Solid-phase Synthesis of 7-Aryl-benzo[*b*][1,4]oxazin-3(4*H*)-one Derivatives on a BOMBA Resin Utilizing the Smiles Rearrangement

Ji Min Lee, Eun-Ae Yu, Joo Yeon Park, In Ae Ryu, Dong Soo Shin,† and Young-Dae Gong*

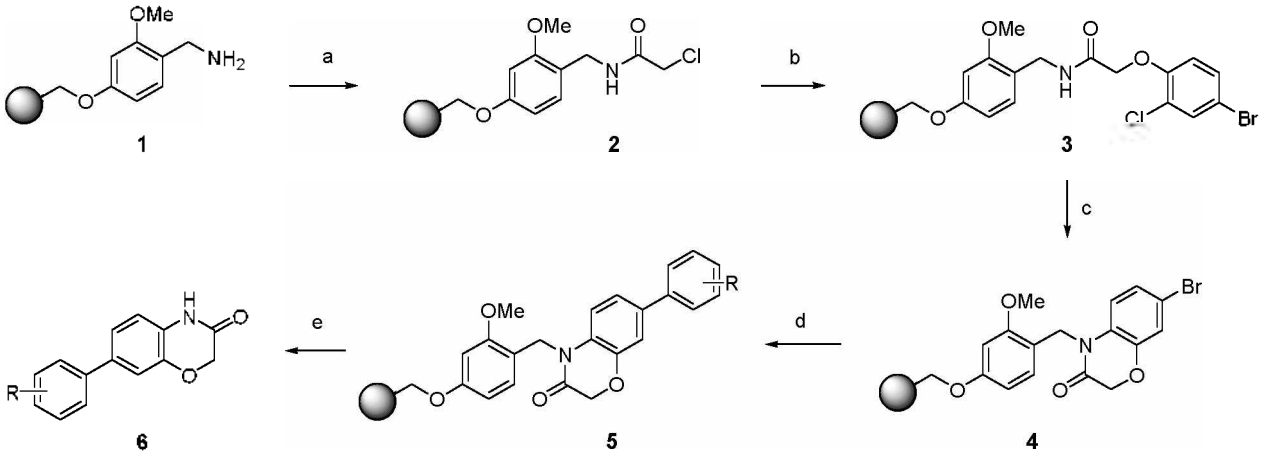
*Center for High Throughput Synthesis Platform Technology, Korea Research Institute of Chemical Technology, P. O. Box 107, Yuseong, Daejon 305-600, Korea. *E-mail: ydgong@krict.re.kr*
†Department of Chemistry, Changwon National University, Changwon, Gyeongnam 641-773, Korea
Received March 12, 2009, Accepted April 27, 2009

A general method has been developed for the solid phase synthesis of drug-like 7-aryl-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives **6**. The method relies on a novel, microwave irradiation promoted cyclization reaction of the BOMBA resin bound, *N*-substituted-α-(2-chloro-4-bromophenoxy)acetamide **3** that takes place *via* a Smiles rearrangement. The 7-bromobenzo[1,4]oxazine **4**, produced in this process is converted to 7-aryloxazin analogs **5** by utilizing Suzuki coupling with various substituted arylboronic acids. Finally, the target 7-aryl-benzo[*b*][1,4]oxazin-3(4*H*)-ones **6** are liberated from the resin by treatment with 5% TFA. The progress of the reactions involved in this preparative route can be monitored by using ATR-FTIR spectroscopy on a single bead. The target compounds, obtained by using this five-step sequence, are produced in high yields and purities.

Key Words: Solid-phase synthesis, Benzo[*b*][1,4]oxazin, Smiles rearrangement, Microwave irradiation, BOMBA resin.

Introduction

Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs.[1] This is especially true for six-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities.[2] In this respect, the utility of the benzo[*b*][1,4]oxazin scaffold as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been amply demonstrated. The benzo[*b*][1,4]oxazin derivatives have been used as the basic framework for substances of interest in numerous therapeutic areas, such as anti-candina albicans,[3] antifungals,[4] and kinase inhibitors.[5] As a part of a research program aimed at drug discovery and high throughput organic synthesis, we needed to develop a facile and rapid solid-phase approach for the construction of drug-like small heterocyclic molecules.[6] A specific focus of this effort was on modulators of kinase inhibitors, which have been identified as allosteric modulators of a wide variety of untreated kinases, including PI3Kinaser.[7] Our interest concentrated on the construction of benzo[*b*][1,4]oxazin derivatives since substances containing this structural platform are known to serve as PI3Kinase γ inhibitors. However, solid-phase synthetic methods to readily generate various aryl substituted benzo[*b*][1,4]oxazin have not been explored. As a matter of fact, most of the known benzo[*b*][1,4]oxazin derivatives have been prepared by solution-phase synthetic routes that employ the Smiles rearrangement.[8] Thus, the goals of the current study were (**1**) to develop a simple and efficient solid-phase synthetic methodology to produce various 7-aryl-benzo[*b*][1,4]oxazin derivatives, and (**2**) to discover novel hit compounds that would be active



Schem 1. Reagents and conditions: (a) 2-Chroloacetyl chloride, pyridine, CH_2Cl_2, rt, 8 hr.; (b) 4-Bromo-2-chlorophenol, Cs_2CO_3, DMF, 80 °C 12 hr.; (c) Cs_2CO_3, DMF, μw, 200 °C, 1 hr.; (d) Substituted phenyl boronic acids, KF, $Pd(PPh_3)_4$, DME, EtOH, 60 °C, 24 hr., R = Halogens, MeO Me, PhO *etc.*; (e) TFA (5% H_2O), CH_2Cl_2, 60 °C, 6 hr.

kinase inhibitors.

