatives **6** is shown in Scheme 2. The bicyclic compound **14** was also synthesized from the acid chloride of **7** by reacting with *N*-[[3,5-bis(trifluoromethyl)benzyl]amino]-*N*′-Boc-1,3-propanediamine and subsequent deprotection with hydrochloric acid and intramolecular cyclization with potassium carbonate. Suzuki coupling reaction of **14** followed by oxidation of sulfide and substitution with



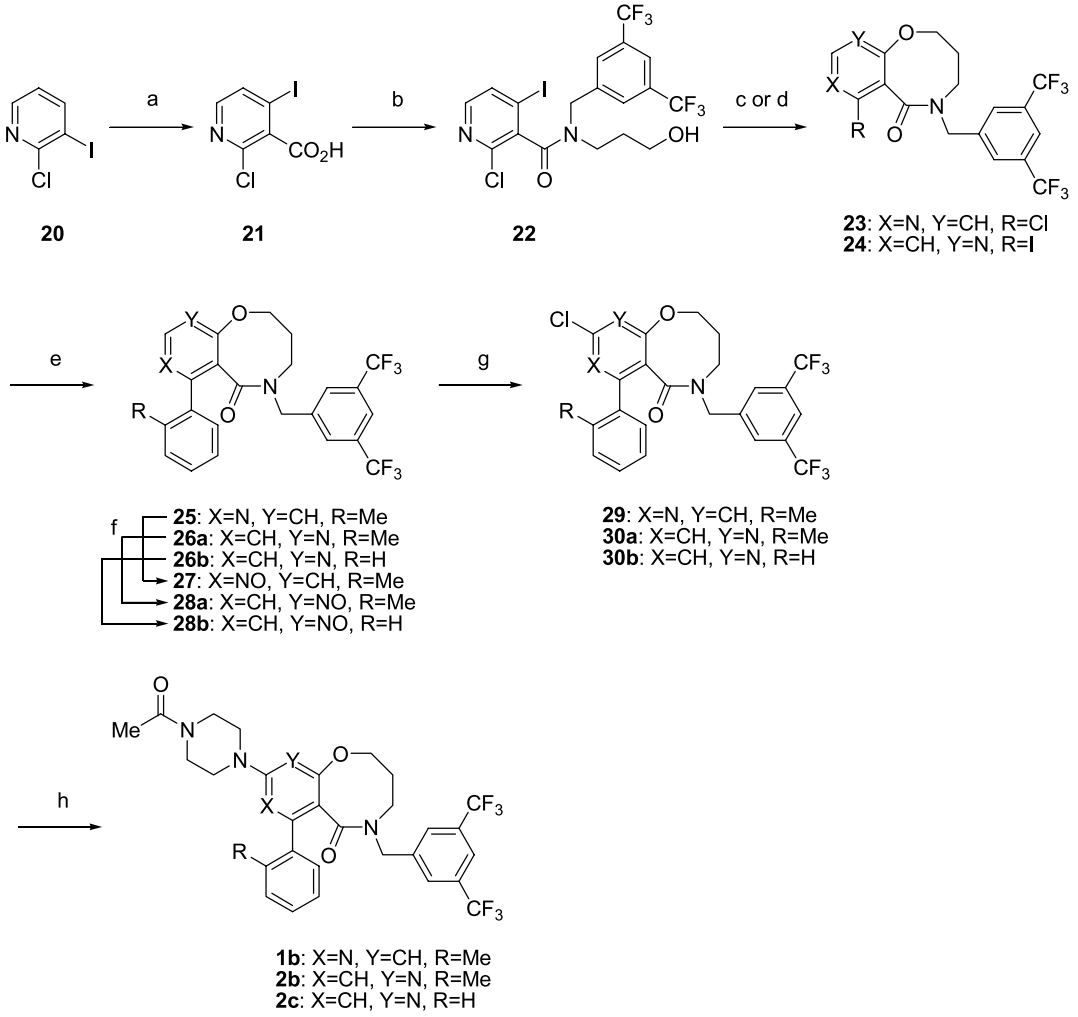
Scheme 1. Reagents: (a) $SOCl_2$, DMF; (b) 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-l-propanol or 2-[[3,5-bis(trifluoromethyl)benzyl]amino]ethanol, THF; (c) K_2CO_3, DMF; (d) 2-methylphenylboronic acid, 10 mol% $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, dioxane; (e) *m*CPBA, THF; (f) R^2H, 1,4-dioxane, diisopropylethylamine; (g) (1) 4-(Boc-amino)piperidine or *N*-Boc-homopiperazine or *N*-Boc-piperazine, (2) 3 M HCl–AcOEt, (3) acetic anhydride or methylsulfonyl chloride.



Scheme 2. Reagents: (a) $SOCl_2$, DMF; (b) *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*′-Boc-l,3-diaminopropane or *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*′-Boc-l,2-diaminoethane; (c) 3 M HCl–AcOEt; (d) K_2CO_3, DMF; (e) 2-methylphenylboronic acid, 10 mol% $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, dioxane; (f) *m*CPBA, THF; (g) acethylpiperazine, 1,4-dioxane; (h) NaH, MeI; (i) acetic anhydride, pyridine.

1-acetylpiperazine provided **5a**. Synthesis of **6**, which contains the diazepine ring, was carried out in a manner similar to that of **5a**. Synthesis of **5b** and **5c** was accomplished by alkylation with methyl iodide or acylation with acetic anhydride, respectively.

As shown in Scheme 3, we synthesized pyrido[4,3-*b*]-1,5-oxazocine derivative **1b** and pyrido[2,3-*b*]-1,5-oxazocine derivatives **2b**,**c** following the procedure for synthesizing **1a** and **2a** reported in our earlier paper.[13a,19] 2-Chloro-4-iodopyridine-3-carboxylic acid **21** was prepared from 2-chloro-3-iodopyridine **20**[20] by a known method[21] with slight modification. Treatment of 2-chloro-3-iodopyridine **20** with LDA, followed by quenching with carbon dioxide, and then hydrolysis with hydrochloric acid gave 2-chloro-4-iodopyridine-3-carboxylic acid **21** in a good yield. Subsequent treatment with thionyl chloride, followed by condensation with 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol afforded the alcohol **22**. Conversion of the alcohol **22** to bicyclic compounds **23**



Scheme 3. Reagents: (a) (1) LDA, THF, (2) CO_2, (3) HCl; (b) (1) $SOCl_2$, DMF, (2) 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-l-propanol, THF; (c) K_2CO_3, EtOH; (d) NaH, THF; (e) 2-methylphenylboronic acid, 10 mol% $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, dioxane; (f) *m*CPBA, CH_2Cl_2; (g) $POCl_3$; (h) acethylpiperazine, 1,4-dioxane.

and **24** was accomplished in a regionselective manner.[19] Suzuki coupling reaction of **23** and **24** with arylboronic acids yielded 7-aryl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]- and [4,3-*b*]-1,5-oxazocin-6-ones (**25** and **26**[8e]) in good yield. Formation of chlorides **29** and **30** via the Meisenheimer reaction[22] was accomplished by treatment of **25** and **26** with *m*CPBA followed by rearrangement with $POCl_3$. Coupling of intermediates **29** and **30** with 1-acetylpiperazine under heat afforded the desired compounds **1** and **2**, respectively.

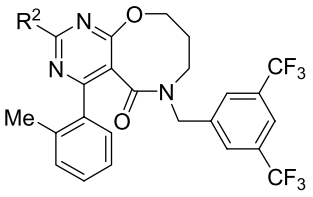
3. Results and discussion

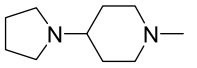
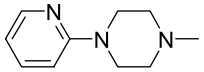
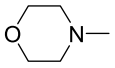
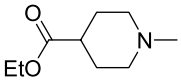
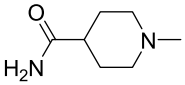
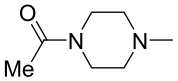
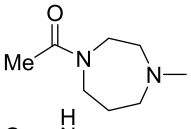
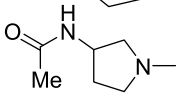
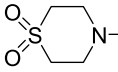
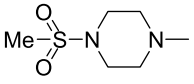
3.1. NK_1 antagonist activity

The NK_1 antagonist activities of the present series of compounds are summarized in Tables 1–3. The NK_1 antagonist activity is displayed as the K_B value measured by the guinea pig ileum contraction assay.[23,24]

To determine the effects of substituents at the C-2 position on the pyrimido[4,5-*b*][1,5]oxazocine ring, the results of the NK_1 antagonist assay for pyrimido[4,5-*b*][1,5]oxazocine **3a** and the newly synthesized derivatives **3b–k** are summarized in Table 1. The pyrimido[4,5-*b*][1,5]oxazocine **3a** bearing a 4-(pyrrolidinyl)piperidino moiety exhibited potent NK_1 antagonist activity. Compounds **3b** and **3e**, carrying an aromatic amine moiety or an ester moiety instead of the aliphatic amine moiety of **3a**, showed a 7- to 10-fold reduction of activity. The NK_1 antagonist activities of **3c**, **3d**, and **3f**, which have a substituted imidazolyl group, a morpholino group, or a 4-carbamoylpiperidino group, were slightly less potent than that of **3a**. The 4-acetylpiperazinyl derivative **3g** showed excellent activity comparable to that of **3a**. The strong NK_1 antagonist activity of **3g** tended to decrease slightly when the position of the acetamide group was changed (**3h**, **i**). The NK_1 antagonist activities of **3j** and **3k**, which have a substituted dioxothiomorpholino group or a methylsulfonylpiperazinyl group, were comparable to that of **3a**, with K_B values within the range of 0.0501–0.0794 nM. Among the compounds with cyclic amino groups, which are substituted at the terminal heteroatom or group at the 2-position on the pyrimidooxazocine ring, 4-(pyrrolidinyl)piperidine **3a**, 4-acetyl-

Table 1. NK_1 antagonist activity of pyrimido[4,5-*b*][1,5]oxazocine derivatives



Compound	R^2	NK_1 antagonist activity[a] K_B (nM)
3a		0.166
3b		1.13
3c		0.459[b]
3d		0.354
3e		1.82
3f		0.341
3g		0.105
3h		0.308
3i		0.440
3j		0.0794
3k		0.0501

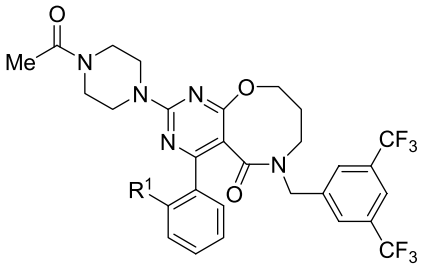
[a] Data present the mean of K_B value of guinea pig ileum contraction assay (n = 3–5). The values of schild plot slope exhibited in 0.81–1.20.
[b] The value of schild plot slope exhibited in 0.44.

piperazine **3g**, dioxothiomorpholine **3j**, and methylsulfonylpiperazine **3k** possessed the most potent activity.

