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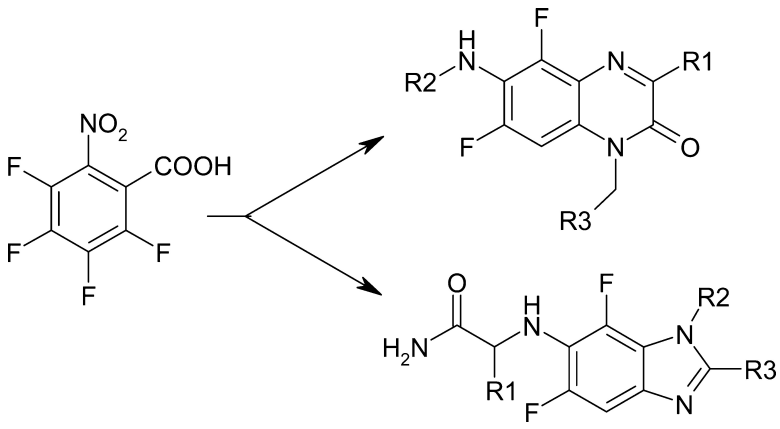


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# Simultaneous Solid-Phase Synthesis of Quinoxalinone and Benzimidazole Scaffold Libraries

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This article describes a method for simultaneous solid-phase synthesis of a quinoxalinone and benzimidazole scaffold library that consists of 240 members. The library was generated by using the solid-phase "split-and-pool" approach and the IRORI sorting system.

## Introduction

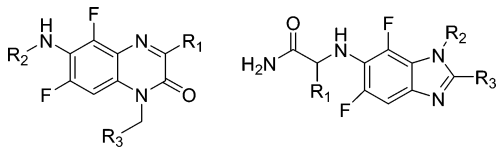
Combinatorial chemistry is a powerful tool for the preparation of large numbers of compounds.[1] In the past decade, small-molecule heterocyclic compound libraries have attracted much interest for their promising biological and pharmacological activities.[2] The large numbers of compounds based on a single scaffold in one library limited the diversity due to their similar chemical information in three-dimensional space.[3] Efficient synthesis of scaffold-diversity libraries will greatly benefit the process of high-throughput generation of "lead-like" compounds.[4] Ji et al.,[5] when he was a postdoctoral fellow in our laboratory, explored the possibility of simultaneous solid-phase synthesis of 2-hydroxyquinoxaline and benzimidazole using 2,3,4,5-tetrafluoro-6-nitrobenzoic acid as the starting material. We herein further describe the simultaneous synthesis of quinoxalinone and benzimidazole library after introducing the symmetric third diversity point to both of two scaffolds.

Unlike 2-hydroxyquinoxaline, quinoxalinone is an attractive, privileged substructure for drug design in medicinal chemistry.[6] The biological activities of quinoxalinones include inhibition of thrombin, aldose reductase, and PDGF receptor tyrosine kinase; antagonism of the AMPA and angiotenism II receptors; and multiple drug resistance, etc.[7] Benzimidazoles also provide a variety of biological activities, including antiulcer, antiviral, and antitumor effects.[8] Thereby, the simultaneous synthesis of these two types of compounds (**1** and **2**, Figure 1) is described in this paper.

## Results and Discussions

The synthetic route is outlined in Scheme 1. According to Ji's method, bead-bound **3** and **4** were synthesized by the commercially available *N*-α-Fmoc-amino acids, aliphatic primary amines, or benzyl amines and subsequently reduced by using 2.0 M $SnCl_2$ and 2.0 M *N*-methylmorpholine in DMF.

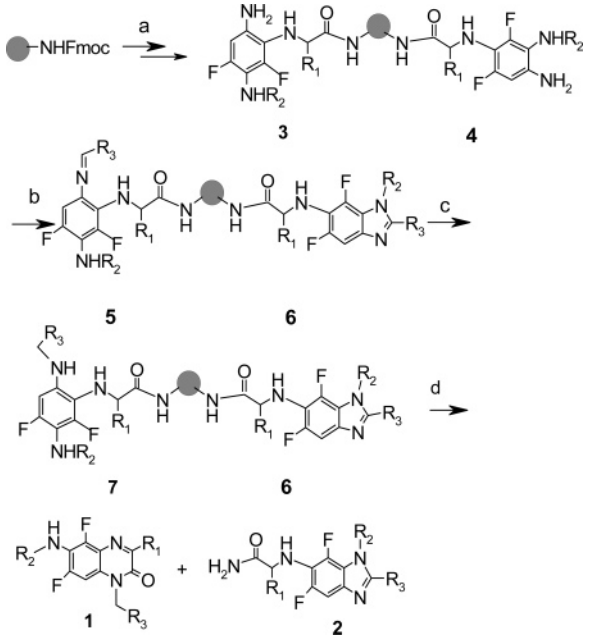
The method that makes the library of 2-hydroxyquinoxaline and benzimidazole scaffolds suffered from the main drawback that the diversity point is unsymmetric to the two scaffolds.[5] This problem obviously makes the repetitive compounds of the 2-hydroxyquinoxaline scaffold in the different final compound wells, whatever the building blocks that were used. For example, using four $R_1$ (amino acids), four $R_2$ (prime amines), and six $R_3$ (aldehydes) as building blocks, the synthesis of a two-scaffold library with unsym-



**1** **2**

**Figure 1.** Scaffolds of 5,7-difluoro-1,3,6-trisubstituted 2-quinoxalinone **1** and 4,6-difluoro-2,3,5-trisubstituted benzimidazole **2**.

