Article

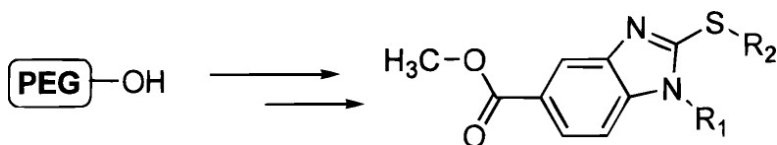# Combinatorial Liquid-Phase Synthesis of Structurally Diverse Benzimidazole Libraries

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Combinatorial Liquid-Phase Synthesis of Structurally Diverse Benzimidazole Libraries

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An expedient liquid-phase synthesis for construction of the diverse benzimidazole libraries is described. Nucleophilic aryl substitution of poly(ethylene glycol)-supported 4-fluoro-3-nitrobenzoic acid **3** with several primary amines under basic conditions, followed by Zn/NH$_4$Cl mediated nitro group reduction, gave the PEG bound diamines **5**. Subsequent cyclization of immobilized *o*-phenylenediamine **5** using thiocarbonyl-diimidazole (TCD) or thiophosgene in dichloromethane furnished benzimidazole-2-thiones **6**. Treatment of **6** with alkyl halides and benzylic halides in the presence of triethylamine provided 1-substituted-2-alkylthio-5-carbamoylbenzimidazoles on the support. The desired products **8** were severed from the PEG under mild conditions in high yield and high purity.

Introduction

Multiple synthetic technology on solid support directed toward the generation of drug-like compounds is now receiving considerable interest as it permits the rapid preparation of compound libraries for lead discovery and optimization.[1] Solid-phase organic synthesis (SPOS) offers several advantages, such as use of excess reagents to drive reactions to completion, easy purification by filtration-washing, and possibility of automation.[2] These benefits make SPOS's utility in organic synthesis attractive and practical. However, several disadvantages have been observed when using cross-linked polystyrenes in solid-supported synthesis, such as the largely reduced rate of the reactions, solvation of the bound species, and the mass transport of reagents and solvents due to the nature of heterogeneous reaction conditions. Although many classical solution-phase organic reactions have been successfully carried out on the solid support,[3] the solid-phase approach still requires extensive development time and effort to establish synthetic conditions on polymer support. Soluble matrixes such as poly(ethylene glycol)-PEG,[4] fluorous supports,[5] and linear poly(styrenes)[6] have recently received increasing attention for their efficiency in generating diverse molecules. We are focusing our research efforts on liquid-phase combinatorial synthesis (LPCS) by the use of soluble polymer support-PEG to generate libraries.[7] This macromolecular carrier, unlike an insoluble matrix, is soluble in most organic solvents and tends to precipitate in diethyl ether or ethanol. To meet all requirements of a stepwise synthesis without intermediate purification, a soluble matrix should be stable across a broad range of reaction conditions. After the reaction is complete, the product remains covalently bound to the support, and purification can be accomplished after precipitation simply by filtering and washing away the low-molecule-weight, solution-phase
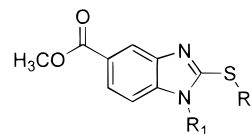
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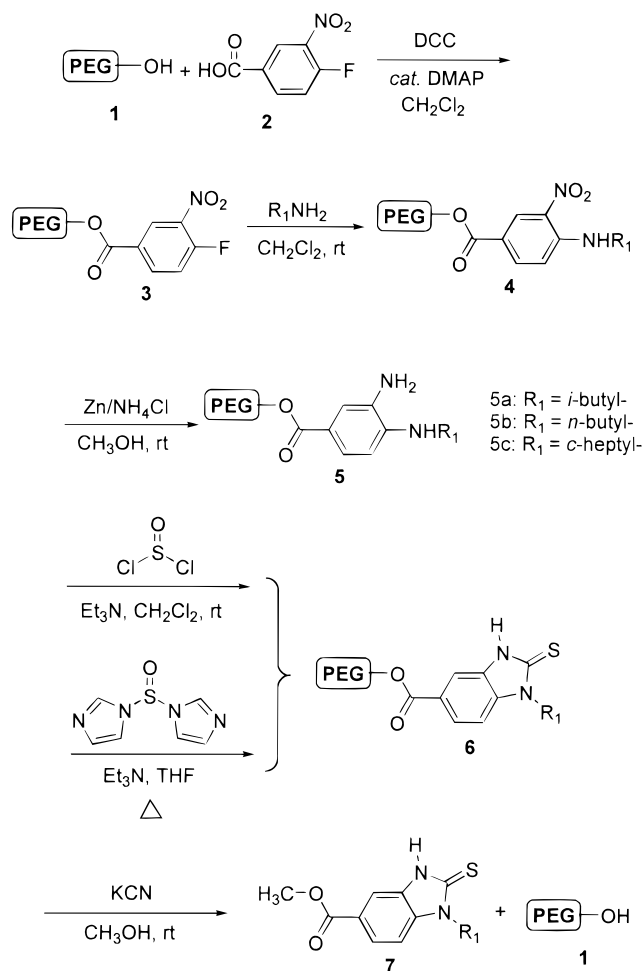

Figure 1.

reagents. Therefore, general difficulties in solid-phase reactions such as lower reactivity and characterization of polymer bound intermediate products could be alleviated by the use of an organic-soluble polymer support.

