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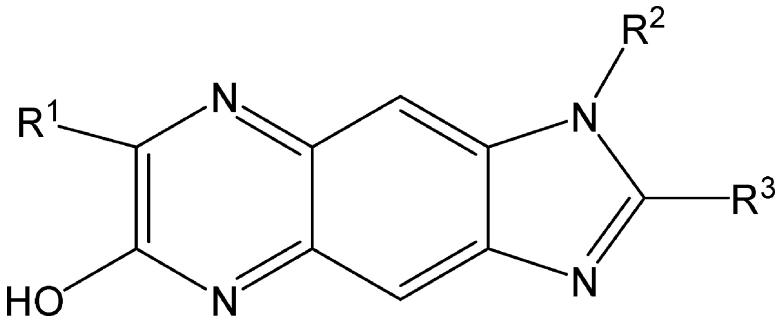

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Solution-Phase Parallel Synthesis of a 1,2,7-Trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol Library Scaffold

Jing Zhang, Liang Zhang, Suode Zhang, Yinghong Wang, and Gang Liu*

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, 1 Xian Nong Tan Street, Beijing 100050, P. R. China

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This paper describes solution-phase parallel synthesis of a library with a novel 1,2,7-trialky-1H-imidazo-[4,5-*g*]quinoxalin-6-ol scaffold and three points of diversity. The library is prepared using 1,5-difluoro-2,4-dinitrobenzene as the starting material and commercially available chemicals as the building blocks. A new, inexpensive, and practical apparatus for parallel filtration is also described.

Introduction

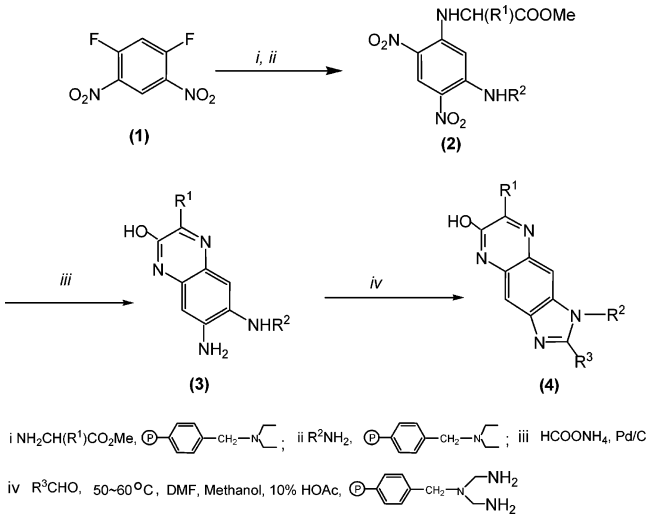
The successes of lead generation and optimization depend on the efficient synthesis of a diverse array of chemical compounds.[1−3] The compound diversities are currently considered as being in three areas, which are compound scaffold diversities, substituent diversities, and stereochemistry diversities on one skeleton. Among them, the scaffold diversity is the key factor. Hence, the development of methods to provide novel scaffolds has been of interest for both academic communities and the pharmaceutical industry. In response, combinatorial chemistry has made significant achievements in this area during the past decade. We recently launched a "scaffold-directed" project to make benzofused chemical libraries using 1,5-difluoro-2,4-dinitrobenzene (DFDNB) as a unique starting material,[4] such as 2-hydroxyquinoxaline and benzimidazole libraries.[5,6] To extend the scope of our recent studies, we report herein the parallel synthesis of a novel 1,2,7-trialky-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol library.

The 1,2,7-trialky-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol scaffold combines two privileged structures of benzimidazole and 2-hydroxyquinoxaline, which possess extensively biological activities. Therefore, combination of these two privileged pharmacophores may provide additional opportunities to discover new lead compounds by one chemical synthetic process.

Results and Discussion

Determination of the Chemistry for Library Synthesis. We have employed DFDNB in the solution-phase parallel synthesis of a 2-hydroxyquinoxaline library.[5] The remaining amino groups of the 2-hydroxyquinoxaline allow us to introduce the third benzofused ring in obtaining the benzimidazole. The synthetic route to the targeted molecule is outlined in Scheme 1. Two fluorine groups of the starting material DFDNB (**1**) were subsequently and quantitatively displaced by nucleophilic amines in the presence of an organic base scavenger resin, such as triethylamine (TEA), *N*-ethyldiisopropylamine (DIPEA), or *N*-methylmorpholine (NMM). We selected the amino acid methyl or ethyl esters with slightly lower nucleophilicity than alkyl primary amines to carry out the first substitution for the purpose of reducing the possibility of disubstitution. Indeed, disubstitution was not observed for the all tested amino acid esters by LC/MS analysis. The second substitution was completed in 18 h at room temperature. Subsequently, the quantitative reduction of two aromatic nitro groups of **2** to offer **3** was achieved in high yield using $HCOONH_4$ and Pd/C or other methods.[4] In the presence of 6−10% acetic acid in DMF, treatment of **3** with aldehydes at 70 °C highly yielded **4**.

Scheme 1. Synthetic Route of the 1,2,7-Trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol Scaffold Library



Design and Manufacture of Highly Efficient Filtering Apparatus.[7] To synthesize the chemical library by solution phase, one of the important techniques is the application of a scavenger resin, a solidified catalyst, or solidified reactants. This provides a simple procedure through filtration operations to remove excess reactants, side products, or catalysts from the reaction solution. Nevertheless, filtering steps are time-consuming and labor-intensive. To solve such a difficulty,

* To whom correspondence should be addressed. Phone: +86-10-63167165. Fax: +86-10-63167165. E-mail: gangliu27@yahoo.com.

