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Solid-phase combinatorial synthesis of benzothiazoles, benzimidazoles, and benzoxazoles using a traceless linker

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Abstract—New methodology for the solid-phase synthesis of benzothiazoles, benzimidazoles, and benzoxazoles has been developed by using a traceless 4-alkoxy-aniline linker. The desired products were released from the polymer support by imine-exchange process coupled with air oxidation. Combinatorial library consisting of 36 members has been synthesized using this linker. The yields are low to good, which highly depend on the building blocks. Recycling of the polymer support was also investigated.

1. Introduction

Benz-fused azoles **1**, such as benzothioazoles, benzimidazoles, and benzoxazoles are an important class of compounds (Fig. 1). They provide a common scaffold to various derivatives, which can be utilized as not only a wide variety of biologically active and medicinally significant compounds[1] but also advanced materials including non-linear optics (NLO),[2] organic light-emitting diodes (OLED),[3] and liquid crystals.[4] Hence, facile preparation of various benz-fused azole derivatives for rapid discovering of new drugs and materials is highly desirable. Solid-phase synthesis is particularly effective for split/mix combinatorial synthesis to generate a large number of compounds. Therefore, solid-phase combinatorial syntheses of these compounds have been reported by some groups.[5]

The selection of an adequate linker in the solid-phase synthesis is one of the key factors for efficiently building the desired libraries.[6] Traceless linkers, in particular, are advantageous because the functional group attached on a solid support is not necessary for the target molecules.[7] We recently developed a new traceless linker **2** suitable for the synthesis of compounds possessing azomethines and applied it to the synthesis of a rod-shaped liquid crystalline library (Fig. 2).[8] In previous studies, the product yields were dependent on the stability balance of the resin-bound azomethines. The overall yields of azomethines were low to moderate because the resin-bound azomethine **4** suffered partial alcoholysis during condensation with alcohols. On the other hand, a resin-bound azomethine **6**, which was loaded on the 4-alkoxyaniline linker **3**, was more stable against alcoholysis than **4**, but the equilibrium for the imine-exchange process was not shifted effectively in favor of the final product **7** at the cleaving step due to comparable stability of **6** and **7** (Scheme 1). In the latter case, it is expected to improve product yields if the resin-bound substrates are cleaved by an irreversible process.

1

X = O, S, NR

Figure 1. Benz-fused azoles.

In general, oxidation is an irreversible process and thus is most likely to be suitable for our solid-phase synthesis. Recently, Hayashi and co-workers reported practical synthesis of 2-arylbenzoxazoles by oxidative coupling of 2-aminophenols and aldehydes in the presence of Darco® KB (a sort of activated carbon) and air.[9] This oxidation does not require any oxidation reagents at cleaving step, and also Darco® KB can be easily removed by simple filtration. This oxidative protocol would be highly advantageous to develop an imine-exchange irreversible process in our solid-phase synthesis of benz-fuzed azoles **1**.

In this paper, we report the solid-phase combinatorial synthesis of 2-arylbenzothiazoles, benzimidazoles, and

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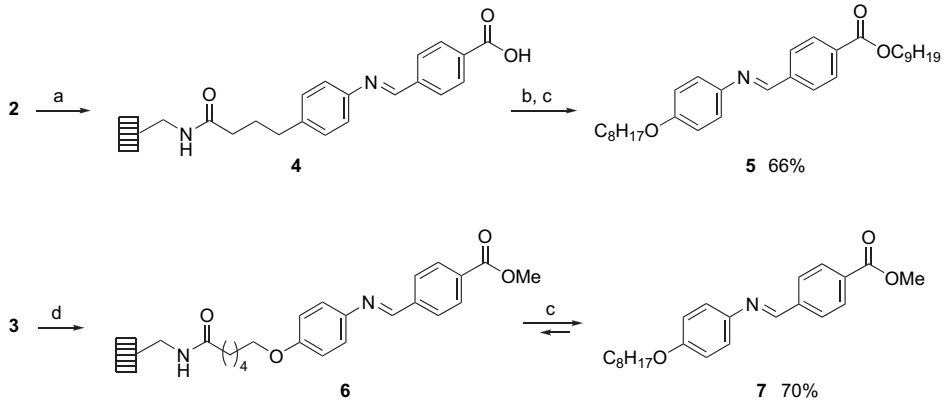


Scheme 1. Synthesis of azomethines using traceless aniline linkers. Reagents: (a) 4-formylbenzoic acid; (b) 1-nonanol, DIC, DMAP; (c) 4-octyloxyaniline; (d) methyl 4-formylbenzoate.

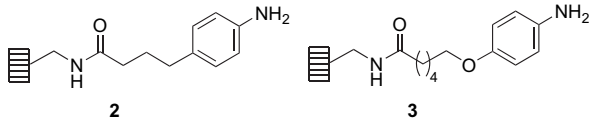


Figure 2. Two traceless aniline linkers.

benzoxazoles by applying oxidative cleavage to release them from a solid support connected through azomethine linkage.[10]

2. Results and discussions

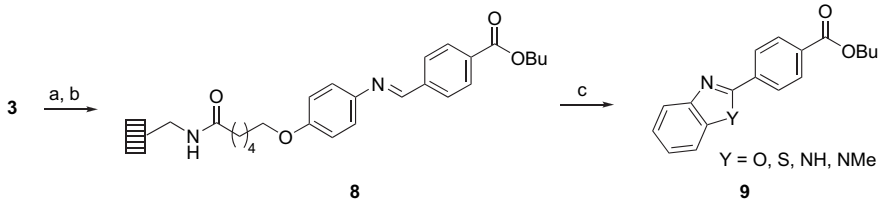
2.1. Oxidative cleavage of resin-bound azomethines using various 2-heteroatom-substituted anilines

First of all, oxidative release of resin-bound azomethines with various 2-heteroatom-substituted anilines was examined to afford benz-fused azoles by applying the Hayashi's process.[9] Solid supported azomethine esters **8** were prepared according to the previously reported procedure (Scheme 2).[8] Yields of three-step synthesis of 2-aryl-benz-fused azoles are summarized in Table 1. By treating **8** with 4 equiv of 2-aminophenol at 100 °C for 1 h in the presence of Darco® KB, 2-arylbenzoxazole **9** (Y=O) was obtained in 22% yield (entry 1). Air oxidation was concomitant with imine-exchange as expected to release the product. The yield was improved up to 58% in a longer period of time (entry 2). Excess 2-aminophenol was consumed during the reaction period. When the resulting resin was treated with 4 equiv of 2-aminophenol again, an additional compound **9** (Y=O) was isolated in 21% yield. Only a trace amount of the product along with 2-aminophenol was obtained in the absence of Darco® KB (entry 3). The results showed that Darco® KB promoted not only oxidative cleavage of a resin-bound substrate but also oxidative decomposition of 2-aminophenol. Unexpectedly, treatment of **8** with 4 equiv of 2-aminothiophenol at room temperature for 18 h produced corresponding 2-arylbenzothiazole **9** (Y=S) in 68% yield under an air atmosphere even in the absence of Darco® KB (entry 4). The yield was improved to 90% on reacting at elevated temperature (entries

Table 1. Isolated yields in three-step synthesis of benzoxazole **9** (Y=O), benzothiazole **9** (Y=S), benzimidazole **9** (Y=NH), and *N*-methylbenzimidazole **9** (Y=NMe) on a solid support

Entry	Y	Conditions[a]			Yield (%)
		Period	Temp (°C)	Additive	
1	O	1 h	100	Darco® KB	22
2		18 h	100	Darco® KB	58 (79)[b]
3		18 h	100	—	1
4	S	18 h	rt	—	68
5		18 h	50	—	82
6		18 h	100	—	90
7		5 min	100	—	76
8		20 min	100	—	91
9		1 h	100	—	90
10[c]		20 min	100	—	51
11	NH	20 min	100	—	5
12		1 h	100	—	14
13		18 h	100	—	84
14	NMe	18 h	100	—	42
15		48 h	100	—	76
16		72 h	100	—	73

[a] Conditions for oxidative cleavage from a solid support (step 3).
[b] A value in a parenthesis refers to combined yield after successive treatment of 2-aminophenol.
[c] Two equivalents of 2-aminothiophenol were used.