As part of our ongoing project devoted toward the development of a rapid synthesis of heterocyclic molecules of biological interest, we explored the possibility of synthesizing benzimidazole libraries (Figure 1) by the liquid-phase methodology. The benzimidazole ring system is structurally related to the widely used benzodiazepine nucleus and has not been widely used in medicinal chemistry.[8] In addition, benzimidazole based compounds have shown broad biological activities, including antiulcer and antiviral effects.[9−12] A general method for the rapid multiple synthesis of benzimidazoles would be of great value and merits investigation for drug discovery. In this full account we describe a liquid-phase synthetic route to the preparation of benzimidazole libraries exploiting two sites of chemical diversity.[13,14]
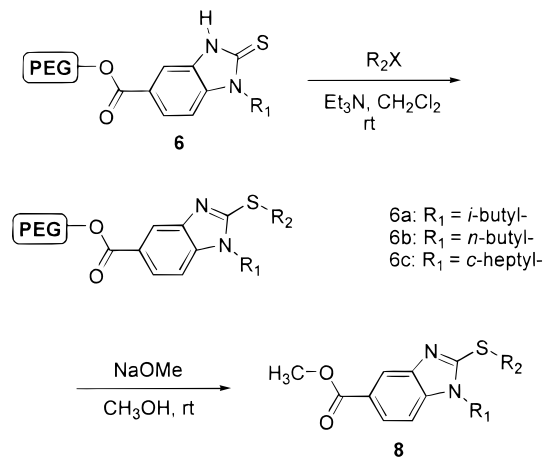
Results and Discussion

The synthetic route described in Scheme 1 was utilized for the synthesis of a representative library. MeO-PEG-OH (MW: 5000) **1** as a soluble support was modified with the commercially available 4-fluoro-3-nitrobenzoic acid **2** through the DCC/DMAP activation to afford the immobilized *o*-fluoronitrobenzene **3** in quantitative yield.[15] This reaction intermediate **3** has previously been shown to undergo facile S$_N$Ar type reaction with secondary nitrogen-nucleophiles.[7a] The first point of diversity was then introduced by nucleophilic aromatic substitution of readily available amines with **3** via an *ipso*-fluoro displacement to give polymer bound

Scheme 1. Synthetic Route to Benzimidazole-2-thione **7**

Scheme 2. Liquid-Phase Synthesis of 1-Alkyl-2-alkylthio-5-carbamoylbenzimidazoles **8**

6a: R₁ = *i*-butyl-
6b: R₁ = *n*-butyl-
6c: R₁ = *c*-heptyl-

transformation with TCD (1,1′-thiocarbonyldiimidazole) required refluxing reaction mixtures to give complete conversion in THF for 3 days. Both conditions gave compound **7** consistently with good yields and good purities after cleavage. To monitor the completion of reaction sequence up to this point, small portions of the PEG bound intermediates **7a**, **7b**, and **7c** were detached from the support by KCN-catalyzed methanolysis.
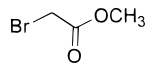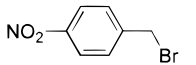
The cleaved products **7a**, **7b**, and **7c** were separated from the MeO-PEG-OH **1** and were analyzed by HPLC, MS, as well as ^{1}H NMR. In all cases, no starting material was observed, and isolated yields of the products were 83∼95% based on the loading yield of **3**. Analysis of products indicated complete cyclization at this stage.

To increase the number of points of chemical diversity in the benzimidazole scaffold, functionalization of the polymer bound benzimidazole **6a** was then investigated with a wide range of alkyl and benzylic halides in the presence of triethylamine as a model study (Scheme 2). To our delight, S-alkylation was performed successfully in CH₂Cl₂ after stirring overnight at room temperature (Table 1).

Carbon-13 NMR experiments indicated that the exclusive product was alkylated on sulfur, but not on nitrogen. After alkylation, the C-2 resonance of compound **7a** was found to show an upfield shift from 170.7 to 154.0 ppm of **8am** (Figure 2).

To follow the course of subsequent reactions without releasing compound from the support, regular proton NMR analysis was used to monitor the success of transformations. This nondestructive method offers considerable advantages to estimate reaction progress compared to that of solid-phase synthesis involving gel-phase,[19] magic-angle spinning NMR,[20] or single-bead FTIR techniques.[21] For example, chemical shifts of α-methylene protons of MeO-PEG-OH are a function of the substrate (4-fluoro-3-nitrobenzoic acid **2**, in this case) linked to the terminal OH group (Figure 3). For unfunctionalized MeO-PEG-OH **1**, the chemical shift of α-methylene protons was δ 3.6 ppm and was shifted to δ 4.4 ppm after **2** was attached. The use of ^{1}H NMR to monitor the reaction course in liquid-phase synthesis was therefore further evaluated for the synthetic sequence leading to compound **8ah**. It was then found at each step that all reagents and solvents were removed during precipitation.

nitroanilines **4**. NMR analysis[16] showed complete conversion of **3** to **4** after a reaction time of 3 h at room temperature. The reaction proceeded efficiently with various amines without cleavage of the O−C=O bon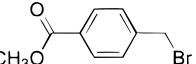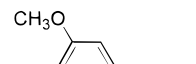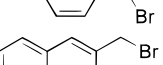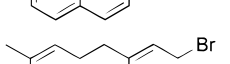d at the polymer attached site. Transamination was not observed when reactions were prolonged over 3 d at ambient temperature or in the refluxing THF for overnight. Reduction of the aryl nitro group in the resulting nitro derivative **3** was successfully accomplished with a suspension of Zn/NH₄Cl in methanol to afford immobilized diamine **5** at room temperature.[17] The heterogeneous catalyst was removed by filtration during the workup, and the PEG bound diamines **5** were purified by selective precipitation. It should be mentioned that another system, namely 2 M SnCl₂·2H₂O mediated nitro reduction recently reported by Pavia and Goff, did not give satisfactory results because the standard purification protocol using diethyl ether resulted in an amorphous solid instead of a regular crystalline PEG bound molecule.[18] Filtration of reaction mixtures containing tin(II) chloride dihydrate was also very difficult, and all attempts to precipitate the PEG bound substrates were unsuccessful. The remaining step completing the synthetic sequence involved key cyclization of **5**. Benzimidazole formation was first attempted with thiophosgene in CH₂Cl₂. Cyclization progress was checked by routine ^{1}H NMR (Figure 4), and we found that reactions proceeded smoothly in the presence of triethylamine after a couple of hours at ambient temperature. However, this