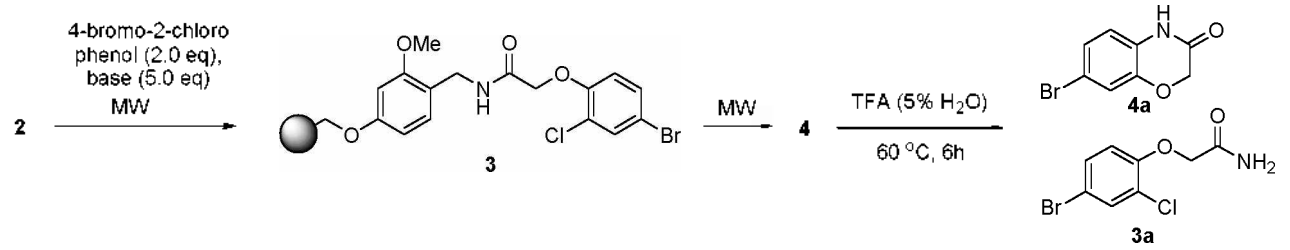
Below, the preparative route relies on a microwave irradiation promoted, Smiles rearrangement type cyclization reaction of a *N*-substituted-α-(2-chloro-4-bromophenoxy)acetamide (**3**) linked to a 4-benzyloxy-2-methoxybenzylamine (BOMBA) resin[9] (Scheme 1). This process generates the benzo[*b*][1,4]-oxazin **4** that is readily converted to the target 7-arylbenzo [*b*][1,4]oxazin derivatives **6** by using Suzuki coupling reactions with various arylboronic acids.

Results and Discussion

The sequence used to prepare the α-chloroacetamide resin **2** employs the BOMBA resin **1** as the starting polymer support. Treatment of the BOMBA resin **1** with α-chloroacetyl chloride in the presence of pyridine at room temperature leads to production of the corresponding α-chloroacetamide resin **2**. The progress of this reaction was monitored by measuring the growth of typical amide stretching band at 1675 cm^{-1} by using ATR-FTIR. Resin **2** is first swollen in DMF and, in a manner that the route employed in the solution-phase counterpart, it is then reacted with 4-chloro-2-bromophenol to give the corresponding BOMBA resin bound, *N*-linked α-(2-chloro-4-bromophenoxy)acetamide **3**. The progress of this reaction was monitored by using ATR-FTIR, which displayed a slightly shift of the amide band from 1675 to 1672 cm^{-1}. The Smiles rearrangement based cyclization of **3** to form the benzo[*b*][1,4]oxazin skeleton found in the key intermediate **4** was explored next. Based on the results of our previous investigation,[10] a suspension of the α-(2-chloro-4-bromophenoxy) acetamide resin **3** in DMF containing Cs_2CO_3 was subjected to microwave irradiation.[11] However, under these conditions the Smiles-cyclization reaction did not take place. And also we could not obtained desired Smiles-cyclization product from the benzo[*b*][1,4]oxazin skeleton found in the key intermediate resin **4** under the same solution-phase reaction condition with three components one pot reaction condition.[12] An exploration of a number of methods to promote this process (Table 1) led to the finding that the optimal conditions to promote the Smiles-cyclization reaction involve the use of much higher temperatures and a microwave irradiation condition.[13] The progress of the cyclization reaction was monitored by observing the shift of the amide band from 1672 cm^{-1} to 1688 cm^{-1} in the ATR-FTIR. In this reaction, we had very difficult to find out each reaction progress using ATR-FTIR. Therefore as shown Figure 1, we had finally confirmed 7-bromo benzo[*b*]-[1,4]oxazin core structure which was obtained from benzo[*b*]-[1,4]oxazine BOMBA resin **5** by X-ray crystallography. A variety of 7-aryl substituted benzo[1,4]oxazine BOMBA resin **5** were then generated by using Suzuki coupling reactions of **4** with a series of substituted phenyl boronic acids. Finally, upon treatment with 5% aqueous TFA cleavage from the resin occurred to furnish the target 7-aryl-[*b*][1,4]oxazin-3(4*H*)-ones derivatives **6** (Table 2).

In summary, an efficient method for the solid phase parallel synthesis of drug-like 7-aryl-benzo[*b*][1,4]oxazin-3(4*H*)-ones **6** has been devised. The preparative sequence employs a microwave promoted Smiles rearrangement-cyclization reaction of BOMBA resin bound α-(2-chloro-4-bromophenoxy) acetamide **3**. Suzuki coupling reactions on the resulting BOMBA resin **4** with arylboronic acids followed by acid cleavage from the resin led to the formation of a series of 7-aryl-benzo[*b*][1,4]oxazin-3(4*H*)-ones **6**.

