Diversity-Oriented Synthesis of Angular Bis-benzimidazole Derivatives under Microwave Irradiation

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Pharmaceutically interesting, angular bis-benzimidazoles with three appendages have been synthesized successfully through a diversity-oriented approach with soluble support under microwave irradiation. Polymer immobilized *o*-phenylenediamine was selectively *N*-acylated with 2-chloro-3-nitrobenzoic acid in a primary aromatic amino moiety. The obtained amide was cyclized to benzimidazole in an acidic condition, and subsequently nucleophilic aromatic substitution with different amines was performed. Successive reduction, cyclization with various aldehydes and activated isothiocyanates yielded angular biheterocyclic benzimidazoles in good quantities. Reaction progress on polymer support was precisely monitored using the conventional proton NMR spectroscopy. Preliminary screening results showed some of these interesting compounds exhibited moderately to good inhibition against vascular endothelial growth factor receptor 3 (VEGFR-3), which is related to invasion and migration of cancer cells.

Introduction

Chemical genetics is a powerful tool for using small molecules to explore biology systematically.[1] Small complex and diverse molecules were generated through a diversity-oriented synthesis to screen indefinite biological targets to discover novel modulators.[2] The diversity-oriented synthesis assisted the initial task of chemical genetics in creating extensive chemical space distributions. On the basis of appendage diversity, various substituent groups were attached to the skeletons to expand the diversity.

Convergent, polymer-supported synthesis of unique chemical entities under microwave irradiation provides a primary lead optimization method to refine biological activity. This approach may significantly reduce the drug development timeline compared with conventional solution-phase synthesis. Solid phase organic synthesis has been extensively used as a platform for the rapid generation of molecular libraries.[3−5] Insoluble polymer-supported reactions improved the synthesis efficiency by reducing purification time. However, optimizing solid phase reaction conditions still requires extensive work and some bottlenecks must be overcome. Using soluble polymer support in combinatorial synthesis facilitates library synthesis and overcomes difficulties with solid phase reactions. It serves as a chemically robust macromolecular protecting group and is carried forward in multistep synthesis, with molecular modifications, until intentional cleavage at the proper stage. To solve these problems arising from the nature of solid support, various kinds of soluble polymer supports have recently emerged.[6] For example, ionic liquids are used to support catalysts or reagents and have been used in synthesizing bio-oligomers and small molecules.[7] Fluorous support and polyethylene glycol have been employed in synthesizing tripeptides,[8] 5-arylidene thiazolidinones,[9a] phthalocyanines,[9b] and other heterocyclic scaffolds.[10] These revolutionary techniques have greatly affected the rapid synthesis of small, complicated molecules. Since conventional heating takes longer duration to complete polymer bound reactions, microwave irradiation obviously accelerates polymer supported library synthesis in high-throughput fashion.[11−17]

Natural products UK-1 and AJI-9561 isolated from *Streptomyces* are topoisomerase II inhibitors (Figure 1). They are also potent cytotoxic metabiotics against many cancer cell lines.[18] One of these derivatives, alkylated UK-1 exhibits antifungal and antibacterial properties.[19,20] Benzimidazole, the analogue of benzoxazole is a privileged skeleton with extensive biological activities. Linear bis-benzimidazole is identified as a selective chelator in the minor groove of dsDNA.[21,22] Angular bis-benzimidazol is expected to be more difficult to construct because of steric hindrance. Chen synthesized UK-1 analogues that showed potent cytotoxicities against BFTV-905 cells and MES-SA cells.[23] Smith and his colleagues prepared UK-1 derivatives as the topoisomerase II inhibitors.[24] Because of the poor understanding about angular bis-benzimidazoles, this study developed a new strategy for rapid synthesis of angular bis-benzimidazoles to probe their biological pathway and modulation in medicinal applications. Interestingly, these synthetic UK-1 derivatives were found to inhibit VEGFR-3, which dominates the formation of lymphatic vessels and the proliferation of lymphatic endothelial cells.[25] Once VEGFR-3 was activated by VEGFR-C, lymphangiogenesis was triggered. The pro-

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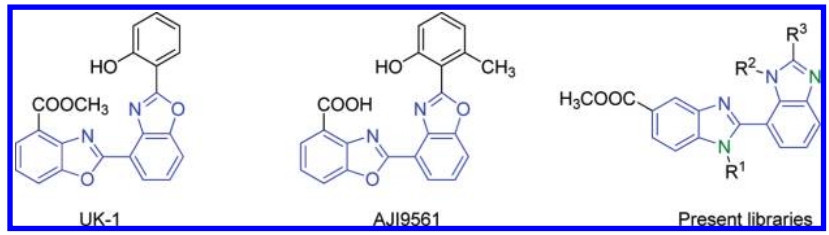
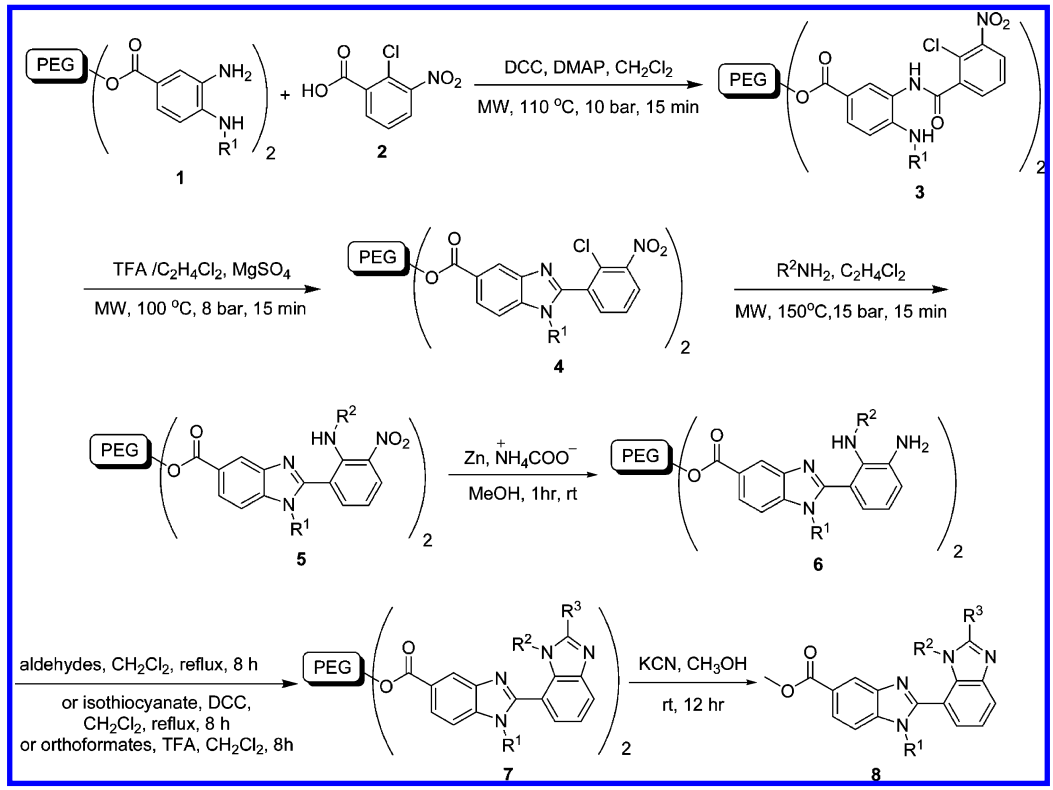


Figure 1. Biological active UK-1 derivatives and angular bis-benzimidazoles.