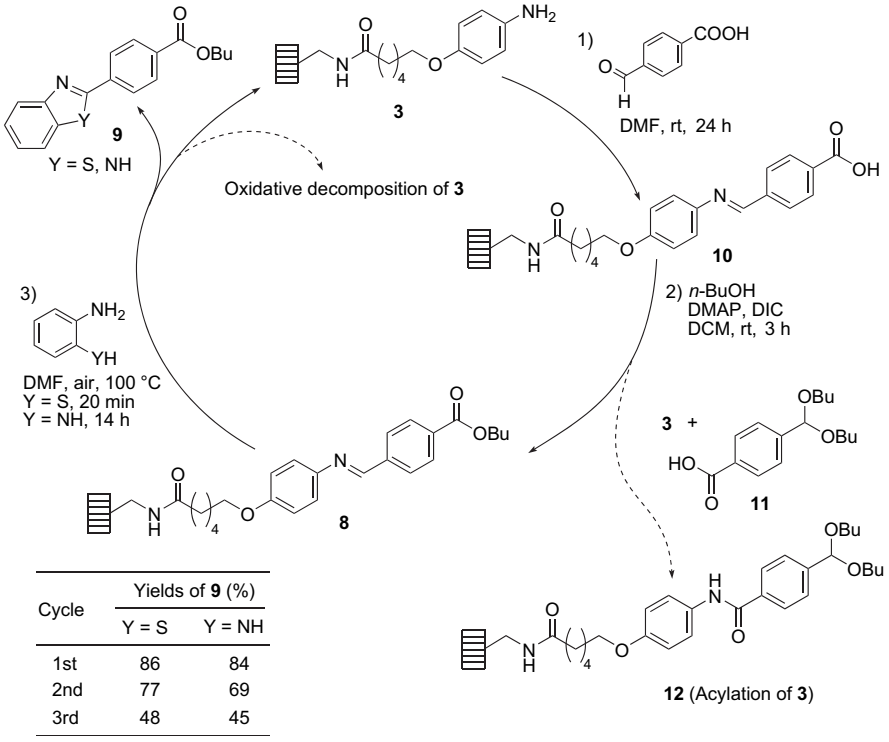


Scheme 2. Three-step synthesis of 2-aryl benz-fuzed azoles including oxidative cleavage of azomethines in the presence or absence of Darco® KB. Reagents and conditions: (a) 4 equiv of 4-formylbenzoic acid, DMF, rt, 24 h; (b) 4 equiv of 1-butanol, DIC, DMAP, DCM, rt, 3 h; (c) 4 equiv of 2-aminophenol (Y=O), 2-aminothiophenol (Y=S), 1,2-phenylenediamine (Y=NH), or *N*-methyl-1,2-phenylenediamine (Y=NMe), air, (Darco® KB), DMF. Yields are shown in Table 1.

5 and 6). The reaction was completed within 20 min at 100 °C (entries 6–9). Two equivalents of 2-aminothiophenol resulted in the decrease of yield (entry 10), indicating that a substantial amount of 2-aminothiophenol was still decomposed under the air oxidation conditions. In the absence of Darco® KB, 2-arylbenzimidazole (Y=NH) was also obtained in good yield, in the case of running the reaction over a longer period of time (entries 11–13). *N*-Methyl-2-arylbenzimidazole (Y=NMe) was also obtained in good yield although much longer reaction time was required (entries 14–16).

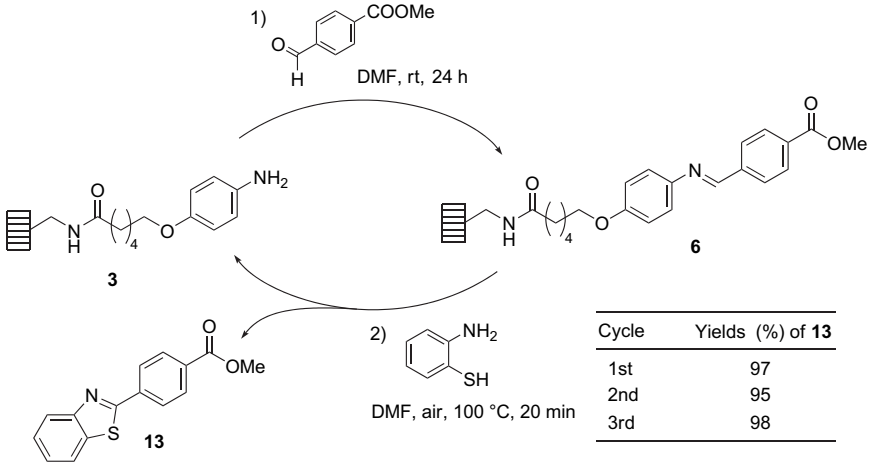
2.2. Recycling of an 4-alkoxyaniline linker

From a point of view of an atom economy, solid-phase synthesis is less efficient than conventional solution-phase synthesis because molecular weight per unit function connecting the substrate is very high. In addition, solid supports are generally expensive. Thus, recycling of the solid support is highly desirable. It should be noted that the solid support **3** can be easily recovered and recycled after cleavage of the resin-bound azomethines **8** as shown in Scheme 3. Thus it is interesting to explore how many times the solid support **3** can be recycled and reused. The synthesis of 2-arylbenzothiazole **9** (Y=S) and 2-arylbenzimidazole **9** (Y=NH) was repeated under optimized conditions by recycling. As results, yields were decreased by 10–20% lower at every recycling (table in Scheme 3). The decreases related to the overall yields were presumed to be due to some decomposition of 4-alkoxyaniline linker **3** during oxidative cleavage of the substrate. However, the recycling process without esterification did not cause the decrease of the yields (table in Scheme 4).



Cycle	Yields of **9** (%)	
	Y = S	Y = NH
1st	86	84
2nd	77	69
3rd	48	45

Scheme 3. Recyclability of solid support **3** for the three-step synthesis of **9**.



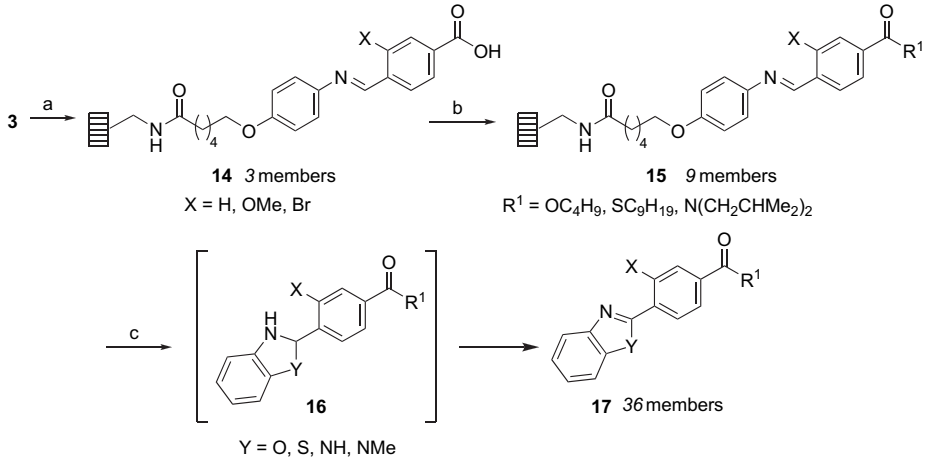
Cycle	Yields (%) of **13**
1st	97
2nd	95
3rd	98

Scheme 4. Recycling of solid support **3** for two-step synthesis of **13**.

Judging from both the results, the drawback to the recycling of **3** is ascribable to partial formation of amide **12** on the solid support via alcoholysis of **10**, followed by consecutive condensation between **3** and **11**. This means that there remains the problem that 4-alkoxyanline linker **3** is not stable enough to suppress a competing alcoholysis of **10**. Recycling is limited to two or three times in the present study.

2.3. Split synthesis of benz-fuzed azole library consisting of 36 members

Next, we attempted combinatorial library synthesis to demonstrate the scope and versatility of our solid-phase reactions (Scheme 5). Three kinds of 4-formylbenzoic acid derivatives (4-formylbenzoic acid, 4-formyl-3-methoxybenzoic acid, and 3-bromo-4-formylbenzoic acid) were prepared. They condensed with a 4-alkoxyaniline linker **3** on the solid support to afford resin-bound azomethines **14** (step 1). In the second step, *n*-butanol, nonanethiols, and diisobutylamines were reacted with **14** to give azomethines **15** (step 2). Finally, the azomethines on the solid support were cleaved by four kinds of 2-heteroatom substituted anilines (2-aminophenol, 2-aminothiophenol, 1,2-phenylenediamine, and *N*-methyl-1,2-phenylenediamine) through an imine-exchange process coupled with air oxidation to give 2-arylbenzoxazoles **17** (Y=O), 2-arylbenzothiazoles **17** (Y=S), and 2-arylbenzimidazoles **17** (Y=NH, NMe) (step 3), which provided a library consisting of 36 members. Oxidative cleavage was performed at 100 °C for 18 h except for *N*-methylbenzimidazole series, which were reacted for 48 h. Darco® KB was employed for the synthesis of 2-arylbenzoxazoles. The reaction rate in the final step highly depended on the substituents at aromatic nuclei. When X was a methoxy group, the reaction rate was the fastest in all the series. On the other hand, when X was bromine, the reaction rate was the slowest. The order of reaction rate seems to reflect the oxidizing potential of cyclic acetal intermediates **16**. The final products were separated from excess reagents and their oxidative decomposition products by silica gel column chromatography. Most of library members were easily purified. The yields are summarized in Table 2. When X was hydrogen, esters and thioesters with 2-arylbenzothiazoles or 2-arylbenzimidazoles were obtained in good yields. When X was bromine or a methoxy group, the yields were slightly reduced. This is presumably explained due to the instability of resin-bound azomethines **14** and **15** in which steric hindrance between X and azomethine linkage causes out-of-plane distortion of the two aromatic rings. Partial aminolysis of thioesters in *N*-methylbenzimidazoles reduced yields, because the reaction time was longest among all the series. Amides were synthesized in low to moderate yields, indicating that substantial amount of imine-exchange reaction between **15** and diisobutylamine was unavoidable even if 4-alkoxyaniline linker **3** was used.