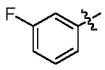
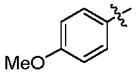
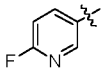
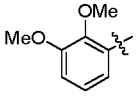
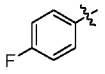
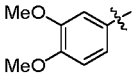
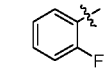
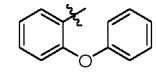
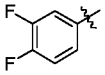
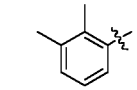
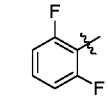
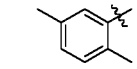
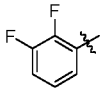
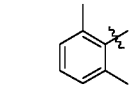
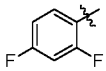
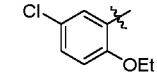
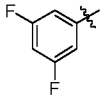
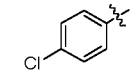
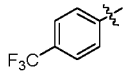
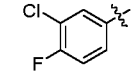
Table 1. Smiles rearrangement cyclization (**2** → **4**) conditions to form benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives on BOMBA resin **4**



Entry	Base	Solvent	Temp (°C)	Conditions	Reaction time	Yields[a](%)	
						4a	**3a**
1[b]	NaH	DMF	200	microwave	1 hr	-	
2[b]	Na_2CO_3	DMF	200	microwave	1 hr	-	7
3[b]	K_2CO_3	DMF	200	microwave	1 hr	trace	14
4[b]	Cs_2CO_3	DMF	200	microwave	1 hr	21	trace
5[b]	Cs_2CO_3	MeCN	70	thermal	12 h	-	8
6[b]	Cs_2CO_3	DMF	80	thermal	12 h	7	29
7[c]	Cs_2CO_3	DMF	80/200	thermal/microwave	12 h/1 hr	34	-

[a]Isolated yields after purification by flash chromatography and three-step overall yield from BOMBA resin 1 (loading capacity 1.25 mmol/g). [b]Three components one pot reaction (from **2** — **4**) performed with thermal and microwave conditions. [c]Step by step reaction performed with thermal (from **2** — **3**) and microwave (from **3** — **4**) conditions.

Table 2. The yields and purities of the 7-aryl-benzo[*b*][1,4]oxazin-3(4*H*)-ones on BOMBA resin **5**

Compound	Structure	Yield[a] (%)	Purity[b] (%)	Compound	Structure	Yield[a] (%)	Purity[b] (%)
1a		20	> 99	**1k**		23	> 99
1b		14	> 99	**1l**		11	> 99
1c		19	> 99	**1m**		21	> 99
1d		19	> 99	**1n**		14	93
1e		20	> 99	**1o**		28	> 99
1f		20	92	**1p**		24	> 99
1g		21	> 99	**1q**		22	90
1h		31	85	**1r**		27	> 99
1i		32	92	**1s**		21	95
1j		19	> 99	**1t**		23	93

[a]Five step overall yield from BOMBA resin **1** (loading capacity 1.25 mmol/g). [b]Purities of the final products were identified by LC/MS.

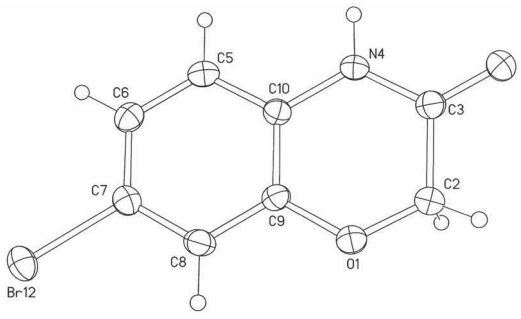


Figure 1. X-ray crystallography of 7-bromo benzo[*b*][1,4]oxazin obtained from BOMBA resin **4**.

Experimental Procedures

General experimental methods. The Merrifield resin (loading capacity 2.00 mmol/g, 100-200 mesh) was obtained from Bead Tech. Most of the reagents were purchased from Sigma-Aldrich. Solvents were purchased from J. T. Baker and were HPLC grade. Suzuki coupling reaction was carried out on the Automated Microwave synthesis system (Emrys Creator).[13] Solvent evaporation was performed on GeneVac Atlas HT-4 centrifugal evaporator. Crude products were purified by parallel chromatography using Quad3™. ATR-FTIR spectra were recorded on Travel IR™ (Sence IR Technology) spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 500 spectrophotometer. LC-UV-MS analyses were performed a Waters ZQ mass spectrometer equipped with PDA (200-400 nm) detection using XterraMS column (C18, 5M, 4.6 × 100 mm) from Waters. A typical gradient was 5-95% CH_3CN/H_2O containing 0.1% trifluoroacetic acid. X-ray crystallography was recorded on SMART Apex II CCD area-detector X-ray Diffractometer and SHELXTL program (Bruker). HRMS data recorded on Micromass Auto Spec MS.

Preparation of BOMBA resin (1) and determination of loading capacity. We had prepare BOMBA resin **1** by known procedure form the Merrifield resin.[9] **(a) Loading**: To an ice cold slurry of BOMBA resin **1** (0.20 g) and *N,N*-Diisopropylethylamine (0.42 mL, 2.40 mmol), was added a solution of 9-fluorenylmethoxycarbonyl chloride (0.41 g, 1.60 mmol) in CH_2Cl_2 (10 mL). The slurry was incubated for 3 h at room