Scheme 1. Microwave Assisted Synthesis of Angular Bis(benzimidazoles) **8**



gression, invasion, and migration of the cancer cells were also stimulated at the same time. Discovery of novel VEGFR-3 modulators has been much less reported.[26] Therefore, further exploration of these biheterocyclic benzimidazoles as novel VEGFR-3 kinase inhibitors for potential cancer-targeted therapeutics is warranted.

Results and Discussion

On the basis of the concept of appendage diversity, our current methodology follows two major steps.[2] The first step is to synthesize the core skeleton angular bis-benzimidazole, which is constructed with a polymer conjugate **1**, 2-Chloro-3-nitrobenzoic acid **2** and aldehydes or isothiocyanates (as described in the graphical abstract). The second step is to expand the distribution of the chemical space and add miscellaneous appendages to the core template to explore diversity. Three reaction steps, such as coupling reaction, nucleophilic aromatic substitution, and nitro reduction, were used to complete the synthesis of soluble support conjugated diamine **1** containing the first appendage. This fundamental building block **1** is a versatile scaffold for constructing biheterocyclic analogues.[22] To generate bis-benzimidazoles, polymer bound *o*-phenylenediamine **1** was selectively reacted in primary aromatic amino moiety using *N*-acylation with 2-chloro-3-nitrobenzoic acid **2**. PEG conjugated amide **3** was obtained from a condensation of diamine **1** with 2-chloro-3-nitrobenzoic acid **2** in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) (Scheme 1). *N*-acylation proceeded by means of the primary amine moiety is due to the less steric congestion and the greater nucleophilicity compared to that of secondary amine. The nucleophilicity of the secondary amine moiety of **1** was reduced by the *para* carbonyl functionality. Furthermore, the steric hindrance of the DMAP-carboxylic acid complex may impede the coupling with a more bulky secondary amine. The coupling reaction was completed in 15 min under microwave irradiation (110 °C, 10 bar, the temperature measured by infrared), whereas traditional refluxing took 16 h to produce **3**. Compared to the synthesis of linear bis-benzimidazole, the coupling reaction took longer and required harsher conditions to achieve the completion.[22,27] Directly monitoring the reaction transformation of the polymer support was feasible using conventional ^{1}H NMR spectroscopy as shown in Figure 2. After coupling diamine **1** with 2-chloro-3-nitrobenzoic acid **2**, three aromatic protons, H_d (7.87 ppm), H_e (7.55 ppm), and H_f (7.87 ppm) emerged, which supported the formation of amide **3** (Figure 2B). Furthermore, the chemical shifts of

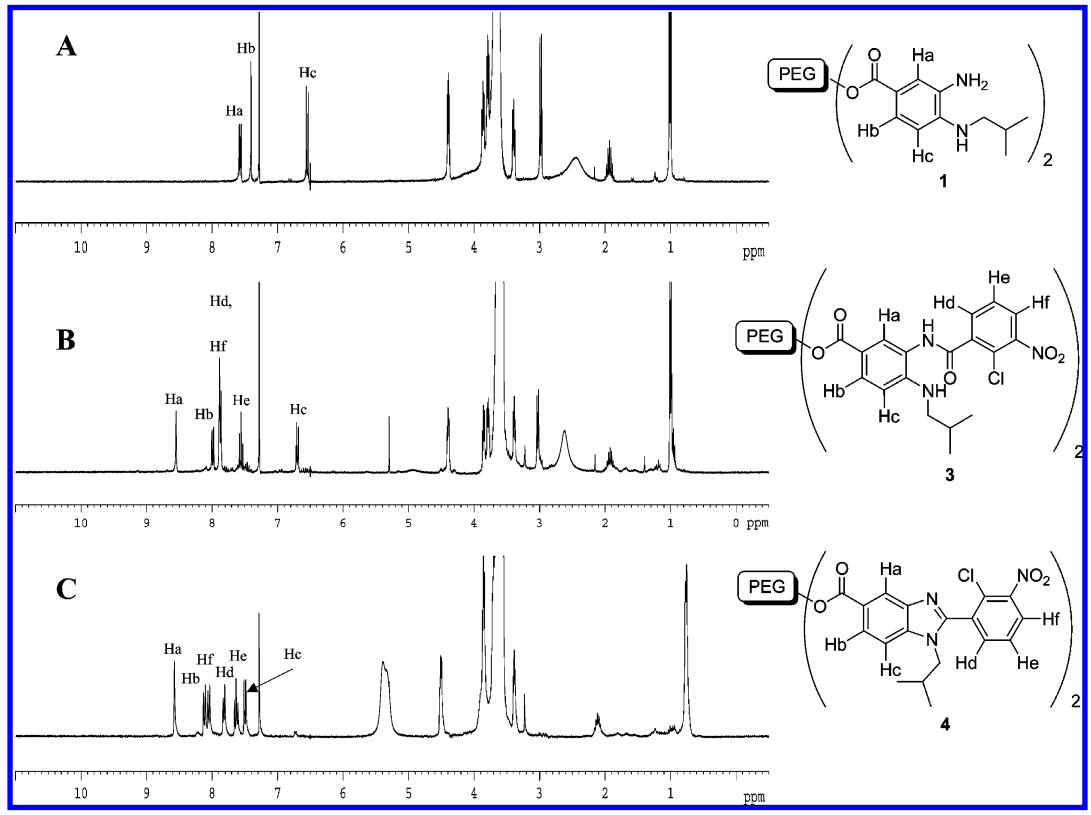


Figure 2. ^{1}H NMR monitoring of the formation of benzimidazole **4**.

the diamine **1** aromatic protons H_a and H_b downfield shifted to δ 8.55 and δ 8.00 in amide **3**, respectively. The decrease in electron density on the aromatic ring where the electron donating amine group of **2** was transformed into the electron withdrawing amide group caused these downfield shifts of H_a and H_b. Following the acid-catalyzed ring cyclization, the polymer-conjugated amide **3** was cyclized in trifluoroacetic acid (TFA) and $MgSO_4$ to produce benzimidazole **4** (Scheme 1). Trifluoroacetic acid served the purpose of dehydrative cyclization to create the first benzimidazole moiety in the present scheme.[28] Cyclization was completed in 12 h under refluxing conditions, but only 15 min were required to complete cyclization using microwave irradiation (100 °C, 8 bar). The functionality transformation was demonstrated by the downfield shift of H_c from 6.67 to 7.47 ppm, which resulted from the conversion of the electron donating amine group of **3** into electron withdrawing nitrogen on the heterocyclic imidazole of **4**.