The effects of substituents at the ortho position on the phenyl ring, which might affect the stacking conformation,[8,16,17] are shown in Table 2. All compounds exhibited potent activities, with K_B values within the range of 0.0584–0.236 nM. The observed effects of introducing substituents at the ortho position on the phenyl ring were not significant.

The NK_1 antagonist activities of the bicyclic pyrimidine derivatives (**3g**, **4**, **5a–c**, and **6**) together with the bicyclic pyridine derivatives (**1b** and **2b**) are shown in Table 3. In general, shortening of the tether length to two methylenes (n = 1) caused a slight loss of activity; an 8-membered ring in the core scaffold was favorable for potent NK_1 antagonist activity in comparison with a 7-membered ring (**3g** vs **4**, **5a** vs **6**). As for the position shown as Z on the 8-membered ring, the NK_1 antagonist activities of **3g** and **5a**, in which the C-10 position shown as Z was substituted by an oxygen atom and a nitrogen atom, respectively, were equal. In contrast to the case of **5b**, the additional methyl group on the nitrogen atom of **5a** slightly debilitated the NK_1 antagonist activity.

Table 2. NK_1 antagonist activity of pyrimido[4,5-*b*][1,5]oxazocine derivatives



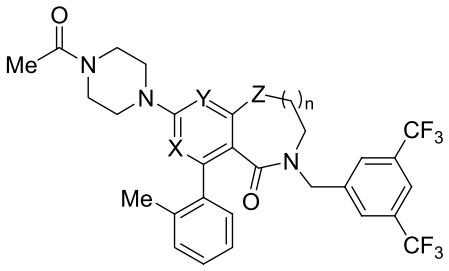
Compound	R^1	NK_1 antagonist activity[a] K_B (nM)
3l	H	0.236
3g	Me	0.105
3m	OMe	0.100
3n	F	0.0584[b]

[a] Data present the mean of K_B value of guinea pig ileum contraction assay (n = 3–5). The values of schild plot slope exhibited in 0.81–1.20.

3.2. Effect on bladder function

Selected compounds with potent NK_1 antagonist activity were examined for their effect on effective bladder

Table 3. NK_1 antagonist activity of bicyclic derivatives bearing 4-acetylpiperazinyl moiety



Compound	X	Y	Z	n	NK_1 antagonist activity[a] K_B (nM)
3g	N	N	O	2	0.105
4	N	N	O	1	0.465
5a	N	N	NH	2	0.148
6	N	N	NH	1	0.480
5b	N	N	NMe	2	0.324
5c	N	N	NAc	2	0.0794
1b	N	CH	O	2	0.275
2b	CH	N	O	2	0.0888

[a] Data present the mean of K_B value of guinea pig ileum contraction assay (n = 3–5). The values of schild plot slope exhibited in 0.81–1.20.

capacity in guinea pigs[25] together with the results for TAK-637,[8d] a representative NK_1 antagonist aimed at the treatment of bladder function disorders. The results are shown in Table 4. The augmentative effects on effective bladder capacity approximately paralleled the corresponding NK_1 antagonist activity. Although the reason is not clear, **3k**, **3m**, and **5c** exhibited significantly weaker augmentative effects in comparison with their corresponding NK_1 antagonist activities. Compounds **3g**, **3j**, and **5a** showed potent increasing effects. Preliminary pharmacokinetic studies were conducted for compounds **3g**, **3j**, and **5a**. The bioavailability (BA) of **3j** in rats was dramatically low (0%), probably due to its low water solubility (0 μg/mL). Compounds **3g** and **5a** exhibited good BA values (41% for **3g**; 38% for **5a**), and therefore they were evaluated for their efficacies in guinea pigs after intraduodenal (id) administration. The augmentative effect of **3g** was more potent than that of **5a** (62.8% vs 29.0%), and the values were comparable to those after iv administration. On the basis of these results, **3g** was selected as a candidate for further evaluation.

On the basis of the study described above, we selected compound **3g** and evaluated its effect on bladder function in comparison with a representative anti-pollakiuria agent, tolterodine (Figs. 4 and 5).

The effect of iv-injected **3g** on distention-induced rhythmic bladder contraction in urethane-anesthetized guinea pigs was examined. Figure 4 shows the percentage contractile frequency and the contractile intravesical

Table 4. Water solubility, effective bladder capacity, and bioavailability of selected compounds

Compound	NK_1 antagonist activity[a] K_B (nM)	Water solubility[b] (μg/mL)	Effective bladder capacity[c] increasing ratio (%)		BA (%)[d]
			iv	id	
2b	0.0888	0	32.3 ± 13.5		
26b	43.3	0	16[e]		
2c	2.21	0	11.9 ± 10.8		
3a	0.166	1453	33.4 ± 11.0		
3d	0.354	0	21.3 ± 3.47		
3g	0.105	6.42	59.4 ± 12.3	62.8 ± 12.0	41
3h	0.308	8.70	36.8 ± 11.6		
3i	0.440	28.3	25.6 ± 3.73		
3j	0.0794	0	40.4 ± 6.65		0
3k	0.0501	0	24.3 ± 12.4		
3m	0.100	25.4	25.3 ± 11.6		
5a	0.148	3.04	43.0 ± 15.4	29.0 ± 0.343	38
5b	0.324	0	34.3 ± 5.46		
5c	0.0794	4.53	24.2 ± 9.41		
TAK-637	0.270		12.0 ± 5.86		

[a] Data present the mean of K_B value of guinea pig ileum contraction assay (n = 3–5). Compounds were screened for antagonist activity on guinea pig ileum as described in the text.
[b] Water solubility value determined by a single experiment run in duplicate.
[c] Data present the mean of increasing ratio (%) of effective bladder capacity measured as the volume of saline injected into spinalized guinea pigs at 0.3 mg/kg (iv) (n = 4–5) and 3 mg/kg (id) (n = 5–6).
[d] BA = (AUC_{0-8}) po/(AUC_{0-8}) iv. AUC values were determined in rats following single intravenous (10 mg/kg, PET solution) or oral (10 mg/kg, CMC Na suspension) administrations (n = 2–5) of the compounds.
[e] The value determined by a single experiment at 1 mg/kg (iv).

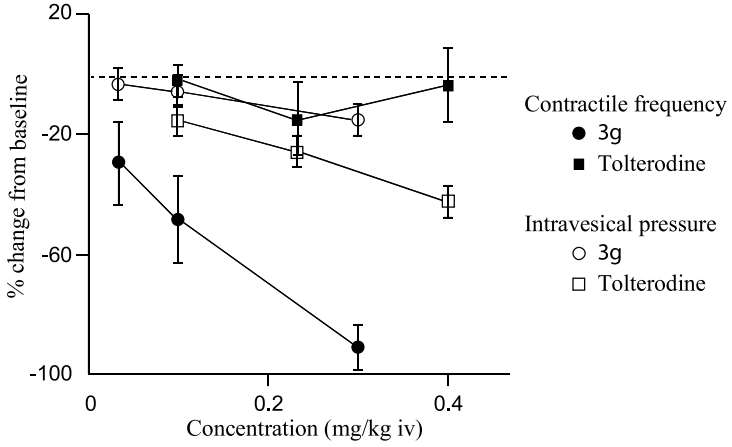


Figure 4. Reductions in contractile frequency and intravesical pressure on distention-induced rhythmic bladder contractions in urethane-anesthetized guinea pigs with ascending concentrations. **3g** (doses: 0.03, 0.1, and 0.3 mg/kg iv); tolterodine (doses: 0.1, 0.2, and 0.4 mg/kg iv).

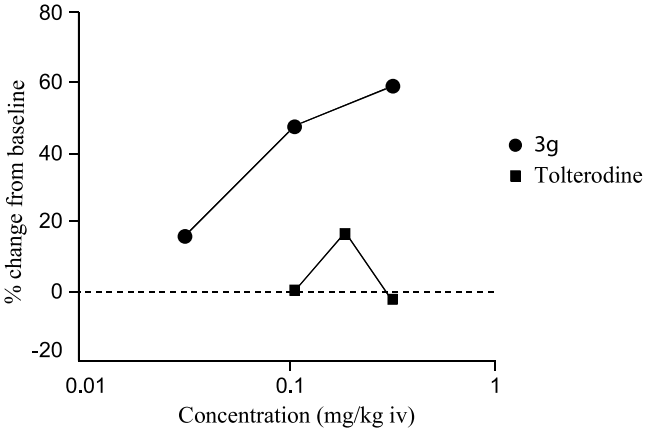


Figure 5. Increasing effect of the effective bladder capacity in spinalized guinea pigs with ascending concentrations. **3g** (doses: 0.03, 0.1, and 0.3 mg/kg iv); tolterodine (doses: 0.1, 0.2, and 0.3 mg/kg iv).

pressure for **3g** in contrast to the predrug value, together with the corresponding data for tolterodine.

In this assay, **3g** decreased the frequency of rhythmic bladder contraction in a dose-dependent manner at doses of 0.03, 0.1, and 0.3 mg/kg, without affecting the contractile intravesical pressure. On the other hand, tolterodine decreased the contractile pressure dose-dependently, without affecting the frequency.

The effect of **3g** on effective bladder capacity was measured as micturition volume in terms of the volume of saline injected into spinalized guinea pigs. Figure 5 shows the ratio of the increase in effective bladder capacity induced by **3g** compared with the predrug value, together with the corresponding data for tolterodine. Compound **3g** increased the effective bladder capacity dose-dependently at 0.03, 0.1, and 0.3 mg/kg. On the other hand, tolterodine was not efficient at doses of 0.1, 0.2, and 0.4 mg/kg.

These results suggested that compound **3g** would not affect the stage of urine storage, but rather the stage of micturition, and would therefore have a low risk of causing urinary retention, one of the side effects of anti-cholinergic agents.

Table 5 shows the binding affinity for the three subtypes of neurokinin receptor in human CHO cells.[26] Compound **3g** showed potent NK_1 antagonist activity, not only in the guinea pig contraction assay, but also in the hNK_1 receptor binding assay ($K_i = 0.0657$ nM), and exhibited high selectivity for the NK_1 receptor.

Compound **3g** showed only a single peak on high-performance liquid chromatography using a chiral column, as far as we were able to ascertain. In addition, C-4 phenyl restricted rotation of **3g** was not observed from the NMR spectrum; and a high-temperature NMR study indicated that the atropisomer induced by oxazocine ring inversion would not be separable at room temperature.[13b,15,27] From these results, it was expected that the chemical properties related to the atropisomerism of **3g** would not create an obstacle for further development.