temperature. Then the resin was removed by filteration and sequentially washed with H_2O, MeOH and CH_2Cl_2. Following a final wash with MeOH, the resin was dried in vacuum oven. The Fmoc-amino resin was obtained as light yellow sold (0.28 g). On bead ATR-FT IR: 3025, 2922, 1708 (amide), 1612, 1589, 1493, 1450, 1421, 1245, 1197, 1159, 1130, 1029, 1019, 823, 758, 736, 699 cm^{-1}. **(b) Deloading**: A suspension of the Fmoc amino resin (0.28 g) and piperidine (2 mL) in CH_2Cl_2 (8 mL) was stirred at room temperature for 2 h. Then the resin was filtered and washed with CH_2Cl_2 (2 × 50.0 mL). The filtrate was concentrated *in vacuo* giving a residue which was subjected to silica gel column chromatography (*n*-hexane-EtOAc, 10:1, v/v) to afford 9-methylene-9*H*-fluorene (45 mg, BOMBA resin loading capacity 1.25 mmol/g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (s, 2H), 7.30-7.33 (td, *J* = 7.5 and 1.1 Hz, 2H), 7.37-7.40 (td, *J* = 7.5 and 1.1 *Hz*, 2H), 7.70-7.71 (dt, *J* = 7.5 and 0.9 Hz, 2H), 7.74-7.76 (dt, *J* = 7.5 and 0.9 Hz, 2H).

***N*-Substituted α-chloroacetamide on BOMBA resin (2).** To a mixture of BOMBA resin **1** (1.00 g, theoretically 1.25 mmol/g) in CH_2Cl_2 (15.0 mL) was added pyridine (0.30 mL, 3.75 mmol) and 2-chloro acetyl chloride (0.30 mL, 3.75 mmol). The mixture was stirred in room temperature. After agitating 12 h, the resin was filtered and washed with CH_2Cl_2, MeOH, H_2O then several times with MeOH and CH_2Cl_2. Following final wash with MeOH, the resin dried in vacuum oven. Resin **2** was obtained as a light brown solid (1.16 g). On bead ATR-FT IR: 3024, 2921, 1675 (C=O, amide), 1611, 1509, 1493, 1451, 1421, 1377, 1286, 1264, 1197, 1160, 1129, 1028, 1018, 822, 759, 737, 698 cm^{-1}.

***N*-Substituted α-(2-chloro-4-bromophenoxy) acetamide on BOMBA resin (3).** To a mixture of resin **2** (1.11 g) in DMF (15.0 mL) was added cesium carbonate (2.42 g, 7.42 mmol) and 4-bromo-2-chlorophenol (1.16 g, 5.56 mmol). The mixture was stirred at 80 °C for 12 h. After which time, the resin was filtered and washed with DMF, MeOH, H_2O, then several times with MeOH and CH_2Cl_2. Following final wash with MeOH, the resin dried in vacuum oven. Resin **3** was obtained as a dark brown solid (1.20 g). On bead ATR-FT IR: 3024, 2922, 1672 (C=O, amide), 1610, 1508, 1493, 1451, 1421, 1376, 1286, 1261, 1196, 1160, 1136, 1127, 1029, 820, 757, 698 cm^{-1}.

7-Bromobenzo[*b*][1,4]oxazin on BOMBA resin (4). To a suspension of resin **3** (0.50 g) in DMF (12.0 mL) was added cesium carbonate (1.02 g, 3.12 mmol) were placed in a Pyrex tube. The tube was sealed, positioned in the cavity and irradiation at 200 °C for 1 h. After which time the reaction mixture was cooled to room temperature. The resin was filtered and washed with DMF, MeOH, H_2O, then several times with MeOH and CH_2Cl_2. Following final wash with MeOH, the resin dried in vacuum oven. Resin **4** was obtained as a dark brown solid (5.05 g). On bead ATR-FT IR: 3024, 2920, 2851, 1688 (C=O, amide), 1603, 1589, 1504, 1493, 1451, 1421, 1389, 1285, 1264, 1195, 1159, 1125, 1115, 1075, 1029, 908, 820, 757, 697 cm^{-1}.

General procedure for the suzuki coupling as applied to the synthesis of 7-(3-fluoro-phenyl)benzo[*b*][1,4]oxazin on BOMBA resin (5a). The resin **4** (0.25 g) was placed reaction vessel with degassed DME (1,2-dimethoxy ethane, 3.00 mL), followed by addition of $Pd(PPh_3)_4$ (36.1 mg, 0.03 mmol). A solution of 3-fluorophenyl boronic acid (0.22 g, 1.56 mmol) in degassed EtOH (0.6 mL) was added to the resin, and the mixture was agitated for 5 min and then potassium fluoride (90.8 mg, 1.56 mmol) was added. The mixture was stirred for 24 h, 60 °C. The resin was filtered and washed with MeOH, H_2O then several times with MeOH and CH_2Cl_2. Following final wash with MeOH, the resin dried in vacuum oven. The dark brown biphenyl resin **5a** (0.27 g) was obtained. On bead ATR-FT IR: 3024, 2919, 1687 (C=O, amide), 1612, 1508, 1493, 1451, 1396, 1287, 1195, 1158, 1030, 819, 758, 697 cm^{-1}.

General procedure for the cleavage as applied to the synthesis of 7-(3-fluoro-phenyl)benzo[*b*][1,4]oxazin(6a). The resin **5a** (0.27 g) was treated with a mixture of TFA/H_2O (95:5, v/v) for 6 h, at 60 °C. After which time, the resin was washed with CH_2Cl_2 several times. The organic filtrates were neutralized by saturated $NaHCO_3$ solution. The filtrate was washed water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc/CH_2Cl_2, 4:1:1) to afford 7-(3-fluoro-phenyl)-4*H*-benzo [*b*][1,4] oxazin-3-one, **6a** (15 mg, 20%, five-step overall yield from BOMBA resin, loading capacity 1.25 mmol/g) as an white solid.