**Scheme 1.** Simultaneous Solid-Phase Synthesis of Quinoxalinone and Benzimidazole Two-sScaffold Compounds from 2, 3, 4, 5-Tetrafluoro-6-nitrobenzoic Acid[a]



[a] Reagents: (a) method reference 5; (b) $R_3CHO$ (10 equiv), 5% AcOH/DMF, r.t., 20 h; (c) $NaBH_3CN$ (20 equiv), 5% AcOH/DMF, r.t., 14 h; (d) 95% TFA/$CH_2Cl_2$, r.t., 1 h.

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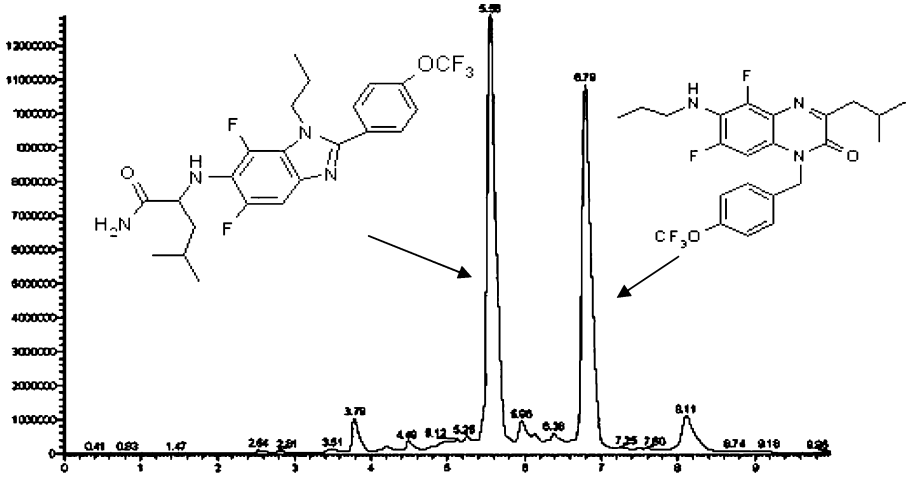


**Figure 2.** HPLC profile of two final products indicating that two different scaffold compounds (**1a** and **2a**) were gained finally.

metric diversity points will only provide 112 compounds ($R_1 \times R_2 \times R_3 + R_1 \times R_2$); however, the symmetric synthesis (recent method) will give 192 compounds ($2 \times R_1 \times R_2 \times R_3$). Such a difference indicates that 80 compounds will be repeatedly synthesized within one chemical process for the simultaneous synthesis of the two-scaffold compound library. Thus, it is necessary to introduce the third diversity point to 2-hydroxyquinoxaline with highly efficient chemistry.

During the studies, we found that the simultaneous benzimidazole formation of **4** and Schiff's base formation of **3** could be subsequently carried out by treatment with an aldehyde to afford bead-bound **5** and **6**. This selective ring formation is probably due to a combination of steric hindrance and electronic deficiency of the nitrogen atom of the amino acid on bead-bound **3**. Bead-bound **5** then was reduced by sodium cyanoboronhydride ($NaBH_3CN$) to offer bead-bound **7**, whereas **6** is stable under this condition. When one-bead-bound **6** and **7** were released from the resin by treatment using a cocktail solution of 95%TFA/DCM, the desired compounds **1** and **2** were simultaneously obtained from a single reaction process (Figure 2).

To equally gain **1** and **2**, we have to overcome a major problem that bead-bound **3** and **7** can be undesiredly self-cleaved from the resin due to the driving force of the six-membered ring formation, and the formation of the benzimidazole ring and Schiff's base has to be performed in a weak acidic environment, such as 5% AcOH/DMF, which probably accelerates self-cleavage of quinoxalinone from the bead-bound **3** and **7**. Another reason is that the reductive alkylation has to be carried out with a long reaction time to ensure that the reaction is completed. This also drives the slow cyclization at the room temperature. Although this self-cleavage was not entirely avoided, aromatic aldehydes were found to be reasonable for simultaneous construction of such two-scaffold library. The explanation is that the corresponding Schiff's base of the aromatic aldehyde is stable by the reason of electron conjugation and the steric hindrance of the aromatic ring, which reduces the tendency of self-cleavage. Using aromatic aldehydes as building blocks to introduce the third diversity, a majority of quinoxalinones could be obtained with 10−60% yield during the total 34 h of benzimidazole formation from **4** and reductive alkylation

