Solid-phase Synthesis and Preliminary Evaluation of 1,6,8-Trisubstituted Tetrahydro-2*H*-pyrazino[1,2-*a*]pyrimidine-4,7-diones as a NF-kB Inhibitor

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The solid-phase synthesis of new series of 1,6,8-trisubstituted tetrahydro-2*H*-pyrazino[1,2-*a*]pyrimidine-4,7-diones as bicyclic β-turn mimetics is described. Their NF-kB inhibition activities were tested and the effect of substituents on bicyclic ring was investigated. Among the prepared compounds, the fluorobenzyl and methoxybenzyl group substituted compounds **26** and **27** at *C*-1 and *C*-8 position showed more inhibitory activities than the others. Tested at a concentration of 10 uM, these two compounds showed a 60% inhibition against the target NF kB 549.

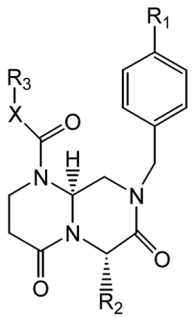
Key Words : Bicyclic β-turn mimetics, NF-kB inhibitor, Solid phase

Introduction

Nuclear factor-kB (NF-kB) has long been known to play a central role in the immune system by regulating the expression of key genes.[1] Moreover, activation of this transcription factor helps a wide variety of cell types survive damage induced by pro-apoptotic stimuli. Because of its crucial role in the regulation of pro-inflammatory genes, NF-kB is a promising target for the discovery of anti-inflammatory drugs. More recently, NF-kB has also emerged as a major culprit in a variety of human cancers mainly because of its ability to protect transformed cells from apoptosis. The pharmaceutical industry should, therefore, seriously consider testing inhibitors of NF-kB, identified as part of their anti-inflammatory drug discovery programs, on combination with other chemotherapeutic drugs on models of cancer.[2-4]

Several compounds which reported to inhibit NF-kB activation have been synthesized and investigated. Among those compounds, heteroaromatic carboxaimides,[5] substituted bezimidazols[6] and indoles[7] were developing in preclinical evaluations.

In order to develop new scaffold of NF-kB inhibitor, we try to apply β-turn peptidomimetic (**I**)[8-13] with the aim of discovering potent enzyme inhibitors and peptide hormone agonists and antagonists.[14]



R_1=OCH_3, -H, -F
R_2=-Isopropyl, isobutyl
R_3=Benzyl derivatives
X=O, S, N

I

In this paper, we described the synthesis and structure-activity relationships of new 1,6,8-trisubstituted tetrahydro-2*H*-pyrazino[1,2-*a*] pyrimidine-4,7-dione derivatives and our approach for preliminary evaluation of bicylic β-turn mimetics as a NF-kB Inhibitor.

Results and Discussion

Chemistry. A focused library of opioid peptide mimetics with these components was prepared according to our previously published solid-phase synthetic protocol.[10] Nucleophilic displacement of the bromide **1** with a number of primary amines gave the corresponding secondary amines **2** which was then coupled with the appropriate Fmoc-α-amino acids using HOBT/DIC in DMF. Treatment of **3** with 20% piperidine in DMF followed by coupling with Fmoc-β-alanine afforded **4**. After deprotection of the Fmoc group of **4** with 20% piperidine, the resin was treated with the *p*-nitrophenyl chloroformate in the presence of DIEA to produce **5**. The urea type compounds **6** were accomplished by treatment of compound **5** with corresponding phenyl amines.

Cleavage from the acetal resin followed by stereoselective tandem acyliminium cyclization was accomplished by treatment with formic acid at room temperature to give the 6,6-bicyclic β-turn mimetic **7**. All the compounds were purified by column chromatography (silica gel) to afford the pure products in good overall yields (27-83%).