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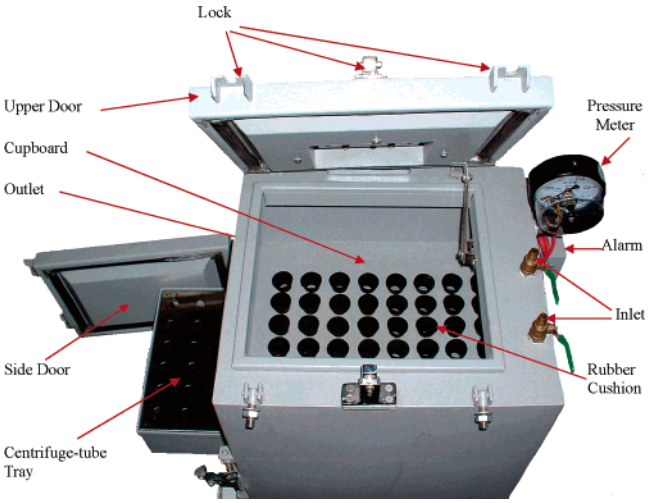


Figure 1. A newly designed apparatus for parallel filtration.

we designed and manufactured an efficient filtering apparatus (Figure 1) that adheres to the guidelines to enforce its extensive utilization, simplicity, and flexibility. This apparatus is capable of (1) parallel filtration of reactants under vacuum or in normal atmosphere, (2) parallel filtration of air-sensitive reactants protected by inert gas, and (3) parallel separation, extraction, and purification of the desired products. This apparatus has greatly accelerated our combinatorial synthesis.

The equipment consists of five components: (1) a stainless steel cupboard with eyelets and a rubber cushion; (2) a changeable septate device; (3) a stainless steel centrifuge tube tray; (4) a warning device that can give an alarm when the pressure is over the limit; and (5) the upper seal door and the side seal door, which allow multiple operations, such as pressured or vacuumed parallel filtration or move the centrifuge tube tray. Whenever or whatever is used, this apparatus allow us to use the reusable filtering funnels to remove scavenger resin, particularly from the air-sensitive reactants. It indeed offers the great benefits of easy and fast separations of the scavenger resin-attached unwanted impurities from the desired compounds.

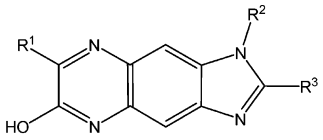
Solution-Phase Parallel Synthesis of the 1,2,7-Trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol Scaffold Library. The synthesis of the 1,2,7-trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol library was explored with the nucleophilic substitutions by amino acid esters and, subsequently, alkyl primary amines. Four equivalent excess DIPEA resin was used as the scavenger to replace the corresponding organic base. The first substitution of the fluorine group by amino acid esters was fast and quantitative with a precise 1:1 molar ratio of reactants at room temperature for 10−30 min. Although the second substitution by alkyl primary amines became slightly slow, the reaction was still quantitative for overnight monitoring with high-performance liquid chromatography (HPLC). We performed this second substitution at 35 °C for several hours, as determined by HPLC analysis. After these two substitution steps, the DIPEA scavenger resin was parallel filtered by our filtering apparatus, described above. The filtrates were parallel and simultaneously collected into other reaction vessels that were located at corresponding positions of the centrifuge tube tray. The reduction of dinitro groups then was carried out in the presence of $HCOONH_4$ and Pd/C at normal pressure on a H+P parallel synthesizer, which allows simultaneous parallel heating and refluxing of all 96 reactions. The reductions were generally finished after 2 h at 65 °C. The remaining $HCOONH_4$ was totally decomposed into N_2, H_2, and CO_2 after an additional 3 h at 65 °C. After removal of Pd/C by our parallel filtration approach again, compound **3** was left in the filtrates, which in turn was analyzed by auto fast LC/MS system (~10 min/compound). Most compounds were >95% in purity when analyzed at UV 254-nm wavelength with the correct molecular weights. For those building blocks which might bring about the debenzylation, dehydroxylation, dechlorination, and debromination, **3** was prepared by the $Na_2S_2O_4$ method or $SnCl_2$/HCl method.[4] In the case of parallel synthesis of a single compound, each **3** was further reacted with 1.2 equiv excess aldehyde in 10% acetic acid/DMF (v:v) overnight at 70 °C. For the parallel synthesis of mixture compounds, five painstakingly selected compounds **3** were combined, diluted with DMF, and split into 72 other reaction vessels. To each one then was added 1.5 equiv excess aldehyde, and they were continuously reacted in 10% acetic acid/DMF (v:v) overnight at 70 °C. The reaction processes were monitored by a fast LC/MS analytical system. This analytic method consisted of a 5-cm reverse C18 column and a 5-min gradient of acetonitrile in water from 5 to 95% containing 0.05% trifluoroacetic acid. The excess aldehyde in each reaction vessel was removed by the addition of an amine scavenger resin[8] at 70 °C for 15 h and then filtered out.

Thirty natural or unnatural amino acid methyl or ethyl esters, 100 alkyl primary amines, and 115 aldehydes were screened before we assembled a library of a large number of compounds. These building blocks were purchased from providers in maximum structural diversity. Six amino acid esters, 34 alkyl primary amines, and 72 aldehydes (Table 1) were finally selected to construct the library following these criteria: (1) the maximum substitution diversity with the minimum combination of building blocks; (2) minor side reactions under Pd/C and $HCOONH_4$ condition, as described in ref 4; (3) avoiding the use of amino acid esters having acid-sensitive protective groups of side chain could introduce some unknown side products; (4) properly combining building blocks with the intermediates which could give the highest conversion and yield; and (5) easy removal of the impurities by scavenger resin.