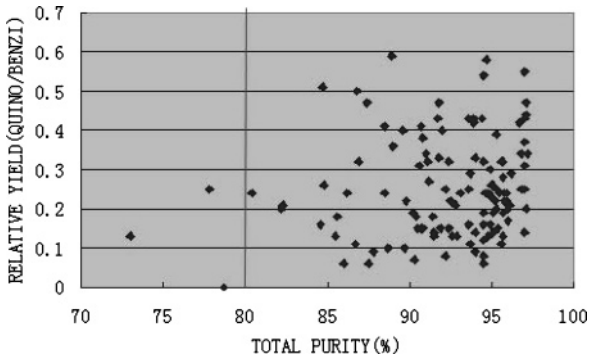



**Figure 3.** Relative yield **1/2** vs total purity of **1** and **2** profile for the two-scaffold library **1** and **2**{*1*−*4*, *1*−*5*, *1*−*6*}. Percent peak areas were determined by UV at 254 nm.

from **3**, whereas over 80% yield of benzimidazoles was mostly received (Figure 3).

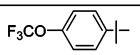
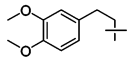
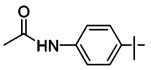
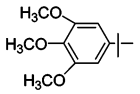
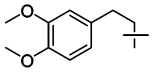
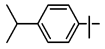
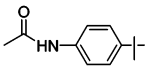
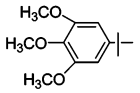
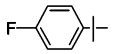
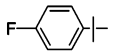
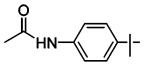
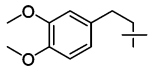
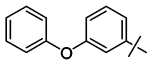
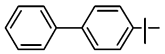
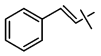
Twelve pairs of representative library compounds (Table 1) were first synthesized and characterized by $^1$H NMR and ESI-MS after purification by preparative thin layer chromatography (PTLC). Compounds **1a**, **2a** and **1g**, **2g**, further characterized by $^{13}$C NMR and element analysis, were used as calibrated standards to estimate the absolute and relative yield of **1**/**2** by UV254 detector according to the reference method by Yan et al.[9]

A medium-sized library of **1** and **2** was synthesized using the above methods employing the IRORI sorting system as a $4 \times 5 \times 6 \times 2$ array containing three substituent-diversity points and two scaffold-diversity elements. The building blocks used in the library are listed in Table 2. All final compounds were analyzed by an automatic LC/MS system to confirm the correct molecular weight, purity, and relative yield. The majority of compounds (117 pairs, 97.5%) were over 80% in total purity. For nine pairs (7.5%), the relative yield (**1**/**2**) was less than 0.1, which means that quinoxalinones **1** was mostly lost during the synthesis due to intramolecular cyclization. Thirty-six pairs had a relative yield between 0.1 and 0.2, and the other 75 pairs had relative yield of over 0.2.

## Conclusion

We have developed a method of simultaneous solid-phase synthesis of quinoxalinone and benzimidazole scaffold

**Table 1.** HPLC Purity and Relative Yield of Compounds Prepared by PTLC **1** and **2** {*a*−*l*}

| Entry | $R_1$ | $R_2$ | $R_3$ | HPLC Total Purity (1+2) (%) | HPLC Relative yield (1/2)[a] |
|---|---|---|---|---|---|
| **1a, 2a** |  |  |  | 94.2 | 0.41 |
| **1g, 2g** |  |  |  | 86.1 | 0.45 |
| **1b, 2b** |  |  |  | 95.3 | 0.44 |
| **1c, 2c** |  |  |  | 91.9 | 0.12 |
| **1d, 2d** |  |  |  | 92.3 | 0.32 |
| **1e, 2e** |  |  |  | 92.6 | 0.24 |
| **1f, 2f** |  |  |  | 97.1 | 0.22 |
| **1h, 2h** |  |  |  | 82.9 | 0.29 |
| **1i, 2i** |  |  |  | 97.7 | 0.25 |
| **1j, 2j** |  |  |  | 88.5 | 0.15 |
| **1k, 2k** |  |  |  | 95.1 | 0.19 |
| **1l, 2l** |  |  |  | 83.0 | 0.24 |

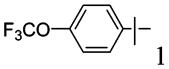
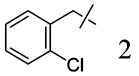
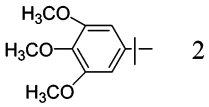
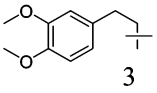
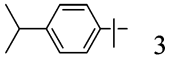
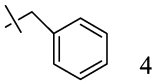
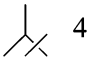
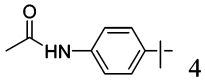
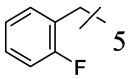
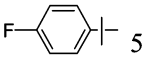
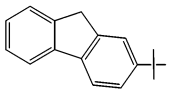
[a] Because of the difference of the chromophores, **1a** and **2a**, **1b** and **2b**, **1f** and **2f** were classified as one group since they have a similar R2 (alkyl). Their peak areas were estimated using a standard curve generated with **1a** and **2a**. Peak areas of the compounds with R2 groups containing aromatic rings were estimated using a standard curve generated with **1g** and **2g**. Standard samples **1a**, **2a**, **1g**, and **2g** were analytically pure, as indicated by HPLC analysis.

libraries via a single synthetic sequence that doubles the scaffold diversity of small molecule heterocycles within one synthetic process.