Benzimidazole conjugated **4** served as a versatile template reacted smoothly with primary amines by *ipso*-fluoro displacement under microwave cavity (150 °C, 15 bar) for 15 min. The harsh condition was required because of the steric hindrance of the *o*-nitro group. We used regular proton NMR to verify the extent of aromatic substitution without detaching the product from the polymer support. In the monitoring model, the proton H_e signal shifted upfield from 7.64 ppm to 6.93 ppm, because the electron withdrawing chloride of **4** was replaced by an electron donating amine. The substitution of the isopropyl group was evident by the appearance of the doublet signal at 0.90 ppm, which was assigned to the methyl protons of the isopropyl group. This study employed various amines as second appendages to increase the diversity, including a normal aliphatic substituent, a steric hindered isopropyl substituent, a phenyl ring containing aliphatic substituent, a heterocycles substituent, and an ether containing aliphatic substituent.

The polymer conjugated *o*-nitro aniline **5** was subsequently reduced to diamine **6** by a convenient Zn-ammonium formate cocktail in methanol. Other reducing agents such as Al-NH_4Cl and 2 M $SnCl_2 \cdot H_2O$ did not reduce the immobilized nitro group successfully. After the reaction was completed, the heterogeneous material was removed by filtration and the PEG-bound diamines were again purified by precipitation.

After the nitro group was reduced to an amine group, the electronic environment on the aromatic ring was altered. Both *para* H_d and *ortho* H_f signals were shifted upfield from 7.64 ppm to 6.83 and 8.31 ppm to 6.83 ppm on the support. Elaboration of compound **6** into the desired second benzimidazole skeleton was readily performed by the cyclization of polymer conjugated *o*-phenylenediamine **6** with aldehydes, orthoformates, and isothiocyanates, respectively, under refluxing condition for 8 h. No trace of the uncyclized compound was observed. For producing compound **7** quantitatively, one-pot cyclization of **6** with a dichloromethane solution of trimethylorthoformate and TFA was adopted which proceeded well. No acidic catalyst was required to finish cyclization with aldehydes. Similar cyclization was applied to construct benzo[1,4]thiazin-3-one tricycles,[29a] benzothiazoles, benzimidazoles, and benzoxazoles.[29b] When the reactions completed, the reaction mixtures were subsequently purified using simple precipitation, filtration, and ether washing to remove unreacted reagents and byproducts.

Compared to the reactivity of aldehydes, isothiocyanates must be activated with DCC to further react with polymer-conjugated diamine **6**. Although the exact intermediates for the DCC-promoted benzimidazole formation were not clear,

the possible in situ generated highly electrophilic carbodimide may be the reactive species. Indirect evidence from a mechanistic study is the isolation of *N,N′*-dicyclohexylthiourea after using DCC to accelerate intramolecular cyclization. In our recent study, one-pot cyclodesulfurization provided a more efficient route toward the formation of second benzimidazole scaffold.

Upon completion of the reaction, insoluble DCU (dicyclohexyl thiourea) was first removed by filtration, and immobilized biheterocyclic benzimidazoles **7** were selectively precipitated out after the addition of diethyl ether to the reaction mixtures. To this end, polymer support was cleaved in a potassium cyanide (1%) solution to deliver methyl ester of trisubstituted angular bis-benzimidazoles **8** in good yields (Table 1). Completed cleavage of the polymer support was verified by observing an upfield shift of α-methylene protons in the polymer attachment site from 4.4 ppm to 3.6 ppm. In most cases, cleavage reactions finished overnight. Their ^{1}H NMR, ^{13}C NMR, and mass spectral data confirmed the structures of all final products. The efficacies of these angular bis(benzimidazoles) **8** were examined with in vitro inhibition of VEGFR-3 kinase cell based assay in the concentration of 3 μM, and preliminary results showed the inhibition of VEGFR-3 kinase from 5.92% to 79.53%.[30]

Synthesis of angular bis-benzimidazole was originally designed by the reaction of diamine conjugated **1** with 3-chloro-2-nitrobenzoic acid **9**. However, benzimidazole conjugated **11** proceeded from a second S_NAr reaction with primary amines, and unexpected nitro group replacement products were obtained (data is shown in the Supporting Information). This result was confirmed by the observing 3:1 ratio of $[M]^+$ and $[M + 2]^+$ peaks in the ESI^+ mass spectra, indicating a chlorine-containing compound.

Conclusions

Microwave-assisted synthesis of angular bis-benzimidazoles on the support with three appendages was achieved in good yields and purities. Compared with conventional thermal heating, microwave irradiation decreased the reaction time from several hours to a few minutes. In contrast to various restrictions on the synthetic progress analysis in solid-phase synthesis, soluble polymer-supported reactions were easily monitored by observing changes in the aromatic region using conventional proton NMR spectroscopy without following *cleave-and-analyze* method.

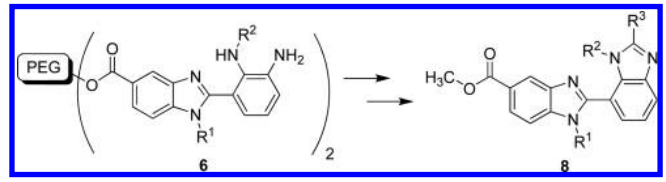
The integration of microwave irradiation and a soluble polymer support strategy provided an efficient and convenient approach for high throughput and diversity-oriented synthesis of drug-like molecules. Preliminary screening results have shown that some of these compounds exhibited moderately to good inhibition against VEGFR 3, which is related to the invasion and migration of cancer cells. These results may lead to the design of more potent VEGFR-3 inhibitors for cancer-targeted therapeutics. Detailed biological data will be reported in due course.

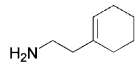
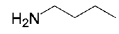
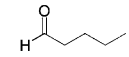
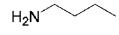
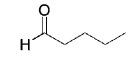
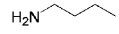
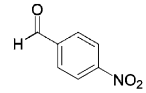
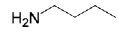
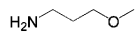
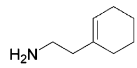
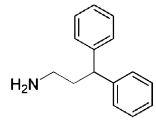
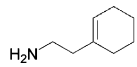
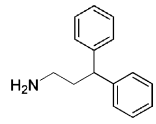
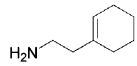
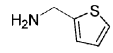
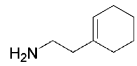
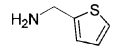
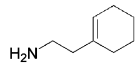
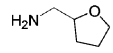
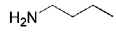
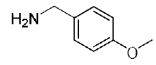
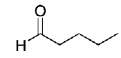
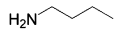
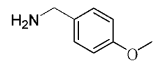
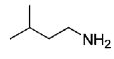
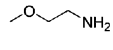
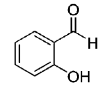
Experimental Section

General Procedures. Dichloromethane was distilled from calcium hydride before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230−400 mesh). Microwave flash heating is performed in CEM Discovery equipment. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per milliom (ppm) on the scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Normal phase HPLC was performed on a Shimadzu LC-10AT series machine with a Hypersil (250 × 4.6 mm) analytical column. PEG was purchased from SHOWA.