Analysis and Identification of Mixed Compounds by HPLC/MS and HPLC/NMR. After individually generated **3**, five compounds were factitiously selected and mixed together. The mixtures then were diluted with DMF in a reaction bottle and split into 72 other reaction tubes encoded by different aldehydes. According to the reaction information gained in the determination of chemistry section, a total of 2500 compounds were synthesized instead of a randomization of **3** with selected aldehydes.

The crude products were analyzed by a HPLC/MS system. The analytic results were determined as the sum of the peak chromatographic areas of five final compounds. All analytic results showed around 70−95% purity, as determined by

Table 1. Diversity of the 1,2,7-Trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol Scaffold Library



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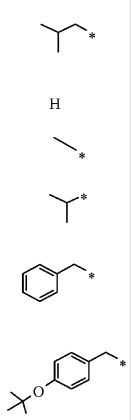
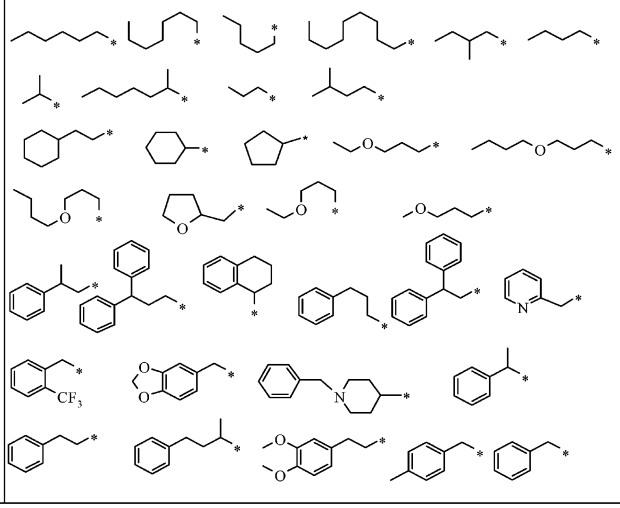
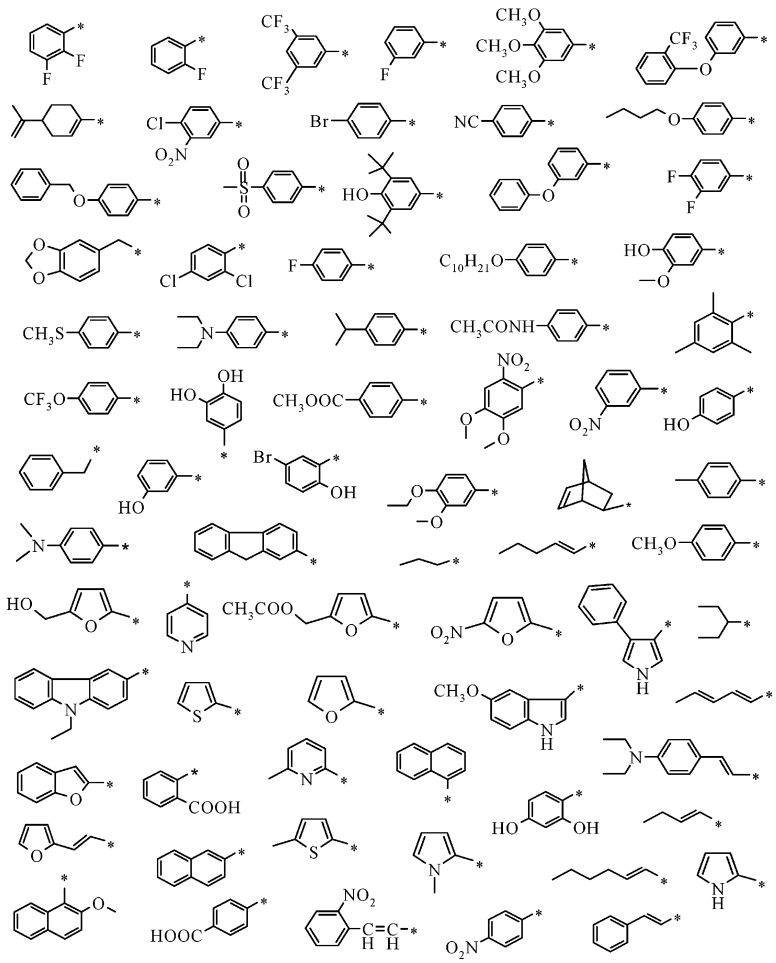
	

R^3


HPLC analysis at UV 254-nm wavelength. As indicated in Figure 2, only 8.0% of the mixture compounds failed to meet our purity standard of ≥80%.

The structure of each compound in the mixture was characterized by HPLC/MS. The structure was typically further confirmed by HPLC/NMR. The former is a powerful

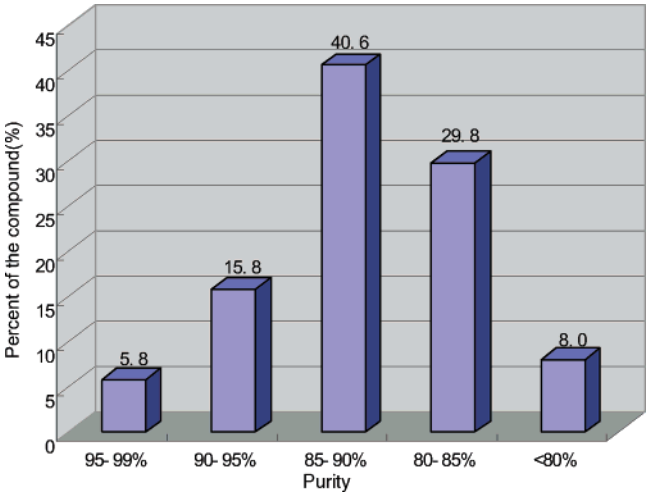


Figure 2. Histogram of purities of product library. Purity was assessed by analytical HPLC monitor at UV 254 -nm wavelength.

tool for analysis of compound mixtures produced by combinatorial chemistry. HPLC/NMR has the ability to show the totality of the sample and is not subject to either ionizing or chromatographic problems, which is particularly useful in the identification of compound mixtures, and complements MS techniques. The utility of HPLC/MS and HPLC/NMR is demonstrated here for a special case of typical mixtures. Figure 3 indicates that (1) five compounds in each well were synthesized as a mixture and (2) the excess aldehyde was completely removed from the final products by the scavenger resin.