Scheme 5. Split synthesis of benzothiazoles, benzimidazoles and benzoxazoles library consisting of 36 members. Reagents and conditions: (a) three kinds of 4-formylbenzoic acids (4-formylbenzoic acid, 4-formyl-3-methoxybenzoic acid, and 3-bromo-4-formylbenzoic acid), DMF, rt, 24 h; (b) n-C_4H_9OH, n-$C_9H_{19}SH$, or $(Me_2CHCH_2)_2NH$, DIC, DMAP, DCM, rt, 3 h; (c) four kinds of 2-substituted anilines (2-aminophenol, 2-aminothiophenol, 1,2-phenylenediamine, *N*-methyl-1,2-phenylenediamine), air, Darco® KB (only for Y=O), DMF, 100 °C, 18–48 h.

Table 2. Isolated yields (%) of all library members **17**

R^1	X	Benzoxazole	Benzothiazole	Benzimdazole	*N*-Methyl benzimidazole
		Y=O	Y=S	Y=NH	Y=NMe
OBu	H	58	87	84	77
	OMe	44	72	80	54
	Br	30	70	64	77
SC_9H_{19}	H	44	88	82	30
	OMe	30	70	70	25
	Br	32	60	74	23
$N(CH_2CHMe_2)_2$	H	15	47	40	23
	OMe	7	33	38	17
	Br	8	31	37	19

3. Conclusion

We have demonstrated that an 4-alkoxyaniline unit is employed as a versatile traceless linker for solid-phase combinatorial syntheses of 2-arylbenzoxazoles, 2-arylbenzothioazoles, and 2-arylbenzimidazoles, which are frequently involved in a number of drugs and advanced materials. It should be emphasized that the products can be released from the solid support only by exposing it to an air atmosphere without any kinds of oxidants under neutral conditions. This new methodology will be widely applicable for combinatorial synthesis because time-consuming work-up is avoided to obtain the final products. Although the recycling of the solid support is limited, the present studies would provide a primary insight into the possibility of increasing the number of recycling the solid support. Further efforts for developing traceless linkers that can stabilize a solid supported azomethine intermediate are under investigation.

4. Experimental

4.1. General

All commercially available chemicals were used without further purification. Solid support **3** was prepared from aminomethylated SynPhase Lantern® purchased from Mimotopes Pty Ltd. (Victoria, Australia) according to the previously reported procedure.[8] Melting points were determined using a Büchi B-545 apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR410 spectrophotometer equipped with SensIR Technologies Durascope® for ATR (attenuated total reflectance) and only characteristic peaks are reported. ^{1}H NMR spectra were recorded at 200 or 300 MHz with Varian Gemini-200 or Mercury-300 spectrometers, using tetramethylsilane as the internal standard. Mass spectra were taken on JEOL AX-500.

4.2. Oxidative cleavage of resin-bound azomethines with 2-hetroatom-substituted anilines

4.2.1. Preparation of a solid supported azomethine 8. Six pieces of the solid supported aniline **3** (loading: 75 μmol×6, 450 μmol) were reacted with 4-formylbenzoic acid (270 mg, 1.8 mmol, 4 equiv) in DMF solution (6 mL) at room temperature for 24 h. The solution was removed by decantation and the resulting resins were washed with DMF (3×0.5 min) and DCM (3×0.5 min). The resulting solid supported azomethine **10** (loading: 75 μmol×6, 450 μmol) was reacted with 4-*N*,*N*-dimethylaminopyridine (13.7 mg, 0.113 mmol, 0.25 equiv), *n*-butanol (133 mg, 1.8 mmol, 4 equiv), and 1,3-diisopropylcarbodiimide (564 μL, 3.6 mmol, 8 equiv) in DCM at room temperature for 3 h. The solution was removed by decantation and the resulting resins were washed with DMF (3×0.5 min) and DCM (3×0.5 min).

4.2.2. Oxidative cleavage of 8. The solid supported azomethine ester **8** (loading: 75 μmol×1, 75 μmol) was reacted with 2-aminophenol (32.7 mg, 0.3 mmol, 4 equiv) and Darco® KB (450 mg) in DMF (3 mL) at 100 °C under an air atmosphere for 18 h. The resulting resins were washed with DMF (3×2 min) and DCM (3×2 min). The combined DMF and DCM solutions were filtered. The filtrate was evaporated and purified by silica gel chromatography (hexane/EtOAc=2:1) to give **9** (Y=O) in 58% yield (12.8 mg, 43.5 μmol) as colorless solid. Butyl 4-(benzothiazol-2-yl)-benzoate **9** (Y=S), butyl 4-(benzimidazol-2-yl)benzoate **9** (Y=NH), and butyl 4-(1-methyl-benzimidazol-2-yl)benzoate **9** (Y=NMe) were synthesized employing the almost same manner as described above. Yields are shown in Table 1 under various reaction conditions.

4.2.2.1. Butyl 4-(benzoxazol-2-yl)benzoate 9 (Y=O). Colorless solid, mp 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.1 Hz), 1.51 (2H, tq, J=7.1, 7.1 Hz), 1.80 (2H, tt, J=6.6, 7.1 Hz), 4.37 (2H, t, J=6.6 Hz), 7.38–7.41 (2H, m), 7.60–7.63 (1H, m), 7.80–7.83 (1H, m), 8.19 (2H, d, J=8.5 Hz), 8.33 (2H, d, J=8.5 Hz); IR (ATR) 1713 cm^{-1}; MS (CI): *m*/*z* 296 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{18}H_{18}NO_3$ ([M+H]$^+$) 296.1287, found 296.1279.

4.2.2.2. Butyl 4-(benzothiazol-2-yl)benzoate 9 (Y=S). Colorless solid, mp 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, t, J=7.4 Hz), 1.50 (2H, tq, J=7.4, 7.4 Hz), 1.79 (2H, tt, J=6.6, 7.4 Hz), 4.37 (2H, t, J=6.6 Hz), 7.42 (1H, ddd, J=1.1, 7.1, 8.0 Hz), 7.52 (1H, ddd, J=1.4, 7.1, 8.2 Hz), 7.93 (1H, ddd, J=0.6, 1.4, 8.0 Hz), 8.11 (1H, ddd, J=0.6, 1.1, 8.2 Hz), 8.16 (4H, s); IR (ATR) 1710 cm^{-1}; MS (EI): *m*/*z* 255 (100%), 311 ([M]$^+$, 53%); HRMS (EI): calcd for $C_{18}H_{17}NO_2S$ ([M]$^+$) 311.0980, found 311.0983.

4.2.2.3. Butyl 4-(benzimidazol-2-yl)benzoate 9 (Y=NH). Colorless solid, mp 211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.1 Hz), 1.48 (2H, tq, J=7.1, 7.1 Hz), 1.76 (2H, tt, J=6.6, 7.1 Hz), 4.34 (2H, t, J=6.6 Hz), 7.26–7.31 (2H, m), 7.66 (2H, br s), 8.09 (2H, d, J=7.7 Hz), 8.15 (2H, d, J=7.7 Hz), 10.9 (1H, s); IR (ATR) 1707 cm^{-1}; MS (EI): *m*/*z* 238 (100%), 294 ([M]$^+$, 94%); HRMS (EI): calcd for $C_{18}H_{18}N_2O_2$ ([M]$^+$) 294.1368, found 294.1371.

4.2.2.4. Butyl 4-(1-methyl-benzimidazol-2-yl)benzoate 9 (Y=NMe). Colorless solid, mp 66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, t, J=7.4 Hz), 1.51 (2H, tq, J=7.4, 7.4 Hz), 1.79 (2H, tt, J=6.6, 7.4 Hz), 3.89 (3H, s), 4.38 (2H, t, J=6.6 Hz), 7.31–7.43 (3H, m), 7.82–7.86 (1H, m), 7.86 (2H, d, J=8.0 Hz), 8.20 (2H, d, J=8.0 Hz); IR (ATR) 1715 cm^{-1}; MS (CI): *m*/*z* 309 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{19}H_{21}N_2O_2$ ([M+H]$^+$) 309.1603, found 309.1606.