Table 5. Neurokinin receptor selectivity

Compound	Binding affinity K_i (nm)		
	hNK_1	hNK_2	hNK_3
3g	0.0657	>1000	>1000

4. Conclusion

As described previously, we have succeeded in synthesizing and evaluating a series of novel bicyclic pyrimidine derivatives as a part of a search for NK_1 antagonists aimed at the treatment of urinary incontinence. Among the diverse chemical modifications performed on the bicyclic pyrimidines, **3g**, a pyrimido[4,5-*b*][1,5]oxazocine derivative bearing a 4-acetylpiperazinyl group and a 2-methylphenyl group, showed potent NK_1 antagonist activity with a K_B value of 0.105 nM, and also exhibited the greatest augmentative effect on effective bladder capacity in guinea pigs (59.4% at 0.3 mg/kg iv and 62.8% at 3 mg/kg id). Furthermore, the effect of **3g** on bladder function appeared to differ from that of tolterodine, another classical anti-pollakiuria agent; **3g** decreased the frequency, but not the amplitude of distention-induced rhythmic bladder contraction using a urethane-anesthetized guinea pig model. Compound **3g**, namely KRP-103, is expected to be a promising compound for the treatment of urinary incontinence. Further investigation of the pharmacological profiles of **3g** is currently in progress.

5. Experimental

5.1. Chemistry

Melting points were determined using a Yamato MP-500 melting point apparatus and are uncorrected. ^1H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS and the solvent peak as internal standards, on a JEOL ECA-400 (400 MHz) spectrometer. Mass spectra (MS) were obtained on a Hitachi M-2000 mass spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60F254 plates, and the compounds were visualized by UV illumination (254 nm) or by heating after spraying with phosphomolybdic acid in ethanol. The data for elemental analysis are within ± 0.4% of theoretical values and were determined by a Yanaco CHN corder MT-5.

5.1.1. 4,6-Dichloro-2-(methylthio)pyrimidine-5-carboxylic acid (7). To a solution of LDA [prepared by reaction of diisopropylamine (3.0 mL, 21.4 mmol) in THF (25 mL) and *n*-butyllithium (13.6 mL, 1.52 M, 20.7 mmol) at −20 °C for 30 min] was added a solution of 4,6-dichloro-2-(methylthio)pyrimidine (2.70 g, 13.8 mmol) in THF (5 mL) at −78 °C. The mixture was stirred at the same temperature for 3 h, and then CO_2 gas was introduced for 10 min. After the reaction had been quenched by addition of water (12 mL) and 2 N HCl (25 mL), the mixture

was extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The residue was recrystallized from toluene to afford **7** as a pale yellow solid (1.93 g, 58%). mp: 160–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (1H, s). HRMS (EI) calcd for $C_6H_4Cl_2N_2O_2S$ (M^+) 237.9371; found, 237.9383. Anal. Calcd for $C_6H_4Cl_2N_2O_2S$: C, 30.14; H, 1.69; N, 11.72. Found: C, 30.07; H, 1.57; N, 11.60.

5.1.2. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-chloro-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (8). To a mixture of **7** (14.0 g, 58.6 mmol) and thionyl chloride (40 mL) was added three drops of DMF and the mixture was refluxed for 2 h and then concentrated. A solution of the residue in THF (80 mL) was added dropwise to a solution of 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol (18.5 g, 61.4 mmol) and triethylamine (40 mL) in THF (100 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. After concentration in vacuo, to a solution of the residue in DMF (60 mL) was added potassium carbonate (24.3 g, 0.176 mol) and the mixture was stirred for 1 h at 80 °C. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt:hexane = 1:1) of the residue gave **8** as a pale yellow solid (17.8 g, 63%). mp: 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.12 (1H, m), 2.20–2.30 (1H, m), 2.60 (3H, s), 3.35 (1H, dd, J = 15.3 and 4.3 Hz), 3.63–3.74 (1H, m), 4.08 (1H, d, J = 15.3 Hz), 4.46–4.58 (2H, m), 5.63 (1H, d, J = 15.3 Hz), 7.88 (3H, s). HRMS (EI) calcd for $C_{18}H_{14}ClF_6N_3O_2S$ (M^+) 485.0399; found, 485.0358. Anal. Calcd for $C_{18}H_{14}ClF_6N_3O_2S$: C, 44.50; H, 2.90; N, 8.65. Found: C, 44.44; H, 2.79; N, 8.54.

5.1.3. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-chloro-2-methylthio-5,6,7,8-tetrahydro-pyrimido[5,4-*f*][1,4]oxazepin-5-one (9). The compound **9** (5.15 g, 52%) was prepared from **7** (5.00 g, 20.9 mmol) and 2-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-ethanol (6.30 g, 21.9 mmol) in a manner similar to that described for the preparation of **8**. mp: 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (3H, s), 3.64 (2H, t, J = 4.9 Hz), 4.50 (2H, t, J = 4.9 Hz), 4.92 (2H, s), 7.81 (2H, s), 7.86 (1H, s). HRMS (EI) calcd for $C_{17}H_{12}ClF_6N_3O_2S$ (M^+) 471.0243; found, 471.0236. Anal. Calcd for $C_{17}H_{12}ClF_6N_3O_2S$: C, 43.28; H, 2.56; N, 8.91. Found: C, 43.14; H, 2.48; N, 8.68.

5.1.4. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-chloro-2-methylthio-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*][1,5]diazocin-5-one (14). To a mixture of **7** (15.0 g, 62.7 mmol) and thionyl chloride (45 mL) was added DMF (0.50 mL) and the mixture was refluxed for 2 h. The mixture was concentrated. The solution of the residue in THF (100 mL) was added dropwise to a solution of 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-(Boc-amino)propane (25.6 g, 63.9 mmol) and triethylamine (40.0 mL, 0.287 mol) in THF (100 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (hexane:AcOEt = 3:1) of residue was dissolved in 20% (w/w) HCl–EtOH (50 mL) and stand for 2 h at room temperature. After concentration in vacuo, to a solution of the residue in DMF (60 mL) was added potassium carbonate (16.5 g, 0.119 mol) and the mixture stirred for 1 h at 80 °C. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (AcOEt:hexane = 1:1) of residue gave **14** as a pale yellow foam (23.4 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80–2.02 (2H, m), 2.49 (3H, s), 3.23–3.36 (2H, m), 3.38–3.49 (1H, m), 3.67–3.78 (1H, m), 3.92 (1H, d, J = 15.3 Hz), 5.59 (1H, d, J = 15.3 Hz), 5.84 (1H, t, J = 7.3 Hz), 7.82 (1H, s), 7.84 (2H, s). HRMS (EI) calcd for $C_{18}H_{15}ClF_6N_4OS$ (M^+) 484.0559; found, 484.0598. Anal. Calcd for $C_{18}H_{15}ClF_6N_4OS$: C, 44.59; H, 3.12; N, 11.56. Found: C, 44.56; H, 3.04; N, 11.46.

5.1.5. trifluoromethyl)benzyl]-4-chloro-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-5-one (15). The compound **15** (6.22 g, 68%) was prepared from **7** (5.00 g, 20.9 mmol) and 2-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-(Boc-amino)ethane (8.24 g, 21.3 mmol) in a manner similar to that described for the preparation of **14**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (3H, s), 3.59–3.68 (4H, m), 4.90 (2H, s), 5.66 (1H, br), 7.84 (2H, s), 7.88 (1H, s). HRMS (EI) calcd for $C_{17}H_{13}ClF_6N_4OS$ (M^+) 470.0403; found, 470.0385. Anal. Calcd for $C_{17}H_{13}ClF_6N_4OS$: C, 43.37; H, 2.78; N, 11.90. Found: C, 43.29; H, 2.69; N, 11.84.

5.1.6. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-methylthio-4-phenyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (10a). To a mixture of **8** (2.43 g, 5.00 mmol) and phenylboronic acid (732 mg, 6.00 mmol) in toluene (15 mL) and 1,4-dioxane (8 mL) were added 2 M Na_2CO_3 (15 mL) and $Pd(PPh_3)_4$ (289 mg, 0.250 mmol), and the mixture was stirred under reflux for 6 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate, then washed with 2 M Na_2CO_3 and brine, and dried over Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (AcOEt:hexane = 1:1) of the residue gave **10a** as a pale yellow solid (2.28 g, 86%). mp: 143–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.22 (2H, m), 2.58 (3H, s), 3.43–3.52 (1H, m), 3.84–3.94 (1H, m), 4.24 (1H, d, J = 15.3 Hz), 4.39–4.46 (2H, m), 5.36 (1H, d, J = 15.3 Hz), 7.25–7.32 (2H, m), 7.37–7.46 (3H, m), 7.76 (2H, s), 7.87 (1H, s). HRMS (EI) calcd for $C_{24}H_{19}F_6N_3O_2S$ (M^+) 527.1102; found, 527.1130. Anal. Calcd for $C_{24}H_{19}F_6N_3O_2S$: C, 54.65; H, 3.63; N, 7.97. Found: C, 54.64; H, 3.64; N, 7.70.

5.1.7. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (10b). The compound **10b** (5.12 g, 95%) was prepared from **8** (4.86 g, 10.0 mmol) in a manner similar to that described for the preparation of **10a**. mp: 144–

145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.07 (1H, m), 2.14–2.26 (1H, m), 2.23 (3H, s), 2.56 (3H, s), 3.33 (1H, dd, J = 15.3 and 4.9 Hz), 3.71–3.81 (1H, m), 3.87 (1H, d, J = 14.7 Hz), 4.37–4.48 (2H, m), 5.31 (1H, d, J = 14.7 Hz), 6.92 (1H, d, J = 7.3 Hz), 7.04 (1H, dd, J = 7.3 and 7.3 Hz), 7.20–7.25 (2H, m), 7.56 (2H, s), 7.82 (1H, s). HRMS (EI) calcd for $C_{25}H_{21}F_6N_3O_2S$ (M^+) 541.1259; found, 541.1241. Anal. Calcd for $C_{25}H_{21}F_6N_3O_2S$: C, 55.45; H, 3.91; N, 7.76. Found: C, 55.39; H, 3.78; N, 7.56.

5.1.8. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methoxylphenyl)-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (10c). The compound **10c** (1.96 g, 88%) was prepared from **8** (1.95 g, 4.01 mmol) in a manner similar to that described for the preparation of **10a**. mp: 164–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.14 (2H, m), 2.56 (3H, s), 3.32–3.43 (1H, m), 3.39 (3H, s), 3.77–3.88 (1H, m), 4.05 (1H, d, J = 14.7 Hz), 4.34–4.49 (2H, m), 5.19 (1H, d, J = 14.7 Hz), 6.74 (1H, d, J = 7.9 Hz), 7.01 (1H, dd, J = 7.9 and 7.9 Hz), 7.34 (2H, dd, J = 7.9 and 7.9 Hz), 7.69 (2H, s), 7.83 (1H, s). HRMS (EI) calcd for $C_{25}H_{21}F_6N_3O_3S$ (M^+) 557.1208; found, 557.1216. Anal. Calcd for $C_{25}H_{21}F_6N_3O_3S$: C, 53.86; H, 3.80; N, 7.54. Found: C, 53.49; H, 3.63; N, 7.28.