**Table 1.** Liquid-Phase Synthesis of 1-(2-Methyl propyl)-2-alkylthio-5-carbamoylbenzimidazoles

Entry	R$_2$X	Observed MS	Crude yield[a] (%)	Crude purity[b] (%)
1	CH$_3$CH$_2$I	293	99(**8aa**)	84
2	CH$_3$CH$_2$CH$_2$I	308[c]	76(**8ab**)	78
3	(isobutyl iodide)	307	74(**8ac**)	41[d]
4	(diiodo branched)	320[c]	72(**8ad**)	40[d]
5	HC≡C-CH$_2$Br	303	80(**8ae**)	89
6	N≡C-CH$_2$Br	289	84(**8af**)	60
7	(prenyl iodide)	332	76(**8ag**)	85
8	BrCH$_2$C(O)OCH$_3$	336	82(**8ah**)	72
9	(cyclohexenyl bromide)	344	72(**8ai**)	87
10	NO$_2$-phenyl-CH$_2$Br	400	78(**8aj**)	87
11	CH$_3$O$_2$C-phenyl-CH$_2$Br	413	81(**8ak**)	81
12	CH$_3$O-phenyl-CH$_2$Br	385[c]	86(**8al**)	90
13	(naphthyl-CH$_2$Br)	405[c]	84(**8aq**)	86
14	(geranyl bromide)	401	85(**8ar**)	75

[a] Based on loading of original resin. [b] Purity determined by HPLC analysis (UV detection at λ = 254 nm) of crude products. Products show satisfactory ^{1}H NMR and MS data. [c] M + 1 peak (FAB). [d] Recovered around 50% of starting material **7a**.
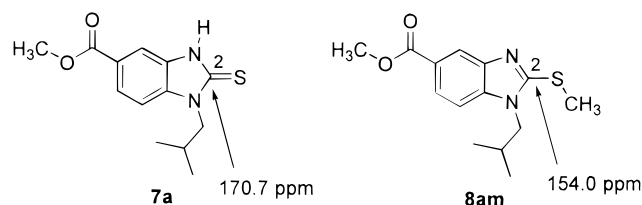
Figure 2. Comparison of C-2 chemical shifts between **7a** and **8am**.

It is clear that there was a significant difference of chemical shift in the aromatic region of the spectrum (A∼D) in the transformations of **4a** to **8ah** (Figure 4). It should also be pointed out that for each conversion performed on the support no remaining peaks from previous material have been observed. This reveals that each step resulted in quantitative conversion, and high-quality spectra were obtained within minutes for PEG bound compounds using an ordinary NMR spectrometer. Furthermore, the sensitivity obtained was enough to estimate the success or failure of reactions when side products were shown by the presence of multiple peaks as inappropriate reaction conditions were applied. The ability
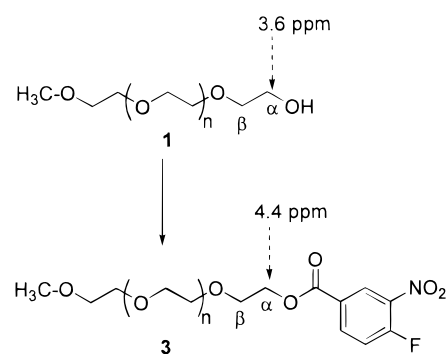
Figure 3. Chemical shift change at α position of **3** after linker **2** was attached to MeO-PEG-OH **1**.

to monitor reactions on PEG without severing compounds from the support will have a significant role in enhancing the development of liquid-phase combinatorial chemistry, since the difficulties of monitoring solid-phase reactions are well recognized.

Following ether and ethanol washes after precipitation in a fritted Buchner funnel, immobilized alkylated products **8** were subjected to a very efficient cleavage from the support with NaOMe in methanol to provide the desired compounds in 72∼99% overall yield for six steps (Table 1). Each crude product was then analyzed by HPLC and gives 40∼90% purity. Low purities in entries 3 and 4 (Table 1) were observed since S-alkylation was not complete. We recovered around 50% of **7a** in both cases after cleavage. No attempts were taken to optimize the reaction conditions, and all reagents were used directly without further purification. Products from validation libraries were characterized by mass spectrometry and ^{1}H NMR, confirming that in each reaction the major compound had a molecular ion corresponding to the appropriate product.

To further expand the library size of targeted molecules, we have shown a structurally diverse set of library (4 × 3) members, which can be prepared in a parallel fashion (Table 2). By employing the desired reaction sequence, a validated library containing a diverse set of compounds was then synthesized. The structures, yields, and purities of compounds obtained were summarized in Table 2. Each crude product was analyzed by HPLC, which showed around 70∼94% purity. Because compound libraries are usually not purified before biological screening, crude products of high purity obtained from our liquid-phase protocol are especially valuable.