## Experimental Section

**General Information.** All chemical reagents were purchased from Acros Organics (Geel, Belgium) and used without further purification. Dry DCM was redistilled from phosphorus pentoxide. DMF was dried by 4-Å molecular sieves and redistilled in vacuum at 30 °C. Fmoc rink-MBHA resin (loading 0.65 mmol/g, 1% DVB cross-linked, 100−200 mesh) was purchased from Tianjin Hecheng Corporation (Tianjin, China). HPLC analysis was performed on a Shimadzu HPLC system equipped with a SPD-10A VP detector, an LC-10AT VP pump, and a DGU-12A degasser. The column employed was a Kromasil C18 column (4.6 $\mu$m, 4.6 × 50 mm) from Dikma. The eluent was a mixture of acetonitrile and water containing 0.05% TFA with a linear gradient from 5:95 v/v acetonitrile/$H_2O$ to 95:5 v/v acetonitrile/water over 5 min at a 1 mL/min flow rate. The UV detection was performed at 254 nm. Auto HPLC/MS analysis was performed on a Thermo Finnigan, LCQ-Advantage mass spectrometer equipped with a Gilson 322 pump, a Gilson UV/vis-152 detector, a Gilson 215 liquid handler, and a fluent splitter. The elution gradient, flow rate, and detection wavelength are the same as above. Five percent of eluent was split into the MS system. Mass spectra were recorded in either positive or negative ion mode using electrospray ionization. All NMR experiments were carried out on a Varian Mercury 300- or 500-MHz NMR spectrometer

**Table 2.** Diversity Reagents: Amino Acid Set {*1*−*4*}, Amine Set {*1*−*5*} and Aldehyde Set {*1*−*6*}

| R1 | R2 | R3 |
|---|---|---|
|  1 |  1 |  1 |
|  2 |  2 |  2 |
|  3 |  3 |  3 |
|  4 |  4 |  4 |
| |  5 |  5 |
| | |  6 |

equipped with an autosampler using $CDCl_3$ or DMSO-$d_6$ as the solvent. The following abbreviations were used: DCM = dichloromethane, DMF = *N*,*N*-dimethylformamide, MeOH = methanol, AcOH = acetic acid, and DIPEA = diisopropylethylamine. The library was constructed using an IRORI Accutag System. MiniKans were filled with 50 mg of Fmoc-rink-MBHA resin. All reactions involving MiniKans were performed in round-bottom flasks. The Accutag-100 was used to sort the MiniKans between combinatorial steps, and cleavage of the library compound was carried out in the Accucleave 96. The validation set of 12-pair compounds was synthesized by using 200 mg of resin under exactly the same conditions that were used for the library.

**General Procedure for the Synthesis of Resins 3 and 4.** One hundred and twenty MiniKans (each MiniKan contained 50 mg of 0.65 mmol/g loaded Fmoc-rink-MBHA resin) were placed into a 0.5-L, round-bottom flask fitted with an overhead stirrer. A solution of 20% piperidine in DMF (300 mL) was added, and the suspension was mixed for 15 min. This Fmoc-deprotection step was repeated. The resin was filtered and washed with DMF (3 × 250 mL), MeOH (3 × 250 mL), and DCM (3 × 250 mL). For each Fmoc-protected amino acid, 30 MiniKans were placed into a 250-mL, round-bottom flask. The Fmoc-protected amino acid (2.5 mmol), HOBt (3.0 mmol), and DIC (3.0 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 3 h. All MiniKans then were combined and washed with DMF (2 × 250 mL). After the deprotection procedure as described above was repeated, the MiniKans were placed into a solution of 2,3,4,5-tetrafluoro-6-nitrobenzoic acid (19.5 mmol) and DIPEA (19.5 mmol) in DMF. The reaction mixture was stirred at room temperature for 6 h. The MiniKans were filtered and washed with DMF (3 × 250 mL), MeOH (3 × 250 mL), and DCM (3 × 250 mL). The MiniKans were dried under a stream of nitrogen gas.

For each primary amine, 24 MiniKans were used. The MiniKans were swelled by DMF, and the primary amine (3.9 mmol) was added along with DIPEA (3.9 mmol). The mixture was stirred at room temperature overnight. All MiniKans were filtered; combined; and washed with DMF (3 × 250 mL), MeOH (3 × 250 mL), and DCM (3 × 250 mL). The MiniKans were dried overnight under a stream of nitrogen gas.

The MiniKans were suspended by DMF and reacted with a solution of 2.0 M $SnCl_2$ and *N*-methylmorpholine in DMF (200 mL) under argon protection. The reaction mixture was stirred at room temperature for 24 h. The MiniKans were washed with 0.5% HCl (1 × 250 mL), DMF (3 × 250 mL), MeOH (3 × 250 mL), and DCM (3 × 250 mL). The MiniKans were dried under a stream of nitrogen gas.