5.1.9. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-fluorophenyl)-2-methylthio-6,7,8, 9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (10d). The compound **10d** (245 mg, 90%) was prepared from **8** (243 mg, 0.501 mmol) in a manner similar to that described for the preparation of **10a**. mp: 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.17 (2H, m), 2.58 (3H, s), 3.33–3.43 (1H, m), 3.75–3.86 (1H, m), 4.02 (1H, d, J = 15.3 Hz), 4.38–4.52 (2 H, m), 5.37 (1H, d, J = 15.3 Hz), 6.90–6.97 (1H, m), 7.22 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.33–7.41 (1H, m), 7.51 (1H, ddd, J = 7.3, 7.3, and 1.8 Hz), 7.74 (2H, s), 7.84 (1H, s). HRMS (FAB^+) calcd for $C_{24}H_{19}F_7N_3O_2S$ (M^++1) 546.1086; found, 546.1108. Anal. Calcd for $C_{24}H_{18}F_7N_3O_2S$: C, 52.85; H, 3.33; N, 7.70. Found: C, 52.87; H, 3.29; N, 7.39.

5.1.10. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-methylthio-5,6,7,8-tetrahydropyrimido[5,4-*f*][1,4]oxazepin-5-one (11). The compound **11** (2.13 g, 81%) was prepared from **9** (2.36 g, 5.00 mmol) in a manner similar to that described for the preparation of **10a**. mp: 209–211 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (3H, s), 2.59 (3H, s), 3.69 (2H, t, J = 4.9 Hz), 4.60 (2H, t, J = 4.9 Hz), 4.76 (2H, s), 7.08 (1H, dd, J = 7.3 and 1.2 Hz), 7.21 (1H, t, J = 7.3 Hz), 7.27–7.37 (2H, m), 7.66 (2H, s), 7.84 (1H, s). HRMS (EI) calcd for $C_{24}H_{19}F_6N_3O_2S$ (M^+) 527.1102; found, 527.1130. Anal. Calcd for $C_{24}H_{19}F_6N_3O_2S \cdot \frac{1}{5}H_2O$: C, 54.28; H, 3.61; N, 7.91. Found: C, 54.23; H, 3.64; N, 7.54.

5.1.11. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(4-fluoro-2-methylphenyl)-2- methylthio-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*][1,5]diazocin-5-one (16). The compound **16** (540 mg, 99%) was prepared from **14** (485 mg, 1.00 mmol) in a manner similar to that described for the preparation of **10a**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77–2.00 (2H, m), 2.15–2.36 (3H, m), 2.48 (3H, s), 3.23–3.42 (3H, m), 3.74 (1H, d, J = 15.3 Hz), 3.77–3.88 (1H, m), 5.34 (1H, d, J = 15.3 Hz), 5.77 (1H, t, J = 7.3 Hz), 6.85–7.08 (2H, m), 7.15–7.24 (2H, m), 7.55 (2H, s), 7.80 (1H, s). HRMS (EI) Calcd for $C_{25}H_{22}F_6N_4OS$ (M^+) 540.1419; found, 540.1390. Anal. Calcd for $C_{25}H_{22}F_6N_4OS$: C, 55.55; H, 4.10; N, 10.37. Found: C, 55.28; H, 4.06; N, 10.19.

5.1.12. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-methylthio-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*e*][1,4]-diazepin-5-one (17). The compound **17** (2.63 g, 99%) was prepared from **15** (2.36 g, 5.01 mmol) in a manner similar to that described for the preparation of **10a**. mp: 248–250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 2.52 (3H, s), 3.64 (4H, br s), 4.69 (2H, br s), 5.59 (1H, br s), 7.11 (1H, dd, J = 7.3 and 1.2 Hz), 7.19 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.23–7.32 (2H, m), 7.63 (2H, s), 7.81 (1H, s). HRMS (EI) calcd for $C_{24}H_{20}F_6N_4OS$ (M^+) 526.1262; found, 526.1232. Anal. Calcd for $C_{24}H_{20}F_6N_4OS$: C, 54.75; H, 3.83; N, 10.64. Found: C, 54.57; H, 3.68; N, 10.46.

5.1.13. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-methylsulfonyl-4-phenyl-6,7,8,9- tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]-oxazocin-5-one (12a). To a solution of **10a** (2.15 g, 4.08 mmol) in THF (8 mL) was added *m*CPBA (2.12 g, 12.3 mmol) portion-wise under ice cooling. The mixture was stirred for 30 min at 0 °C and then for 3 h at room temperature. The resulting mixture was diluted with ethyl acetate, then washed with saturated sodium hydrogen carbonate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt) of the residue gave **12a** as a colorless solid (17.8 g, 63%). mp: 239–241 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10–2.32 (2H, m), 3.36 (3H, s), 3.52–3.61 (1H, m), 3.78–3.88 (1H, m), 4.10 (1H, d, J = 15.3 Hz), 4.48–4.59 (2H, m), 5.36 (1H, d, J = 15.3 Hz), 7.29 (2H, dd, J = 7.9 and 7.9 Hz), 7.42–7.50 (3 H, m), 7.77 (2H, s), 7.90 (1H, s). HRMS (EI) calcd for $C_{24}H_{19}F_6N_3O_4S$ (M^+) 559.1000; found, 559.0974. Anal. Calcd for $C_{24}H_{19}F_6N_3O_4S$: C, 51.52; H, 3.42; N, 7.51. Found: C, 51.39; H, 3.32; N, 7.29.

5.1.14. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-methylsulfonyl-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]-[1,5]oxazocin-5-one (12b). The compound **12b** (4.98 g, 100%) was prepared from **10b** (4.50 g, 8.31 mmol) in a manner similar to that described for the preparation of **12a**. mp: 211–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03–2.14 (1H, m), 2.23 (3H, s), 2.17–2.33 (1H, m), 3.34 (3H, s), 3.44 (1H, dd, J = 15.3 and 5.5 Hz), 3.66–3.77 (1H, m), 3.91 (1H, d, J = 14.7 Hz), 4.48–4.60 (2H, m), 5.29 (1H, d, J = 14.7 Hz), 6.88 (1H, d, J = 7.3 Hz), 7.02 (1H, dd, J = 7.3 and 7.3 Hz), 7.22–7.32 (2H, m), 7.57 (2H, s), 7.84 (1H, s). HRMS (EI) calcd for $C_{25}H_{21}F_6N_3O_4S$ (M^+) 573.1157; found, 573.1144. Anal. Calcd for $C_{25}H_{21}F_6N_3O_4S$: C, 52.36; H, 3.69; N, 7.33. Found: C, 52.40; H, 3.52; N, 7.05.

5.1.15. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methoxylphenyl)-2-methylsulfonyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (12c). The compound **12c**

(1.75 g, 85%) was prepared from **10c** (1.80 g, 3.23 mmol) in a manner similar to that described for the preparation of **12a**. mp: 202–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06–2.23 (2H, m), 3.35 (6H, s), 3.41–3.48 (1H, m), 3.72–3.82 (2H, m), 4.05 (1H, d, J = 14.7 Hz), 4.45–4.60 (2H, m), 5.52 (1H, d, J = 14.7 Hz), 6.73 (1H, d, J = 7.3 Hz), 7.04 (1H, dd, J = 7.3 and 7.3 Hz), 7.35–7.43 (2H, m), 7.69 (2H, s), 7.86 (1H, s). HRMS (EI) calcd for $C_{25}H_{21}F_6N_3O_5S$ (M^+) 589.1106; found, 589.1082. Anal. Calcd for $C_{25}H_{21}F_6N_3O_5S$: C, 50.94; H, 3.59; N, 7.13. Found: C, 50.77; H, 3.43; N, 6.90.

5.1.16. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-fluorophenyl)-2-methylsulfonyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (12d). The compound **12d** (215 mg, 92%) was prepared from **10d** (221 mg, 0.405 mmol) in a manner similar to that described for the preparation of **12a**. mp: 202–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07–2.26 (2H, m), 3.36 (3H, s), 3.43–3.53 (1H, m), 3.71–3.82 (1H, m), 4.06 (1H, d, J = 14.7 Hz), 4.50–4.62 (2H, m), 5.36 (1H, d, J = 14.7 Hz), 6.90–6.97 (1H, m), 7.25 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.39–7.47 (1H, m), 7.55 (1H, ddd, J = 7.3, 7.3, and 1.8 Hz), 7.75 (2H, s), 7.87 (1H, s). HRMS (FAB$^+$) calcd for $C_{24}H_{19}F_7N_3O_4S$ (M^++1) 578.0985; found, 578.1015. Anal. Calcd for $C_{24}H_{18}F_7N_3O_4S$: C, 49.92; H, 3.14; N, 7.28. Found: C, 49.91; H, 3.07; N, 7.17.

5.1.17. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-methylsulfonyl-5,6,7,8-tetrahydropyrimido[5,4-*f*][1,4]-oxazepin-5-one (13). The compound **13** (1.73 g, 84%) was prepared from **11** (1.95 g, 3.70 mmol) in a manner similar to that described for the preparation of **12a**. mp: 197–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, s), 3.37 (3H, s), 3.77 (2H, t, J = 4.9 Hz), 4.71 (2H, t, J = 4.9 Hz), 4.79 (2H, s), 7.05 (1H, brd, J = 7.3 Hz), 7.23 (1H, t, J = 7.3 Hz), 7.33 (1H, d, J = 7.3 Hz), 7.40 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.68 (2H, s), 7.88 (1H, s). HRMS (EI) calcd for $C_{24}H_{19}F_6N_3O_4S$ (M^+) 559.1000; found, 559.1016. Anal. Calcd for $C_{24}H_{19}F_6N_3O_4S \cdot \frac{1}{10}H_2O$: C, 51.36; H, 3.41; N, 7.49. Found: C, 51.02; H, 3.39; N, 7.19.

5.1.18. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-methylsulfonyl-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*]-[1,5]diazocin-5-one (18). The compound **18** (335 mg, 65%) was prepared from **16** (490 mg, 0.907 mmol) in a manner similar to that described for the preparation of **12a**. mp: 276–279 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87–2.07 (2H, m), 2.24 (3H, s), 3.27 (3H, s), 3.33–3.46 (3H, m), 3.71–3.83 (1H, m), 3.78 (1H, d, J = 15.3 Hz), 5.32 (1H, d, J = 15.3 Hz), 6.41 (1H, t, J = 7.3 Hz), 6.85–6.94 (1H, br), 7.02 (1H, t, J = 7.3 Hz), 7.20–7.28 (2H, m), 7.55 (2H, s), 7.82 (1H, s). HRMS (EI) calcd for $C_{25}H_{22}F_6N_4O_3S$ (M^+) 572.1317; found, 572.1290. Anal. Calcd for $C_{25}H_{22}F_6N_4O_3S \cdot \frac{1}{20}H_2O$: C, 52.36; H, 3.87; N, 9.77. Found: C, 52.73; H, 3.85; N, 9.37.