Conclusions

In summary, we have demonstrated that liquid-phase methodology can be applied efficiently in parallel synthesis of benzimidazole libraries. Although the benzimidazoles prepared have two points of diversity, additional diversity could be introduced on the methyl ester part of the phenyl ring. This method should decrease the difficulties of adapting established solution-phase precedents to polymer-supported reactions since reactions can be carried out in homogeneous solution. It is also worthy to note that, in contrast to the various restrictions on the analysis of reactions developed in solid-phase synthesis, liquid-phase synthesis allows routine analytical instruments to monitor reaction progress without
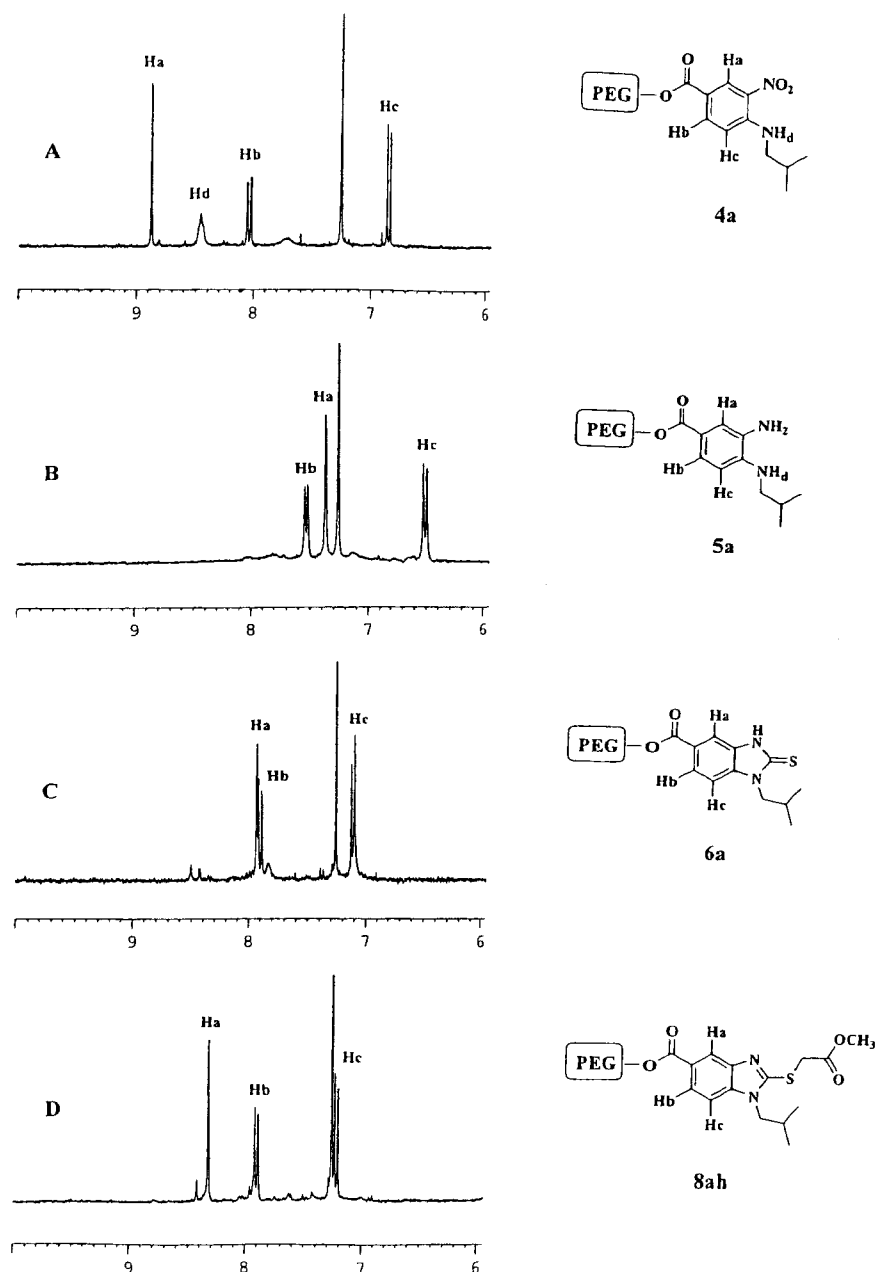
Figure 4. Conventional ^{1}H NMR monitoring of a stepwise benzimidazole formation.

following the *cleave-and-analyze* technique. This nondestructive approach to monitor reaction progress makes the LPCS method even more valuable.

All reactions involved here are highly efficient in giving the desired compounds at room temperature. Crude products are usually obtained in high purity and high yield just by simple precipitation and washings, providing their direct use in biological assays without any purification. This method of synthesis is flexible and robust and produces compounds with known pharmacophoric scaffolds, which are then easily adaptable for the parallel synthesis of the targeted molecules on the soluble support.
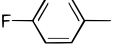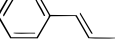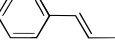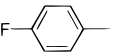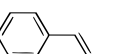
Experimental Section

General. THF and CH_2Cl_2 were distilled from sodium/benzophenone ketyl 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. Visulalization of the chromatogram was by UV absorbance, aqueous cerium molybdate, and ethanolic phosphomolybdic acid. Flash chromatography was performed using compressed air with the indicated solvent system and silica gel 60 (Merk, 230−400 mesh). ^{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 million (ppm) on the δ scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spetrometer. Normal phase HPLC was performed on a Shimadzu LC-10AT series machine with a Sphereclone (250 × 4.6 mm) analytical column. PEG was purchased from Aldrich.

General Procedure for the S-Alkylation with Alkyl and Aryl Halides. A typical procedure for the synthesis of **8aq**

Table 2. Liquid-Phase Synthesis of 1-Alkyl-2-alkylthio-5-carbamoylbenzimidazoles

Entry	R$_1$	R$_2$	Crude yield[a]	Crude purity[b]
1		CH$_3$	64(**8am**)[c]	94
2			76(**8an**)	80
3		F—	85(**8ao**)	91
4			80(**8ap**)	92
5		CH$_3$	79(**8bm**)	81
6			76(**8bn**)	81
7		F—	80(**8bo**)	83
8			81(**8bp**)	90
9		CH$_3$	92(**8cm**)	83
10			84(**8cn**)	87
11		F—	71(**8co**)	70
12			85(**8cp**)	86

a Determined based on weight of crude sample (%). *b* Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm) of crude products (%). Products show satisfactory ^{1}H NMR and MS data. *c* Product number.

(Table 1, entry 13) was as follows: PEG-supported benzimidazole-2-thione **6a** (506 mg, 0.1 mmol), 2-(bromomethyl)-naphthalene (32.1 mg, 0.145 mmol), and triethylamine (0.054 mL, 0.39 mmol) were stirred in 5 mL of CH$_2$Cl$_2$ for 8 h. After completion, the solution was concentrated by rotary evaporation and the reaction mixture was precipitated by addition of ether. Polymer bound product was then filtered under aspirator pressure using a fritted funnel. The crude PEG product was redissolved, precipitated twice, and dried in vacuo for the next sequence. The transesterification of alkylated product in NaOMe/methanol was representative for the cleavage procedure: 425.4 mg of polymer bound S-alkylated benzimidazole was dissolved in 5 mL of CH$_3$OH and NaOMe (15.7 mg, 0.29 mmol) and stirred at room temperature overnight. The solution was evaporated under vacuum to remove methanol, and PEG product was precipitated into ether. The polymer was filtered, and the combined filtrate was dried to give crude product **8aq** as a bright yellow solid (32.8 mg, 84%). The crude purity of this compound was determined to be 86% by HPLC analysis (250 × 4.6 mm Sphereclone 5 μm Si, gradient elution 50% ethyl acetate/hexane, 1 mL/min; UV detection at $\lambda = 254$ nm): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.45 (d, $J = 1.2$ Hz, 1H), 7.95 (dd, $J = 8.7$, 1.2 Hz, 1H), 7.89~7.43 (m, 7H), 7.245 (d, $J = 8.7$ Hz, 1H), 4.83 (s, 2H), 3.95 (s, 3H), 3.84 (d, $J = 7.8$ Hz, 2H), 2.19 (m, 1H), 0.90 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 154.0, 142.7, 139.7, 133.7, 133.2, 132.8, 128.5, 128.0, 127.8, 127.6, 126.9, 126.3, 126.1, 124.0,