Figure 4 shows a stacked plot of the five compounds for the NMR region from $\delta = 1$ to 8.5. The protons of each compound were assigned by stopped-flow HPLC/NMR. As each of the components was captured in the probe, the chromatography was stopped, and the NMR data collection was initiated. The unintegral protons of eluents acetonitrile and H_2O were assigned at 2.00 and 3.20 ppm, respectively. The triplet at $\delta = 1.19$ and the quartet at $\delta = 2.39$ were from the impurity of a trace amount of propionitrile from the eluent acetonitrile. To obtain the signals of the compounds, we synchronously presaturated at 2.00 and 3.20 ppm to suppress these two very high peaks. Although the presaturation resulted in the distorted assignments from $\delta = 1.70-2.20$ and $\delta = 3.10-4.40$, the determination of the structure for each anticipated compound was straightforward by consideration of the other chemical shifts. The detailed proton assignments of this mixture are described in the Experimental Section. Thus, from the experiments, we could draw the conclusion that HPLC/MS and HPLC/NMR can efficiently and quickly determine the synthetic mixture compounds and their purities.

Conclusions

In summary, a protocol for solution-phase synthesis of the novel 1,2,7-trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol library scaffold was developed. The library was incorporated into three diversity points and prepared using commercially available building blocks. By utilizing scavenger resin and a highly efficient filtering apparatus, we obtained compounds in good yields and reasonable purities. The biological screening results from this library for the identification of active compounds will be reported soon.

Experimental Section

All amino acids methyl or ethyl esters were purchased from Chem-Impex International, Inc. (Wood Dale, IL). All alkyl primary amines and aldehydes were purchased from Acros Organics (Geel, Belgium). All organic solvents were

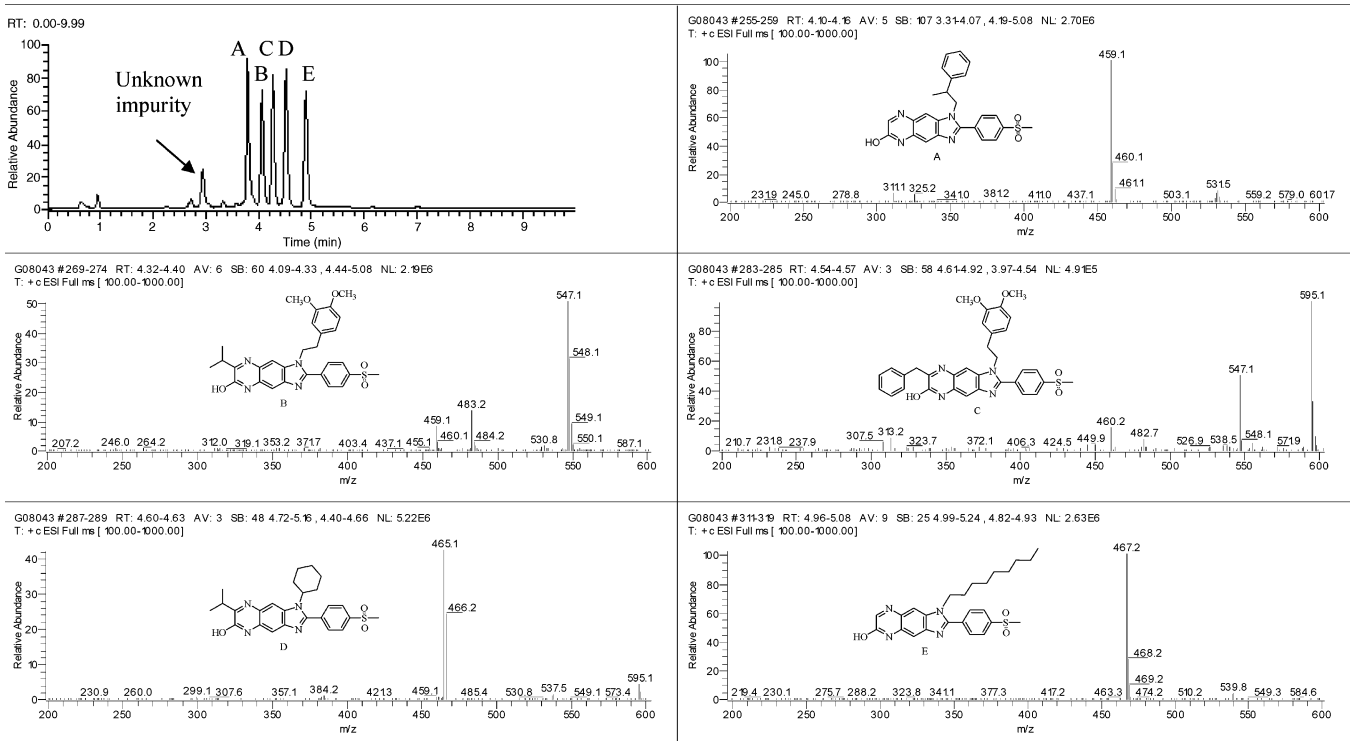


Figure 3. HPLC/MS analysis of five compounds/well and their corrected molecular weights.