Biological studies. All new 1,6,8-trisubstituted tetrahydro-2*H*-pyrazino[1,2-*a*] pyrimidine-4,7-dione derivatives (**1-35**) were subjected to preliminary *in vitro* NF-kB inhibitory activity screening[15] exhibited different biological properties, depending on the kind of substituents at the 1, 6 and 8 positions of the main bicyclic system. Based on the

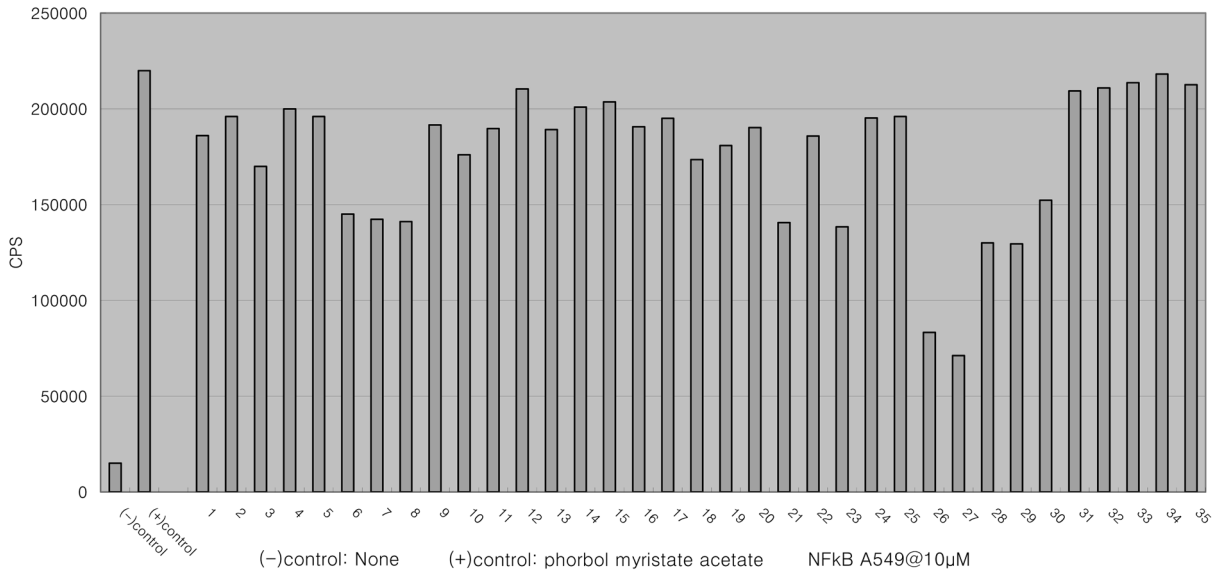
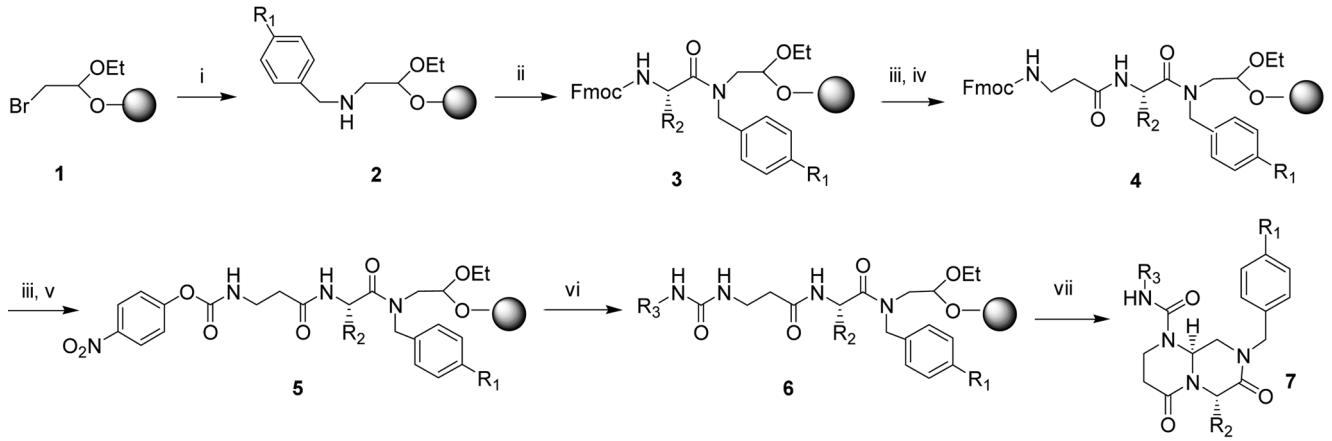