123.6, 120.3, 108.8, 52.1, 51.3, 37.5, 29.0, 20.1; IR (cm^{-1}, neat) 2957, 2871, 1715; mass spectrum (FAB) *m/z* 405 (MH$^+$). Exact mass calcd for C$_{24}$H$_{24}$N$_2$O$_2$S: *m/z* 404.1558. Found 404.1558.

Methyl 2-ethylthio-1-(2-methylpropyl)benzimidazole-5-carboxylate (8aa): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 (d, $J = 1.2$ Hz, 1H), 7.93 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 3.92 (s, 3H), 3.89 (d, $J = 7.8$ Hz, 2H), 3.43 (m, 2H), 2.26 (m, 1H), 1.47 (t, $J = 7.5$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 154.6, 142.4, 139.5, 124.0, 123.59, 120.0, 108.7, 52.0, 51.8, 28.9, 27.1, 20.2, 14.7; IR (cm^{-1}, neat) 2960, 2872, 1713, 1433; mass spectrum (EI) *m/z* 293 (M$^+$). Exact mass calcd for C$_{15}$H$_{20}$N$_2$O$_2$S: *m/z* 292.1245. Found 292.1247.

Methyl 1-(2-methylpropyl)-2-propylthiobenzimidazole-5-carboxylate (8ab): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.47 (d, $J = 1.2$ Hz, 1H), 7.93 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 3.93 (s, 3H), 3.90 (d, $J = 7.5$ Hz, 2H), 3.41 (t, $J = 7.2$ Hz, 2H), 2.26 (m, 1H), 1.84 (m, 2H), 1.08 (t, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 154.8, 142.2, 139.4, 124.0, 123.6, 121.7, 114.6, 52.0, 51.8, 34.6, 28.9, 22.6, 20.2, 13.3; IR (cm^{-1}, neat) 2962, 1714; mass spectrum (FAB) *m/z* 307 (MH$^+$). Exact mass calcd for C$_{16}$H$_{22}$N$_2$O$_2$S: *m/z* 306.1402. Found 306.1400.

Methyl 2-(methylethylthio)-1-(2-methylpropyl)benzimidazole-5-carboxylate (8ac): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.42 (d, $J = 1.2$ Hz, 1H), 7.94 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 4.27 (m, 1H), 3.93 (s, 3H), 3.90 (d, $J = 7.8$ Hz, 2H), 2.25 (m, 1H), 1.50 (d, $J = 6.6$ Hz, 6H), 0.96 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 154.3, 139.0, 124.1, 123.7, 120.1, 108.8, 107.4, 52.1, 51.8, 39.0, 29.0, 23.0, 20.2; IR (cm^{-1}, neat) 2963, 2871, 1716; mass spectrum (EI) *m/z* 307 (M$^+$). Exact mass calcd for C$_{16}$H$_{22}$N$_2$O$_2$S: *m/z* 306.1402. Found 306.1404.

Methyl 1-(2-methylpropyl)-2-(2-methylpropylthio)benzimidazole-5-carboxylate (8ad): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.41 (d, $J = 1.5$ Hz, 1H), 7.94 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 1H), 3.93 (s, 3H), 3.92 (d, $J = 6.6$ Hz, 2H), 3.40 (d, $J = 6.6$ Hz, 2H), 2.28 (m, 1H), 2.08 (m, 1H), 1.09 (d, $J = 6.6$ Hz, 6H), 0.97 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.4, 167.6, 128.9, 121.7, 119.9, 114.6, 108.7, 107.4, 70.5, 52.1, 51.8, 28.9, 28.4, 21.8, 20.2; IR (cm^{-1}, neat) 2961, 1716; mass spectrum (EI) *m/z* 320 (M$^+$). Exact mass calcd for C$_{17}$H$_{24}$N$_2$O$_2$S: *m/z* 320.1558. Found 320.1557.

Methyl 1-(2-methylpropyl)-2-prop-2-ynylthiobenzimidazole-5-carboxylate (8ae): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.45 (d, $J = 2.1$ Hz, 1H), 7.98 (dd, $J = 9.0$, 2.1 Hz, 1H), 7.29 (d, $J = 9.0$ Hz, 1H), 4.20 (d, $J = 2.4$ Hz, 1H), 3.93 (s, 3H), 3.92 (d, $J = 7.2$ Hz, 2H), 2.26 (m, 1H), 1.25 (s, 1H) 0.98 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 211.4, 166.6, 152.9, 137.4, 125.6, 119.0, 109.7, 110.3, 81.1, 80.1, 77.2, 52.6, 52.4, 29.0, 20.1; IR (cm^{-1}, neat) 2956, 1712; mass spectrum (EI) *m/z* 303 (M$^+$). Exact mass calcd for C$_{16}$H$_{18}$N$_2$O$_2$S: *m/z* 302.1089. Found 302.1089.

Methyl 2-(cyanomethyl)-1-(2-methylpropyl)benzimidazole-5-carboxylate (8af): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.35 (d, $J = 1.2$ Hz, 1H), 7.93 (dd, $J = 8.4$, 1.2 Hz, 1H),

7.26 (d, J = 8.4 Hz, 1H), 4.25 (s, 2H), 3.93 (s, 3H), 2.27 (m, 1H), 0.97 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 155.1, 143.0, 140.3, 124.0, 123.6, 120.6, 114.0, 108.8, 52.0, 51.9, 34.4, 29.0, 20.2; IR (cm^{-1}, neat) 2962, 2870, 1715; mass spectrum (FAB) m/z 305 (MH$^+$). Exact mass calcd for C$_{15}$H$_{17}$N$_3$O$_2$S: m/z 303.1041. Found 303.1044.