General Procedures for the Synthesis of Methyl 2-(1-alkyl-2-substutional-1*H*-benzo[*d*]imidazol-7-yl)-1-alkyl-1*H*-benzo[*d*]imidazole-5-carboxylate (8). Activated ester was prepared by dissolving 2-chloro-3-nitrobenzoic acid **2** 0.09 g (2.6 equiv., 0.44 mmol) in dry dichloromethane and DCC 0.09 g (2.6 equiv., 0.44 mmol) as well as 4-dimethylaminopyridine (DMAP) (0.001 g) were added to the solution. After 30 min, the solution was filtered and poured into the solution of polymer supported diamine **1** (PEG 6000) 1.0 g (1.0 equiv., 0.17 mmol) in dry dichloromethane (10 mL). The reaction mixtures were subjected to microwave irradiation at 110 °C for 15 min, and the crude products were purified by precipitating and washing with excess cold ether (50 mL × 3). To a solution of PEG supported amide **3** in dichloroethane in a microwave vial, trifluoroacetic acid (10.0 equiv., 1.7 mmol) and 0.5 g of magnesium sulfate were added. The vial was sealed and irradiated in a microwave reactor at 100 °C (8 bar) for 15 min. The reaction mixtures were then passed through a thin layer of Celite to remove $MgSO_4$. The solvent was removed under reduced pressure and diluted with slow addition of excess of cold ether (100 mL). The precipitated benzoimidazole conjugate **4** was filtered through a fritted funnel and washed with ether. Various primary amines (7.0 equiv., 1.19 mmol) were added to a solution of PEG bounded benzimidazole **4** in dichloroethane. After irradiation in a microwave reactor at 150 °C (15 bar) for 15 min, the conjugate **5** was purified using the same procedures described previously. Zinc 0.3 g (30.0 equiv., 5.1 mmol) and ammonium formate 0.15 g (15.0 equiv., 2.6 mmol) were added to a solution of **5** in methanol, and the reaction mixtures were stirred for 1 h at room temperature. The mixtures were filtered with Celite to remove zinc, and the filtrate was collected and concentrated under reduced pressure. Then dichloromethane (50 mL) was added to precipitate ammonium formate, and the mixtures were again passed through a thin layer of Celite to remove ammonium formate. To a solution of conjugate **6** in dichloromethane, aldehydes or orthoformates or isothiocyanates (10.0 equiv., 1.7 mmol) were added. The reaction mixtures were irradiated by microwave for several minutes until the reaction was complete. The solvent was removed under reduced pressure and washed with ether to deliver PEG bound angular bis(benzimidazoles) **7**. Potasium cyanide (0.01 equiv., 0.0017 mmol) was added to a solution of conjugate

Table 1. Synthesis of Angular Biheterocyclic Benzimidazoles **8** with Three Different Appendages



Entry	H_2N-R^1	H_2N-R^2	Aldehyde, orthoformate or isothiocyanate	LRMS	Isolated yield (%)
8a				513 (M+1)	70
8b				461 (M+1)	70
8c				526 (M+1)	75
8d				470	72
8e				488	75
8f				595 (M+1)	67
8g				676	65
8h				496	72
8i				579 (M+1)	70
8j				567 (M+1)	75
8k				525 (M+1)	75
8l				511 (M+1)	71
8m				513	67
8n				513	63
8o				513	67
8p				562 (M+1)	67
8q				512 (M+1)	59
8r				700 (M+1)	61

7 in methanol (10 mL). The mixtures were stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure, and the mixtures were precipitated and washed with ether (50 mL × 3). The filtrates were collected, and products **8** were obtained in good yields after column choromatography purification.

Methyl 2′,3′-Dibutyl-1-(2-cyclohexenylethyl)-2,4′-bi (1*H*-benzo[*d*]imidazole)-5-carboxylate (8a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.46−7.28 (m, 2H), 5.33 (s, 1H), 4.10 (t, J = 7.5 Hz, 2H), 4.00 (s, 3H), 2.84 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.92−1.86 (m, 4H), 1.82−1.76 (m, 2H), 1.55−1.46 (m, 6H), 1.31−1.21 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H), 0.90−0.82 (m, 2H), 0.78−0.70 (m, 2H), 0.52 (t, J = 7.3 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 155.8, 152.2, 142.9, 141.5, 136.8, 132.4, 124.8, 124.3, 124.2, 123.7, 121.8, 120.7, 120.4, 112.1, 108.9, 108.5, 52.6, 44.2, 43.7, 38.0, 32.4, 29.8, 28.4, 27.4, 25.0, 22.7, 22.6, 21.8, 19.8, 13.8, 13.3; IR (cm^{-1}, neat): 2925, 1719, 1300; MS (ESI) *m*/*z*: 513.35 (M+H)$^+$; HRMS (EI) calcd for $C_{32}H_{20}N_4O_2$: *m*/*z* 512.3151, found 512.3157.

Methyl 2′,3′-Dibutyl-1-isobutyl-2,4′-bi(1*H*-benzo[*d*]imidazole)-5- arboxylate (8b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 1.1 Hz, 1H), 8.08 (dd, J = 8.6, 1.1 Hz, 1H), 7.88 (dd, J = 7.3, 1.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.35−7.26 (m, 2H), 3.98 (s, 3H), 3.84 (d, J = 4.7 Hz, 2H), 3.72−3.62 (m, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.09 (m, 1H), 1.94−1.85 (m, 2H), 1.53−1.43 (m, 2H), 1.40−1.30 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H), 0.79 (d, J = 6.6 Hz, 6H), 0.80−0.70 (m, 2H), 0.55 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 157.2, 153.0, 144.1, 142.7, 138.7, 133.2, 125.5, 125.1, 124.9, 122.7, 121.7, 121.6, 113.4, 110.5, 52.6, 52.6, 44.8, 32.7, 31.3, 30.1, 29.5, 27.7, 23.1, 20.6, 20.2, 14.2, 13.7; IR (cm^{-1}, neat): 2959, 1717, 1301; MS (ESI) *m*/*z*: 461.32 (M+H)$^+$; HRMS (EI) calcd for $C_{28}H_{36}N_4O_2$: *m*/*z* 460.2838, found 460.2843.

Methyl 3′-Butyl-1-isobutyl-2′-(4-nitrophenyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.38 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H), 8.03 (m, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.54−7.47 (m, 3H), 3.98 (s, 3H), 3.98−3.94 (m, 4H), 2.19−2.14 (m, 1H), 1.25−1.05 (m, 2H), 0.85 (d, J = 6.5 Hz, 6H), 0.60−0.50 (m, 2H), 0.38 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 153.6, 152.4, 149.0, 144.7, 142.7, 138.8, 137.1, 133.9, 131.0, 127.2, 125.2, 125.1, 124.4, 122.9, 122.8, 114.8, 110.7, 110.7, 52.7, 52.6, 46.3, 32.8, 29.6, 20.7, 19.9, 13.4; IR (cm^{-1}, neat): 2960, 1717, 1524, 1349; MS (ESI) *m*/*z*: 526.3 (M+H)$^+$; HRMS (EI) calcd for $C_{30}H_{31}N_5O_4$: *m*/*z* 525.2376, found 525.2384.