4.3. Recycling of the solid support 3

4.3.1. Recycling for the three-step synthesis of 9. The solid supported ester **8** was prepared as described above. It (loading: 75 μmol×1, 75 μmol) was reacted with 2-aminothiophenol (32.1 μL, 0.3 mmol, 4 equiv) in DMF (3 mL) at 100 °C under an air atmosphere for 20 min. The resulting resins were washed with DMF (3×2 min) and DCM (3×2 min). The combined DMF and DCM solutions were evaporated and purified by silica gel chromatography (hexane/EtOAc=15:1) to give **9** (Y=S) in 86% yield (21.0 mg, 64.5 μmol) as colorless solid. The resulting resins, which were washed with 15% TFA in DCM (1×30 min), DMF

(3×2 min) and DCM (3×2 min), were treated twice in the same manner as described above to give **9** (Y=S) in 77% yield (18.0 mg, 57.8 μmol) at second recycling and in 48% yield (11.2 mg, 36.0 μmol) at third recycling. Oxidative cleavage to give **9** (Y=NH) was performed at 100 °C under an air atmosphere for 14 h by employing 1,2-phenylenediamine. Work-up and recycling were accomplished in the same manner. Yields for each recycling are shown in Scheme 3.

4.3.2. Simple loading and cleavage on the solid support 3. One piece of the solid supported aniline **3** (loading: 75 μmol×1, 75 μmol) was reacted with methyl 4-formylbenzoate (49.2 mg, 0.3 mmol, 4 equiv) in DMF solution (3 mL) at room temperature for 24 h. The solution was removed by decantation and the resulting resins **6** were washed with DMF (3×0.5 min) and DCM (3×0.5 min). Oxidative cleavage and purification of the compound were accomplished in the same manner as described above to give **13** in 97% yield (19.6 mg, 72.8 μmol) as colorless solid. The resulting resins, which were washed with 15% TFA in DCM (1×30 min), DMF (3×2 min), and DCM (3×2 min) were treated twice following the same procedure as above to give **13** in 95% yield (19.2 mg, 71.3 μmol) at second recycling and in 98% yield (19.8 mg, 73.5 μmol) at third recycling.

4.3.2.1. Methyl 4-(benzothiazol-2-yl)benzoate 13. Colorless solid, mp 164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (3H, s), 7.42 (1H, ddd, J=1.1, 7.4, 8.0 Hz), 7.52 (1H, ddd, J=1.4, 7.4, 8.2 Hz), 7.93 (1H, ddd, J=0.6, 1.4, 8.0 Hz), 8.10 (1H, ddd, J=0.6, 1.1, 8.2 Hz), 8.16 (4H, s); IR (ATR) 1715 cm^{-1}; MS (EI): m/z 269 ([M]$^+$, 53%); HRMS (EI): calcd for $C_{15}H_{11}NO_2S$ ([M]$^+$) 269.0511, found 269.0511.

4.4. Library synthesis

4.4.1. Syntheses of building blocks. All building blocks except for the following two reagents are commercially available.

4.4.1.1. Synthesis of 3-methoxy-4-formylbenzoic acid. Water (120 mL) and sodium carbonate (4.68 g, 44.2 mmol) were added to a solution of methyl 4-formyl-3-methoxybenzoate[11] (4.29 g, 22.1 mmol) in ethanol (140 mL). The mixture was refluxed for 2.5 h. After being cooled to room temperature, the reaction mixture was quenched slowly by addition of 1 mol L^{-1} HCl (100 mL). The mixture was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated to furnish the crude product, which was purified by flash chromatography (silica gel 40 g, EtOAc) followed by recrystallization (EtOAc). The product (2.47 g, 13.7 mmol, 62%) was obtained as light yellow needles; mp 233 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.10 (3H, s), 7.73 (1H, dd, J=1.4, 8.0 Hz), 7.79 (1H, d, J=1.4 Hz), 7.91 (1H, d, J=8.0 Hz), 10.5 (1H, s); IR (ATR) 1699, 1651 cm^{-1}; MS (EI): m/z 180 ([M]$^+$, 100%); HRMS (EI): calcd for $C_9H_8O_4$ ([M]$^+$) 180.0422, found 180.0430.

4.4.1.2. Synthesis of 3-bromo-4-formylbenzoic acid. *N*-Bromosuccinimide (46.9 g, 0.264 mol) and benzoyl peroxide (2.05 g, 8.46 mmol) were added by portions to a refluxing solution of methyl 3-bromo-4-methylbenzoate (25.3 g, 0.11 mol) in benzene (250 mL). After refluxing for 1.5 h, the reaction mixture was cooled to room temperature. The precipitate was filtered and the filtrate was evaporated to leave the residue to which 200 mL of brine was added. The mixture was extracted with toluene (3×150 mL). The combined organic layers were dried over sodium sulfate and concentrated to afford the crude methyl 3-bromo-4-(dibromomethyl)benzoate. Water (100 mL) and sodium carbonate (116 g, 1.1 mol) were added to a solution of the crude product in ethanol (120 mL). The reaction mixture was stirred at 90 °C for 72 h. After being cooled to room temperature, the reaction mixture was quenched slowly by addition of 10 mol L^{-1} HCl (250 mL) at 0 °C. After stirring for 16 h at room temperature, 500 mL of water was added to the mixture, which was filtered to afford the solid crude product. Brine of 200 mL was added to the solid and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated to furnish crude product, which was purified by flash chromatography followed by recrystallization (DMF/EtOAc/hexane). The product (12.4 g, 54.3 mmol, 49% for two steps) was obtained as light brown needles; mp 239 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.06 (1H, d, J=8.0 Hz), 8.17 (1H, dd, J=1.6, 8.0 Hz), 8.32 (1H, d, J=1.6 Hz), 10.4 (1H, s); IR (ATR) 1680 cm^{-1}; MS (CI): m/z 229 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_8H_6BrO_3$ ([M+H]$^+$) 228.9500, found 228.9492.

4.4.2. General procedures for the synthesis of the library. The library was prepared by general 'Split and Pool Synthesis' using color coded tags.[12]

4.4.2.1. Synthesis of 14 (X=OMe) on solid support 3. Six pieces of the solid supported aniline **3** (loading: 75 μmol×6, 450 μmol) were reacted with 4-formyl-3-methoxybenzoic acid (325 mg, 1.8 mmol, 4 equiv) in DMF (6 mL) at room temperature for 24 h. The solution was removed by decantation and the resulting resins were washed with DMF (3×0.5 min) and DCM (3×0.5 min). 4-Formylbenzoic acid and 3-bromo-4-formylbenzoic acid were also loaded by the same procedure.

4.4.2.2. Synthesis of 15 (R^1=SC_9H_{19}) on solid support 14 with 1-nonanethiol. Six pieces of the solid supported azomethine **14** (loading: 75 μmol×6, 450 μmol) were reacted with 4-*N*,*N*-dimethylaminopyridine (13.7 mg, 0.113 mmol, 0.25 equiv), 1-nonanethiol (289 mg, 1.8 mmol, 4 equiv), and 1,3-diisopropylcarbodiimide (564 μL, 3.6 mmol, 8 equiv) in DCM at room temperature for 3 h. The solution was removed by decantation and the resulting resins were washed with DMF (3×0.5 min) and DCM (3×0.5 min). Butylesters **15** (R^1=OBu) and *N*,*N*-diisobutylamides **15** (R^1=$N(CH_2CHMe_2)_2$) were also prepared by the same procedure described above.

4.4.2.3. Oxidative cleavage from the solid support. The solid supported ester **15** (X=H, R^1=OBu, loading: 75 μmol×1, 75 μmol) was reacted with 2-aminophenol (32.7 mg, 0.3 mmol, 4 equiv) and Darco® KB (450 mg) in DMF (3 mL) at 100 °C under an air atmosphere for 18 h. The resulting resins were washed with DMF (3×2 min) and

DCM (3×2 min). The combined DMF and DCM solutions were filtered. The filtrate was evaporated and purified by silica gel chromatography (hexane/EtOAc=10:1) to give **17** (X=H, R^1=OBu, Y=O) in 58% yield (12.8 mg, 43.3 μmol) as colorless solid. Benzothiazoles **17** (Y=S) and benzimidazoles **17** (Y=NH) were synthesized by the same procedure described above but in the absence of Darco® KB. *N*-Methylbenzimidazoles **17** (Y=NMe) were synthesized in the same manner as the preparation of benzimidazoles **17** (Y=NH) but for longer reaction period (48 h). Yields for all library members are shown in Table 2.

*4.4.2.3.1. S-Nonyl 4-(2-benzoxazol-2-yl)benzoate **17** (X=H, R^1=SC_9H_{19}, Y=O).* Colorless solid, mp 111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.1 Hz), 1.28 (10H, m), 1.44 (2H, m), 1.70 (2H, tt, *J*=6.9, 7.1 Hz), 3.11 (2H, t, *J*=7.1 Hz), 7.38–7.41 (2H, m), 7.60–7.63 (1H, m), 7.80–7.83 (1H, m), 8.12 (2H, d, *J*=8.8 Hz), 8.34 (2H, d, *J*=8.8 Hz); IR (ATR) 1657 cm^{-1}; MS (CI): *m/z* 222 (100%), 382 ($[M+H]^+$, 70%); HRMS (CI): calcd for $C_{23}H_{28}NO_2S$ ($[M+H]^+$) 382.1841, found 382.1847.