**General Procedure for the Synthesis of Resins 6 and 7.** For each aldehyde, 20 MiniKans were used. MiniKans were swelled by 5%AcOH/DMF (200 mL), and the aldehyde (6.5 mmol) was added into the reaction system. The mixture was stirred at room temperature for 20 h. Afterward, sodium cyanoboronhydride ($NaBH_3CN$) (13 mmol) was added. The mixture was continuously stirred at room temperature for 14 h. All MiniKans were combined and washed with 1% AcOH/DMF (1 × 250 mL), DMF (3 × 250 mL), MeOH (3 × 250 mL), and DCM (3 × 250 mL). The MiniKans were dried under a stream of nitrogen gas.

**Cleavage of Compounds Attached to the Resin.** The MiniKans were sorted into cleavage racks. Each MiniKan was treated with a solution of 95% TFA in DCM (1.5 mL). The mixture was shaken for 1.5 h and drained. The MiniKans were rinsed with DCM (2 × 1 mL), and the filtrate was

exposed to the air for oxidation within 1 h. Then the resulting solution was concentrated under reduced pressure to afford **1** and **2**.

**5,7-Difluoro-3-isobuyl-6-propylamino-1-(4-trifluoromethoxylbenzyl)-1*H*-quinoxalin-2-one (1a).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.25 (d, $J = 7$ Hz, 2H), 7.17 (d, $J = 7$ Hz, 2H), 6.66 (d, $J = 13$ Hz, 1H), 5.36 (s, 2H), 3.30 (t, $J = 6$ Hz, 2H), 2.88 (d, $J = 7$ Hz, 2H), 2.38 (m, 1H), 1.59 (m, 2H), 1.02 (d, $J = 6$ Hz, 6H), 0.96 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 470$ $[M + H]^+$. $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 160.2, 155.7, 154.6, 152.5, 148.7, 133.6, 128.9, 124.8, 123.0, 121.8, 109.8, 96.6, 96.3, 48.4, 45.6, 42.9, 27.0, 23.8, 22.6, 11.1. Element analysis: C, 58.7%; H, 5.1%; N, 8.7%.

**2-(4,6-Difluoro-3-propyl-2-(4-trifluoromethoxylphenyl)-3*H*-benzoimidazol-5-ylamino)-4-methylpentanamide (2a).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.69 (d, $J = 9$ Hz, 2H), 7.36 (d, $J = 9$ Hz, 2H), 7.26 (d, $J = 10$ Hz, 1H), 6.72 (brs, 1H), 5.61 (brs, 1H), 4.21 (t, $J = 8$ Hz, 2H), 3.94 (d, $J = 9$ Hz, 1H), 1.85 (m, 1H), 1.81 (m, 2H), 1.65 (t, 2H), (m, 3H), 0.99 (d, $J = 5$ Hz, 3H), 0.90 (d, $J = 6$ Hz, 3H), 0.81 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 485$ $[M + H]^+$. $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 153.0, 150.7, 149.8, 140.6, 135.2, 131.3, 128.0, 126.9, 122.0, 120.9, 118.6, 101.6, 101.3, 53.7, 48.1, 24.9, 24.4, 23.1, 18.5, 11.7, 10.8. Element analysis: C, 57.2%; H, 5.2%; N, 11.4%.

**5,7-Difluoro-3-isobuyl-6-propylamino-1-(3,4,5-trimethoxylbenzyl)-1*H*-quinoxalin-2-one (1b).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 6.76 (d, $J = 12$ Hz, 1H), 6.42 (s, 2H), 5.30 (s, 2H), 3.78−3.83 (9H), 3.31 (t, $J = 7$ Hz, 2H), 2.90 (d, $J = 7$ Hz, 2H), 2.38 (m, 1H), 1.61 (m, 2H), 1.02 (d, $J = 6$ Hz, 6H), 0.96 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 476$ $[M + H]^+$.

**2-[4,6-Difluoro-3-propyl-2-(3,4,5-trimethoxylphenyl)-3*H*-benzoimidazol-5-ylamino]-4-methylpentanamide (2b).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.31 (d, $J = 11$ Hz, 1H), 6.86 (s, 2H), 6.70 (brs, 1H), 5.50 (brs, 1H), 4.25 (t, $J = 7$ Hz, 2H), 3.95 (d, 1H), 3.91−3.94 (9H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (t, 2H), (m, 3H), 1.00 (d, $J = 6$ Hz, 3H), 0.90 (d, $J = 6$ Hz, 3H), 0.86 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 491$ $[M + H]^+$.

**6-2-(3,4-Dimethoxyphenyl)-ethylamino-5,7-difluoro-3-isobuyl-1-(4-isopropyl-benzyl)-1*H*-quinoxalin-2-one (1c).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.16 (d, $J = 7$ Hz, 4H), 6.74−6.82 (3H), 6.69 (d, $J = 11$ Hz, 1H), 5.34 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.58 (t, $J = 7$ Hz, 2H), 2.89 (d, $J = 7$ Hz, 2H), 2.84 (t, $J = 9$ Hz, 2H), 2.38 (m, 2H), 1.22 (d, $J = 9$ Hz, 6H), 1.01 (d, $J = 6$ Hz, 6H); MS (ESI) $m/z = 550$ $[M + H]^+$.