Methyl 3′-Butyl-2′-(furan-2-yl)-1-isobutyl-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 7.4 Hz, 1H), 7.62 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.45−7.36 (m, 2H), 7.24 (s, 1H), 6.62 (d, J = 1.4 Hz, 1H), 4.03−3.96 (m, 2H), 4.00 (s, 3H), 3.90−3.80 (m, 2H), 2.10 (m, 1H), 1.59−1.43 (m, 2H), 0.80 (d, J = 6.5 Hz, 6H), 0.81−0.73 (m, 2H), 0.56 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 152.8, 146.2, 145.6, 144.5, 142.8, 141.9, 138.7, 133.7, 126.7, 125.2, 125.0, 122.9, 122.6, 122.5, 114.1, 113.7, 112.4, 110.5, 52.6, 46.1, 32.8, 30.1, 29.5, 20.6, 20.1, 13.6; IR (cm^{-1}, neat): 2959, 1715, 1302; MS (EI) *m*/*z*: 470 (M$^+$); HRMS (EI) calcd for $C_{28}H_{30}N_4O_3$: *m*/*z* 470.2318, found 470.2322.

Methyl 3′-Isopropyl-1-(3-methoxypropyl)-2′-(thiophen-2-yl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 1.0 Hz, 1H), 8.13 (dd, J = 8.5, 1.0 Hz, 1H), 8.00 (dd, J = 8.0, 1.2 Hz, 1H), 7.59−7.53 (m, 2H), 7.45−7.39 (m, 2H), 7.32 (dd, J = 7.4, 1.2 Hz, 1H), 7.16 (dd, J = 5.1, 3.7 Hz, 1H), 4.35 (sept, J = 7.0 Hz, 1H), 4.18−4.12 (m, 2H), 3.99 (s, 3H), 3.27−3.23 (m, 2H), 3.23 (s, 3H), 1.94−1.84 (m, 2H), 1.19 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 153.4, 149.7, 144.3, 142.6, 138.6, 134.5, 133.4, 130.4, 129.1, 127.6, 126.7, 125.3, 125.2, 122.9, 122.8, 122.5, 114.3, 110.3, 69.1, 59.0, 52.6, 50.3, 42.1, 30.5, 22.4; IR (cm^{-1}, neat): 2927, 1715, 1301; MS (EI) *m*/*z*: 488 (M$^+$); HRMS (EI) calcd for $C_{27}H_{28}N_4O_3S$: *m*/*z* 488.1882, found 488.1890.

Methyl 1-(2-Cyclohexenylethyl)-3′-(3,3-diphenylpropyl)-2,4′-bi (1*H*-benzo[*d*]imidazole)-5-carboxylate (8f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 1.3 Hz, 1H), 8.16 (dd, J = 8.5, 1.5 Hz, 1H), 8.01 (d, J = 7.0 Hz, 1H), 7.81 (s, 1H), 7.45−7.37 (m, 3H), 7.20−7.10 (m, 6H), 6.87 (d, J = 1.9 Hz, 2H), 6.85 (s, 2H), 5.19 (s, 1H), 4.04 (s, 3H), 4.03−3.91 (m, 4H), 3.17 (t, J = 7.9 Hz, 1H), 2.16 (t, J = 8.0 Hz, 2H), 2.09−1.90 (m, 2H), 1.90−1.80 (m, 2H), 1.68−1.60 (m, 2H), 1.54−1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 152.3, 146.0, 145.5, 143.3, 142.7, 138.4, 133.4, 132.2, 129.0, 127.7, 127.0, 125.8, 125.4, 125.1, 124.8, 123.1, 122.9, 122.2, 114.2, 110.6, 52.6, 49.0, 46.1, 44.2, 38.2, 35.9, 28.5, 25.5, 22.9, 22.3; IR (cm^{-1}, neat): 2929, 1716, 1301; MS (ESI) *m*/*z*: 595.2 (M+H)$^+$; HRMS (EI) calcd for $C_{39}H_{38}N_4O_2$: *m*/*z* 594.2995, found 594.2996.

Methyl 1-(2-Cyclohexenylethyl)-3′-(3,3-diphenylpropyl)-2′-(thiophen-2-yl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 1.1 Hz, 1H), 8.13 (dd, J = 8.6, 1.1 Hz, 1H), 8.00 (dd, J = 7.9, 1.1 Hz, 1H), 7.47 (dd, J = 5.0, 1.0 Hz, 1H), 7.43−7.37 (m, 3H), 7.15−7.10 (m, 6H), 7.05 (dd, J = 3.7, 1.0 Hz, 1H), 6.98 (dd, J = 5.0, 3.7 Hz, 1H), 6.93−6.72 (m, 4H), 5.24 (s, 1H), 4.03 (s, 3H), 4.04−3.99 (m, 4H), 2.90 (t, J = 7.6 Hz, 2H), 2.25 (t, J = 7.6 Hz, 2H), 2.14−2.05 (m, 2H), 1.98−1.90 (m, 2H), 1.71−1.63 (m, 2H), 1.55−1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 152.2, 149.4, 144.5, 143.4, 142.7, 138.2, 134.0, 133.4, 131.8, 129.3, 128.8, 128.7, 128.2, 127.7, 126.8, 126.2, 125.4, 125.2, 125.0, 122.9, 122.6, 122.5, 113.9, 110.5, 52.6, 49.3, 45.5, 44.2, 38.3, 36.2, 28.6, 25.5, 23.0, 22.3; IR (cm^{-1}, neat): 2932, 1716, 1301; MS (EI) *m*/*z*: 676 (M$^+$); HRMS (EI) calcd for $C_{43}H_{40}N_4O_2S$: *m*/*z* 676.2872, found 676.2867.

Methyl 1-(2-Cyclohexenylethyl)-3′-(thiophen-2-ylmethyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8h). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 1.0 Hz, 1H), 8.11 (dd, J = 8.6, 1.0 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.37−7.33 (m, 2H), 6.98 (dd, J = 5.1, 1.0 Hz, 1H), 6.56 (dd, J = 5.1, 3.5 Hz, 1H), 5.82 (d, J = 2.7 Hz, 1H), 5.56 (s, 2H), 5.31 (s, 1H), 4.01 (s, 3H), 3.72−3.66 (m, 2H), 2.14 (t, J = 7.4 Hz, 2H), 1.96−1.88 (m, 2H), 1.80−1.72 (m, 2H), 1.60−1.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

168.0, 151.8, 142.7, 139.2, 139.2, 138.5, 133.8, 133.8, 127.1, 125.9, 125.6, 125.2, 125.0, 125.0, 124.9, 124.6, 123.1, 122.7, 122.4, 114.5, 110.5, 52.6, 46.4, 43.9, 38.0, 28.8, 25.5, 23.0, 22.4; IR (cm^{-1}, neat): 2929, 1714, 1301; MS (EI) *m/z*: 496 (M^+); HRMS (EI) calcd for $C_{29}H_{28}N_4O_2S$: *m/z* 496.1933, found 496.1936.