7-(3-Fluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6a). **6a** was isolated as an white solid (15 mg, 20%). ^{1}H NMR (500 MHz, acetone-d_6) δ 4.68 (s, 2H), 7.08-7.09 (d, *J* = 8.1 Hz, 1H), 7.08-7.12 (m, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.30-7.32 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.38-7.41 (m, 1H), 7.46-7.48 (m, 2H), 9.74 (br s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 68.0, 114.0, 114.6, 115.6, 117.1, 122.0, 123.3, 131.5, 135.7, 143.5, 145.1, 163.2, 165.3; MS (ESI) *m/z* 244 ($[M+H]^-$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{14}H_{10}NO_2F$ 243.0696, found 243.0691.

7-(6-Fluoro-pyridin-3-yl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6b). **6b** was isolated as an white solid (11 mg, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (s, 2H), 6.91-6.89 (d, *J* = 8.1 Hz, 1H), 6.99-7.01 (dd, *J* = 8.5 and 3.1 Hz, 1H), 7.14-7.16 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 7.90-7.94 (m, 1H), 8.06 (br s, 1H), 8.38 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.5, 109.6, 109.9, 115.7, 116.5, 121.5, 126.2, 133.2, 139.5, 139.6, 144.3, 145.7, 145.8, 165.4; MS (ESI) *m/z* 245 ($[M+H]^-$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{13}H_9N_2O_2F$ 244.0648, found 244.0642.

7-(4-Fluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6c). **6c** was isolated as an white solid (14 mg, 19%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (s, 2H), 6.84-6.86 (d, *J* = 8.1 Hz, 1H), 7.10-7.13 (t, *J* = 8.7 Hz, 2H), 7.14-7.16 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.47-7.50 (dd, *J* = 8.8 and 5.3 Hz, 2H), 7.95 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.6, 115.6, 115.8, 116.0, 116.2, 121.4, 128.5, 128.5, 136.9, 144.1, 165.3; MS (ESI) *m/z* 244 ($[M+H]^+$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{14}H_{10}NO_2F$ 243.0696, found 243.0691.

7-(2-Fluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6d). **6d** was isolated as an white solid (14 mg, 19%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.91 (s, 3H), 4.67 (s, 2H), 6.86-6.87 (d, *J* = 8.1 Hz, 1H), 6.90-6.93 (m, 2H), 7.08-7.11 (dd, *J* = 8.2 and, 8.2 Hz, 1H), 7.17-7.19 (dd, *J* = 8.1, 1.8 Hz,

1H), 7.21 (d, J = 1.8 Hz, 1H), 8.09 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.0, 116.3, 116.5, 118.5, 121.2, 124.7, 128.5, 129.6, 129.6, 130.5, 161.5; MS (ESI) m/z 244 ($[M+H]^+$); HRMS (EI) m/z $[M]^-$ calcd for $C_{14}H_{10}NO_2F$ 243.0696, found 243.0693.

7-(3,4-Difluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6e). 6e was isolated as an white solid (16 mg, 20%), ^{1}H NMR (500 MHz, acetone-d_6) δ 4.62 (2H, s), 7.07-7.09 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.28-7.30 (dd, J = 8.1, 2.0 Hz, 1H), 7.36-7.41 (m, 1H), 7.46-7.49 (m, 1H), 7.58-7.62 (m, 1H), 9.73 (br s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 67.8, 115.2, 117.3, 118.5, 121.8, 123.9, 128.7, 135.3, 138.6, 145.2, 149.5, 165.4; MS (ESI) m/z 262 ($[M+H]^-$); HRMS (EI) m/z $[M]^-$ calcd for $C_{14}H_9NO_2F_2$ 261.0601, found 261.0605.

7-(2,6-Difluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6f). 6f was isolated as an white solid (16 mg, 20%), ^{1}H NMR (500 MHz, acetone-d_6) δ 4.62 (s, 2H), 7.07-7.09 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 1.9 Hz, 1H), 7.28-7.30 (dd, J = 8.1, 2.0 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.35-7.39 (t, J = 8.7 Hz, 1H), 7.61-7.64 (dq, J = 8.6, 2.3 Hz, 1H), 7.75-7.57 (dd, J = 7.0, 2.3 Hz, 1H), 9.73 (br s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 68.0, 115.7, 117.2, 117.8, 118.0, 121.9, 127.8, 129.5, 134.7, 138.8, 145.1, 157.2, 159.2, 165.3; MS (ESI) m/z 262 ($[M+H]^+$); HRMS (EI) m/z $[M]^+$ calcd for $C_{14}H_9NO_2F_2$ 261.0601, found 261.0604.

7-(2,3-Difluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6g). 6e was isolated as an white solid (17 mg, 21%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (s, 2H), 6.87-6.88 (d, J = 8.1 Hz, 1H), 7.12-7.18 (m, 4H), 7.20 (m, 1H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 19.9, 22.4, 31.4, 48.9, 54.0, 59.6, 67.1, 116.0, 116.8, 123.1, 124.7, 125.4, 127.7, 129.5, 130.4, 143.8, 164.5, 170.0; MS (ESI) m/z 262 ($[M+H]^+$); HRMS (EI) m/z $[M]^-$ calcd for $C_{14}H_9NO_2F_2$ 261.0601, found 261.0604.