Figure 1. *In vitro* NFkB A549 activity of β-turn mimetics.



Scheme 1. (i) Benzyl amine derivatives. DMSO; (ii) Fmoc-Leu-OH (R_2 = isobutyl) or Fmoc-Val-OH (R_2 = isopropyl), 1,3-diisopropylcarbodiimide/1-hydroxybenzotriazole hydrate, DMF; (iii) 20% Piperidine in DMF; (iv) Fmoc-β-alanine, 1,3-diisopropylcarbodiimide/1-hydroxybenzotriazole hydrate, DMF; (v) *p*-Nitrophenyl chloroformate, diisopropylethylamine, THF/CH_2Cl_2 = 1/1; (vi) Phenyl amines, DMF; (vii) Formic acid.

results assembled in Figure 1, it can be shown that compounds (**21**-**30**) containing a methoxybenzyl group at *C*-8 position exhibited a little better activity than their benzyl group (**11**-**20**) and compounds (**11**, **13**, **16**, **17** and **19**) having a isobutyl group at *C*-6 position showed slight differences to their isopropyl group (**31**-**35**).

Among the prepared compounds, the fluorobenzyl and methoxybenzyl group substituted compounds **26** and **27** at *C*-1 and *C*-8 position showed more inhibitory activities than the others. Tested at a concentration of 10 uM, these two compounds showed a 60% inhibition against the target NFkB 549.

Experimental Section

^{1}H NMR spectra: Varian Gemini 300 spectrometer, tetramethylsilane (TMS), as an internal standard. The mass spectrometry system was based on a HP5989A MS Engine (Palo Alto, CA, USA).

N-Benzylamino-Resin (2). The resin **1**[16] (1.0 g, 1.3 mmol/g) and a solution of a benzylamine in DMSO (10 mL, 2 M) were placed in 20 mL vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 10-24 h. The resin was collected by filtration, and washed with DMF and CH_2Cl_2. For the storage, the resin was dried *in vacuo* at room temperature.

Fmoc-α-Amino Acid Coupled Resin (3). A solution of Fmoc-amino acid (Fmoc-Leu-OH (R_2 = isobutyl) or Fmoc-Val-OH (R_2 = isopropyl, 3.9 mmol), HOBT (0.60 g, 3.9 mmol) and DIC (0.60 mL, 3.9 mmol) in DMF was added to the resin (**2**) prepared above. After the reaction mixture was shaken for 3 h at room temperature, the resin was filtered and washed with DMF, MC, and then DMF. The resin was dried *in vacuo* at room temperature.

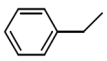
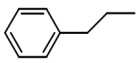
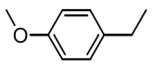
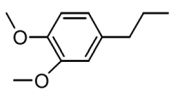
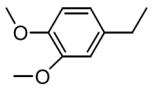
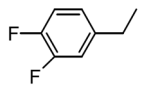
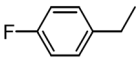
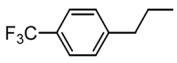
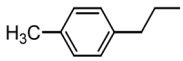
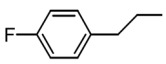
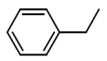
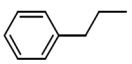
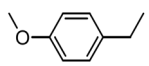
Fmoc-β-Amino Acid Coupled Resin (4). To the above resin (**3**) was added 20% piperidine in DMF (10 mL for 1 g

of the resin). After the reaction mixture was shaken for 20 min at room temperature, the resin was filtered and washed with DMF, MC, and then DMF. A solution of Fmoc-β-Alanine (1.20 g, 3.9 mmol) HOBT (0.60 g, 3.9 mmol) and DIC (0.60 mL, 3.9 mmol) in DMF was added to the resin prepared above. After being shaken for 3 h at room temperature, the resin was filtered and washed with DMF, MC, and then DMF. The resin was dried *in vacuo* at room temperature.