Methyl 1-(2-Cyclohexenylethyl)-2′-(thiophen-2-yl)-3′-(thiophen-2-ylmethyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8i). ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.11 (dd, J = 7.3, 2.1 Hz, 2H), 7.59 (d, 5.0 Hz, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.35−7.31 (m, 2H), 7.16 (m, 1H), 6.94 (d, J = 5.0 Hz, 1H), 6.56 (dd, J = 5.0, 3.5 Hz, 1H), 5.89−5.81 (m, 3H), 5.32 (s, 1H), 4.02 (s, 3H), 3.55 (t, J = 7.7 Hz, 2H), 2.17 (t, J = 7.7 Hz, 2H), 1.98−1.88 (m, 2H), 1.83−1.73 (m, 2H), 1.63−1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 151.2, 149.7, 143.8, 141.9, 139.5, 138.1, 133.6, 133.6, 133.1, 130.4, 130.0, 128.5, 127.1, 126.5, 125.5, 125.2, 125.1, 124.7, 124.0, 123.1, 122.5, 122.4, 114.0, 110.6, 52.6, 46.1, 44.0, 38.0, 28.8, 25.5, 23.0, 22.3; IR (cm^{-1}, neat): 2927, 1715, 1300; MS (FAB) *m/z*: 579 $(M+H)^+$; HRMS (FAB) calcd for $C_{33}H_{31}N_4O_2S_2$: *m/z* 579.1888, found 579.1895.

Methyl 1-(2-Cyclohexenylethyl)-3′-((tetrahydrofuran-2-yl)methyl)-2′-(thiophen-2-yl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8j). ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 1.1 Hz, 1H), 8.12 (dd, J = 8.5, 1.1 Hz, 1H), 8.00 (dd, J = 7.6, 1.4 Hz, 1H), 7.63 (d, J = 3.2 Hz, 1H), 7.54−7.52 (m, 1H), 7.50 (s, 1H), 7.44−7.36 (m, 2H), 7.16 (dd, J = 5.1, 3.7 Hz, 1H), 5.40 (s, 1H), 4.45−4.24 (m, 2H), 4.13 (t, J = 7.7, 2H), 4.00 (s, 3H), 3.63 (br, 1H), 3.40 (m, 1H), 3.29 (br, 1H), 2.46 (t, J = 7.7 Hz, 2H), 1.97−1.81 (m, 6H), 1.61−1.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 152.8, 150.3, 144.7, 142.6, 138.4, 134.1, 133.6, 132.5, 129.8, 129.3, 128.0, 126.2, 125.2, 125.1, 125.0, 122.7, 122.7, 122.4, 114.2, 110.3, 68.3, 52.6, 50.0, 44.6, 38.5, 31.4, 29.3, 28.7, 25.6, 25.5, 23.0, 22.4; IR (cm^{-1}, neat): 2930, 1715, 1301; MS (ESI^+) *m/z*: 567.3 $(M+H)^+$; HRMS (EI) calcd for $C_{33}H_{34}N_4O_3S$: *m/z* 566.2352, found 566.2353.

Methyl 1,2′-Dibutyl-3′-(4-methoxybenzyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8k). ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.06 (dd, J = 8.5, 1.1 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.21−7.16 (m, 2H), 6.38 (d, J = 8.5 Hz, 2H), 6.00 (d, J = 8.5 Hz, 2H), 5.26 (br, 2H), 4.01 (s, 3H), 3.66 (s, 3H), 3.20 (t, J = 7.6 Hz, 2H), 2.93 (t, J = 7.6 Hz, 2H), 1.93−1.83 (m, 2H), 1.53−1.37 (m, 4H), 1.22−1.10 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 159.1, 159.1, 157.7, 152.0, 144.0, 142.7, 138.4, 132.8, 128.3, 126.3, 125.2, 125.0, 124.7, 122.6, 121.9, 121.6, 114.0, 110.3, 55.6, 52.6, 47.6, 44.6, 31.8, 30.3, 27.8, 23.0, 20.4, 14.1, 13.8; IR (cm^{-1}, neat): 2957, 2933, 1716, 1300; MS (ESI^+) *m/z*: 525.4 $(M+H)^+$; HRMS (EI) calcd for $C_{32}H_{36}N_4O_3$: *m/z* 524.2787, found 524.2782.

Methyl 1-Butyl-3′-(4-methoxybenzyl)-2′-propyl-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8l). ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 1.0 Hz, 1H), 8.11−8.05 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.27−7.21 (m, 2H), 6.39 (d, J = 8.6 Hz, 2H), 6.00 (d, J = 8.6 Hz, 2H), 5.34 (br, 2H), 4.03 (s, 3H), 3.67 (s, 3H), 3.22 (t, J = 7.6 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.01−1.93 (m, 2H), 1.47−1.37 (m, 2H), 1.27−1.15 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 159.3, 157.0, 151.3, 142.6, 141.4, 138.4, 132.0, 127.5, 126.3, 126.0, 125.2, 124.9, 123.0, 122.6, 120.9, 114.7, 114.2, 110.4, 55.7, 52.6, 47.9, 44.6, 31.9, 29.4, 21.8, 20.4, 14.4, 13.9; IR (cm^{-1}, neat): 2958, 2930, 1716; MS (ESI^+) *m/z*: 511.3 $(M+H)^+$; HRMS (EI) calcd. for $C_{31}H_{34}N_4O_3$: *m/z* 510.2631, found 510.2633.

Methyl-2-[2-(2-Hydroxyphenyl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazol-7-yl]-1-isopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate (8m). ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 1.2 Hz, 1H), 8.12 (dd, J = 8.6, 1.2 Hz, 1H), 7.96 (dd, J = 7.8, 1.0 Hz, 1H), 7.71 (dd, J = 7.8, 1.5 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.49−7.27 (m, 3H), 7.13 (d, J = 7.8 Hz, 1H), 6.91 (dd, J = 8.0, 6.9 Hz, 1H), 4.35 (br, 2H), 4.10 (t, J = 8.0 Hz, 2H), 3.98 (s, 3H), 3.13 (t, J = 5.7 Hz, 2H), 2.84 (s, 3H), 1.78−1.64 (m, 3H), 1.56 (m, 1H), 0.84 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 158.6, 154.5, 152.2, 143.0, 142.7, 138.3, 133.7, 132.2, 128.6, 126.5, 125.3, 125.2, 123.0, 122.9, 121.9, 119.5, 118.4, 114.5, 114.0, 110.3, 70.7, 59.0, 52.6, 46.4, 43.9, 39.0, 26.4, 22.6; IR (cm^{-1}, neat): 2956, 1716, 1618; MS (ESI^+) *m/z*: 513 $(M+H)^+$; HRMS (ESI^+) calcd. for $C_{30}H_{32}N_4O_4$: *m/z* 512.2424, found 512.2422.