7-(2,4-Difluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6h). 6h was isolated as an white solid (21 mg, 25%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (2H s), 6.87-6.88 (d, J = 8.1 Hz, 1H), 7.12-7.18 (m, 4H), 7.20 (m, 1H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.1, 104.3, 116.0, 117.1, 123.2, 124.0, 125.5, 126.0, 130.1, 143.5, 165.9; MS (ESI) m/z 262 ([M+ H]$^-$); HRMS (EI) m/z $[M]^+$ calcd for $C_{14}H_9NO_2F_2$ 261.0601, found 261.0607.

7-(3,5-Difluoro-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6i). 6i was isolated as an white solid (26 mg, 32%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (s, 2H), 6.75-6.80 (tt, J = 8.8 and 2.3 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 7.04-06 (dd, J = 8.7, 2.2 Hz), 7.15-7.17 (dd, J = 8.1, 2.0 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 8.51 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.4, 93.0, 106.5, 116.0, 117.3, 123.4, 125.0, 126.6, 130.9, 133.8, 168.9; MS (ESI) m/z 262 ($[M+H]^+$); HRMS (EI) m/z $[M]^-$ calcd for $C_{14}H_9NO_2F_2$ 261.0601, found 261.0603.

7-(4-Trifluoromethyl-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6j). 6j was isolated as an white solid (17 mg, 19%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (s, 2H), 7.11-7.13 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.35-7.37 (dd, J = 8.1, 2.0 Hz, 1H), 7.76-7.78 (d, J = 8.2 Hz, 2H), 7.85-7.87 (d, J = 8.2 Hz, 2H), 9.78 (br s, 1H); ^{13}C NMR(125 MHz, acetone-d_6) δ 55.0, 68.0, 115.9, 117.3, 122.2, 126.6, 128.3, 135.4, 144.9, 145.2, 165.4; MS (ESI) m/z 294 ($[M+H]^-$); HRMS (EI) m/z $[M]^-$ calcd for $C_{15}H_{10}NO_2F_3$ 293.0664, found 293.0667

7-(4-Methoxy-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6k). 6k was isolated as an white solid (18 mg, 23%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.66 (s, 2H), 6.85-6.86 (d, J = 8.1 Hz, 1H), 6.95-6.97 (d, J = 8.8 Hz, 2H), 7.15-7.17 (dd, J = 8.1, 1.9 Hz, 1H), 7.18 (d, J = 1.9 Hz, 1H), 7.46-7.48 (d, J = 8.9 Hz, 2H), 8.42 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.5, 67.5, 114.4, 115.2, 116.3, 121.1, 124.8, 128.0, 132.7, 137.6, 144.1, 159.4, 165.7; MS (ESI) m/z 256 ($[M+H]^+$); HRMS (EI) m/z $[M]^+$ calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0898.

7-(2,3-Dimethoxy-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6l). 6l was isolated as an white solid (10 mg, 11%), ^{1}H NMR(500 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.91 (s, 3H), 4.67 (s, 2H), 6.86-6.87 (d, J = 8.1 Hz, 1H), 6.90-6.93 (m, 2H), 7.08-7.11 (dd, J = 8.2, 8.2 Hz, 1H), 7.17-7.19 (dd, J = 8.1, 1.8 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 8.09 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 60.7, 67.5, 111.8, 115.7, 117.8, 122.5, 123.9, 124.3, 125.1, 134.8, 134.8, 143.4, 146.7, 153.3, 166.0; MS (ESI) m/z 286 ($[M+H]^+$); HRMS (EI) m/z $[M]^-$ calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.0995.

7-(3,4-Dimethoxy-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6m). 6m was isolated as an white solid (20 mg, 21%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (2, 3H), 3.94 (s, 3H), 4.67 (s, 2H), 6.87-6.88 (d, J = 8.1 Hz, 1H), 6.92-6.94 (d, J = 8.4 Hz, 1H), 7.04-7.05 (d, J = 2.1 Hz, 1H), 7.08-7.10 (dd, J = 8.3, 2.2 Hz, 1H), 7.15-7.18 (dd, J = 8.1, 2.0 Hz, 1H), 7.18-7.19 (d, J = 1.9 Hz, 1H), 8.88 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1, 67.4, 110.3, 111.7, 115.3, 116.4, 119.3, 121.2, 125.0, 133.1, 137.8, 144.0, 148.9, 149.4, 166.0; MS (ESI) m/z 286 ($[M+H]^-$); HRMS (EI) m/z $[M]^-$ calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1006.

7-(2-Phenoxy-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6n). 6n was isolated as an white solid (14 mg, 14%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (s, 2H), 6.91-6.93 (m, 2H), 6.97-6.99 (dd, J = 8.2, 1.2 Hz, 1H), 7.02-7.05 (tt, J = 7.6, 1.0 Hz, 1H), 7.16-7.18 (dd, J = 8.2, 1.9 Hz, 1H), 7.18-7.20 (dd, J = 7.5, 1.3 Hz, 1H), 7.21 (d, J = 1.7 Hz, 1H), 7.27-7.29 (m, 3H), 7.41-7.43 (dd, J = 7.7, 1.8 Hz, 1H), 8.22 (br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.4, 115.7, 117.8, 118.3, 120.3, 123.0, 123.8, 124.2, 125.2, 129.0, 129.8, 131.1, 132.5, 134.2, 143.4, 153.8, 157.7, 166.0; MS (ESI) m/z 318 ($[M+H]^+$); HRMS (EI) m/z $[M]^-$ calcd for $C_{20}H_{15}NO_3$ 317.1052, found 317.1055.