5.1.19. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)methylsulfonyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-5-one (19). The compound **19** (410 mg, 15%) was prepared from **17** (2.50 g, 4.75 mmol) in a manner similar to that described for the preparation of **12a**. mp: 307–310 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (3H, s), 3.30 (3H, s), 3.51–3.58 (2H, m), 3.76–3.87 (2H, br), 4.62–4.74 (2H, br), 7.05 (1H, t, J = 7.3 Hz), 7.17–7.24 (2H, m), 7.27 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.84 (2H, s), 8.06 (1H, s), 8.68–8.73 (1H, br). HRMS (EI) calcd for $C_{24}H_{20}F_6N_4O_3S$ (M^+) 558.1160; found, 558.1156. Anal. Calcd for $C_{24}H_{20}F_6N_4O_3S$: C, 51.61; H, 3.61; N, 10.03. Found: C, 51.38; H, 3.45; N, 9.95.

5.1.20. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-[4-(1- pyrrolodinyl)piperidino]-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3a). To a solution of **12b** (1.50 g, 2.62 mmol) in 1,4-dioxane (10 mL) were added diisopropylethylamine (1 mL) and 4-(pyrrolidinyl)piperidine (485 mg, 3.14 mmol) at room temperature and the mixture was refluxed for 3 h. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt:MeOH = 3:1) of the residue gave **3a** as a colorless foam (1.08 g, 64%). ^{1}H 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). HRMS (EI) calcd for $C_{33}H_{35}F_6N_5O_2$ (M^+) 647.2695; found, 647.2707. Anal. Calcd for $C_{33}H_{35}F_6N_5O_2 \cdot \frac{1}{5}H_2O$: C, 60.86; H, 5.42; N, 10.75. Found: C, 60.47; H, 5.40; N, 10.47.

5.1.21. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)pyridyl)-1-piperazinyl]-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3b). The compound **3b** (77.1 mg, 88%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.03 (1H, m), 2.08–2.20 (1H, m), 2.27 (3H, s), 3.29 (1H, dd, J = 15.3 and 4.3 Hz), 3.53–3.66 (4H, m), 3.78–3.89 (1H, m), 3.85 (1H, d, J = 15.3 Hz), 3.92–4.03 (4H, m), 4.30–4.43 (2H, m), 5.33 (1H, d, J = 15.3 Hz), 6.63–6.69 (2H, m), 6.93–6.99 (1H, m), 7.02–7.08 (1H, m), 7.20–7.28 (2H, m), 7.46–7.53 (1H, m), 7.57 (2H, s), 7.80 (1H, s), 8.20 (1H, dd, J = 4.9 and 1.2 Hz). HRMS (EI) calcd for $C_{33}H_{30}F_6N_6O_2$ (M^+) 656.2334; found, 656.2310. Anal. Calcd for $C_{33}H_{30}F_6N_6O_2$: C, 60.36; H, 4.61; N, 12.80. Found: C, 60.25; H, 4.63; N, 12.92.

5.1.22. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-(1-imidazolyl)-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]-[1,5]oxazocin-5-one (3c). The compound **3c** (53.8 mg, 64%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.12 (1H, m), 2.21–2.32 (4H, m), 3.41 (1H, dd, J = 15.6 and 4.9 Hz), 3.74–3.85 (1H, m), 3.91 (1H, d, J = 14.6 Hz), 4.45–4.57 (2H, m), 5.32 (1H, d, J = 14.6 Hz), 6.94 (1H,

d, $J = 7.8$ Hz), 7.07 (1H, dd, $J = 7.8$ and 7.8 Hz), 7.14 (1H, d, $J = 1.0$ Hz), 7.27–7.33 (2H, m), 7.59 (2H, s), 7.84 (1H, s), 7.86 (1H, d, $J = 1.0$ Hz), 8.58 (1H, s). HRMS (EI) calcd for $C_{27}H_{21}F_6N_5O_2$ (M^+) 561.1599; found, 561.1597. Anal. Calcd for $C_{27}H_{21}F_6N_5O_2$: C, 57.76; H, 3.77; N, 12.47. Found: C, 57.53; H, 3.69; N, 12.31.

5.1.23. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)morpholino-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]-oxazocin-5-one (3d). The compound **3d** (50.4 mg, 87%) was prepared from **12b** (57.4 mg, 0.100 mmol) in a manner similar to that described for the preparation of **3a.** Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91–2.03 (1H, m), 2.08–2.19 (1H, m), 2.25 (3H, s), 3.28 (1H, dd, $J = 15.3$ and 4.3 Hz), 3.68–3.76 (4H, m), 3.76–3.89 (6H, m), 4.30–4.42 (2H, m), 5.32 (1H, d, $J = 15.3$ Hz), 6.92–6.97 (1H, m), 7.01–7.08 (1H, m), 7.19–7.27 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{28}H_{26}F_6N_4O_3$ (M^+) 580.1909; found, 580.1948. Anal. Calcd for $C_{28}H_{26}F_6N_4O_3$: C, 57.93; H, 4.51; N, 9.65. Found: C, 57.80; H, 4.41; N, 9.52.

5.1.24. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-[4-(ethoxycarbonyl)piperidino]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3e). The compound **3e** (64.6 mg, 68%) was prepared from **12 b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, $J = 7.3$ Hz), 1.62–1.75 (2H, m), 1.87–2.01 (4H, m), 2.07–2.17 (1H, m), 2.26 (3H, s), 2.50–2.60 (1H, m), 3.00–3.11 (2H, m), 3.27 (1H, dd, $J = 14.7$ and 4.3 Hz), 3.77–3.88 (1H, m), 3.84 (1H, d, $J = 15.3$ Hz), 4.14 (2H, q, $J = 7.3$ Hz), 4.28–4.40 (2H, m), 4.60–4.72 (2H, m), 5.32 (1H, d, $J = 15.3$ Hz), 6.93–6.98 (1H, m), 7.02–7.08 (1H, m), 7.18–7.28 (1H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{32}H_{32}F_6N_4O_4$ (M^+) 650.2328; found, 650.2351. Anal. Calcd for $C_{32}H_{32}F_6N_4O_4$: C, 59.07; H, 4.96; N, 8.61. Found: C, 58.82; H, 5.00; N, 8.55.

5.1.25. 2-(4-Carbamoylpiperidino)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3f). The compound **3f** (70.0 mg, 75%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a.** Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62–1.77 (2H, m), 1.86–2.02 (3H, m), 2.07–2.18 (1H, m), 2.25 (3H, s), 2.37–2.47 (1H, m), 2.90–3.02 (2H, m), 3.28 (1H, dd, $J = 15.3$ and 4.9 Hz), 3.77–3.89 (1H, m), 3.85 (1H, d, $J = 15.3$ Hz), 4.28–4.42 (2H, m), 4.77–4.88 (2H, m), 5.32 (1H, d, $J = 15.3$ Hz), 5.38–5.49 (2H, brs), 6.92–6.99 (1H, m), 7.01–7.09 (1H, m), 7.19–7.25 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{30}H_{29}F_6N_5O_3$ (M^+) 621.2175; found, 621.2142. Anal. Calcd for $C_{30}H_{29}F_6N_5O_3 \cdot \frac{1}{2}H_2O$: C, 57.14; H, 4.64; N, 11.11. Found: C, 57.18; H, 4.61; N, 11.02.

5.1.26. piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]-[1,5]oxazocin-5-one (3g). The compound **3g** (60.7 mg, 65%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. mp: 162–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.04 (1H, m), 2.10–2.20 (1H, m), 2.13 (3H, s), 2.25 (3H, s), 3.30 (1H, dd, $J = 15.1$ and 4.4 Hz), 3.50 (2H, dd, $J = 4.4$ and 4.4 Hz), 3.63–3.70 (2H, m), 3.76–3.95 (6H, m), 4.30–4.43 (2H, m), 5.32 (1H, d, $J = 15.1$ Hz), 6.95 (1H, br d, $J = 7.3$ Hz), 7.05 (1H, br dd, $J = 7.3$ and 7.3 Hz), 7.20–7.25 (2H, m), 7.57 (2H, s), 7.81 (1H, s). HRMS (EI) calcd for $C_{30}H_{29}F_6N_5O_3$ (M^+) 621.217500; found, 621.2192. Anal. Calcd for $C_{30}H_{29}F_6N_5O_3$: C, 57.97; H, 4.70; N, 11.27. Found: C, 57.90; H, 4.70; N, 11.33.

5.1.27. 2-(4-Acetamido-1-homopiperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3h). To a solution of **12b** (86.0 mg, 0.150 mmol) in 1,4-dioxane (1 mL) were added diisopropylethylamine (0.1 mL) and 4-(*tert*-butoxycarbonylamino)homopiperazine (36.1 mg, 0.180 mmol) at room temperature and the mixture was refluxed for 5 h. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. To the resulting residue was added 3 M HCl–AcOEt (1 mL) under ice cooling. The mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. The resulting mixture was concentrated in vacuo. To a solution of the residue in THF (1 mL) were added triethylamine (0.1 mL) and acetic anhydride (0.05 mL) portion-wise under ice cooling. The mixture was stirred for 30 min at 0 °C. The resulting mixture was diluted with ethyl acetate, then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt) of the residue gave **3h** as a pale yellow foam (39.5 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83–2.06 (4H, m), 2.12 (3H, s), 2.25 (3H, d, $J = 3.9$ Hz), 3.29 (1H, dd, $J = 15.1$ and 4.4 Hz), 3.33–4.15 (10H, m), 4.29–4.42 (2H, m), 5.31 (1H, d, $J = 15.1$ Hz), 6.91–6.98 (1H, m), 7.01–7.08 (1H, m), 7.19–7.25 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{31}H_{31}F_6N_5O_3$ (M^+) 635.2331; found, 635.2313. Anal. Calcd for $C_{31}H_{31}F_6N_5O_3$: C, 58.58; H, 4.92; N, 11.02. Found: C, 58.25; H, 4.81; N, 10.72.

5.1.28. 2-(3-Acetamido-1-pyrrolidinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3i). The compound **3i** (65.0 mg, 70%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. mp: 134–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90–2.03 (5H, m), 2.07–2.19 (1H, m), 2.19–2.32 (4H, m), 3.28 (1H, dd, $J = 15.1$ and 4.9 Hz), 3.49 (1H, dd, $J = 11.7$ and 4.4 Hz), 3.69 (2H, dd, $J = 6.8$ and 6.8 Hz), 3.74–3.91 (3H, m), 4.29–4.42 (2H, m), 4.52–4.62 (1H, m), 5.32 (1H, d, $J = 14.6$ Hz), 5.63 (1H, br s), 6.91–6.98 (1H, m), 7.01–7.08 (1H, m), 7.18–7.26 (2H, m), 7.57 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{30}H_{29}F_6N_5O_3$ (M^+) 621.2175; found, 621.2173. Anal. Calcd for $C_{30}H_{29}F_6N_5O_3 \cdot H_2O$: C, 56.34; H, 4.57; N, 10.95. Found: C, 56.64; H, 4.62; N, 10.96.