Methyl-2-[2-(3-Hydroxyphenyl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazol-7-yl]-1-isopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate (8n). ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 1.2 Hz, 1H), 8.12 (dd, J = 8.6, 1.2 Hz, 1H), 8.03 (dd, J = 7.8, 0.7 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.47−7.33 (m, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 1.5 Hz,1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 4.11 (t, J = 7.8 Hz, 4H), 3.96 (s, 3H), 2.94 (t, J = 5.4 Hz, 2H), 2.74 (s, 3H), 1.85−1.70 (m, 3H), 1.61 (m, 1H), 0.89 (d, J = 6.5 Hz, 6H); ^{13}C NMR 75 MHz, $CDCl_3$)δ 167.8, 158.1, 156.8, 152.4, 143,9, 142.2, 138.2, 133.6, 130.8, 130.2, 126.0, 125.5, 125.2, 122.5, 122.5, 122.4, 121.1, 118.4, 117.5, 114.0, 110.4, 70.9, 58.9, 52.6, 45.3, 44.0, 39.0, 26.6, 22.7; IR (cm^{-1}, neat): 3060, 2954, 1716; LRMS (ESI^+): *m/z* 513 $(M+H)^+$; HRMS (ESI^+) calcd. for $C_{30}H_{32}N_4O_4$: *m/z* 512.2424, found 512.2428.

Methyl 2-[2-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-1*H*-benzo[*d*]imidazol-7-yl]-1-isopentyl-1*H*-benzo[*d*]imidazole-5-carboxylate (8o). ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.47−7.31 (m, 4H), 6.79 (d, J = 7.8 Hz, 2H), 4.26−4.07 (m, 4H), 3.98 (s, 3H), 3.00 (t, J = 5.4 Hz, 2H), 2.80 (s, 3H), 1.82−1.66 (m, 3H), 1.59 (m, 1H), 0.88 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 160.1, 157.4, 152.4, 143.8, 142.5, 138.3, 133.6, 131.5, 125.8, 125.3, 125.2, 122.7, 122.6, 121.9, 120.1, 116.5, 114.2, 110.3, 70.7, 58.9, 52.6, 45.5, 43.9, 39.0, 26.5, 22.7; IR (cm^{-1}, neat): 2954, 1716; LRMS (ESI^+): *m/z* 513 $(M+H)^+$; HRMS (ESI^+) calcd. for $C_{30}H_{32}N_4O_4$: *m/z* 512.2424, found 512.2426.

Methyl 2′-(Benzylamino)-3′-butyl-1-(2-cyclohexenylethyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8p). ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.07 (dd, J = 8.5, 1.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.39−7.27 (m, 5H), 6.97 (d, J = 7.6 Hz, 1H), 6.88 (dd, J = 7.6, 1.1 Hz, 1H), 5.40 (s, 1H), 5.04 (dd, J = 15.1, 5.7 Hz, 1H), 4.84 (dd, J = 15.1,

5.7 Hz, 1H), 4.14−4.10 (m, 4H), 3.99 (s, 3H), 3.89−3.67 (m, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.00−1.92 (m, 2H), 1.92−1.86 (m, 2H), 1.65−1.54 (m, 4H), 1.38−1.21 (m, 2H), 1.12−1.02 (m, 2H), 0.70 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 152.7, 145.3, 145.3, 142.7, 138.7, 138.3, 133.8, 130.5, 129.4, 128.9, 128.0, 127.6, 127.6, 125.0, 124.9, 124.8, 122.9, 120.7, 118.5, 110.4, 54.0, 52.5, 50.1, 44.4, 38.3, 30.5, 28.9, 25.5, 23.1, 22.4, 20.3, 14.2; IR (cm^{-1}, neat): 2928, 1716; MS (ESI^+) m/z: 562 $(M+H)^+$; HRMS (ESI^+) calcd for $C_{35}H_{39}N_5O_2$: m/z 562.3181, found 562.3184.

Methyl 2′-(Benzylamino)-3′-isopropyl-1-(3-methoxypropyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8q). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 1.0 Hz, 1H), 8.05 (dd, J = 8.5, 1.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.44−7.25 (m, 6H), 6.94 (dd, J = 8.1, 1.1 Hz, 1H), 6.85 (dd, J = 7.5, 1.1 Hz, 1H), 5.36 (sept, J = 6.6 Hz, 1H), 5.11 (dd, J = 15.3, 5.3 Hz, 1H), 4.87 (dd, J = 15.3, 5.3 Hz, 1H), 4.32 (t, J = 7.6 Hz, 2H), 3.99 (s, 3H), 3.47 (t, J = 5.0 Hz, 2H), 3.34 (s, 3H), 2.30−2.12 (m, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.44 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6, 168.0, 153.3, 146.7, 142.6, 138.9, 138.5, 131.7, 129.4, 128.8, 127.9, 127.5, 125.7, 125.0, 124.9, 122.9, 120.0, 118.2, 110.4, 69.7, 59.2, 53.1, 52.5, 49.9, 42.8, 30.6, 22.1, 19.7; IR (cm^{-1}, neat): 3357, 2928, 1714; MS (FAB) m/z: 512 $(M+H)^+$; HRMS (EI) calcd for $C_{30}H_{33}N_5O_3$: m/z 511.2583, found 511.2585.

Methyl 2′-(Benzylamino)-1-(2-cyclohexenylethyl)-3′-(3,3-diphenylpropyl)-2,4′-bi(1*H*-benzo[*d*]imidazole)-5-carboxylate (8r). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 1.1 Hz, 1H), 8.06 (dd, J = 8.5, 1.5 Hz, 1H), 7.40−7.26 (m, 7H), 7.19−7.06 (m, 6H), 7.06−6.96 (m, 5H), 6.84 (dd, J = 7.4, 1.1 Hz, 1H), 5.36 (s, 1H), 5.03 (dd, J = 15.0, 5.5 Hz, 1H), 4.82 (dd, J = 15.0, 5.5 Hz, 1H), 4.15 (s, 1H), 4.01 (s, 3H), 3.80−3.66 (m, 4H), 3.56 (m, 1H), 2.43−2.31 (m, 2H), 2.22−2.10 (m, 2H), 2.04−1.96 (m, 2H), 1.89−1.80 (m, 2H), 1.70−1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 168.0, 152.6, 145.2, 144.7, 144.3, 142.8, 138.7, 138.2, 133.7, 130.5, 129.4, 128.9, 128.8, 128.8, 128.0, 128.0, 128.0, 127.6, 126.6, 125.0, 125.0, 124.7, 123.0, 120.4, 118.6, 110.5, 53.3, 52.5, 50.1, 49.0, 44.2, 38.4, 33.6, 28.8, 25.6, 23.1, 22.4; IR(cm^{-1}, neat): 3332, 2927, 1716; MS (ESI^+) m/z: 700 $(M+H)^+$; HRMS (ESI^+) calcd. for $C_{46}H_{45}N_5O_2$: m/z 700.3651 (M+1), found 700.3655.