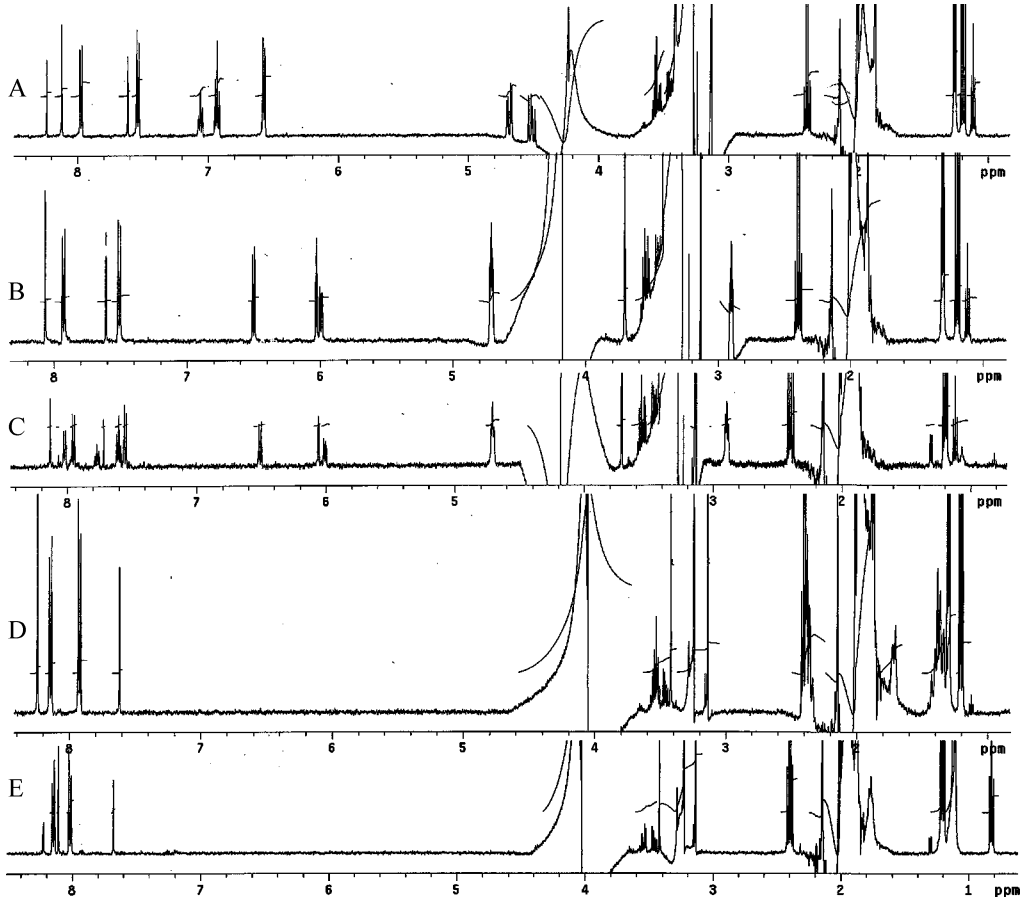


Figure 4. HPLC/NMR analysis of five compounds/well and typical assignments of ^{1}H NMR.

redistilled after a proper drying program. HPLC analysis was carried out by a Shimzdzu HPLC equipped with a SPD-10A VP detector, a LC-10AT VP pump, and a DGU-12A degasser. The analytic gradient was acetonitrile in water from 5 to 95% containing 0.05% trifluoroacetic acid (TFA) in 5 min with a flow rate of 1.0 mL/min and detected by UV at 254-nm wavelength. Auto LC/MS/MS analysis was carried out on a ThermoFinnigan 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 (LC gradient, flow rate, UV detection wavelength are the same as above; 5% eluent was split into the MS system). The employed column was a Kromasil C18 column (4.6 μm, 4.6 × 50 mm) from DIKMA. Mass spectra were recorded in positive ion mode using electrospray ionization. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian Mercury 300 spectrometer at 300 MHz. Chemical shifts are reported as σ values (ppm). HPLC NMR analysis was performed on a Varian INOVA (500 MHz), which consisted of a Varian Prostar 230 solvent delivery system and a Varian Prostar 330 photodiode array detector. The solvent gradient was 45−100% acetonitrile in D_2O for 70 min at a flow rate of 1 mL/min. The detection wavelength was at UV 254 nm, and the column was an Inertsil ODS-3 C_{18} HPLC column (250 × 4.6 mm). The parallel synthesis was carried out on an H+P Labortechnik GmbH parallel synthesizer, which was equipped with a reflux cooler 96.16 and DLSB-20/40 low temperature (max. −40 °C) liquid circulator by Zheng-Zou Great Wall Ke-Mao Corp.

General Procedure for Parallel Compounds Filtration without Inert Gas Production. Forty-eight test tubes with reactants were placed in a test tube rack specially made for this filtering apparatus and arranged in an 8 × 6 array. This reflects the positions of half of the test tubes in the H+P parallel synthesizer and minimizes the opportunities of reacting solution in a test tube being filtered into the wrong centrifuge tube. To prevent the labels from being dissolved by the solvent during the filtering steps, the 48 test tubes were labeled with the corresponding compound codes using indelible ink and covered with clear inert tape. Forty-eight new centrifuge tubes then were placed in the centrifuge tube tray with the same codes in the exact positions of the first rack.

The centrifuge tube tray with centrifuge tubes was pushed into the filtering apparatus, and the side door then was closed. Forty-eight filter-cushion pads then were inserted into the wells of the cupboard, and the filtering funnels were next inserted into the filter-cushion pad. The end of the funnels was sure to be plugged into ∼3.0 cm of the corresponding tubes. Forty-eight reactants from the test tubes then were poured into the corresponding funnels. Then the air was slowly drained out of the outlet. After the liquids were drained into the corresponding centrifuge tubes completely, the same operation was repeated for washing the filter cakes with a small volume of solvent; however, the total amount never exceeded 8 mL. The centrifuge tubes containing the anticipated compounds were then centrifuged in a vacuum to obtain the final products. If there are fewer than 48

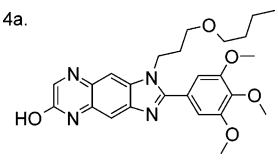
solutions, surplus wells in the middle board can be locked with a rubber stopper.