*4.4.2.3.2. N,N-Diisobutyl 4-(benzoxazol-2-yl)benzamide **17** (X=H, R^1=$N(CH_2CHMe_2)_2$, Y=O).* Colorless solid, mp 158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (6H, d, *J*=6.6 Hz), 1.02 (6H, d, *J*=6.6 Hz), 1.87 (1H, m), 2.15 (1H, m), 3.11 (2H, d, *J*=7.4 Hz), 3.39 (2H, d, *J*=7.7 Hz), 7.36–7.41 (2H, m), 7.52 (2H, d, *J*=8.2 Hz), 7.60–7.63 (1H, m), 7.78–7.81 (1H, m), 8.29 (2H, d, *J*=8.0 Hz); IR (ATR) 1632 cm^{-1}; MS (CI): *m/z* 351 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{22}H_{27}N_2O_2$ ($[M+H]^+$) 351.2073, found 351.2070.

*4.4.2.3.3. Butyl 4-(2-benzoxazol-2-yl)-3-bromobenzoate **17** (X=Br, R^1=OBu, Y=O).* Colorless solid, mp 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, t, *J*=7.1 Hz), 1.50 (2H, tq, *J*=7.1, 7.1 Hz), 1.79 (2H, tt, *J*=6.6, 7.1 Hz), 4.38 (2H, t, *J*=6.6 Hz), 7.39–7.47 (2H, m), 7.63–7.67 (1H, m), 7.87–7.90 (1H, m), 8.11 (1H, dd, *J*=1.6, 8.2 Hz), 8.20 (1H, d, *J*=8.2 Hz), 8.43 (1H, d, *J*=1.6 Hz); IR (ATR) 1720 cm^{-1}; MS (CI): *m/z* 374 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{18}H_{17}BrNO_3$ ($[M+H]^+$) 374.0391, found 374.0389.

*4.4.2.3.4. S-Nonyl 4-(benzoxazol-2-yl)-3-bromobenzoate **17** (X=Br, R^1=SC_9H_{19}, Y=O).* Colorless solid, mp 68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=6.9 Hz), 1.28 (10H, m), 1.44 (2H, m), 1.70 (2H, tt, *J*=6.9, 7.4 Hz), 3.12 (2H, t, *J*=7.4 Hz), 7.39–7.48 (2H, m), 7.63–7.67 (1H, m), 7.87–7.90 (1H, m), 8.03 (1H, dd, *J*=1.6, 8.2 Hz), 8.21 (1H, d, *J*=8.2 Hz), 8.35 (1H, d, *J*=1.6 Hz); IR (ATR) 1657 cm^{-1}; MS (CI): *m/z* 460 ($[M+H]^+$, 97%); HRMS (CI): calcd for $C_{23}H_{27}BrNO_2S$ ($[M+H]^+$) 460.0946, found 460.0944.

*4.4.2.3.5. N,N-Diisobutyl 4-(benzoxazol-2-yl)-3-bromobenzamide **17** (X=Br, R^1=$N(CH_2CHMe_2)_2$, Y=O).* Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (6H, d, *J*=6.6 Hz), 1.01 (6H, t, *J*=6.6 Hz), 1.89 (1H, m), 2.13 (1H, m), 3.10 (2H, d, *J*=7.7 Hz), 3.37 (2H, d, *J*=7.4 Hz), 7.40–7.45 (3H, m), 7.62–7.65 (1H, m), 7.74 (1H, d, *J*=1.6 Hz), 7.85–7.88 (1H, m), 8.13 (1H, d, *J*=8.0 Hz); IR (ATR) 1633 cm^{-1}; MS (CI): *m/z* 429 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{22}H_{26}BrN_2O_2$ ($[M+H]^+$) 429.1178, found 429.1184.

*4.4.2.3.6. Butyl 4-(2-benzoxazol-2-yl)-3-methoxybenzoate **17** (X=OMe, R^1=OBu, Y=O).* Colorless solid, mp 98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, *J*=7.1 Hz), 1.51 (2H, tq, *J*=7.1, 7.1 Hz), 1.80 (2H, tt, *J*=6.6, 7.1 Hz), 4.10 (3H, s), 4.38 (2H, t, *J*=6.6 Hz), 7.36–7.40 (2H, m), 7.60–7.64 (1H, m), 7.75–7.78 (2H, m), 7.84–7.87 (1H, m), 8.22 (1H, d, *J*=8.2 Hz); IR (ATR) 1717 cm^{-1}; MS (CI): *m/z* 326 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{19}H_{20}NO_4$ ($[M+H]^+$) 326.1392, found 326.1396.

*4.4.2.3.7. S-Nonyl 4-(benzoxazol-2-yl)-3-methoxybenzoate **17** (X=OMe, R^1=SC_9H_{19}, Y=O).* Colorless solid, mp 77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=7.1 Hz), 1.28 (10H, m), 1.45 (2H, m), 1.71 (2H, tt, *J*=7.4, 7.4 Hz), 3.12 (2H, t, *J*=7.4 Hz), 4.10 (3H, s), 7.35–7.42 (2H, m), 7.60–7.63 (1H, m), 7.65 (1H, s), 7.72 (1H, d, *J*=8.0 Hz), 7.84–7.87 (1H, m), 8.24 (1H, d, *J*=8.0 Hz); IR (ATR) 1662 cm^{-1}; MS (CI): *m/z* 252 (100%), 412 ($[M+H]^+$, 70%); HRMS (CI): calcd for $C_{24}H_{30}NO_3S$ ($[M+H]^+$) 412.1946, found 412.1939.

*4.4.2.3.8. N,N-Diisobutyl 4-(benzoxazol-2-yl)-3-methoxybenzamide **17** (X=OMe, R^1=$N(CH_2CHMe_2)_2$, Y=O).* Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (6H, d, *J*=6.6 Hz), 1.02 (6H, d, *J*=6.9 Hz), 1.89 (1H, m), 2.15 (1H, m), 3.12 (2H, d, *J*=7.4 Hz), 3.39 (2H, d, *J*=7.4 Hz), 4.04 (3H, s), 7.05 (1H, dd, *J*=4.4, 7.7 Hz), 7.08 (1H, d, *J*=1.4 Hz), 7.58–7.63 (1H, m), 7.78–7.86 (1H, m), 8.15 (1H, d, *J*=8.0 Hz); IR (ATR) 1631 cm^{-1}; MS (CI): *m/z* 381 ($[M+H]^+$, 100%); HRMS (CI): calcd for $C_{23}H_{29}N_2O_3$ ($[M+H]^+$) 381.2178, found 381.2180.

*4.4.2.3.9. S-Nonyl 4-(benzothiazol-2-yl)benzoate **17** (X=H, R^1=SC_9H_{19}, Y=S).* Colorless solid, mp 83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=6.6 Hz), 1.22–1.39 (10H, m), 1.44 (2H, m), 1.70 (2H, tt, *J*=7.4, 7.4 Hz), 3.10 (2H, t, *J*=7.4 Hz), 7.42 (1H, ddd, *J*=1.1, 7.1, 8.0 Hz), 7.52 (1H, ddd, *J*=1.1, 7.1, 8.0 Hz), 7.93 (1H, ddd, *J*=0.6, 1.1, 8.0 Hz), 8.08 (2H, d, *J*=8.8 Hz), 8.11 (1H, d, *J*=0.6, 1.1, 8.0 Hz), 8.17 (2H, d, *J*=8.8 Hz); IR (ATR) 1645 cm^{-1}; MS (EI): *m/z* 238 (100%), 397 ($[M]^+$, 7.0%); HRMS (EI): calcd for $C_{23}H_{27}NOS_2$ ($[M]^+$) 397.1534, found 397.1549.

*4.4.2.3.10. N,N-Diisobutyl 4-(benzothiazol-2-yl)benzamide **17** (X=H, R^1=$N(CH_2CHMe_2)_2$, Y=S).* Colorless solid, mp 142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (6H, d, *J*=6.3 Hz), 1.01 (6H, d, *J*=6.3 Hz), 1.87 (1H, m), 2.15 (1H, m), 3.12 (2H, d, *J*=7.4 Hz), 3.39 (2H, d, *J*=7.4 Hz), 7.41 (1H, dd, *J*=7.4, 8.0 Hz), 7.48 (2H, d, *J*=8.2 Hz), 7.52 (1H, dd, *J*=7.4, 7.4 Hz), 7.93 (1H, d, *J*=8.0 Hz), 8.09 (1H, d, *J*=7.4 Hz), 8.12 (2H, d, *J*=8.2 Hz); IR (ATR) 1623 cm^{-1}; MS (EI): *m/z* 238 (100%), 366 ($[M]^+$, 71%); HRMS (EI): calcd for $C_{22}H_{26}N_2OS$ ($[M]^+$) 366.1766, found 366.1769.