**2-[3-[2-(3,4-Dimethoxyphenyl)-ethyl]-4,6-difluoro-2-(4-isopropylphenyl)-3*H*-benzoimidazol-5-ylamino]-4-methylpentanamide (2c).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.43 (d, $J = 10$ Hz, 1H), 7.24−7.28 (6H), 6.59 (d, $J = 11$ Hz, 1H), 6.68 (brs, 1H), 5.70 (brs, 1H), 4.55 (t, $J = 7$ Hz, 2H), 3.99 (m, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 2.85−2.95 (m, 3H), 1.28 (d, $J = 8$ Hz, 6H), 0.97 (d, $J = 7$ Hz, 6H); MS (ESI) $m/z = 565$ $[M + H]^+$.

***N*-{4-[5,7-Difluoro-6-(2-fluorobenzylamino-3-methyl-2-oxo)-2*H*-quinoxalin-1-ylmethyl]-phenyl}-acetamide (1d).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.46 (d, $J = 9$ Hz, 2H), 7.31 (t, $J = 7$ Hz, 1H), 7.16−7.22 (3H), 7.02 (m, 2H), 6.69 (d, $J = 12$ Hz, 2H), 5.31 (s, 2H), 4.54 (s, 2H), 2.64 (s, 3H), 2.40−2.60 (brs), 2.16 (s, 3H); MS (ESI) $m/z = 467$ $[M + H]^+$

**2-[2-(4-Acetylaminophenyl)-4,6-difluoro-3-(2-fluorobenzyl)-3*H*-benzoimidazol-5-ylamino]-propionamide (2d).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 11.05 (brs), 8.31 (brs, 1H), 7.64 (d, $J = 9$ Hz, 2H), 7.51 (d, $J = 9$ Hz, 2H), 7.32 (d, $J = 11$ Hz, 2H), 6.63 (brs, 1H), 7.00−7.10 (3H), 7.02 (m, 1H), 5.54 (s, 2H), 3.95 (q, $J = 7$ Hz, 1H), 2.16 (s, 3H), 1.45 (d, 3H); MS (ESI) $m/z = 482$ $[M + H]^+$.

**6-(2-Chlorobenzylamino)-5,7-difluoro-3-methyl-1-(3,4,5-trimethoxylbenzyl)-1*H*-quinoxalin-2-one (1e).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.33−7.37 (2H), 7.17−7.20 (2H), 6.76 (dd, $J = 13.2$ Hz, 1H), 6.41 (s, 2H), 5.28 (s, 2H), 4.59 (s, 2H), 3.81 (s, 3H), 3.80 (s, 6H), 2.65 (s, 3H); MS (ESI) $m/z = 516$ $[M + H]^+$.

**2-[3-(2-Chlorobenzyl)-4,6-difluoro-2-(3,4,5-trimethoxylphenyl)-3*H*-benzoimidazol-5-ylamino]-propionamide (2e).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.40−7.49 (2H), 7.22−7.32 (2H), 6.85 (d, $J = 8$ Hz, 1H), 6.75 (s, 2H), 6.58 (brs, 1H), 5.58 (s, 2H), 5.51 (brs, 1H), 3.87 (s, 3H), 3.62 (s, 6H), 1.48 (d, $J = 6$ Hz, 3H); MS (ESI) $m/z = 531$ $[M + H]^+$.

**5,7-Difluoro-1-(4-fluorobenzyl)-6-isopropylamino-3-methyl-1*H*-quinoxalin-2-one (1f).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta_H$ 7.33 (dd, $J = 8,6$ Hz, 2H), 7.10−7.16 (3H), 5.37 (s, 2H), 3.65 (m, 1H), 2.47 (s, 3H), 1.11 (d, $J = 6$ Hz, 6H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 168.8, 160.4, 157.4, 154.3, 153.5, 147.7, 131.8, 129.1, 125.1, 120.5, 115.4, 97.4, 47.0, 44.4, 23.2, 21.4; MS (ESI) $m/z = 362$ $[M + H]^+$.

**2-[4,6-Difluoro-2-(4-fluorophenyl)-3-isopropyl-3*H*-benzoimidazol-5-ylamino-propionamide (2f).** $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta_H$ 7.68 (dd, $J = 8,6$ Hz, 2H), 7.57 (brs, 1H), 7.40 (t, $J = 8$ Hz, 2H), 7.34 (d, $J = 11$ Hz, 1H), 7.11 (brs, 1H), 4.68 (brs, 1H), 4.61 (m, 1H), 4.12 (m, 1H), 1.47 (d, $J = 7$ Hz, 6H), 1.28 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) $\delta$ 175.4, 163.9, 161.9, 152.9, 151.9, 150.0, 137.6, 131.8, 126.9, 119.8, 115.8, 101.3, 54.2, 48.8, 21.7, 19.9; MS (ESI) $m/z = 377$ $[M + H]^+$.