General Procedure for Parallel Filtration of Compounds under an Atmosphere of Inert Gas. As described above, the centrifuge tube tray was pushed into the filtering apparatus, and the side door was closed, then 48 filter-cushion pads were inserted into the wells, after which the filtering funnels were inserted. After the upper door was closed, nitrogen or argon gas was pressed in through the inlet, and air was let out through the outlet for half an hour. Then the upper door was opened, and 48 reaction solutions were quickly poured into the corresponding funnels. The upper door was closed again, and an inert gas pressure was gently applied. The liquids were forced out of the funnels into the corresponding centrifuge-tubes below. The procedure of washing and collecting the final compounds were the same as above. Sounds from alarm indicated that the pressure inside is over the pressure limitation.

General Procedure for the Parallel Preparation of 1,2,7-Trialkyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol Single Compound. To each reaction tube of a 96-well H+P parallel synthesizer, 0.1 mmol 1,5-difluoro-2,4-dinitrobenzen (20.4 mg) in 2 mL of redistilled DMF, 4.0 equiv of DIPEA resin, and precisely 0.1 mmol of amino acid methyl or ethyl ester hydrogen chloride in DMF were added in order. The reactions then were continued for 30 min at room temperature with gentle stirring. Continuously, precisely 0.1 mmol of alkyl primary amine was added to each reaction tube for an additional 18 h at 35 °C. After that, the scavenger resin was parallel filtered out using our apparatus, and 10% Pd/C then was added, followed by the immediate addition of ammonium formic acid (120 mg). The suspensions were continuously stirred at 70 °C for 5 h. After the Pd/C was filtered, compounds **3** were gained in DMF. To the solution of each **3**, 0.15 mmol of aldehyde was added sequentially for an additional 15 h at 75 °C. The excessive aldehyde was removed from the reaction system by the amino scavenger resin[8] at 65 °C overnight. This scavenger resin was finally filtered out of the reaction system. The filtrates were analyzed by an automatic LC/MS system. Selected compounds were further characterized by ^{1}H NMR. Ten typically resulting compounds are compounds **4a**−**j**.

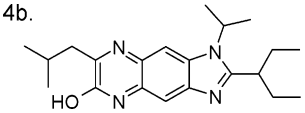
4a. 1-(3-Butoxypropyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{25}H_{30}N_4O_5$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 7.2 Hz, 3H), 1.21 (m 2H), 1.34 (m, 2H), 1.97 (m, 2H), 3.18 (t, J = 6.6 Hz, 2H), 3.27 (t, J = 5.7 Hz, 2H), 3.75 (s, 3H), 3.86 (s, 6H), 4.47 (t, J = 7.2 Hz, 2H), 7.08 (s, 2H), 7.51 (s, 1H), 8.08 (s, 1H), 8.11 (s, 1H). MS (*m*/*z*): calcd, 466.54; found, 467.2 [M + H]$^+$.

4a.



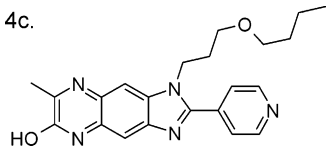
4b. 2-(1-Ethylpropyl)-7-isobutyl-1-isopropyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{21}H_{30}N_4O$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76 (t, J = 7.5 Hz, 6H), 0.93 (d, J = 6.6 Hz, 6H), 1.58 (d, J = 6.9 Hz, 6H), 1.75 (m, 4H), 2.24 (m, 1H), 2.66 (d, J = 7.2 Hz, 2H), 2.99 (m, 1H), 4.93 (m, 1H), 7.40 (s, 1H), 7.97 (s, 1H). MS (*m*/*z*): calcd, 354.50; found, 355.1 [M + H]$^+$.

4b.



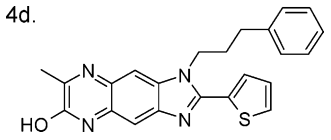
4c. 1-(3-Butoxypropyl)-7-methyl-2-pyridin-4-yl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{22}H_{25}N_5O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81 (t, J = 7.2 Hz, 2H), 1.20 (m, 2H), 1.31 (m, 2H), 1.94 (m, 2H), 2.43 (s, 3H), 3.12 (t, J = 6.6 Hz, 2H), 3.19 (t, J = 5.7 Hz, 2H), 4.50 (t, J = 7.2 Hz, 2H), 7.53 (s, 1H), 7.84 (d, J = 6.0 Hz, 2H), 8.06 (s, 1H), 8.78 (d, J = 6.0 Hz, 2H). MS (*m*/*z*): calcd, 391.48; found, 392.1 [M + H]$^+$.

4c.



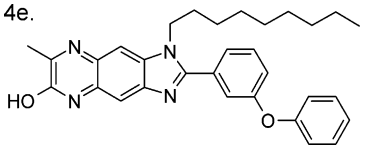
4d. 7-Methyl-1-(3-phenylpropyl)-2-thiophen-2-yl-1*H*-imidazo[4.5-*g*]quinoxalin-6-ol. Molecular formula, $C_{23}H_{20}N_4OS$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.09 (m, 2H), 2.41 (s, 3H), 2.72 (t, J = 7.5 Hz, 2H), 4.53 (t, J = 7.5 Hz, 2H), 7.16−7.30 (m, 6H), 7.42 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 7.82 (d, J = 4.8 Hz, 1H), 7.99 (s, 1H), 12.18 (bs, 1H). MS (*m*/*z*): calcd, 400.51; found, 401.1 [M + H]$^+$.