*4.4.2.3.11. Butyl 4-(benzothiazol-2-yl)-3-bromobenzoate **17** (X=Br, R^1=OBu, Y=S).* Colorless solid, mp 95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, t, *J*=7.4 Hz), 1.49

(2H, tq, *J*=7.4, 7.4 Hz), 1.79 (2H, tt, *J*=6.9, 7.4 Hz), 4.37 (2H, t, *J*=6.9 Hz), 7.47 (1H, dd, *J*=7.1, 7.4 Hz), 7.56 (1H, dd, *J*=7.1, 8.2 Hz), 7.97 (1H, d, *J*=7.4 Hz), 8.08 (1H, dd, *J*=1.6, 7.4 Hz), 8.15 (1H, d, *J*=7.4 Hz), 8.16 (1H, d, *J*=8.2 Hz), 8.40 (1H, d, *J*=1.6 Hz); IR (ATR) 1712 cm^{-1}; MS (EI): *m/z* 333 (92%), 335 (100%), 389 ($[M]^+$, 67%), 391 ($[M+2]^+$, 69%); HRMS (EI): calcd for $C_{18}H_{16}BrNO_2S$ ($[M]^+$) 389.0085, found 389.0089.

4.4.2.3.12. S-Nonyl 4-(benzothiazol-2-yl)-3-bromobenzoate ***17*** *(X=Br, R^1=SC_9H_{19}, Y=S).* Colorless solid, mp 64 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=6.6 Hz), 1.28–1.38 (10H, m), 1.44 (2H, m), 1.70 (2H, tt, *J*=7.4, 7.4 Hz), 3.11 (2H, t, *J*=7.4 Hz), 7.47 (1H, ddd, *J*=1.4, 7.4, 8.0 Hz), 7.56 (1H, ddd, *J*=1.4, 7.4, 8.0 Hz), 7.97 (1H, ddd, *J*=0.6, 1.4, 8.0 Hz), 8.01 (1H, dd, *J*=1.4, 8.1 Hz), 8.16 (1H, ddd, *J*=0.6, 1.4, 8.0 Hz), 8.18 (1H, d, *J*=8.2 Hz), 8.32 (1H, d, *J*=1.4 Hz); IR (ATR) 1662 cm^{-1}; MS (EI): *m/z* 316 (97%), 318 (100%), 475 ($[M]^+$, 11%), 477 ($[M+2]^+$, 12%); HRMS (EI): calcd for $C_{23}H_{26}BrNOS_2$ ($[M]^+$) 475.0639, found 475.0639.

4.4.2.3.13. N,N-Diisobutyl 4-(benzothiazol-2-yl)-3-bromobenzamide ***17*** *(X=Br, R^1=$N(CH_2CHMe_2)_2$, Y=S).* Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (6H, d, *J*=6.3 Hz), 1.01 (6H, t, *J*=6.4 Hz), 1.90 (1H, m), 2.14 (1H, m), 3.12 (2H, d, *J*=7.4 Hz), 3.38 (2H, d, *J*=7.4 Hz), 7.42 (1H, dd, *J*=1.4, 8.0 Hz), 7.46 (1H, ddd, *J*=1.1, 7.1, 8.0 Hz), 7.56 (1H, ddd, *J*=1.1, 7.1, 8.2 Hz), 7.72 (1H, d, *J*=1.4 Hz), 7.97 (1H, d, *J*=8.0 Hz), 8.06 (1H, d, *J*=8.0 Hz), 8.15 (1H, d, *J*=8.2 Hz); IR (ATR) 1628 cm^{-1}; MS (EI): *m/z* 316 (99%), 318 (100%), 444 ($[M]^+$, 13%), 446 ($[M+2]^+$, 13%); HRMS (EI): calcd for $C_{22}H_{25}BrN_2OS$ ($[M]^+$) 444.0871, found 444.0854.

4.4.2.3.14. Butyl 4-(benzothiazol-2-yl)-3-methoxybenzoate ***17*** *(X=OMe, R^1=OBu, Y=S).* Colorless solid, mp 92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, *J*=7.4 Hz), 1.50 (2H, tq, *J*=7.4, 7.4 Hz), 1.79 (2H, tt, *J*=6.6, 7.4 Hz), 4.12 (3H, s), 4.37 (2H, t, *J*=6.6 Hz), 7.40 (1H, ddd, *J*=1.1, 7.1, 8.0 Hz), 7.51 (1H, ddd, *J*=1.4, 7.1, 8.2 Hz), 7.74 (1H, d, *J*=1.4 Hz), 7.78 (1H, dd, *J*=1.4, 8.2 Hz), 7.94 (1H, ddd, *J*=0.6, 1.4, 8.0 Hz), 8.12 (1H, ddd, *J*=0.6, 1.1, 8.2 Hz), 8.61 (1H, d, *J*=8.2 Hz); IR (ATR) 1705 cm^{-1}; MS (EI): *m/z* 341 ($[M]^+$, 100%); HRMS (EI): calcd for $C_{19}H_{19}NO_3S$ ($[M]^+$) 341.1086, found 341.1069.

4.4.2.3.15. S-Nonyl 4-(benzothiazol-2-yl)-3-methoxybenzoate ***17*** *(X=OMe, R^1=SC_9H_{19}, Y=S).* Colorless solid, mp 80 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=6.6 Hz), 1.28–1.38 (10H, m), 1.44 (2H, m), 1.70 (2H, tt, *J*=7.1, 7.1 Hz), 3.10 (2H, t, *J*=7.1 Hz), 4.12 (3H, s), 7.40 (1H, ddd, *J*=1.0, 7.1, 7.7 Hz), 7.51 (1H, ddd, *J*=1.0, 7.1, 8.0 Hz), 7.63 (1H, d, *J*=1.6 Hz), 7.74 (1H, dd, *J*=1.6, 8.2 Hz), 7.94 (1H, d, *J*=7.7 Hz), 8.11 (1H, d, *J*=8.0 Hz), 8.62 (1H, d, *J*=8.2 Hz); IR (ATR) 1645 cm^{-1}; MS (EI): *m/z* 268 (100%), 427 ($[M]^+$, 18%); HRMS (EI): calcd for $C_{24}H_{29}NO_2S_2$ ($[M]^+$) 427.1640, found 427.1624.

4.4.2.3.16. N,N-Diisobutyl 4-(benzothiazol-2-yl)-3-methoxybenzamide ***17*** *(X=OMe, R^1=$N(CH_2CHMe_2)_2$, Y=S).* Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (6H, d, *J*=6.3 Hz), 1.02 (6H, d, *J*=6.3 Hz), 1.89 (1H, m), 2.15 (1H, m), 3.14 (2H, d, *J*=7.4 Hz), 3.39 (2H, d, *J*=7.4 Hz), 4.08 (3H, s), 7.08 (1H, d, *J*=8.6 Hz), 7.09 (1H, s), 7.39 (1H, ddd, *J*=1.4, 7.4, 8.0 Hz), 7.50 (1H, ddd, *J*=1.4, 7.4, 8.0 Hz), 7.94 (1H, ddd, *J*=0.8, 1.4, 8.0 Hz), 8.10 (1H, ddd, *J*=0.8, 1.4, 8.0 Hz), 8.54 (1H, d, *J*=8.6 Hz); IR (ATR) 1628 cm^{-1}; MS (EI): *m/z* 268 (100%), 396 ($[M]^+$, 45%); HRMS (EI): calcd for $C_{23}H_{28}N_2O_2S$ ($[M]^+$) 396.1871, found 396.1881.

4.4.2.3.17. S-Nonyl 4-(benzimidazol-2-yl)benzoate ***17*** *(X=H, R^1=SC_9H_{19}, Y=NH).* Colorless solid, mp 190 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=6.6 Hz), 1.26–1.36 (10H, m), 1.41 (2H, m), 1.66 (2H, tt, *J*=7.1, 7.1 Hz), 3.07 (2H, t, *J*=7.1 Hz), 7.26–7.31 (2H, m), 7.65 (2H, br s), 7.98 (2H, d, *J*=8.0 Hz), 8.16 (2H, d, *J*=8.0 Hz); IR (ATR) 1660 cm^{-1}; MS (EI): *m/z* 221 (100%), 380 ($[M]^+$, 44%); HRMS (EI): calcd for $C_{23}H_{28}N_2OS$ ($[M]^+$) 380.1922, found 380.1919.

4.4.2.3.18. N,N-Diisobutyl 4-(benzimidazol-2-yl)benzamide ***17*** *(X=H, R^1=$N(CH_2CHMe_2)_2$, Y=NH).* Colorless solid, mp 192 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (6H, d, *J*=6.6 Hz), 1.03 (6H, d, *J*=6.6 Hz), 1.84 (1H, m), 2.19 (1H, m), 3.09 (2H, d, *J*=7.4 Hz), 3.46 (2H, d, *J*=7.7 Hz), 7.21–7.27 (2H, m), 7.22 (2H, d, *J*=8.5 Hz), 7.63 (2H, br s), 7.89 (2H, d, *J*=8.5 Hz), 12.15 (1H, br s); IR (ATR) 1606 cm^{-1}; MS (EI): *m/z* 221 (100%), 349 ($[M]^+$, 16%); HRMS (EI): calcd for $C_{22}H_{27}N_3O$ ($[M]^+$) 349.2154, found 349.2153.