***p*-Nitrophenyl Coupled Resin (5).** To the above resin (**4**) was added 20% piperidine in DMF (10 mL for 1 g of the resin). After the reaction mixture was shaken for 20 min at room temperature, the resin was filtered and washed with DMF, MC, and then DMF. A solution of *p*-Nitrophenyl chloroformate (1.30 g, 6.5 mmol) and DIEA (0.68 mL, 3.9 mmol) in THF/CH_2Cl_2 was added to the resin prepared above. After being shaken for 2 h at room temperature, the resin was filtered and washed with DMF, MC, and then DMF. The resin was dried *in vacuo* at room temperature.

Benzylurea Coupled Resin (6). To the above resin (**5**)

Table 1. Bicyclic β-turn mimetics by solid-phase synthetic method

Entry	R_2	R_1	R_3	yield[a]	^{1}H-NMR ($CDCl_3$, δ) and MS data
1	isobutyl	F		70	0.92, 0.98 (2 × 3H, d, J = 6.3 Hz), 1.62 (1H, m), 1.82 (2H, m), 2.38 (2H, m), 3.30 (4H, m), 4.37 (2H, m), 4.64 (1H, m), 5.27 (2H, m), 5.96 (1H, t, J = 7.2 Hz), 6.98 (2H, t, J = 8.4 Hz), 7.25 (7H, m). -MS(FAB) m/z 467.2 $(MH)^+$
2	isobutyl	F		83	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.62 (1H, m), 1.78 (2H, m), 2.38 (2H, m), 2.83 (2H, m), 3.29 (2H, m), 3.52 (4H, m), 4.75 (2H, t, J = 6.0 Hz), 5.34 (1H, dd, J = 3.0 and 9.0 Hz), 5.97 (1H, q, J = 9.0 Hz), 7.03 (2H, t, J = 8.7 Hz), 7.25 (7H, m). -MS(FAB) m/z 481.3 $(MH)^+$
3	isobutyl	F		42	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.53 (2H, m), 3.31 (4H, m), 3.80 (3H, s), 4.35 (4H, m), 5.35 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.89 (2H, d, J = 8.7 Hz), 7.03 (2H, t, J = 8.7 Hz), 7.23 (4H, m). -MS(FAB) m/z 497.3 $(MH)^+$
4	isobutyl	F		50	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 2.78 (2H, t, J = 6.0 Hz), 3.30 (2H, m), 3.46 (4H, m), 3.86 (6H, s), 4.76 (2H, m), 5.37(1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.69 (2H, d, J = 6.3 Hz), 6.80 (1H, d, J = 8.47 Hz), 7.03 (2H, t, J = 8.7 Hz), 7.21 (2H, m). -MS(FAB) m/z 541.3 $(MH)^+$
5	isobutyl	F		45	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.39 (4H, m), 3.86 (6H, s), 4.36 (4H, m), 5.37 (1H, dd, J = 3.0 and 9.0 Hz), 6.00 (1H, q, J = 9.0 Hz), 6.83 (3H, s), 7.03 (2H, t, J = 8.7 Hz), 7.21 (2H, m). -MS(FAB) m/z 527.3 $(MH)^+$
6	isobutyl	F		35	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.65 (1H, m), 1.82 (2H, m), 2.43 (2H, m), 3.33 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01(1H, q, J = 6.0 Hz), 7.15 (7H, m). -MS(FAB) m/z 503.2 $(MH)^+$
7	isobutyl	F		53	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.34 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.03 (4H, t, J = 8.7 Hz), 7.21 (4H, m). -MS(FAB) m/z 485.2 $(MH)^+$
8	isobutyl	F		33	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.34 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.03 (2H, m), 7.21 (4H, m), 7.39 (2H, d, J = 9.0 Hz), 7.60 (2H, d, J = 9.0 Hz). -MS(FAB) m/z 535.23 $(MH)^+$
9	isobutyl	F		32	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.34 (3H, s), 2.39 (2H, m), 2.80 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 4.74 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 6.0 Hz), 7.06 (4H, m), 7.21 (4H, m). -MS(FAB) m/z 495.3 $(MH)^+$
10	isobutyl	F		36	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.63 (1H, m), 1.82 (2H, m), 2.44 (2H, m), 2.81 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 4.70 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.98 (1H, q, J = 6.0 Hz), 7.14 (8H, m). -MS(FAB) m/z 499.2 $(MH)^+$
11	isobutyl	H		80	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.78 (2H, m), 2.37 (2H, m), 3.29 (4H, m), 4.38 (3H, m), 5.33 (2H, m), 6.03 (1H, q, J = 2.3 Hz), 7.29 (10H, m). -MS(FAB) m/z 449.2 $(MH)^+$
12	isobutyl	H		52	0.98, 1.03 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.78 (2H, m), 2.38 (2H, m), 2.83 (2H, m), 3.29 (2H, m), 3.52 (4H, m), 4.75 (2H, t, J = 6.0 Hz), 5.34 (1H, dd, J = 3.0 and 9.0 Hz), 5.97 (1H, q, J = 9.0 Hz), 7.31 (10H, m). -MS(FAB) m/z 463.3 $(MH)^+$
13	isobutyl	H		55	0.97, 1.02 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.53 (2H, m), 3.31 (4H, m), 3.80 (3H, s), 4.35 (4H, m), 5.35 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.86 (2H, d, J = 6.0 Hz), 7.30 (7H, m). -MS(FAB) m/z 479.2 $(MH)^+$