4d.



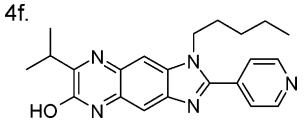
4e. 7-Methyl-1-nonyl-2-(3-phenoxyphenyl)-1*H*-imidazo-[5,6-*g*]quinoxalin-6-ol. Molecular formula, $C_{31}H_{34}N_4O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 6.9 Hz, 3H), 1.07−1.25 (m, 12H), 1.62 (m, 2H), 2.41 (s, 3H), 4.31 (t, J = 7.2 Hz, 2H), 7.08−7.60 (m, 10H), 7.99 (s, 1H). MS (*m*/*z*): calcd, 494.64; found, 495.2 [M + H]$^+$.

4e.



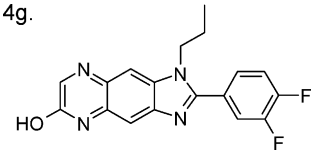
4f. 7-Isopropyl-1-pentyl-2-pyridin-4-yl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{22}H_{25}N_5O$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 6.9 Hz, 3H), 1.07−1.25 (m, 12H), 1.62 (m, 2H), 2.41 (s, 3H), 4.31 (t, J = 7.2 Hz, 2H), 7.08−7.60 (m, 10H), 7.99 (s, 1H). MS (*m*/*z*): calcd, 494.64; found, 495.2 [M + H]$^+$.

4f.



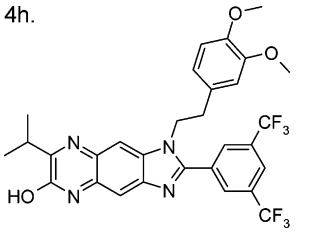
4g. 2-(3,4-Difluorophenyl)-1-propyl-1*H*-imidazo[4,5-*g*]-quinoxalin-6-ol. Molecular formula, $C_{18}H_{14}F_2N_4O$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 6.9 Hz, 3H), 1.07−1.25 (m, 12H), 1.62 (m, 2H), 2.41 (s, 3H), 4.31 (t, J = 7.2 Hz, 2H), 7.08−7.60 (m, 10H), 7.99 (s, 1H). MS (*m*/*z*): calcd, 494.64; found, 495.2 $[M + H]^+$.

4g.



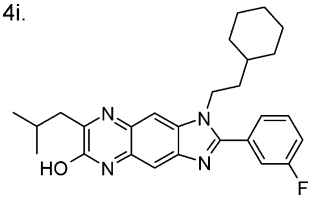
4h. 2-(3,5-Bis-trifluoromethylphenyl)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-7-isopropyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{30}H_{26}F_6N_4O_3$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 6.9 Hz, 3H), 1.07−1.25 (m, 12H), 1.62 (m, 2H), 2.41 (s, 3H), 4.31 (t, J = 7.2 Hz, 2H), 7.08−7.60 (m, 10H), 7.99 (s, 1H). MS (*m*/*z*): calcd, 494.64; found, 495.2 $[M + H]^+$.

4h.



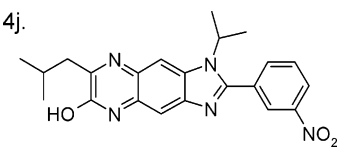
4i. 1-(2-Cyclohexylethyl)-2-(3-fluorophenyl)-7-isobutyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{27}H_{31}FN_4O$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 6.9 Hz, 3H), 1.07−1.25 (m, 12H), 1.62 (m, 2H), 2.41 (s, 3H), 4.31 (t, J = 7.2 Hz, 2H), 7.08−7.60 (m, 10H), 7.99 (s, 1H). MS (*m*/*z*): calcd, 494.64; found, 495.2 $[M + H]^+$.

4i.



4j. 2-(3-Nitrophenyl)-7-isobutyl-1-isopropyl-1*H*-imidazo-[54,5-*g*]quinozalin-6-ol. Molecular formula, $C_{22}H_{23}N_5O_3$. ^{1}H NMR (300 MHz DMSO-d_6): δ 0.95 (d, J = 6.3 Hz, 6H), 1.64 (d, J = 6.9 Hz, 6H), 2.27 (m, 1H), 2.69 (d, J = 7.2 Hz, 2H), 4.76 (m, 1H), 7.53 (s, 1H), 7.89 (t, J = 8.1 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.17 (s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.48 (s, 1H). MS (*m*/*z*): calcd, 405.46; found, 406.1 $[M + H]^+$.

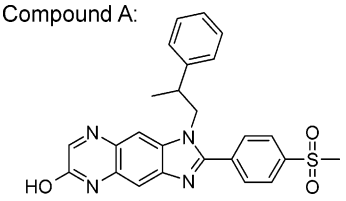
4j.



General Procedure for the Parallel Preparation of Mixed Compounds. Intermediates **3** in Scheme 1 were prepared using the same procedure described above. After being analyzed by LC/MS and showing purity over 90%, five anticipated compounds were grouped, mixed, and distributed into the different reaction tubes after proper dilution in DMF. Each mixture then was reacted with 1.5 equiv of the selected aldehyde for 18 h at 75 °C. An automatic LC/MS system traced the reaction until all intermediates **3** disappeared. The excessive aldehyde was removed from the reaction system by the amino scavenger resin overnight at 65 °C. The filtrates were analyzed again by LC/MS. Selected reaction wells were identified by HPLC/NMR. Assignments of ^{1}H NMR and LC/MS results of each compound, **A**−**E**, are indicated in Figures 3 and 4.