Methyl 2-(2-methylpropyl-1-enylthio)-1-(2-methylpropyl)benzimidazole-5-carboxylate (8ag): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.38 (d, J = 1.5 Hz, 1H), 7.93 (dd, J = 8.4, 1.5 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 5.42 (m, 1H), 4.07 (d, J = 8.1 Hz, 2H), 3.93 (s, 3H), 3.88 (d, J = 7.8 Hz, 2H), 2.25 (m, 1H), 1.75 (s, 6H), 0.95 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 154.8, 143.0, 139.7, 138.6, 123.7, 123.4, 120.2, 117.7, 108.6, 52.0, 51.7, 31.1, 29.0, 25.7, 20.2, 17.9; IR (cm^{-1}, neat) 2960, 1717; mass spectrum (FAB) m/z 333 (MH$^+$). Exact mass calcd for C$_{18}$H$_{24}$N$_2$O$_2$S: m/z 332.1558. Found 332.1561.

Methyl 2-(5-(methoxycarbonyl)-1-(2-methylpropyl)benzimidazol-2-ylthio)acetate (8ah): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.36 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 8.7, 1.2 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 4.28 (s, 2H), 3.93 (d, J = 7.8 Hz, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 2.27 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.0, 167.5, 152.7, 142.4, 139.8, 124.1, 123.8, 120.4, 108.5, 53.0, 52.1, 51.9, 34.5, 29.0, 20.2; IR (cm^{-1}, neat) 2957, 2874, 1724, 1714; mass spectrum (FAB) m/z 337 (MH$^+$). Exact mass calcd for C$_{16}$H$_{20}$N$_2$O$_4$S: m/z 336.1143. Found 336.1143.

Methyl 2-cyclohex-2-enylthio-1-(2-methylpropyl)benzimidazole-5-carboxylate (8ai): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 (d, J = 1.2 Hz, 1H), 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 5.96~5.85 (m, 2H), 4.81 (br, 1H), 3.93 (s, 3H), 3.89 (d, J = 7.8 Hz, 2H), 2.25 (m, 1H), 2.18~1.70 (m, 6H), 1.00 (dd, J = 6.6, 1.5 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 154.8, 143.0, 139.7, 138.6, 123.7, 123.4, 120.2, 117.7, 108.6, 52.0, 51.7, 43.1, 29.3, 29.0, 24.9, 20.2, 19.4; IR (cm^{-1}, neat) 2958, 2869, 1716; mass spectrum (FAB) m/z 345 (MH$^+$). Exact mass calcd for C$_{19}$H$_{24}$N$_2$O$_2$S: m/z 344.1558. Found 344.1561.

Methyl 2-[(4-nitrophenyl)methylthio]-1-(2-methylpropyl)benzimidazole-5-carboxylate (8aj): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 (d, J = 1.2 Hz, 1H), 8.15 (d, J = 8.7 Hz, 2H), 7.94 (dd, J = 8.4, 1.2 Hz, 1H), 7.64 (d, J = 8.7, 1.2 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 4.7 (s, 2H), 3.94 (s, 3H), 3.84 (d, J = 7.5 Hz, 2H), 2.19 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.2, 152.6, 147.4, 144.3, 139.2, 130.1, 124.7, 124.3, 123.8, 120.1, 119.11, 109.1, 52.7, 52.0, 36.0, 29.0, 20.1; IR (cm^{-1}, neat) 2956, 2823, 1713; mass spectrum (EI) m/z 400 (M$^+$). Exact mass calcd for C$_{20}$H$_{21}$N$_3$O$_4$S: m/z 399.1252. Found 399.1250.

Methyl 4-((5-(methoxycarbonyl)-1-(2-methylpropyl)-benzimidazol-2-ylthio)methyl)benzoate (8ak): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.40 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.94 (dd, J = 8.1, 1.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.1 Hz, 1H), 4.68 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.83 (d, J = 7.5 Hz, 2H), 2.19 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 166.7, 153.4, 142.7, 142.0, 139.7, 130.3, 129.5, 129.1, 124.0, 123.7, 120.8, 109.2, 52.5, 52.4, 52.2, 37.0, 29.4, 20.5;

IR (cm^{-1}, neat) 2955, 2872, 1716; mass spectrum (EI) m/z 413 (M$^+$). Exact mass calcd for C$_{22}$H$_{24}$N$_2$O$_4$S: m/z 412.1457. Found 412.1456. Anal. Calcd for C$_{22}$H$_{24}$N$_2$O$_4$S: C, 64.00; H, 5.80; N, 6.80. Found: C, 63.88; H, 6.23; N, 6.42.

Methyl 2-[(3-methoxyphenyl)methyl]-1-(2-methylpropyl)benzimidazole-5-carboxylate (8al): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.41 (d, J = 1.2 Hz, 1H), 7.94 (dd, J = 8.4, 1.2 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 10.8 Hz, 1H), 6.99 (s, 1H), 6.81 (dd, J = 8.4, 2.1 Hz, 1H), 4.62 (s, 3H), 3.94 (s, 3H), 3.84 (d, J = 7.8 Hz, 2H), 3.76 (s, 3H), 2.20 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 159.7, 154.0, 142.9, 139.7, 137.8, 129.7, 123.8, 123.5, 121.4, 120.3, 114.5, 113.4, 108.7, 55.2, 52.0, 51.7, 37.1, 28.9, 20.1; IR (cm^{-1}, neat) 2961, 2872, 1716; mass spectrum (FAB) m/z 385 (MH$^+$). Exact mass calcd for C$_{21}$H$_{24}$N$_2$O$_3$S: m/z 384.1508. Found 384.1508.