[a]Yield of product 7 based upon original loading of resin 1.

Table 1. (continued)

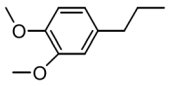
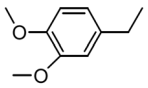
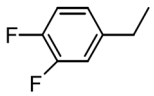
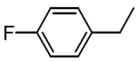
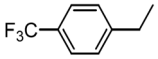
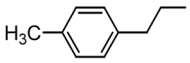
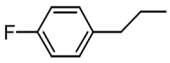
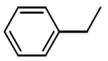
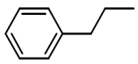
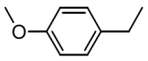
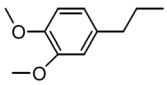
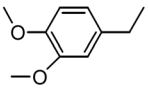
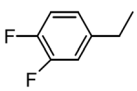
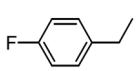
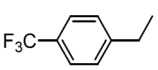
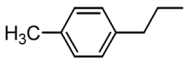
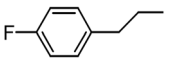
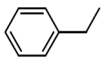
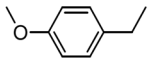
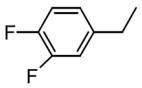
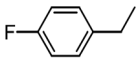
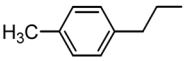
Entry	R_2	R_1	R_3	yield[a]	^{1}H-NMR ($CDCl_3$, δ) and MS data
14	isobutyl	H		43	0.98, 1.04 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 2.78 (2H, t, J = 6.0 Hz), 3.30 (2H, m), 3.46 (4H, m), 3.86 (6H, d, J = 3.0 Hz), 4.76 (2H, m), 5.37 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.75 (3H, dd, J = 9.0 and 33.0 Hz), 7.28 (5H, m). -MS(FAB) m/z 523.3 $(MH)^+$
15	isobutyl	H		34	0.97, 1.03 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.39 (4H, m), 3.86 (6H, d, J = 3.0 Hz), 4.36 (4H, m), 5.37 (1H, dd, J = 3.0 and 9.0 Hz), 6.00 (1H, q, J = 9.0 Hz), 6.82 (2H, s), 7.28 (6H, m). -MS(FAB) m/z 509.3 $(MH)^+$
16	isobutyl	H		31	0.94, 0.99 (2 × 3H, d, J = 6.6 Hz), 1.65 (1H, m), 1.82 (2H, m), 2.43 (2H, m), 3.33 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.17 (8H, m). -MS(FAB) m/z 485.2 $(MH)^+$
17	isobutyl	H		37	0.96, 1.01 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.34 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.00 (2H, t, J = 8.7 Hz), 7.27 (7H, m). -MS(FAB) m/z 467.2 $(MH)^+$
18	isobutyl	H		36	0.96, 1.02 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.34 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.30 (7H, m), 7.58 (2H, d, J = 9.0 Hz). -MS(FAB) m/z 517.2 $(MH)^+$
19	isobutyl	H		32	0.98, 1.04 (2 × 3H, d, J = 6.6 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.34 (3H, s), 2.39 (2H, m), 2.80 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 4.74 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 6.0 Hz), 7.09 (4H, dd, J = 7.8 and 21.9 Hz), 7.28 (5H, m). -MS(FAB) m/z 477.3 $(MH)^+$