***N*-(4-{6-[2-(3,4-Dimethoxylphenyl)-ethylamino]-[5,7-difluoro-3-methyl-2-oxo)-2*H*-quinoxalin-1-ylmethyl]-phenyl}-acetamide (1g).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.46 (d, $J = 8$ Hz, 2H), 7.31 (s, 1H), 7.18 (d, $J = 8$ Hz, 2H), 6.80 (d, $J = 7$ Hz, 1H), 6.72 (d, $J = 7$ Hz, 1H), 6.70 (d, $J = 13$ Hz, 1H), 5.34 (s, 2H), 3.83−3.86 (6H), 3.58 (t, $J = 6$ Hz, 2H), 2.81 (t, $J = 6$ Hz, 2H), 2.66 (s, 3H), 3.00 (brs), 2.17 (s, 3H); MS (ESI) $m/z = 523$ $[M + H]^+$. Element analysis: C, 64.0%; H, 5.8%; N, 10.0%.

**2-{2-(4-Acetylaminophenyl)-3-[2-(3,4-dimethoxylphenyl)-ethyl]-4,6-difluoro-3*H*-benzoimidazol-5-ylamino}-propionamide (2g).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 10.92 (brs), 7.63 (d, $J = 8$ Hz, 2H), 7.34 (d, $J = 8$ Hz, 2H), 7.20 (d, $J = 8$ Hz, 1H), 6.86 (brs, 1H), 6.55 (d, $J = 10$ Hz, 1H), 6.63 (brs, 1H), 6.15 (d, $J = 8$ Hz, 1H), 6.10 (s, 1H), 4.56 (t, $J = 6$ Hz, 2H), 4.16 (m, 1H), 4.15 (brs), 3.79 (s, 3H), 3.57 (s, 3H), 2.88 (t, $J = 6$ Hz, 2H), 2.18 (s, 3H), 1.54 (d, $J = 7$ Hz, 3H); MS (ESI) $m/z = 538$ $[M + H]^+$. Element analysis: C, 62.03%; H, 5.8%; N, 12.8%.

**3-Benzyl-6-(2-chlorobenzylamino)-5,7-difluoro-1-(4-fluorobenzyl)-1*H*-quinoxalin-2-one (1h).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.47 (d, $J = 7$ Hz, 2H), 6.9−7.2 (11H), 6.64 (d, $J = 13$ Hz, 1H), 5.33 (s, 2H), 4.58 (s, 2H), 4.30 (s, 2H); MS (ESI) $m/z = 520$ $[M + H]^+$.

**2-[3-(2-Chlorobenzyl)-4,6-difluoro-2-(4-fluorophenyl)-3*H*-benzoimidazol-5-ylamino]-3-phenylpropionamide (2h).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 8.00 (brs, 1H), 7.52 (d, $J =$ 8 Hz, 2H), 7.43 (d, $J = 8$ Hz, 1H), 7.1−7.4 (10H), 6.66 (d, $J = 11$ Hz, 1H), 5.51 (s, 2H), 4.16 (t, $J = 4$ Hz, 1H), 3.13 (d, $J = 9$ Hz, 2H); MS (ESI) $m/z = 535$ $[M + H]^+$.

***N*-(4-[6-(2-Chlorobenzylamino)-5,7-difluoro-3-isopropyl-2-oxo-2*H*-quinoxalin-1-ylmethyl]-phenyl}-acetamide (1i).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.44 (d, $J = 8$ Hz, 2H), 7.36 (d, $J = 8$ Hz, 2H), 7.20 (d, $J = 6$ Hz, 2H), 7.15 (d, $J = 7$ Hz, 2H), 6.67 (dd, $J = 12.1$ Hz, 1H), 5.31 (s, 2H), 4.57 (s, 2H), 3.63 (m, 1H), 2.16 (s, 2H), 1.35 (d, $J = 8$ Hz, 6H); MS (ESI) $m/z = 511$ $[M + H]^+$.

**2-[2-(4-Acetylaminophenyl)-3-(2-cholrobenzyl)-4,6-difluoro-3*H*-benzoimidazol-5-ylamino}-3-methylbutyramide (2i).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 8.38 (brs), 7.63 (d, $J = 8$ Hz, 2H), 7.45 (d, $J = 8$ Hz, 2H), 7.10−7.30 (4H), 6.68 (d, $J = 9$ Hz, 1H),6.61 (brs, 1H), 5.68 (brs, 1H), 5.51 (s, 2H), 3.92 (brs), 3.65 (m, 1H), 2.34 (m, 1H), 1.44 (d, $J =$ 7 Hz, 6H); MS (ESI) $m/z = 526$ $[M + H]^+$.