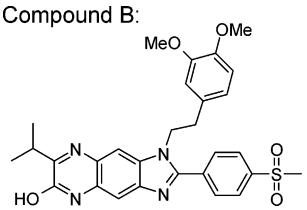
Compound A. 2-(4-Methanesulfonylphenyl)-1-(2-phenyl-propyl)-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{25}H_{22}N_4O_3S$. ^{1}H NMR (500 MHz, CH_3CN/D_2O): 1.26 (d, J = 6.5 Hz, 3H), 3.23 (s, 3H), 4.51 (dd, J = 10 Hz, 14.5 Hz, 1H), 4.68 (dd, J = 4.5 Hz, 14.5 Hz, 1H), 6.57 (d, J = 7.5 Hz, 2H), 6.93 (t, J = 7.5 Hz, 2H), 7.06 (t, J = 7.5 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 8.12 (s, 1H), 8.24 (s, 1H). MS (*m*/*z*): calcd 458.54; found, 459.1 $[M + H]^+$.

Compound A:



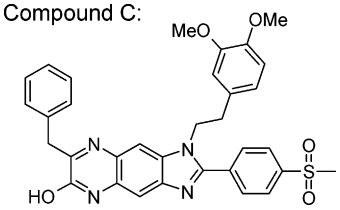
Compound B. 7-Isopropyl-2-(4-methanesylfonylphenyl)-1-3,4-dimethoxyphenethyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{29}H_{30}N_4O_5S$. ^{1}H NMR (500 MHz, CH_3CN/D_2O): 1.30 (d, J = 7.0 Hz, 6H), 2.90 (t, J = 6.0 Hz, 2H), 3.21 (s, 3H), 3.40 (s, 3H), 3.71 (s, 3H), 4.71 (t, J = 6.0 Hz, 2H), 6.01 (d, J = 8.0 Hz, 1H), 6.03 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.61 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 8.07 (s, 1H). MS (*m*/*z*): cald, 546.65; found, 547.1 $[M + H]^+$.

Compound B:



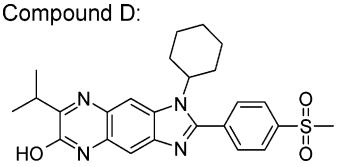
Compound C. 7-Benzyl-2-(4-methanesulfonylphenyl)-1-dimethoxyphenethyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{32}H_{30}N_4O_5S$. ^{1}H NMR (500 MHz, CH_3CN/D_2O): 2.89 (t, J = 6.0 Hz, 2H), 3.23 (s, 3H), 3.40 (s, 3H), 3.71 (s, 3H), 4.71 (t, J = 6.0 Hz, 2H), 6.01 (d, J = 8.0 Hz, 1H), 6.06 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.60 (t, J = 8.0 Hz, 2H), 7.72 (s, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H), 8.13 (s, 1H). MS (*m*/*z*): cald, 594.69; found 595.1, $[M + H]^+$.

Compound C:



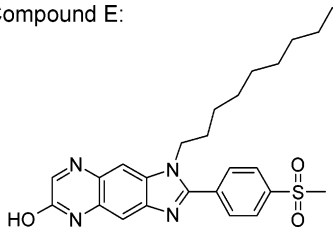
Compound D. 1-Cyclohexyl-7-isopropyl-2-(4-methanesulfonylphenyl)-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{25}H_{28}N_4O_3S$. ^{1}H NMR (500 MHz, CH_3CN/D_2O): 1.30 (d, $J = 7.0$ Hz, 6H), 3.24 (s, 3H), 7.62 (s, 1H), 7.92 (d, $J = 8.5$ Hz, 2H), 8.14 (d, $J = 8.5$ Hz, 2H), 8.24 (s, 1H). MS (*m*/*z*): calcd, 464.59; found, 465.1 $[M + H]^+$.

Compound D:



Compound E. 2-(4-Methanesulfonylphenyl)-1-nonyl-1*H*-imidazo[4,5-*g*]quinoxalin-6-ol. Molecular formula, $C_{25}H_{30}N_4O_3S$. ^{1}H NMR (500 MHz, CH_3CN/D_2O): 0.82 (t, $J = 7.0$ Hz, 3H), 3.23 (s, 3H), 7.68 (s, 1H), 8.02 (d, $J = 8.0$ Hz, 2H), 8.11 (s, 1H), 8.15 (d, $J = 8.0$Hz, 2H), 8.22 (s, 1H). MS (*m*/*z*): cald, 466.61; found, 467.2 $[M + H]^+$.

Compound E:



General Procedure for the Parallel Analysis of Mixed Compounds by LC/NMR. LC/NMR data were acquired using a Varian INOVA 500-MHz spectrometer equipped with a H{^{13}C} pulsed-field gradient LC/NMR flow probe with a 60-μL flow cell. ^{1}H NMR spectra were obtained in stopped-flow mode at 500.13 MHz. Varian WET solvent suppression and its related sequences were used to suppress the acetonitrile, its ^{13}C satellites, and the residual water peaks. Free induction decays were collected with 16-K data points, a spectral width of 7500 Hz, a 1.5-s acquisition time, and a 1-s pulse delay. Before Fourier transformation, 256 transients were acquired to obtain the ^{1}H NMR data. The exponential apodization function was applied to the FID, corresponding to a line broadening of 0.5 Hz. The HPLC system consisted of a Varian Prostar 230 solvent delivery system and a Varian Prostar 330 photodiode array detector. The HPLC method used an Inertsil ODS-3 C_{18} HPLC column (250 × 4.6 mm) and a solvent gradient of 45−100% acetonitrile in D_2O in 70 min at a flow rate of 1.02002 mL/min. A 20-μL injection (2 mg/200 μL) of the mixture was used for the LC/NMR stopped-flow experiment.

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References and Notes

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