20	isobutyl	H		31	0.98, 1.04 (2 × 3H, d, J = 6.6 Hz), 1.63 (1H, m), 1.82 (2H, m), 2.44 (2H, m), 2.81 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 4.70 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.98 (1H, q, J = 6.0 Hz), 7.00 (2H, t, J = 8.4 Hz), 7.23 (7H, m). -MS(FAB) m/z 481.2 $(MH)^+$
21	isobutyl	OCH_3		48	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.62 (1H, m), 1.82 (2H, m), 2.38 (2H, m), 3.30 (4H, m), 3.76 (3H, s), 4.37 (2H, m), 4.64 (1H, m), 5.27 (2H, m), 5.96 (1H, t, J = 7.2 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz), 7.27(5H, m). -MS(FAB) m/z 479.2 $(MH)^+$
22	isobutyl	OCH_3		32	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.62 (1H, m), 1.78 (2H, m), 2.38 (2H, m), 2.83 (2H, m), 3.29 (2H, m), 3.52 (4H, m), 3.76 (3H, s), 4.75 (2H, t, J = 6.0 Hz), 5.34 (1H, dd, J = 3.0 and 9.0 Hz), 5.97 (1H, q, J = 9.0 Hz), 6.96(4H, dd, J = 8.4 and 7.3 Hz), 7.27 (5H, m). -MS(FAB) m/z 493.2 $(MH)^+$
23	isobutyl	OCH_3		31	0.96, 1.02 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.53 (2H, m), 3.31 (4H, m), 3.80 (6H, s), 4.35 (4H, m), 5.35 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.96 (8H, m). -MS(FAB) m/z 509.3 $(MH)^+$
24	isobutyl	OCH_3		33	0.97, 1.04 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 2.78 (2H, t, J = 6.0 Hz), 3.30 (2H, m), 3.46 (4H, m), 3.86 (9H, s), 4.76 (2H, m), 5.37 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.75 (3H, dd, J = 9.0 and 3.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz).-MS(FAB) m/z 553.3 $(MH)^+$
25	isobutyl	OCH_3		31	0.97, 1.03 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.39 (4H, m), 3.86 (9H, s), 4.36 (4H, m), 5.37 (1H, dd, J = 3.0 and 9.0 Hz), 6.00 (1H, q, J = 9.0 Hz), 6.75 (3H, dd, J = 9.0 and 3.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz). -MS(FAB) m/z 539.3 $(MH)^+$
26	isobutyl	OCH_3		31	0.98, 1.04 (2 × 3H, d, J = 6.3 Hz), 1.65 (1H, m), 1.82 (2H, m), 2.43 (2H, m), 3.33 (4H, m), 3.81 (3H, s), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz), 7.34 (3H, m). -MS(FAB) m/z 515.2 $(MH)^+$
27	isobutyl	OCH_3		37	0.98, 1.04 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.34 (4H, m), 3.81 (3H, s), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz), 7.27 (4H, m). -MS(FAB) m/z 497.2 $(MH)^+$
28	isobutyl	OCH_3		30	0.98, 1.04 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.48 (2H, m), 3.34 (4H, m), 3.80 (3H, s), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.00 (1H, q, J = 6.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz), 7.14 (2H, m), 7.58 (2H, m). -MS(FAB) m/z 547.2 $(MH)^+$