7-(2,3-Dimethyl-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6o). 6o was isolated as an white solid (22 mg, 28%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.33 (s, 3H), 4.66 (s, 2H), 6.81-6.83 (d, J = 8.0 Hz, 1H), 6.89-6.91 (dd, J = 8.0, 1.8 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 7.05-7.04 (d, J = 7.3 Hz, 1H), 7.11-7.17 (m, 2H), 7.91 (br s, 1H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 16.9, 20.7, 67.4, 115.3, 117.9, 123.8, 125.3, 127.5, 129.1, 134.0, 139.1, 141.0, 143.2, 165.3; MS (ESI) m/z 254 ($[M+H]^-$); HRMS (EI) m/z $[M]^-$ calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1106.

7-(2,5-Dimethyl-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6p). 6p was isolated as an white solid (20 mg, 24%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.35 (s, 3H), 4.68 (s, 2H), 6.89-6.90 (d, J = 8.0 Hz, 1H), 6.92-6.94 (dd, J = 8.0, 1.7 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 7.03(s, 1H), 7.07-7.08 (dd, J =

7.8, 1.1 Hz, 1H), 7.14-7.16 (d, J = 7.8 Hz, 1H), 9.32 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 21.0, 67.4, 115.7, 117.7, 123.8, 124.8, 128.3, 130.5, 132.3, 135.4, 138.7, 140.7, 143.4, 166.2; MS (ESI) *m/z* 254 ($[M+H]^-$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1108.

7-(2,6-Dimethyl-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6q). 6q was isolated as an white solid (17 mg, 22%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 6H), 4.68 (s, 2H), 6.77-6.79 (dd, J = 7.9, 1.7 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 7.12 (s, 1H), 7.13 (s, 1H), 7.17-7.20 (m, 1H), 8.43 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 67.5, 116.0, 117.7, 123.6, 124.7, 127.4, 127.5, 136.3, 137.6, 140.8, 143.8, 165.5; MS (ESI) *m/z* 254 ($[M+H]^+$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1101.

7-(5-Chloro-2-ethoxy-phenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6r). 6r was isolated as an white solid (26 mg, 27%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34-1.37 (t, J = 7.0 Hz, 3H), 4.00-4.04 (q, J = 7.0 Hz, 2H), 4.66 (2H, s), 6.84-6.85 (d, J = 8.1 Hz, 1H), 6.87-6.89 (d, J = 8.8 Hz, 1H), 7.13-7.15 (dd, J = 8.1, 1.9 Hz, 1H), 7.19 (d, J = 1.7 Hz, 1H), 7.21-7.27 (m, 2H), 8.54 (br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 64.6, 67.5, 114.0, 115.6, 118.1, 124.0, 125.3, 125.8, 128.3, 130.4, 133.8, 143.4, 154.6, 165.9; MS (ESI) *m/z* 304 ($[M+H]^-$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{16}H_{14}NO_3Cl$ 303.0662, found 303.0655.

7-(4-Chlorophenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6s). 6s was isolated as a yellow solid (17 mg, 21%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (2H, s), 7.15-7.17 (dd, J = 8.1, 2.0 Hz, 1H), 7.19 (d, J = 1.9 *Hz*, 1H), 7.38-7.40 (d, J = 8.7 Hz, 2H), 7.45-7.47 (d, J = 8.7 Hz, 2H), 7.80 (br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 64.5, 67.4, 113.9, 115.4, 118.0, 123.9, 125.2, 125.8, 128.3, 130.3, 131.1, 133.7, 143.3, 154.5, 165.6; MS (ESI) *m/z* 260 ($[M+H]^-$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{14}H_{10}NO_2Cl$ 259.0400, found 259.0391.

7-(3-Chloro-4-fluorophenyl)-4*H*-benzo[*b*][1,4]oxazin-3-one (6t). 6t was isolated as a yellow solid (20 mg, 23%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (2H, s), 7.12-7.14 (dd, J = 8.1, 2.0 Hz, 1H), 7.15 (d, J = 1.9 Hz, 1H), 7.21-7.17 (t, J = 8.7 Hz, 1H), 7.36-7.39 (m, 1H), 7.55-7.57 (dd, J = 6.9, 2.4 Hz, 1H), 8.22(br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.5, 115.6, 116.4, 117.0, 117.1, 121.4, 126.5, 126.6, 129.1, 135.6, 144.2, 165.4; MS (ESI) *m/z* 278 ($[M+H]^-$); HRMS (EI) *m/z* $[M]^-$ calcd for $C_{14}H_9ClFNO_2$ 277.0306, found 277.0299.

Supporting Information Available. Full analytical data of compounds, copies of ^{1}H NMR, ^{13}C NMR spectra, LC-MS, and ATR-FTIR spectra of compounds **1-5** and BOMBA resins **5a-5k**, and X-ray crystallography of 7-bromo benzo[*b*][1,4]-oxazin obtained from BOMBA resin **4**.