Methyl 2-(3,7-dimethylocta-2,6-dienylthio)-1-(2-methylpropyl)benzimidazole-5-carboxylate (8ar): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.38 (d, J = 1.2 Hz, 1H), 7.93 (dd, J = 9.3, 1.2 Hz, 1H), 7.24 (d, J = 9.3 Hz, 1H), 5.41 (t, J = 7.8 Hz, 1H), 5.05 (t, J = 5.8 Hz, 1H), 4.08 (d, J = 7.8 Hz, 2H), 3.93 (s, 3H), 3.88 (d, J = 7.5 Hz, 2H), 2.25 (m, 1H), 2.06 (m, 4H), 1.75 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 154.8, 142.9, 142.2, 139.7, 131.8, 123.7, 123.4, 121.7, 120.3, 117.5, 108.6, 52.0, 51.7, 39.5, 31.1, 29.0, 26.3, 26.6, 25.7, 20.2, 17.7, 16.3; IR (cm^{-1}, neat) 2961, 2873, 1715; mass spectrum (FAB) m/z 401 (MH$^+$). Exact mass calcd for C$_{23}$H$_{32}$N$_2$O$_2$S: m/z 400.2184. Found 400.2182.

Methyl 1-(2-methylpropyl)2-methylthiobenzimidazole-5-carboxylate (8am): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.38 (d, J = 1.2 Hz, 1H), 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.88 (d, J = 7.5 Hz, 2H), 2.81 (s, 3H), 2.27 (m, 1H), 0.97 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.5, 155.9, 143.4, 140.5, 124.2, 123.8, 120.6, 108.9, 52.4, 52.1, 29.3, 20.6, 15.1; IR (cm^{-1}, neat) 2959, 2872, 1713; mass spectrum (EI) m/z 279 (M$^+$). Exact mass calcd for C$_{14}$H$_{18}$N$_2$O$_2$S: m/z 278.1089. Found 278.1089.

Methyl 1-(2-methylpropyl)-2-prop-2-enylthiobenzimidazole-5-carboxylate (8an): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.40 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 6.09~5.96 (m, 1H), 5.38 (d, J = 17.1 Hz, 1H), 5.18 (d, J = 10.2 Hz, 1H), 4.10 (d, J = 6.9 Hz, 2H), 3.93 (s, 3H), 3.91 (d, J = 7.5 Hz, 2H), 2.26 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 153.9, 139.6, 132.4, 124.1, 123.7, 120.2, 119.1, 108.8, 107.4, 52.0, 51.8, 35.5, 29.0, 20.2; IR (cm^{-1}, neat) 3085, 2959, 2872, 1714; mass spectrum (EI) m/z 305 (M$^+$). Exact mass calcd for C$_{16}$H$_{20}$N$_2$O$_2$S: m/z 304.1245. Found 304.1245.

Methyl 2-((4-fluorophenyl)methylthio)-1-(2-methylpropyl)benzimidazole-5-carboxylate (8ao): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.44 (d, J = 1.2 Hz, 1H), 7.96 (dd, J = 8.4, 1.2 Hz, 1H), 7.42 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 6.99 (m, 2H), 4.67 (s, 2H), 3.94 (s, 3H), 3.85 (d, J = 7.5 Hz, 2H), 2.20 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.5, 163.9, 153.7, 139.3, 130.9, 103.8, 124.3, 124.0, 120.1, 115.7, 115.4, 108.9, 52.1, 51.9, 36.5,

29.0, 20.1; IR (cm^{-1}, neat) 2959, 2871, 1714; mass spectrum (EI) m/z 373 (M$^+$). Exact mass calcd for C$_{20}$H$_{21}$N$_2$O$_2$SF: m/z 372.1308. Found 372.1309.

Methyl 1-(2-methylpropyl)-2-(3-phenylvinylthio)benzimidazole-5-carboxylate (8ap): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.43 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 8.4, 1.2 Hz, 1H), 7.36~7.21 (m, 6H), 6.70 (d, J = 15.6 Hz, 1H), 6.39 (m, 1H), 4.28 (d, J = 7.5 Hz, 2H), 3.94 (s, 3H), 3.90 (d, J = 8.7 Hz, 2H), 2.26 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 153.9, 139.7, 136.4, 134.2, 128.5, 127.9, 126.5, 124.0, 123.6, 121.7, 102.2, 108.8, 107.4, 52.6, 51.8, 35.5, 29.0, 20.2; IR (cm^{-1}, neat) 3023, 2959, 1713; mass spectrum (EI) m/z 381 (M$^+$). Exact mass calcd for C$_{22}$H$_{24}$N$_2$O$_2$S: m/z 380.1558. Found 380.1557.

Methyl 1-butyl-2-methylthiobenzimidazole-5-carboxylate (8bm): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.40 (d, J = 1.5 Hz, 1H), 7.95 (dd, J = 8.4, 1.5 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 4.08 (t, J = 4.5 Hz, 2H), 3.93 (s, 3H), 2.84 (s, 3H), 1.79 (m, 2H), 1.39 (m, 2H), 0.96 (t, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 155.0, 145.5, 139.4, 124.0, 123.7, 120.0, 108.2, 52.0, 44.2, 31.2, 20.1, 14.7, 13.8; IR (cm^{-1}, neat) 2958, 2873, 1715; mass spectrum (FAB) m/z 280 (MH$^+$). Exact mass calcd for C$_{14}$H$_{18}$N$_2$O$_2$S: m/z 278.1089. Found 278.1086.

Methyl 1-butyl-2-prop-2-enylthiobenzimidazole-5-carboxylate (8bn): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.38 (d, J = 1.5 Hz, 1H), 7.94 (dd, J = 8.4, 1.5 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 6.10~5.96 (m, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.17 (d, J = 9.9 Hz, 1H), 4.09 (t, J = 7.5 Hz, 4H), 3.93 (s, 3H), 1.78 (m, 2H), 1.38 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 153.5, 142.8, 139.3, 132.5, 123.9, 123.6, 120.3, 119.0, 108.3, 52.0, 44.2, 35.3, 31.4, 20.1, 13.7; IR (cm^{-1}, neat) 2956, 2875, 1715; mass spectrum (FAB) m/z 305 (MH$^+$). Exact mass calcd for C$_{16}$H$_{20}$N$_2$O$_2$S: m/z 304.1245. Found 304.1247.