Table 1. (continued)

Entry	R_2	R_1	R_3	yield[a]	^{1}H-NMR ($CDCl_3$, δ) and MS data
29	isobutyl	OCH_3		27	0.98, 1.04 (2 × 3H, d, J = 6.3 Hz), 1.60 (1H, m), 1.82 (2H, m), 2.34 (3H, s), 2.39 (2H, m), 2.80 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 3.80 (3H, s), 4.74 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 6.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz), 7.10 (4H, dd, J = 7.8 and 21.9 Hz). -MS(FAB) m/z 507.3 $(MH)^+$
30	isobutyl	OCH_3		31	0.98, 1.04 (2 × 3H, d, J = 6.3 Hz), 1.63 (1H, m), 1.82 (2H, m), 2.44 (2H, m), 2.81 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 3.80 (3H, s), 4.70 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.98 (1H, q, J = 6.0 Hz), 6.96 (4H, dd, J = 8.4 and 7.3 Hz), 7.23 (4H, m). -MS(FAB) m/z 511.3 $(MH)^+$
31	isopropyl	H		56	0.99, 1.11 (2 × 3H, d, J = 6.7 Hz), 1.60 (1H, m), 2.37 (2H, m), 3.29 (4H, m), 4.38 (3H, m), 5.33 (2H, m), 6.03 (1H, q, J = 2.3 Hz), 7.29 (10H, m). -MS(FAB) m/z 435.2 $(MH)^+$
32	isopropyl	H		56	0.99, 1.11 (2 × 3H, d, J = 6.7 Hz), 1.60 (1H, m), 2.53 (2H, m), 3.31 (4H, m), 3.80 (3H, s), 4.35 (4H, m), 5.35 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 9.0 Hz), 6.86 (2H, d, J = 6.0 Hz), 7.30 (7H, m). -MS(FAB) m/z 465.2 $(MH)^+$
33	isopropyl	H		27	0.99, 1.11 (2 × 3H, d, J = 6.7 Hz), 1.65 (1H, m), 2.43 (2H, m), 3.33 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.17 (8H, m). -MS(FAB) m/z 471.2 $(MH)^+$
34	isopropyl	H		29	0.99, 1.11 (2 × 3H, d, J = 6.7 Hz), 1.60 (1H, m), 2.48 (2H, m), 3.34 (4H, m), 4.35 (4H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 6.01 (1H, q, J = 6.0 Hz), 7.00 (2H, t, J = 8.7 Hz), 7.27 (7H, m). -MS(FAB) m/z 453.6 $(MH)^+$
35	isopropyl	H		31	0.99, 1.11 (2 × 3H, d, J = 6.7 Hz), 1.60 (1H, m), 2.34 (3H, s), 2.39 (2H, m), 2.80 (2H, t, J = 6.6 Hz), 3.30 (2H, m), 3.48 (4H, m), 4.74 (2H, m), 5.32 (1H, dd, J = 3.0 and 9.0 Hz), 5.99 (1H, q, J = 6.0 Hz), 7.09 (4H, dd, J = 7.8 and 21.9 Hz), 7.28 (5H, m). -MS(FAB) m/z 463.3 $(MH)^+$

was added benzyl amine in DMF (10 mL for 1 g of the resin). After the reaction mixture was shaken for 3 h at room temperature, the resin was filtered and washed with DMF, MC, and then DMF. The resin was dried *in vacuo* at room temperature