Acknowledgments. This research was supported by a grant (CBM32-B1000-01-00-00) from the Center for Biological Modulators of the 21st Century Frontier R&D Program, the Ministry of Education Science and Technology, Korea and Korea Research Institute of Chemical Technology.

References

1. (a) Hermakens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Foder, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.
2. (a) Avendano, C.; Menendez, J. C. *Medicinal Chemistry of Anticancer Drugs*; Elsevier: 2008. (b) Doherty, A. M. *Annual Reports in Medicinal Chemistry*; Academic press: 2000; p 35. (c) Patrick, G. L. *An Introduction to Medicinal Chemistry*; Oxford University: 1995. (d) Ganellin, C. R.; Roberts, S. M. *Medicinal Chemistry*; Academic press: 1993.
3. (a) Fringuelli, R.; Pietrella, D.; Schiaffella, F.; Guarrac, I. A.; Perito, S.; Bistoni, F.; Vecchiarelli, A. *Bioorg. Med. Chem.* **2002**, *10*, 1681.
4. (a) Macchiarulo, A.; Costantino, G.; Fringuelli, F.; Vecchiarelli, A.; Schiaffella, F.; Fringuelli, R. *Bioorg. Med. Chem.* **2002**, *10*, 3415.
5. (a) Adams, N. D.; Darcy, M. G.; Dhanak, D.; Duffy, K. J.; Fitch, D. M.; Knight, S. D.; Newlander, K. A.; Shaw, A. N. *Int. Patent, WO 2006113432*, **2006**; *Chem. Abstr.* **2006**, *145*, 438652.
6. (a) Seo, J.-S.; Yoon, C. M.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *9*, 366. (b) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Yoo, S.-E.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 136. (c) Hwang, J.-S.; Choi, H.-S.; Seo, J.-S.; La, H.-J.; Kim, D.-S.; Jeon, H. S.; Jeon, M.-K.; Lee, H. L.; Gong, Y.-D. *J. Org. Chem.* **2005**, *70*, 10151. (d) Hwang, J. Y.; Choi, H.-S.; Gong, Y.-D. *Tetrahedron Lett.* **2005**, *46*, 3107. (e) Lee, I. Y.; Kim, S. Y.; Lee, J. Y.; Yu, C.-M.; Lee, D. H.; Gong, Y.-D. *Tetrahedron Lett.* **2004**, *45*, 9319. (f) Gong, Y.-D.; Seo, J.-S.; Chon, Y. -S.; Hwang, J.-Y.; Park, J.-Y.; Yoo, S.-E. *J. Comb. Chem.* **2003**, *5*, 577.
7. (a) Lanni, Jr., T. B.; Greene, K. L.; Kolz, C. N.; Para, K. S.; Visnick, M.; Mobley, J. L.; Dudley, D. T.; Baginski, T. J.; Liimatta, M. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 756.
8. (a) Breznik, M.; Mrcina, A.; Kikelj, D. *Tetrahedron: Asymmetry* **1998**, *9*, 1115. (b) Breznik, M.; Hrast, V.; Mrcina, A.; Kikelj, D. *Tetrahedron: Asymmetry* **1999**, *10*, 153. (c) Breznik, M.; Grdadolnik, S. G.; Giester, G.; Leban, I.; Kikelj, D. *J. Org. Chem.* **2001**, *66*, 7044. (d) Lee, C. L.; Chan, K. P.; Lam, Y.; Lee, S. Y. *Tetrahedron Lett.* **2001**, *42*, 1167. (e) Ma, C.; Cho, S.-D.; Flack, J. R.; Shin, D.-S. *Heterocycles* **2004**, *63*, 75.
9. (a) Fivush, A. M.;Willson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151. (b) Larsen, S. D.; Dipaolo, B. A. *Org. Lett.* **2001**, *3*, 3341. (c) Pietta, P. G.; Cavallo, P. F.; Takahashi, K.; Marshall, G. R. *J. Org. Chem.* **1972**, *39*, 44. (d) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404. (e) Bunin, B. *Combinatorial Index*; Cloth. Academic Press: London, 1997; pp 219-220.
10. (a) Cho, S.-D.; Song, S.-Y.; Park, Y.-D.; Kim, J.-Y.; Joo, W.-H.; Shiro, M.; Falck, J. R.; Shin, D.-S.; Yoon, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 8995. (b) Cho, S.-D.; Song, S.-Y.; Park, Y.-D.; Kim, J.-Y.; Joo, W.-H.; Shiro, M.; Esser, L.; Falck, J. R.; Ahn, C.; Shin, D.-S.; Yoon, Y.-J. *Tetrahedron* **2004**, *60*, 3763.
11. (a) Zuo, H.; Meng, L.; Ghate, M.; Hwang, K. H.; Cho, Y. K.; Chandrasekhar, S.; Ch, R. R.; Shin, D.-S. *Tetrahedron Lett.* **2008**, *49*, 3827.
12. (a) Cho, S.-D.; Park, Y.-D.; Kim, S.-G.; Chen, M.; Song, S.-Y.; Joo, W.-H.; W.-H.; Falck, J. R.; Shiro, M.; Shin, D.-S.; Yoon, Y.-J. *J. Org. Chem.* **2003**, *68*, 7918.
13. (a) Emerys creator microwave reactor is computer controlled system for temperature and pressure during microwave irradiation. (b) Schanche, J.-S. *Molecular Diversity* **2003**, *7*, 293.