5.1.29. 6-[3,5-Bis(trifluoromethyl)benzyl]-2-(1,1-dioxothiomorpholino)-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3j). The compound **3j** (12.5 mg, 13%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. mp: 227–230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.05 (1H, m), 2.11–2.21 (1H, m), 2.23 (3H, s), 3.00–3.09 (4H, m), 3.29–3.37 (1H, m), 3.75–3.83 (1H, m), 3.86 (1H, d, J = 14.6 Hz), 4.33–4.44 (6H, m), 5.31 (1H, d, J = 14.6 Hz), 6.93 (1H, d, J = 6.8 Hz), 7.06 (1H, dd, J = 6.8 and 6.8 Hz), 7.21–7.30 (2H, m), 7.57 (2H, s), 7.81 (1H, s). HRMS (EI) calcd for $C_{28}H_{26}F_6N_4O_4S$ (M^+) 628.1579; found, 628.1523. Anal. Calcd for $C_{28}H_{26}F_6N_4O_4S$ H_2O: C, 52.01; H, 4.05; N, 8.66. Found: C, 52.34; H, 4.11; N, 8.80.

5.1.30. 6-[3,5-Bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-2-[4-(methylsulfonyl)-1-piperazinyl]-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3k). The compound **3k** (54.6 mg, 55%) was prepared from **12b** (86.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3h**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.04 (1H, m), 2.07–2.20 (1H, m), 2.24 (3H, s), 2.79 (3H, s), 3.20–3.33 (5H, m), 3.73–3.84 (1H, m), 3.85 (1H, d, J = 15.3 Hz), 3.96–4.03 (4H, m), 4.31–4.43 (2H, m), 5.31 (1H, d, J = 15.3 Hz), 6.92–6.97 (1H, m), 7.03–7.08 (1H, m), 7.19–7.25 (2H, m), 7.56 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{29}H_{29}F_6N_5O_4S$ (M^+) 657.1844; found, 657.1843. Anal. Calcd for $C_{29}H_{29}F_6N_5O_4S$: C, 52.96; H, 4.44; N, 10.65. Found: C, 52.77; H, 4.32; N, 10.46.

5.1.31. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-phenyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]-[1,5]oxazocin-5-one (3l). The compound **3l** (53.7 mg, 59%) was prepared from **12a** (84.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. mp: 215–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.20 (2H, m), 2.14 (3H, s), 3.40–3.48 (1H, m), 3.48–3.54 (2H, m), 3.65–3.71 (2H, m), 3.84–4.00 (5H, m), 4.03 (1H, d, J = 15.3 Hz), 4.33–4.40 (2H, m), 5.36 (1H, d, J = 15.3 Hz), 7.24–7.31 (2H, m), 7.35–7.43 (3H, m), 7.76 (2H, s), 7.86 (1H, s). HRMS (EI) calcd for $C_{29}H_{27}F_6N_5O_3$ (M^+) 607.2018; found, 607.2049. Anal. Calcd for $C_{29}H_{27}F_6N_5O_3$: C, 57.33; H, 4.48; N, 11.53. Found: C, 56.99; H, 4.36; N, 11.49.

5.1.32. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3m). The compound **3m** (86.2 mg, 90%) was prepared from **12c** (88.5 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93–2.12 (2H, m), 2.13 (3H, s), 3.28–3.37 (1H, m), 3.41 (3H, s), 3.48–3.53 (2H, m), 3.63–3.70 (2H, m), 3.82–3.94 (5H, m), 4.04 (1H, d, J = 14.7 Hz), 4.28–4.43 (2H, m), 5.17 (1H, d, J = 14.7 Hz), 6.76 (1H, d, J = 7.3 Hz), 7.01 (1H, dd, J = 7.3 and 7.3 Hz), 7.27–7.37 (2H, m), 7.69 (2H, s), 7.82 (1H, s). HRMS (EI) calcd for $C_{30}H_{29}F_6N_5O_4$ (M^+) 637.2124; found, 637.2085. Anal. Calcd for $C_{30}H_{29}F_6N_5O_4 \cdot \frac{1}{2}H_2O$: C, 55.73; H, 4.52; N, 10.83. Found: C, 55.49; H, 4.47; N, 10.87.

5.1.33. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-fluorophenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*][1,5]oxazocin-5-one (3n). The compound **3n** (65.7 mg, 88%) was prepared from **12d** (68.5 mg, 0.119 mmol) in a manner similar to that described for the preparation of **3g**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.12 (2H, m), 2.14 (3H, s), 3.30–3.38 (1H, m), 3.52 (2H, t, J = 5.5 Hz), 3.65–3.72 (2H, m), 3.80–3.94 (5H, m), 3.99 (1H, d, J = 15.3 Hz), 4.33–4.45 (2H, m), 5.36 (1H, d, J = 15.3 Hz), 6.92–6.98 (1H, m), 7.19 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.32–7.38 (1H, m), 7.46 (1H, ddd, J = 7.3, 7.3, and 1.8 Hz), 7.73 (2H, s), 7.82 (1H, s). HRMS (FAB$^+$) calcd for $C_{29}H_{27}F_7N_5O_3$ (M^++1) 626.2002; found, 626.2012. Anal. Calcd for $C_{29}H_{26}F_7N_5O_3 \cdot \frac{1}{5}H_2O$: C, 55.36; H, 4.17; N, 11.13. Found: C, 54.96; H, 4.11; N, 10.88.

5.1.34. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-5,6,7,8-tetrahydropyrimido-[5,4-*f*][1,4]oxazepin-5-one (4). The compound **4** (62.2 mg, 68%) was prepared from **13** (84.0 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. mp: 231–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (3H, s), 2.31 (3H, s), 3.52 (2H, t, J = 4.9 Hz), 3.64–3.73 (4H, m), 3.86–3.98 (4H, m), 4.54 (2H, t, J = 4.9 Hz), 4.73 (2H, s), 7.10 (1H, dd, J = 7.3 and 1.2 Hz), 7.22 (1H, t, J = 7.3 Hz), 7.27 (1H, d, J = 7.3 Hz), 7.32 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.65 (2H, s), 7.82 (1H, s). HRMS (EI) calcd for $C_{29}H_{27}F_6N_5O_3$ (M^+) 607.2018; found, 607.2026. Anal. Calcd for $C_{29}H_{27}F_6N_5O_3$: C, 57.33; H, 4.48; N, 11.53. Found: C, 57.13; H, 4.38; N, 11.41.

5.1.35. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*][1,5]diazocin-5-one (5a). The compound **5a** (70.0 g, 75%) was prepared from **18** (85.9 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–1.85 (1H, m), 1.85–1.97 (1H, m), 2.12 (3H, s), 2.18–2.38 (3H, br), 3.18–3.38 (3H, m), 3.42–3.49 (2H, m), 3.59–3.68 (2H, m), 3.69–3.94 (6H, m), 5.36 (1H, d, J = 15.3 Hz), 5.47 (1H, t, J = 7.3 Hz), 6.85–7.10 (2H, m), 7.16–7.24 (2H, m), 7.79 (2H, s), 8.02 (1H, s). HRMS (EI) calcd for $C_{30}H_{30}F_6N_6O_2$ (M^+) 620.2334; found, 620.2319. Anal. Calcd for $C_{30}H_{30}F_6N_6O_2 \cdot \frac{1}{5}H_2O$: C, 57.73; H, 4.84; N, 13.46. Found: C, 57.40; H, 4.82; N, 13.22.

5.1.36. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*e*][1,4]diazepin-5-one (6). The compound **6** (43.8 g, 46%) was prepared from **19** (83.8 mg, 0.150 mmol) in a manner similar to that described for the preparation of **3a**. mp: 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (3H, s), 2.34 (3H, s), 3.48 (2H, dd, J = 5.5 and 5.5 Hz), 3.61 (4H, s), 3.65 (2H, dd, J = 5.5 and 5.5 Hz), 3.82 (2H, dd, J = 5.5 and 5.5 Hz), 3.88 (2H, dd, J = 5.5 and 5.5 Hz), 4.68 (2H, br), 5.29 (1H, s), 7.14 (1H, dd, J = 7.3 and 1.2 Hz), 7.20 (1H, ddd, J = 7.3, 7.3, and 1.2 Hz), 7.23–7.31 (2H, m), 7.63 (2H, s), 7.80 (1H, s). HRMS (EI) calcd for $C_{29}H_{28}F_6N_6O_2$ (M^+) 606.2178; found, 606.2166. Anal. Calcd for $C_{29}H_{28}F_6N_6O_2 \cdot \frac{1}{2}H_2O$: C, 56.58; H, 4.58; N, 13.65. Found: C, 56.28; H, 4.53; N, 13.26.

5.1.37. 2-(4-Acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-10-methyl- 4-(2-methylphenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*][1,5]diazocin-5-one (5b). To a solution of **5a** (25.0 mg, 40.3 μmol) in DMF (0.5 mL) was added sodium hydride (2.5 mg, 62.5 μmol, 60% oil suspension) portion-wise under ice cooling. The mixture was stirred for 30 min at room temperature, and then iodomethane (4.0 μl, 64.3 μmol) was added and stirred for 1 h at room temperature. The resulting mixture was diluted with ethyl acetate, then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography (AcOEt) of the residue gave **5b** as a colorless foam (10.8 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.90 (2H, m), 2.13 (3H, s), 2.35 (3H, br s), 3.13–3.24 (2H, m), 3.26 (3H, s), 3.58 (2H, dd, J = 4.9 and 4.9 Hz), 3.53–3.92 (9H, m), 5.25 (1H, d, J = 14.7 Hz), 6.75–7.00 (2H, br), 7.14–7.25 (2H, m), 7.58 (2H, br s), 7.78 (1H, s). HRMS (EI) calcd for $C_{31}H_{32}F_6N_6O_2$ (M^+) 634.2491; found, 634.2451. Anal. Calcd for $C_{31}H_{32}F_6N_6O_2 \cdot \frac{1}{10}H_2O$: C, 58.50; H, 5.07; N, 13.21. Found: C, 58.17; H, 5.02; N, 13.01.

5.1.38. 10-Acetyl-2-(4-acetyl-1-piperazinyl)-6-[3,5-bis(trifluoromethyl)benzyl]-4-(2-methylphenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*][1,5]diazocin-5-one (5c). To a solution of **5a** (25.0 mg, 40.3 μmol) in 1,4-dioxane (0.5 mL) were added pyridine (0.1 mL) and acetic anhydride (0.2 mL) at room temperature. The mixture was stirred for 3 h at 100 °C. The resulting mixture was diluted with ethyl acetate, and then washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt) of the residue gave **5c** as a colorless foam (26.0 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51–1.64 (1H, m), 1.93 (3H, s), 2.16 (3H, s), 2.22–2.33 (1H, m), 2.28 (3H, s), 3.02–3.12 (1H, m), 3.24–3.33 (1H, m), 3.53–3.66 (3H, m), 3.68–3.78 (2H, m), 3.86–4.00 (5H, m), 4.61–4.69 (1H, m), 5.36 (1H, d, J = 15.9 Hz), 6.98 (1H, d, J = 7.3 Hz), 7.11 (1H, t, J = 7.3 Hz), 7.27–7.35 (2H, m), 7.49 (2H, s), 7.78 (1H, s). HRMS (EI) calcd for $C_{32}H_{32}F_6N_6O_3$ (M^+) 662.2440; found, 662.2435. Anal. Calcd for $C_{32}H_{32}F_6N_6O_3$ H_2O: C, 56.47; H, 4.74; N, 12.35. Found: C, 56.76; H, 4.79; N, 12.55.