(6S)-8-Benzyl-6-isobutyl-1-[(benzylamino)carbonyl]-tetrahydro-2H-pyrazino[1,2-a] pyrimidine-4,7-dione (Entry 11). The resin **6** was treated with formic acid (15 mL for 1 g of resin) for 10 h at room temperature. After the resin was removed by filteration, the filterate was condensed under reduced pressure to give oily residue, which was then purified by column chromatography (silica gel, ethyl acetate-methanol). ^{1}H-NMR and mass data results of compounds **1-35** are given in Table 1.

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References

1. Haefner, B. *Drug discovery today* **2002**, *7*, 653.
2. Karin, M.; Cao, Y.; Greten, F. R.; Li, Z.-W. *Nat. Rev. Cancer* **2002**, *2*, 301.
3. O'Byrne, K. J.; Dalgleish, A. G. *Br. J. Cancer* **2001**, *85*, 473.
4. Balkwill, F.; Mantovani, A. *Lancet*. **2001**, *357*, 539.
5. Baxter, A.; Brough, S.; Faull, A.; Johnstone, C.; Mcinally, T. *WO0158890*.
6. Ritzeler, O.; Stilz, H. U.; Neises, B.; Bock, W. J.; Walser, A.; Flynn, G. A. *WO0100610*.
7. Ritzeler, O.; Stilz, H. U.; Neises, B.; Jaehne, G.; Habermann, J. *WO0130774*.
8. Kahn, M. *Synlett*. **1993**, *11*, 821.
9. (a) Souers, A. J.; Virgilio, A. A.; Schürer, S. S.; Ellman, J. A.; Kogan, T. P.; Ankener, H. W.; Vanderslice, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2297. (b) Souers, A. J.; Virgilio, A. A.; Rosenquist, A.; FenuikJ. A.; Ellman, A. *J. Am. Chem. Soc.* **1999**, *121*, 1817.
10. Masakatsu, E.; Lee, M. S.; Hiroshi, N.; Marcin, S.; Scott, L.; Kahn, M. *J. Am. Chem. Soc.* **1999**, *121*, 12204.
11. Masakatsu, E.; Lee, M. S.; Richard, Y. W.; Shea, J. P.; Marcin, S.; Scot, L.; Kahn, M. *J. Med. Chem.* **2002**, *45*, 1395.
12. Masakatsu, E.; Lee, M. S.; Stasiak, M.; Kahn, M. *Tetrahedron Lett.* **2001**, *42*, 1237.
13. Kee, K. S.; Jois, D. S. *Current Pharmaceutical Design* **2003**, *9*, 1209.
14. (a) Kahn, M. Ed. *Tetrahedron* **1993**, *49*, Symposia 50, 3433. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (c) Gillespie, P.; Cicariello, J.; Olson, G. L. *Biopolymers* **1997**, *43*, 191. (d) Hanessian, S.; Huynh, H. K.; Reddy, G. V.; McNaughton-Smith, G.; Ernst, B.; Sweeley, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2803. (e) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334. (f) Hirschmann, R.; Hynes, J.; Cichy-Knight, M. A.; Pietranico-Cole, S.; Smith, A. B. *J. Med. Chem.* **1998**, *41*, 1382.
15. Jeong, D.-W.; Yoo, M.-H.; Kim, T. S.; Kim, J.-H.; Kim, I. Y. *The J. of Biol. Chem.* **2002**, *277*, 17871.
16. Bromoacetal Resin (1) was purchased from Advanced ChemTech.