Methyl 1-butyl-2-((4-fluorophenyl)methylthio)benzimidazole-5-carboxylate (8bo): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.43 (d, J = 1.2 Hz, 1H), 7.96 (dd, J = 8.7, 1.2 Hz, 1H), 7.42 (m, 2H), 7.27 (d, J = 8.7 Hz, 1H), 6.99 (m, 2H), 4.64 (s, 2H), 4.04 (t, J = 7.5 Hz, 2H), 3.94 (s, 3H), 1.72 (m, 2H), 1.32 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 153.3, 142.6, 139.2, 130.9, 130.8, 124.1, 123.8, 120.2, 115.7, 115.4, 108.5, 52.1, 44.2, 36.2, 31.3, 20.0, 13.6; IR (cm^{-1}, neat) 2959, 1715; mass spectrum (FAB) m/z 373 (MH$^+$). Exact mass calcd for C$_{20}$H$_{21}$N$_2$O$_2$SF: m/z 372.1308. Found 372.1310.

Methyl 1-butyl-2-(3-phenylprop-2-enylthio)benzimidazole-5-carboxylate (8bp): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.42 (d, J = 1.5 Hz, 1H), 7.52 (dd, J = 8.4, 1.5 Hz, 1H), 7.37~7.20 (m, 5H), 7.26 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 15.6 Hz, 1H), 6.40 (m, 1H), 4.26 (d, J = 7.5 Hz, 2H), 4.09 (t, J = 7.5 Hz, 2H), 3.94 (s, 3H), 1.78 (m, 2H), 1.37 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 153.5, 142.8, 139.3, 136.4, 134.1, 128.5, 127.8, 126.4, 124.0, 123.7, 123.6, 120.2, 52.0, 44.2, 35.2, 31.4, 20.0; IR (cm^{-1}, neat) 2956, 2872, 1714; mass spectrum (FAB) m/z 381 (MH$^+$). Exact mass calcd for C$_{22}$H$_{24}$N$_2$O$_2$S: m/z 380.1558. Found 380.1559.

Methyl 1-cycloheptyl-2-methylthiobenzimidazole-5-carboxylate (8cm): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.37 (d, J = 1.5 Hz, 1H), 7.88 (dd, J = 8.4, 1.5 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 4.36 (m, 1H), 3.92 (s, 3H), 2.81 (s, 3H), 2.35~1.62 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 154.2, 143.4, 138.1, 123.5, 123.0, 120.1, 110.1, 59.2, 52.0, 33.4, 27.3, 25.7, 12.9; IR (cm^{-1}, neat) 2929, 2855, 1716; mass spectrum (FAB) m/z 319 (MH$^+$). Exact mass calcd for C$_{17}$H$_{22}$N$_2$O$_2$S: m/z 318.1402. Found 318.1403. Anal. Calcd for C$_{17}$H$_{22}$N$_2$O$_2$S: C, 64.10; H, 6.90; N, 8.80. Found: C, 63.54; H, 7.00; N, 8.54.

Methyl 1-cycloheptyl-2-prop-2-enylthiobenzimidazole-5-carboxylate (8cn): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.36 (d, J = 1.5 Hz, 1H), 7.88 (dd, J = 8.7, 1.5 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 6.11~5.97 (m, 2H), 5.36 (dd, J = 17.1, 1.2 Hz, 1H), 5.17 (d, J = 9.9 Hz, 1H), 4.40 (m, 1H), 4.06 (d, J = 6.9 Hz, 2H), 3.92 (s, 2H), 2.34~1.55 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 152.7, 143.4, 137.9, 132.6, 123.6, 123.1, 120.4, 119.0, 110.2, 59.2, 52.0, 35.6, 33.4, 27.3, 25.8; IR (cm^{-1}, neat) 3082, 2930, 2858, 1716; mass spectrum (FAB) m/z 345 (MH$^+$). Exact mass calcd for C$_{19}$H$_{24}$N$_2$O$_2$S: m/z 344.1558. Found 344.1560.

Methyl 1-cycloheptyl-2-[(4-fluorophenyl)methylthio]benzimidazole-5-carboxylate (8co): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.40 (d, J = 1.2 Hz, 1H), 7.90 (dd, J = 8.7, 1.2 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.41 (m, 2H), 7.00 (m, 2H), 4.62 (s, 2H), 4.33 (m, 1H), 3.94 (s, 3H), 2.30~1.54 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.6, 152.6, 143.0, 137.7, 130.9, 130.8, 123.8, 123.3, 120.3, 115.7, 115.4, 110.4, 59.4, 52.1, 36.6, 33.4, 27.2, 25.7; IR (cm^{-1}, neat) 2930, 2857, 1715; mass spectrum (FAB) m/z 413 (MH$^+$). Exact mass calcd for C$_{23x}$H$_{25}$N$_2$O$_2$SF: m/z 412.1621. Found 412.1621.

Methyl 1-cycloheptyl-2-(3-phenylprop-2-enylthio)benzimidazole-5-carboxylate (8cp): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 (d, J = 1.5 Hz, 1H), 7.89 (dd, J = 8.4, 1.5 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.38~7.20 (m, 5H), 6.68 (d, J = 15.6 Hz, 1H), 6.41 (m, 1H), 4.41 (m, 1H), 4.23 (d, J = 7.5 Hz, 2H), 3.93 (s, 3H), 2.34~1.54 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 152.8, 143.5, 138.0, 136.4, 134.1, 128.5, 127.8, 126.4, 123.8, 123.6, 123.1, 120.4, 110.2, 59.3, 52.0, 35.5, 33.4, 27.3, 25.8; IR (cm^{-1}, neat) 2929, 2858, 1715; mass spectrum (FAB) m/z 421 (MH$^+$). Exact mass calcd for C$_{25}$H$_{28}$N$_2$O$_2$S: m/z 420.1872. Found 420.1872.

Supporting Information Available. Experimental details and ^{1}H NMR and HPLC data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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