5.1.39. 2-Chloro-4-iodo-3-pyridinecarboxylic acid (21). The compound **21** (22.7 g, 81%) was prepared from **20** (23.8 g, 99.3 mmol) in a manner similar to that described for the preparation of **7**. mp: 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (1H, d, J = 5.4 Hz), 8.09 (1H, d, J = 5.4 Hz). HRMS (EI) calcd for $C_6H_3ClINO_2$ (M^+) 282.8897; found, 282.8896. Anal. Calcd for $C_6H_3ClINO_2$: C, 25.42; H, 1.07; N, 4.94. Found: C, 25.36; H, 0.97; N, 4.71.

5.1.40. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-4-iodo-3-pyridinecarboxamide (22). To a mixture of **21** (8.40 g, 29.6 mmol) and thionyl chloride (20 mL) was added three drops of DMF and the mixture was refluxed for 2 h, then concentrated. A solution of the residue in THF (150 mL) was added dropwise to a solution of 3-[[3,5-bis(trifluoromethyl)benzyl]amino]-1-propanol (10.7 g, 35.5 mmol) and triethylamine (20 mL) in THF (50 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt:hexane = 3:1) of the residue gave **22** as a colorless solid (15.4 g, 92%). mp: 99–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.30 (1H, m), 1.70–1.90 (2H, m), 3.20–3.85 (4H, m), 4.54 (0.6H, s), 4.90 (0.7H, d, J = 15.3 Hz), 4.99 (0.7H, d, J = 15.3 Hz), 7.70–8.08 (5H, m). HRMS (EI) calcd for $C_{18}H_{14}ClF_6IN_2O_2$ (M^+) 565.9693; found, 565.9731. Anal. Calcd for $C_{18}H_{14}ClF_6IN_2O_2$: C, 38.15; H, .2.49; N, 4.94. Found: C, 37.95; H, 2.35; N, 5.01.

5.1.41. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-chloro-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]-1,5-oxazocin-6-one (23). To a solution of **22** (1.74 g, 3.07 mmol) in EtOH (30 mL) was added K_2CO_3 (2.12 g, 15.3 mmol), and the mixture was stirred under reflux for 6 h. The resulting mixture was extracted with ethyl acetate, and the extract was washed with brine, then dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel chromatography (AcOEt:hexane = 2:1 v/v) to give compound **23** (950 mg, 71%). mp: 197–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.18 (2H, m), 3.23–3.32 (1H, m), 3.63–3.74 (1H, m), 4.06 (1H, d, J = 15.3 Hz), 4.22–4.30 (1H, m), 4.44–4.53 (1H, m), 5.64 (1H, d, J = 15.3 Hz), 6.80 (1H, d, J = 5.5 Hz), 7.84 (1H, s), 7.88 (2H, s), 8.17 (1H, d, J = 5.5 Hz). HRMS (EI) calcd for $C_{18}H_{13}ClF_6N_2O_2$ (M^+) 438.0570; found, 438.0571. Anal. Calcd for $C_{18}H_{13}ClF_6N_2O_2$ H_2O: C, 47.33; H, 2.87; N, 6.13. Found: C, 47.17; H, 2.88; N, 6.33.

5.1.42. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-iodo-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (24). To a solution of **22** (6.86 g, 12.1 mmol) in THF (60 mL) was added NaH (581 mg, 14.5 mmol) at 0 °C, and the mixture was stirred for 0.5 h and then at room temperature for 1 h. The reaction mixture was cooled at 0 °C, and water was added. The subsequent work-up procedure as described above afforded compound **24** (7.69 g, 42%). mp: 203–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–1.81 (1H, m), 2.21–2.34 (1H, m), 3.18–3.27 (1H, m), 3.40–3.50 (1H, m), 4.14 (1H, d, J = 15.6 Hz), 4.22–4.30 (1H, m), 4.46–4.68 (1H, m), 5.71 (1H, d, J = 15.6 Hz), 7.69 (1H, d, J = 5.3 Hz), 7.83 (1H, s), 7.94 (2H, s), 8.01 (1H, d, J = 5.3 Hz). HRMS (EI) calcd for $C_{18}H_{13}F_6IN_2O_2$ (M^+) 529.9926; found, 529.9907. Anal. Calcd for $C_{18}H_{13}F_6IN_2O_2$: C, 40.78; H, 2.47; N, 5.28. Found: C, 40.88; H, 2.30; N, 5.19.

5.1.43. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]-1,5-oxazocin-6-one (25). The compound **25** (330 mg, 98%) was prepared from **23** (300 mg, 0.684 mmol) in a manner similar to that described for the preparation of **10a**. mp: 151–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.12 (2H, m), 2.18 (3H, s), 3.24–3.32 (1H, m), 3.75–3.85 (1H, m), 3.91 (1H, d, J = 15.3 Hz), 4.19–4.27 (1H, m), 4.38–4.46 (1H, m), 5.33 (1H, d, J = 15.3 Hz), 6.85 (1H,

d, J = 5.5 Hz), 6.92–7.09 (2H, m), 7.18–7.25 (2H, m), 7.57 (2H, s), 7.81 (1H, s), 8.44 (1H, d, J = 5.5 Hz). HRMS (EI) calcd for $C_{25}H_{20}F_6N_2O_2$ (M^+) 494.1429; found, 494.1443. Anal. Calcd for $C_{25}H_{20}F_6N_2O_2 \cdot \frac{1}{5}H_2O$: C, 60.29; H, 4.05; N, 5.62. Found: C, 60.01; H, 4.07; N, 5.40.

5.1.44. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (26a). The compound **26a** (278 mg, 99%) was prepared from **24** (300 mg, 0.566 mmol) in a manner similar to that described for the preparation of **10a**. mp: 138–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75–1.97 (2H, m), 2.17–2.34 (3H, brs), 3.17–3.32 (1H, m), 3.50–3.73 (1H, m), 4.02 (1H, d, J = 15.3 Hz), 4.31–4.41 (1H, m), 4.60–4.68 (1H, m), 5.44 (1H, d, J = 15.3 Hz), 6.73–7.70 (5H, m), 7.02 (1H, d, J = 4.9 Hz), 7.78 (1H, s), 8.40 (1H, d, J = 4.9 Hz). HRMS (EI) for $C_{25}H_{20}F_6N_2O_2$ (M^+): calcd, 494.1429; found, 494.1441. Anal. calcd for $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.88; H, 4.01; N, 5.32.

5.1.45. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (26b). The compound **26b** (729 mg, 80%) was prepared from **24** (1.00 g, 1.89 mmol) in a manner similar to that described for the preparation of **10a**. mp: 185–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–1.82 (1H, m), 2.26–2.39 (1H, m), 3.32–3.40 (1H, m), 3.69–3.78 (1H, m), 4.17 (1H, d, J = 15.3 Hz), 4.27–4.37 (1H, m), 4.63–4.70 (1H, m), 5.51 (1H, d, J = 15.3 Hz), 7.16 (1H, d, J = 5.5 Hz), 7.25–7.70 (5H, m), 7.71 (2H, s), 7.83 (1H, s), 8.41 (1H, d, J = 5.5 Hz). HRMS (EI) calcd for $C_{24}H_{18}F_6N_2O_2$ (M^+) 480.1272; found 480.1286. Anal. Calcd for $C_{24}H_{18}F_6N_2O_2$: C, 60.00; H, 3.78; N, 5.83. Found: C, 59.83; H, 3.71; N, 5.76.

5.1.46. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-(2-methylphenyl)-8-oxo-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]-1,5-oxazocin-6-one (27). To a solution of **25** (360 mg, 0.728 mmol) in dichloromethane (2 mL) was added *m*CPBA (251 mg, 1.45 mmol) portion-wise under ice cooling. The mixture was stirred for 30 min at 0 °C and then for 24 h at room temperature. Flash chromatography (AcOEt:-MeOH = 5:1 v/v) of the mixture gave **27** as a colorless solid (259 g, 70%). mp: 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.15 (2H, m), 2.36 (3H, s), 1.31–3.38 (1H, m), 3.77–3.86 (1H, m), 3.94 (1H, d, J = 14.7 Hz), 4.12–4.20 (1H, m), 4.44–4.51 (1H, m), 5.25 (1H, d, J = 14.7 Hz), 6.79 (1H, d, J = 7.3 Hz), 6.94 (1H, d, J = 7.3 Hz), 7.01–7.07 (1H, m), 7.24–7.37 (3H, m), 7.53 (2H, s), 7.82 (1H, s), 8.24 (1H, d, J = 7.3 Hz). HRMS (EI) calcd for $C_{25}H_{20}F_6N_2O_3$ (M^+) 510.1378; found, 510.1413. Anal. Calcd for $C_{25}H_{20}F_6N_2O_3 \cdot H_2O$: C, 56.82; H, 3.81; N, 5.30. Found: C, 57.00; H, 3.83; N, 5.27.

5.1.47. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-(2-methylphenyl)-10-oxo-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (28a). The compound 28a (231 mg, 83%) was prepared from **26a** (270 mg, 0.546 mmol) in a manner similar to that described for the preparation of **27**. mp: 188–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75–1.84 (1H, m), 1.90–2.44 (4H, m), 3.27–3.38 (1H, m), 3.57–3.75 (1H, m), 4.06 (1H, d, J = 15.3 Hz), 4.28–4.39 (1H, m), 4.73–4.81 (1H, m), 5.45 (1H, d, J = 15.3 Hz), 6.68–7.33 (4H, m), 7.01 (1H, d, J = 6.7 Hz), 7.52 (2H, s), 7.79 (1H, s), 8.31 (1H, d, J = 6.7 Hz). HRMS (FAB$^+$) calcd for $C_{25}H_{21}F_6N_2O_3$ (M^++1) 511.1456; found, 511.1469. Anal. Calcd for $C_{25}H_{20}F_6N_2O_3 \cdot \frac{1}{5}H_2O$: C, 58.41; H, 3.92; N, 5.45. Found: C, 58.03; H, 3.79; N, 5.38.

5.1.48. 5-[3,5-Bis(trifluoromethyl)benzyl]-10-oxo-7-phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (27b). The compound **27b** (411 mg, 54%) was prepared from **26b** (729 mg, 1.52 mmol) in a manner similar to that described for the preparation of **27**. mp: 207–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77–1.84 (1H, m), 2.35–2.48 (1H, m), 3.46 (1H, dd, J = 15.9 and 6.1 Hz), 3.79 (1H, dd, J = 15.9 and 11.6 Hz), 4.19 (1H, d, J = 15.3 Hz), 4.30 (1H, ddd, J = 12.8, 12.8, and 3.7 Hz), 4.79 (1H, dd, J = 12.8 and 5.5 Hz), 5.51 (1H, d, J = 15.3 Hz), 7.16 (1H, d, J = 6.7 Hz), 7.24–7.69 (5H, m), 7.71 (2H, s), 7.85 (1H, s), 8.35 (1H, d, J = 6.7 Hz). HRMS (FAB$^+$) calcd for $C_{24}H_{19}F_6N_2O_3$ (M^++1) 497.1300; found 497.1291. Anal. Calcd for $C_{24}H_{18}F_6N_2O_3 \cdot \frac{1}{2}H_2O$: C, 57.03; H, 3.59; N, 5.54. Found: C, 57.43; H, 3.54; N, 5.39.