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Supporting Information Available. Proton and carbon NMR spectrum of compounds **8a**−**8r** and **13a**−**13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969. (b) Walsh, D. P.; Chang, Y. T. *Chem. Rev.* **2006**, *106*, 2476–2530. (c) Ahn, Y. H.; Chang, Y. T. *Acc. Chem. Res.* **2007**, *40*, 1025–1033.

(2) (a) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152–154. (b) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272–3276. (c) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.

(3) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997–10998.

(4) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149−2150.

(5) (a) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157. (b) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607–2624.

(6) (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S. Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826. (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509. (c) Sun, C. M. *Comb. Chem. High Throughput Screening* **1999**, *2*, 299–309. (d) Sun, C. M. Soluble Polymer-Supported Synthesis of Heterocyclic Libraries. In *Combinatorial Chemistry Methods and Protocols*; Bellavance, L., Ed.; Methods in Molecular Biology Series; The Humana Press Inc.: NJ, 2002; Chapter 10, pp 345−371. (e) Zhang, W. *Chem. Rev.* **2004**, *104*, 2531–2556. (f) Martins, M. P. A.; Frizzo, C. P.; Moreira, D. N.; Zanztta, N.; Bonacorsa, H. G. *Chem. Rev.* **2008**, *108*, 2015–2050.

(7) Miao, W.; Chan, T. H. *Acc. Chem. Res.* **2006**, *39*, 897−908.

(8) Zhang, C. X.; Tong, H. B.; Yan, C. G. *J. Comb. Chem.* **2007**, *9*, 924–925.

(9) (a) Liu, Z.; Huang, Y.; Zhang, W.; Ma, L.; Li, J.; Wang, X.; Li, J.; Shen, J. *J. Comb. Chem.* **2008**, *10*, 632–636. (b) Erdem, S. S.; Nesterova, I. V.; Soper, S. A.; Hammer, R. P. *J. Org. Chem.* **2008**, *73*, 5003–5007.

(10) (a) Zhang, W.; Lu, Y.; Chen, C. H. T.; Zeng, L.; Kassel, D. B. *J. Comb. Chem.* **2006**, *8*, 687–695. (b) James, K. M.; Willetts, N.; Procter, D. J. *Org. Lett.* **2008**, *10*, 1203–1206. (c) Leach, S. G.; Cordier, C. J.; Morton, D.; McKiernan, G. J.; Warriner, S.; Nelson, A. *J. Org. Chem.* **2008**, *73*, 2753–2759.

(11) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 51–64.

(12) (a) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417–1424. (b) Guillena, G.; del Cramen Hita, M.; Nájera, Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933–5943. (c) Xie, H.; Zu, L.; Queis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1923–1926.

(13) (a) Maloobi, M.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 275–284. (b) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 285–291. (c) Pisani, L.; Prokopcoá, H.; Kremsner, J. M.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 415–421. (d) Machetti, F.; Bucelli, I.; Indiani, G.; Kappe, C. O.; Guarna, A. *J. Comb. Chem.* **2007**, *9*, 454–461.

(14) Dollinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.

(15) (a) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Shishkina, S. V.; Shishkin, O. V.; Kobzar, K. M.; Kappe, C. O. *Org. Lett.* **2007**, *9*, 1691–1694. (b) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 5110–5118.

(16) (a) Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun.* **2007**, *28*, 368. (b) Bogdald, D.; Prociak, A. *Microwave-Enhanced Polymer Chemistry and Technology*; Blackwell Publishing: Oxford, U.K. 2007. (c) Lee, K. S.; Myung, S. K.; Sun, Y. K. *Chem. Mater.* **2007**, *19*, 2727–2729. (d) Parada, C.; Morán, E. *Chem. Mater.* **2006**, *18*, 2719–2825. (e) Lin, S.; Yun, D.; Qi, D.; Deng, C.; Li, Y.; Zhang, H. *J. Proteome Res.* **2008**, *7*, 1297–1307. (f) Hauser, N.; Han, H.; McLuckey, S. A.; Basile, F. *J. Proteome Res.* **2008**, *7*, 1867–1872.

(17) (a) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36–47. (b) Razzaq, T.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 6321–6329.

(18) (a) Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.; Taniguchi, M.; Oi, S. *J. Antibiot.* **1993**, *46*, 1089–1094. (b)

Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayasho, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102–104. (c) Kumar, D.; Jacob, M. R.; Reynold, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3994–4123 .

(19) Ueki, M.; Shibata, K.; Taniguchi, M. *J. Antibiot.* **1998**, *51*, 883–885.

(20) Ueki, M.; Taniguchi, M. *J. Antibiot.* **1997**, *50*, 788–790.

(21) (a) Reddy, P. M.; Jindra, P. T.; Satz, A. L.; Bruice, T. C. *J. Am. Chem. Soc.* **2003**, *125*, 7843–7848. (b) Joubert, A.; Sun, X. W.; Johansson, E.; Bailly, C.; Mann, J.; Neidle, S. *Biochemistry* **2003**, *42*, 5984–5992.

(22) (a) Lin, M. J.; Sun, C. M. *Synlett* **2004**, 663–666. (b) Yeh, W. B.; Lin, M. J.; Sun, C. M. *Comb. Chem. High Throughput Screening* **2004**, *7*, 251–255.

(23) Huang, S. T.; Hsei, I. J.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106–6119.

(24) Wang, B. B.; Maghami, N.; Goodlin, V. L.; Smith, P. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3221–3226.

(25) (a) Plate, K. *Nat. Med.* **2001**, *7*, 151–152. (b) Witte, D.; Thomas, A.; Ali, N.; Carlson, N.; Younes, M. *Anticancer Res.* **2002**, *22*, 1463–1466. (c) Su, J. L.; Yen, C. J.; Chen, P. S.; Chuang, S. E.; Hong, C. C.; Kuo, I. H.; Chen, H. Y.; Hung, M. C.; Kuo, K. L. *Br. J. Cancer* **2007**, *96*, 541–545.

(26) Patel, P. H.; Chaganti, R. S.; Motzer, R. J. *Br. J. Cancer* **2006**, *94*, 614–619.

(27) Chang, C. M.; Kulkarni, M. V.; Chen, C. H.; Wang, C. H.; Sun, C. M. *J. Comb. Chem.* **2008**, *10*, 466–474.

(28) (a) Thimmegowda, N. R.; Swamy, S. N.; Kumar, C. S. A.; Kumar, Y. C. S.; Chandrappa, S.; Yip, G. W.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 432–435. (b) Morningstar, M. L.; Roth, T.; Farnsworth, D. W.; Smith, M. K.; Watson, K.; Buckheit, R. W.; Das, K.; Zhang, W.; Arnold, E.; Julias, J. G.; Hughes, S. H.; Michejda, C. J. *J. Med. Chem.* **2007**, *50*, 4003–4015.

(29) (a) Li, L.; Wang, Z.; Chen, Y.; Yuan, Y.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 959–972. (b) Hioki, H.; Matsushita, K.; Kubo, M.; Harada, K.; Kodama, M.; Fukuyama, Y. *Tetrahedron* **2007**, *63*, 11315–11324.

(30) The standard method to measure VEGFR3 inhibition is described in the Supporting Information.

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