**6-[2-(3,4-Dimethoxylphenyl)-ethylamino]-5,7-difluoro-3-methyl-1-(4-phenoxylbenzyl)-1*H*-quinoxalin-2-one (1j).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.24−7.35 (2H), 7.11 (t, $J$ $= 7$ Hz, 1H), 6.97 (d, $J = 8$ Hz, 2H), 6.86−6.92 (3H), 6.81 (d, $J = 8$ Hz, 1H), 6.65−6.74 (4H), 5.36 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.59 (t, $J = 6$ Hz, 2H), 2.82 (t, $J = 6$ Hz, 2H), 2.65−2.75 (brs), 2.65 (s, 3H); MS (ESI) $m/z = 558$ $[M + H]^+$.

**2-[2-(3,4-Dimethoxylphenyl)-ethyl]-4,6-difluoro-2-(4-phenoxylphenyl)-3*H*-benzoimidazol-5-ylamino]-propionamide (2j).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.30−7.39 (5H), 7.00−7.14 (5H), 6.75 (brs, 1H), 6.60 (d, $J = 8$ Hz, 1H), 6.27 (d, $J = 9$ Hz, 1H), 5.71 (brs, 1H), 4.49 (t, $J = 8$ Hz, 2H), 3.80 (s, 3H), 3.64 (s, 3H), 2.59 (t, $J = 8$ Hz, 2H), 1.50 (d, $J = 7$ Hz, 3H); MS (ESI) $m/z = 573$ $[M + H]^+$.

**1-Biphenyl-4-ylmethyl-3-*sec*-butyl-6-(2-chlorobenzylamino)-5,7-difluoro-1*H*-quinoxalin-2-one (1k).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.54 (d, $J = 8$ Hz, 3H), 7.20−7.42 (10H), 7.20 (d, $J = 6$ Hz, 2H), 6.74 (d, $J = 12$ Hz, 1H), 5.40 (s, 2H), 4.45 (s, 2H), 3.47 (m, 1H), 3.12 (brs, 1H), 1.64 (m, 2H), 1.32 (d, $J = 6$ Hz, 3H), 0.98 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 545$ $[M + H]^+$.

**2-[2-Biphenyl-4-yl-3-(2-chlorobenzyl)-4,6-difluoro-3*H*-benzoimidazol-5-ylamino]-3-methylpentanamide (2k).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 7.56−7.65 (5H), 7.34−7.46 (4H), 7.18−7.28 (4H), 6.74 (d, $J = 9$ Hz, 1H), 6.56 (brs, 1H), 5.61 (s, 2H), 3.78 (d, $J = 4$ Hz, 1H), 3.67 (brs, 1H), 3.10 (m, 1H), 1.60 (m, 2H), 1.50 (d, $J = 7$ Hz, 3H), 0.95 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 560$ $[M + H]^+$.

**5,7-Difluoro-3-isobutyl-1-(3-phenylallyl)-[(pyridin-2-ylmethyl)-amino]-1*H*-quinoxalin-2-one (1l).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 8.65 (d, $J = 4$ Hz, 1H), 7.82 (t, $J = 7$ Hz, 1H), 7.49 (d, $J = 7$ Hz, 2H), 7.23−7.30 (5H), 6.85 (d, $J =$ 12 Hz, 1H), 6.57 (d, $J = 15$ Hz, 1H), 6.20 (dd, $J = 15.6$ Hz, 1H), 4.93 (d, $J = 6$ Hz, 2H), 4.74 (s, 2H), 2.85 (d, $J = 7$ Hz, 2H), 2.34 (m, 1H), 1.00 (d, $J = 6$ Hz, 6H); MS (ESI) $m/z = 461$ $[M + H]^+$.

**2-(4,6-Difluoro-3-pyridin-2-ylmethyl-2-styryl-3*H*-benzoimidazol-5-ylamino)-4-methylpentanamide (2l).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$ 8.60 (d, $J = 5$ Hz, 1H), 7.87 (d, $J =$ 16 Hz, 1H), 7.62 (t, $J = 7$ Hz, 1H), 7.52 (d, $J = 7$ Hz, 2H), 7.15−7.38 (5H), 7.10 (d, $J = 16$ Hz, 1H), 6.92 (d, $J = 9$ Hz, 1H), 6.54 (brs, 1H), 5.68 (s, 2H), 5.58 (brs, 1H), 3.78 (d, $J = 4$ Hz, 1H), 3.67 (brs, 1H), 3.90 (1H), 1.86 (t, $J = 7$ Hz, 2H), 1.64 (m, 1H), 0.96 (d, $J = 6$ Hz, 3H), 0.87 (t, $J =$ 7 Hz, 3H); MS (ESI) $m/z = 476$ $[M + H]^+$.

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**Note Added after ASAP Publication.** This article was released ASAP on August 29, 2006, with errors in the General Procedure paragraph headings and description in the Experimental Section. References 9−12 were deleted and ref 13 was renumbered as 9. The version posted on September 13, 2006, and the print version are correct.

## References and Notes

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M.; Krueger, C. A.; Collins, N. *J. Comb. Chem.* **2003**, *5*, 547−559. The standard $UV_{254nm}$ calibration curves of two-pair compounds (**1a**, **2a** and **1g**, **2g**) were made to estimate their absolute and relative yield that indicates the real situation without consideration of the loss by the purification process.

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