4.4.2.3.19. Butyl 4-(benzimidazol-2-yl)-3-bromobenzoate ***17*** *(X=Br, R^1=OBu, Y=NH).* Colorless solid, mp 143 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, t, *J*=7.1 Hz), 1.49 (2H, tq, *J*=7.1, 7.1 Hz), 1.78 (2H, tt *J*=6.6, 7.1 Hz), 4.36 (2H, t *J*=6.6 Hz), 7.31–7.36 (2H, m), 7.60 (1H, br s), 7.81 (1H, br s), 8.03 (1H, d, *J*=8.2 Hz), 8.31 (1H, s), 8.33 (1H, d, *J*=8.2 Hz), 10.64 (1H, br s); IR (ATR) 1724 cm^{-1}; MS (EI): *m/z* 372 ($[M]^+$, 100%), 374 ($[M+2]^+$, 99%); HRMS (EI): calcd for $C_{18}H_{17}BrN_2O_2$ ($[M]^+$) 372.0473, found 372.0482.

4.4.2.3.20. S-Nonyl 4-(benzimidazol-2-yl)-3-bromobenzoate ***17*** *(X=Br, R^1=SC_9H_{19}, Y=NH).* Colorless solid, mp 144 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.1 Hz), 1.28–1.38 (10H, m), 1.43 (2H, m), 1.69 (2H, tt, *J*=7.1, 7.1 Hz), 3.10 (2H, t, *J*=7.1 Hz), 7.30–7.36 (2H, m), 7.70 (2H, br s), 7.94 (1H, dd, *J*=1.6, 8.2 Hz), 8.21 (1H, d, *J*=1.6 Hz), 8.30 (1H, d, *J*=8.2 Hz), 10.76 (1H, br s); IR (ATR) 1657 cm^{-1}; MS (EI): *m/z* 299 (100%), 301 (96%), 458 ($[M]^+$, 18%), 460 ($[M+2]^+$, 19%); HRMS (EI): calcd for $C_{23}H_{27}BrN_2OS$ ($[M]^+$) 458.1027, found 458.1013.

4.4.2.3.21. N,N-Diisobutyl 4-(benzimidazol-2-yl)-3-bromobenzamide ***17*** *(X=Br, R^1=$N(CH_2CHMe_2)_2$, Y=NH).* Colorless solid, mp 173 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (6H, d, *J*=6.3 Hz), 1.02 (6H, d, *J*=6.6 Hz), 1.89 (1H, m), 2.16 (1H, m), 3.10 (2H, d, *J*=7.4 Hz), 3.42 (2H, d, *J*=7.4 Hz), 7.31–7.34 (2H, m), 7.33 (1H, d, *J*=8.0 Hz), 7.62 (1H, br s), 7.64 (1H, s), 7.83 (1H, br s), 8.10 (1H, d, *J*=8.0 Hz), 11.10 (1H, br s); IR (ATR) 1627 cm^{-1}; MS (EI): *m/z* 299 (99%), 301 (100%), 427 ($[M]^+$, 16%), 429

([M+2]$^+$, 16%); HRMS (EI): calcd for $C_{22}H_{26}BrN_3O$ ([M]$^+$) 427.1259, found 427.1240.

4.4.2.3.22. Butyl 4-(benzimidazol-2-yl)-3-methoxybenzoate ***17*** *(X=OMe, R^1=OBu, Y=NH).* Colorless solid, mp 220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.4 Hz), 1.50 (2H, tq, J=7.4, 7.4 Hz), 1.79 (2H, tt, J=6.9, 7.4 Hz), 4.16 (3H, s), 4.37 (2H, t, J=6.9 Hz), 7.28–7.33 (2H, m), 7.52–7.54 (1H, m), 7.76 (1H, d, J=1.4 Hz), 7.80 (1H, dd, J=1.4, 8.2 Hz), 7.83–7.85 (1H, m), 8.67 (1H, d, J=8.2 Hz), 10.70 (1H, br s); IR (ATR) 1701 cm^{-1}; MS (EI): m/z 324 ([M]$^+$, 100%); HRMS (EI): calcd for $C_{19}H_{20}N_2O_3$ ([M]$^+$) 324.1474, found 324.1470.

4.4.2.3.23. S-Nonyl 4-(benzimidazol-2-yl)-3-methoxybenzoate ***17*** *(X=OMe, R^1=SC_9H_{19}, Y=NH).* Colorless solid, mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=6.6 Hz), 1.26–1.39 (10H, m), 1.45 (2H, m), 1.70 (2H, tt, J=7.4, 7.4 Hz), 3.10 (2H, t, J=7.4 Hz), 4.15 (3H, s), 7.28–7.32 (2H, m), 7.52 (1H, m), 7.64 (1H, d, J=1.4 Hz), 7.77 (1H, dd, J=1.4, 8.2 Hz), 7.84 (1H, br s), 8.67 (1H, d, J=8.2 Hz), 10.68 (1H, br s); IR (ATR) 1661 cm^{-1}; MS (EI): m/z 251 (100%), 410 ([M]$^+$, 55%); HRMS (EI): calcd for $C_{24}H_{30}N_2O_2S$ ([M]$^+$) 410.2028, found 410.2029.

4.4.2.3.24. N,N-Diisobutyl 4-(benzimidazol-2-yl)-3-methoxybenzamide ***17*** *(X=OMe, R^1=N(CH_2CHMe_2)$_2$, Y=NH).* Colorless solid, mp 173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (6H, d, J=6.0 Hz), 1.02 (6H, d, J=6.0 Hz), 1.88 (1H, m), 2.15 (1H, m), 3.15 (2H, d, J=6.9 Hz), 3.39 (2H, d, J=7.1 Hz), 4.08 (3H, s), 7.09 (1H, d, J=8.2 Hz), 7.10 (1H, s), 7.26–7.31 (2H, m), 7.66 (2H, br s), 8.58 (1H, d, J=8.2 Hz), 10.67 (1H, br s); IR (ATR) 1617 cm^{-1}; MS (EI): m/z 251 (100%), 379 ([M]$^+$, 41%); HRMS (EI): calcd for $C_{23}H_{29}N_3O_2$ ([M]$^+$) 379.2260, found 379.2268.

4.4.2.3.25. S-Nonyl 4-(1-methyl-benzimidazol-2-yl)benzoate ***17*** *(X=H, R^1=SC_9H_{19}, Y=NMe).* Colorless solid, mp 64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J=6.9 Hz), 1.25–1.37 (10H, m), 1.45 (2H, m), 1.71 (2H, tt, J=7.4, 7.4 Hz), 3.12 (2H, t, J=7.4 Hz), 3.90 (3H, s), 7.31–7.44 (3H, m), 7.82–7.86 (1H, m), 7.88 (2H, d, J=8.2 Hz), 8.13 (2H, d, J=8.2 Hz); IR (ATR) 1658 cm^{-1}; MS (CI): m/z 395 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{24}H_{31}N_2OS$ ([M+H]$^+$) 395.2157, found 395.2167.

4.4.2.3.26. N,N-Diisobutyl 4-(1-methyl-1-methyl-benzimidazol-2-yl)benzamide ***17*** *(X=H, R^1=N(CH_2CHMe_2)$_2$, Y=NMe).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (6H, d, J=6.6 Hz), 1.02 (6H, d, J=6.9 Hz), 1.89 (1H, m), 2.16 (1H, m), 3.14 (2H, d, J=7.4 Hz), 3.40 (2H, d, J=7.7 Hz), 3.88 (3H, s), 7.30–7.44 (3H, m), 7.52 (2H, d, J=8.2 Hz), 7.80 (2H, d, J=8.2 Hz), 7.80–7.86 (1H, m); IR (ATR) 1631 cm^{-1}; MS (CI): m/z 364 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{23}H_{30}N_3O$ ([M+H]$^+$) 364.2389, found 364.2389.

4.4.2.3.27. Butyl 4-(1-methyl-benzimidazol-2-yl)-3-bromobenzoate ***17*** *(X=Br, R^1=OBu, Y=NMe).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.4 Hz), 1.50 (2H, tq, J=7.4, 7.4 Hz), 1.80 (2H, tt, J=6.6, 7.4 Hz), 3.68 (3H, s), 4.39 (2H, t, J=6.6 Hz), 7.32–7.46 (3H, m), 7.63 (1H, d, J=8.0 Hz), 7.82–7.88 (1H, m), 8.12 (1H, dd, J=1.7, 8.0 Hz), 8.38 (1H, d, J=1.7 Hz); IR (ATR) 1717 cm^{-1}; MS (CI): m/z 388 (100%), 387 ([M+H]$^+$, 96%); HRMS (CI): calcd for $C_{19}H_{20}BrN_2O_2$ ([M+H]$^+$) 387.0709, found 387.0709.