5.1.49. 5-[3,5-Bis(trifluoromethyl)benzyl]-9-chloro-7-(2-methylphenyl)-3,4,5,6- tetrahydro-2*H*-pyrido[4,3-*b*]-1,5-oxazocin-6-one (29). A mixture of **27** (243 mg, 0.476 mmol) and phosphorus oxychloride (2 mL) was refluxed for 1 h. After concentration in vacuo, the residue was poured into H_2O and filtered in vacuo to give **29** as a yellow foam (252 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.31 (2H, m), 2.20 (3H, s), 3.28–3.36 (1H, m), 3.72–3.83 (1H, m), 3.89 (1H, d, J = 15.3 Hz), 4.27–4.33 (1H, m), 4.39–4.48 (1H, m), 5.27 (1H, d, J = 15.3 Hz), 6.92–6.99 (2H, m), 6.99–7.07 (1H, m), 7.17–7.25 (2H, m), 7.54 (2H, s), 7 81 (1H, s). HRMS (EI) calcd for $C_{25}H_{19}ClF_6N_2O_2$ (M^+) 528.1039; found, 528.1013. Anal. Calcd for $C_{25}H_{19}ClF_6N_2O_2 \cdot 7H_2O$: C, 45.84; H, 2.92; N, 4.28. Found: C, 46.17; H, 3.28; N, 4.14.

5.1.50. 5-[3,5-Bis(trifluoromethyl)benzyl]-9-chloro-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (30a). The compound **30a** (1.80 g, 98%) was prepared from **28a** (1.77 g, 3.47 mmol) in a manner similar to that described for the preparation of **29**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81–1.94 (1H, m), 2.14–2.34 (4H, m), 3.20–3.33 (1H, m), 3.40–3.73 (1H, m), 3.98 (1H, d, J = 15.3 Hz), 4.32–4.42 (1H, m), 4.56–4.65 (1H, m), 5.40 (1H, d, J = 15.3 Hz), 6.68–7.38 (5H, m), 7.52 (2H, s), 7.78 (1H, s). HRMS (EI) calcd for $C_{25}H_{19}ClF_6N_2O_2$ (M^+) 528.1039; found, 528.1063. Anal. Calcd for $C_{25}H_{19}ClF_6N_2O_2 \cdot 3H_2O$: C, 51.51; H, 3.29; N, 4.81. Found: C, 51.38; H, 3.43; N, 4.74.

5.1.51. 5-[3,5-Bis(trifluoromethyl)benzyl]-9-chloro-7-phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (30b). The compound **30b** (440 mg, 99%) was prepared from **28b** (400 mg, 0.806 mmol) in a manner similar to that described for the preparation of **29**. mp: 177–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78–1.88 (1H,

m), 2.23–2.36 (1H, m), 3.33–3.42 (1H, m), 3.69–3.79 (1H, m), 4.12 (1H, d, J = 15.3 Hz), 4.28–4.37 (1H, m), 4.60–4.68 (1H, m), 5.46 (1H, d, J = 15.3 Hz), 7.19 (1H, s), 7.23–7.47 (5H, m), 7.69 (2H, s), 7.83 (1H, s). HRMS (EI) calcd for $C_{24}H_{17}ClF_6N_2O_2$ (M^+) 514.0883; found, 514.0865. Anal. Calcd for $C_{24}H_{17}ClF_6N_2O_2$: C, 55.99; H, 3.33; N, 5.44. Found: C, 55.98; H, 3.24; N, 5.25.

5.1.52. 9-(4-Acetylpiperazinyl)-5-[3,5-bis(trifluoromethyl)benzyl]-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]-1,5-oxazocin-6-one (1b). A mixture of **29** (79.4 mg, 0.150 mmol) and 1-acetylpiperazine (38.5 mg, 0.300 mmol) was heated at 150 °C for 5 h. The resulting mixture was diluted with ethyl acetate, then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt:MeOH = 10:1) of the residue gave **1b** as a colorless foam (51.4 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90–2.10 (2H, m), 2.13 (3H, s), 2.23 (3H, s), 3.21–3.29 (1H, m), 3.45–3.62 (4H, m), 3.62–3.78 (4H, m), 3.78–3.89 (1H, m), 3.92 (1H, d, J = 15.3 Hz), 4.10–4.18 (1H, m), 4.36–4.44 (1H, m), 5.34 (1H, d, J = 15.3 Hz), 6.11 (1H, s), 6.92–7.01 (1H, m), 7.01–7.08 (1H, m), 7.17–7.24 (2H, m), 7.57 (2H, s), 7.79 (1H, s). HRMS (EI) calcd for $C_{31}H_{30}F_6N_4O_3$ (M^+) 620.2222; found, 620.2244. Anal. Calcd for $C_{31}H_{30}F_6N_4O_3 \cdot \frac{1}{5}H_2O$: C, 59.65; H, 4.84; N, 8.98. Found: C, 59.27; H, 4.72; N, 8.76.

5.1.53. 9-(4-Acetylpiperazinyl)-5-[3,5-bis(trifluoromethyl)benzyl]-7-(2-methylphenyl)-3,4,5,6-tetrahydro-2*H*-pyrido[2,3-*b*]-1,5-oxazocin-6-one (2b). The compound **2b** (44.6 mg, 38%) was prepared from **30a** (100 mg, 0.189 mmol) in a manner similar to that described for the preparation of **1b**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81–1.95 (2H, m), 2.05–2.20 (4H, m), 2.27–2.35 (2H, m), 3.15–3.23 (1H, m), 3.52–3.62 (4H, m), 3.62–3.82 (5H, m), 3.93 (1H, d, J = 15.3 Hz), 4.28–4.36 (1H, m), 4.42–4.52 (1H, m), 5.31–5.43 (1H, m), 6.24 (1H, s), 6.75–7.33 (4H, m), 7.52 (2H, s), 7.77 (1H, s). HRMS (EI) calcd for $C_{31}H_{30}F_6N_4O_3$ (M^+) 620.2222; found, 620.2224. Anal. Calcd for $C_{31}H_{30}F_6N_4O_3$: C, 60.00; H, 4.87; N, 9.03. Found: C, 59.69; H, 4.73; N, 8.90.

5.1.54. 5-[3,5-bis(trifluoromethyl)benzyl]-9-morpholino-7-phenyl-3,4,5,6-tetrahydro-2*H*-pyrido[4,3-*b*]-1,5-oxazocin-6-one (2c). The compound **2c** (47.3 mg, 57%) was prepared from **30b** (75.0 mg, 0.146 mmol) in a manner similar to that described for the preparation of **1b**. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84–1.93 (1H, m), 2.07–2.20 (1H, m), 3.35–3.43 (1H, m), 3.50–3.63 (4H, m), 3.76–3.83 (4H, m), 3.92–4.01 (1H, m), 4.03–4.10 (1H, m), 4.13 (1H, d, J = 15.3 Hz), 4.40–4.52 (1H, m), 5.40 (1H, d, J = 15.3 Hz), 6.14 (1H, s), 7.24–7.37 (3H, m), 7.41–7.47 (2H, m), 7.78 (2H, s), 7.84 (1H, s). HRMS (EI) calcd for $C_{28}H_{25}F_6N_3O_3$ (M^+) 565.1800; found 565.1761. Anal. Calcd for $C_{28}H_{25}F_6N_3O_3$: C, 59.47; H, 4.46; N, 7.43. Found: C, 59.45; H, 4.50; N, 7.19.

5.2. Biology

5.2.1. NK_1 receptor antagonist test.[23] Guinea pigs were stunned by a blow on the head and then exsanguinated from the carotid artery and the ileum was isolated. The ileum was mounted in an organ bath containing Tyrode's solution, which was maintained at 32 °C and gased with 95% O_2 and 5% CO_2. The ileum was subjected to a resting tension of 1 g and allowed to equilibrate for 20 min before the experiment was started. As a control, a concentration–response curve for substance P obtained in the absence of test compounds was used. The NK_1 receptor antagonist activity of each test compound was determined from a concentration–response curve obtained by pretreatment with at least three concentrations of a test compound in DMSO solution for 10 min and subsequently applying substance P in a cumulative manner. The activity was expressed as a K_B value determined by the Schild method.[24]

5.2.2. Water solubility test. A sample solution of test compound (10 g/mL) was prepared by adding a test compound (2.0–4.0 mg) in dimethylsulfoxide (0.2–0.4 mL). The solution was added to aqueous buffer solution, pH 6.8, and the mixture was shaken vigorously for 15 min at room temperature, followed by filtering off the precipitate using a 96-well filterplate. An HPLC equipped with a photodiode array detector was used to measure the concentration of the sample solution.

5.2.3. Cystometry test[25]**.** Guinea pigs were anesthetized with halothane and the spinal cord was cut at the tenth cervical vertebra level in each animal. After restriction in a Ballman cage for more than 2 h, room-temperature saline was injected through a bladder catheter into the bladder at a rate of 6 mL/h to conduct a cystometry test. After the effective bladder capacity had stabilized, a DMSO solution of a test compound was administered intravenously from the jugular vein. The effective bladder capacity was defined as the volume of saline injected from the time of one micturition to the next. The effect of each test compound was regarded as the increase in the average bladder volume, determined by taking the difference between the average bladder volume measured 30 min prior to administration of the test compound and that measured every 30 min after administration of the test compound.

5.2.4. Rhythmic bladder contraction test. Rhythmic bladder contraction was observed when saline (1–2 mL) was injected into a balloon placed in the bladder of urethane-anesthetized guinea pigs. After rhythmic bladder contraction had stabilized, a DMSO solution of a test compound was administered by iv injection. The effect on rhythmic bladder contraction was evaluated in terms of frequency and amplitude of contraction.

Acknowledgments

The authors thank Dr. H. Miyachi, currently at the University of Tokyo, for many valuable suggestions and encouragement, and also Dr. T. Ishizaki, Dr. Y. Fukuda, and Dr. M. Segawa of Kyorin Pharmaceutical Co., Ltd., for helpful discussion.

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27. The ^{1}H NMR spectrum of **3g** showed an AB pattern for the benzylic and oxazocine ring methylene protons at room temperature. Each pair of methylene protons deteriorated to a very broad peak at 100 °C and collapsed to one peak but with distinct fission patterns at 150 °C. These results indicate that attempts to isolate the atropisomers about the oxazocine ring would give only racemic products due to rapid interconversion.