4.4.2.3.28. S-Nonyl 4-(1-methyl-benzimidazol-2-yl)-3-bromobenzoate ***17*** *(X=Br, R^1=SC_9H_{19}, Y=NMe).* Colorless solid, mp 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J=6.9 Hz), 1.28 (10H, m), 1.45 (2H, m), 1.70 (2H, tt, J=7.1, 7.4 Hz), 3.12 (2H, t, J=7.4 Hz), 3.66 (3H, s), 7.31–7.37 (2H, m), 7.39–7.44 (1H, m), 7.63 (1H, d, J=8.0 Hz), 7.83–7.86 (1H, m), 8.03 (1H, dd J=1.6, 8.0 Hz), 8.29 (1H, d, J=1.6 Hz); IR (ATR) 1655 cm^{-1}; MS (CI): m/z 473 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{24}H_{30}BrN_2OS$ ([M+H]$^+$) 473.1263, found 473.1262.

4.4.2.3.29. N,N-Diisobutyl 4-(1-methyl-benzimidazol-2-yl)-3-bromobenzamide ***17*** *(X=Br, R^1=N(CH_2CHMe_2)$_2$, Y=NMe).* Colorless solid, mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (6H, d, J=6.9 Hz), 1.01 (6H, t, J=6.6 Hz), 1.91 (1H, m), 2.14 (1H, m), 3.12 (2H, d, J=7.7 Hz), 3.39 (2H, d, J=7.7 Hz), 3.67 (3H, s), 7.32–7.39 (2H, m), 7.40–7.46 (1H, m), 7.43 (1H, dd, J=1.6, 7.7 Hz), 7.58 (1H, d, J=7.7 Hz), 7.70 (1H, d, J=1.6 Hz), 7.81–7.87 (1H, m); IR (ATR) 1630 cm^{-1}; MS (CI): m/z 442 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{23}H_{29}BrN_3O$ ([M+H]$^+$) 442.1494, found 442.1490.

4.4.2.3.30. Butyl 4-(1-methyl-benzimidazol-2-yl)-3-methoxybenzoate ***17*** *(X=OMe, R^1=OBu, Y=NMe).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.1 Hz), 1.50 (2H, tq, J=7.1, 7.1 Hz), 1.80 (2H, tt, J=6.6, 7.1 Hz), 3.66 (3H, s), 3.90 (3H, s), 4.38 (2H, t, J=6.6 Hz), 7.28–7.43 (3H, m), 7.67 (1H, d, J=7.7 Hz), 7.71 (1H, s), 7.79 (1H, d, J=7.7 Hz), 7.82–7.85 (1H, m); IR (ATR) 1714 cm^{-1}; MS (CI): m/z 339 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{20}H_{23}N_2O_3$ ([M+H]$^+$) 339.1708, found 339.1701.

4.4.2.3.31. S-Nonyl 4-(1-methyl-benzimidazol-2-yl)-3-methoxybenzoate ***17*** *(X=OMe, R^1=SC_9H_{19}, Y=NMe).* Colorless solid, mp 54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, J=6.9 Hz), 1.26–1.37 (10H, m), 1.45 (2H, m), 1.68 (2H, m), 3.12 (2H, t, J=7.4 Hz), 3.66 (3H, s), 3.90 (3H, s), 7.28–7.43 (3H, m), 7.60 (1H, d, J=1.4 Hz), 7.68 (1H, d, J=8.0 Hz), 7.75 (1H, dd, J=1.4, 8.0 Hz), 7.82–7.85 (1H, m); IR (ATR) 1662 cm^{-1}; MS (CI): m/z 425 ([M+H]$^+$, 100%); HRMS (CI): calcd for $C_{25}H_{33}N_2O_2S$ ([M+H]$^+$) 425.2262, found 425.2244.

4.4.2.3.32. N,N-Diisobutyl 4-(1-methyl-benzimidazol-2-yl)-3-methoxybenzamide ***17*** *(X=OMe, R^1=N(CH_2CHMe_2)$_2$, Y=NMe).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (6H, d, J=6.6 Hz), 1.02 (6H, d, J=6.3 Hz), 1.91 (1H, m), 2.15 (1H, m), 3.16 (2H, d, J=7.1 Hz), 3.40 (2H, d, J=7.4 Hz), 3.65 (3H, s), 3.84 (3H, s), 7.04 (1H, s), 7.06 (1H, d, J=7.4 Hz), 7.28–7.37 (2H, m), 7.39–7.43 (1H, m), 7.60 (1H, d, J=7.4 Hz), 7.79–7.84 (1H, m); IR (ATR) 1626 cm^{-1}; MS (CI): m/z 394 ([M+H]$^+$, 100%); HRMS

(CI): calcd for $C_{24}H_{32}N_3O_2$ ([M+H]$^+$) 394.2494, found 394.2494.

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References and notes

1. For some examples, see: (a) Sondhi, S. M.; Singh, N.; Kumar, A.; Lozach, O.; Meijer, L. *Bioorg. Med. Chem.* **2006**, *14*, 3758–3765; (b) Vinsova, J.; Cermakova, K.; Tomeckova, A.; Ceckova, M.; Jampilek, J.; Cermak, P.; Kunes, J.; Dolezal, M.; Staud, F. *Bioorg. Med. Chem.* **2006**, *14*, 5850–5865; (c) Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455–1459.
2. Rodembusch, F. S.; Buckup, T.; Segala, M.; Tavares, L.; Correia, R. R. B.; Stefani, V. *Chem. Phys.* **2004**, *305*, 115–121.
3. (a) Gong, J.-R.; Wan, L.-J.; Lei, S.-B.; Bai, C.-L.; Zhang, X.-H.; Lee, S.-T. *J. Phys. Chem. B* **2005**, *109*, 1675–1682; (b) Chen, T.-R. *J. Mol. Struct.* **2005**, *737*, 35–41.
4. Wang, C.-S.; Wang, I.-W.; Cheng, K.-L.; Lai, C. K. *Tetrahedron* **2006**, *62*, 9383–9392.
5. (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930; (b) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Rao, M. V. *Mini Rev. Med. Chem.* **2006**, *6*, 71–89; (c) Carpenter, R. D.; DeBerdt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006**, *8*, 907–914; (d) Choi, S. J.; Park, H. J.; Lee, S. K.; Kim, S. W.; Han, G.; Choo, H.-Y. P. *Bioorg. Med. Chem.* **2006**, *14*, 1229–1235; (e) Beebe, X.; Wodka, D.; Sowin, T. J. *J. Comb. Chem.* **2001**, *3*, 360–366; (f) Hwang, J. Y.; Gong, Y.-D. *J. Comb. Chem.* **2006**, *8*, 297–303; (g) Matsushita, H.; Lee, S.-H.; Joung, M.; Clapham, B.; Janda, K. D. *Tetrahedron Lett.* **2004**, *45*, 313–316; (h) Yokum, T. S.; Alsina, J.; Barany, G. *J. Comb. Chem.* **2000**, *2*, 282–292; (i) Wu, Z.; Ede, N. J.; Mathieu, M. N. *Tetrahedron Lett.* **2003**, *44*, 2293–2296; (j) Kilburn, J. P.; Lau, J.; Jones, R. C. F. *Tetrahedron Lett.* **2000**, *41*, 5419–5421.
6. For some examples, see: (a) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2158; (b) Scott, P. J. H.; Steel, P. G. *Eur. J. Org. Chem.* **2006**, 2251–2268.
7. (a) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607–2624; (b) .Gil, C.; BräseCurr, S. *Opin. Chem. Biol.* **2004**, *8*, 230–237; (c) Bräse, S.; Dahmen, S. *Chem.—Eur. J.* **2000**, *6*, 1899–1905.
8. (a) Hioki, H.; Fukutaka, M.; Takahashi, H.; Kodama, M.; Kubo, K.; Ideta, K.; Mori, A. *Tetrahedron Lett.* **2004**, *45*, 7591–7594; (b) Hioki, H.; Fukutaka, M.; Takahashi, H.; Kubo, M.; Matsushita, K.; Kodama, M.; Kubo, K.; Ideta, K.; Mori, A. *Tetrahedron* **2005**, *61*, 10643–10651.
9. Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713–3715.
10. The preliminary account has been published. Hioki, H.; Matsushita, K.; Kubo, M.; Kodama, M. *J. Comb. Chem.* **2006**, *8*, 462–463.
11. Adediran, S. A.; Cabaret, D.; Drouillat, B.; Pratt, R. F.; Wakselman, M. *Bioorg. Med. Chem.* **2001**, *9*, 1175–1183.
12. See the following web site for generating a Lantern® library using color coded tags; http://www.mimotopes.com/PageContent.aspx?linkId=158.