A Highly Automated, Polymer-Assisted Strategy for the Preparation of 2-Alkylthiobenzimidazoles and *N,N′*-Dialkylbenzimidazolin-2-ones

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Received October 26, 2004

A multistep, polymer-assisted solution phase strategy for the highly automated (auto-PASP) synthesis of 2-alkylthiobenzimidazole and *N,N′*-dialkylbenzimidazolin-2-one libraries is presented. The approach incorporates in-line purification techniques to afford library products directly with high purities and is exemplified by the preparation of a 96-member 2-alkylthiobenzimidazoline library **1**{*1*−*12,1*−*8*} and a 72-member *N,N′*-dialkylbenzimidazolin-2-one library **9**{*1*−*12,1*−*6*}.

Introduction

The identification of suitable lead structures as starting points for new medicinal chemistry programs represents a recurring challenge within the pharmaceutical industry. In an attempt to address this problem and reduce costs by improving throughput, high-throughput screening (HTS) approaches have been widely adopted within the industry.[1] This has served to focus attention on the need to develop high-throughput chemistries (HTC) that are able to both supply large numbers of new compounds to drive these primary screens and facilitate the rapid preparation of focused compound sets required for subsequent lead optimization.

Solid-phase synthesis techniques continue to be widely exploited for the preparation of large compound libraries.[2] This strategy has been further enhanced by the incorporation of automated compound synthesis and processing protocols.[3] However, in many cases, difficulty in monitoring solid-phase chemistries, the inability to purify resin-bound intermediates, and protracted chemistry development times have focused attention on the need to develop complementary solution-phase strategies for HTC.[4]

Toward this goal, polymer-assisted solution phase (PASP) synthesis has emerged as an important enabling technique and has been demonstrated to facilitate the preparation of a wide variety of chemotypes.[5] Moreover, because this approach exploits a repetitive cycle of filtration and incubation steps, it is particularly well-suited to automation. The appeal of this strategy is further enhanced by the ability to incorporate in-line purification protocols such as reagent and byproduct scavenging,[6] and catch-and-release[7] protocols. This introduces the possibility for the direct high-throughput synthesis of compounds with intrinsically high purities that are suitable for immediate biological screening without the need for further purification, thereby bypassing the chromatographic bottleneck.

We have initiated a program to develop automated PASP protocols for reactions that are commonly exploited within medicinal chemistry. By combining such procedures on the same robotic synthesizer, it is possible to perform highly automated multistep syntheses that, once initiated, require minimal end-user intervention.

Benzimidazoles[8] and related heterocyclics represent chemotypes that are often targeted in drug discovery programs and have well-precedented biological activities, such as the modulation of ion channels[9a−c] and antiviral[9d] and antihistamine activity.[9e] Recently, we have reported an automated polymer-assisted synthesis of benzimidazolinones and 2-alkylthiobenzimidazoles.[10] However, this synthesis was performed in a *stepwise* manner, was limited in regard to throughput, and required a considerable amount of end-user intervention to implement. To address these shortcomings, we now describe in detail a further development of this work which has culminated in a more efficient, fully automated, *multistep* PASP approach. Individual synthesis steps are integrated on a single synthesis robot that is able to perform multiple steps in an unattended manner and thereby maximize the advantages inherent in the use of polymer-supported reagents (Scheme 1).

To enable reliable, fully automated multistep synthesis, a key objective is to reduce operational complexity. We have previously established that this may be achieved in practice through the combination of PASP synthesis techniques with a top-filtration robot equipped with high-speed vortexers to ensure efficient mixing of the resin suspensions.[11] In this way, aqueous workups can be avoided and in-line purification protocols incorporated to simplify the work process and thereby largely eliminate the need for intermediate manual

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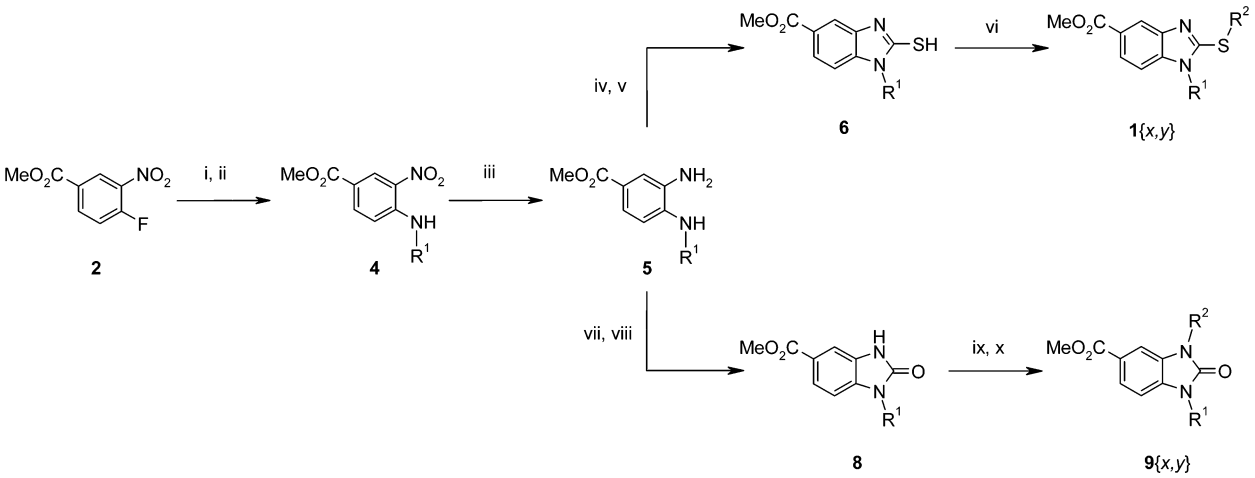
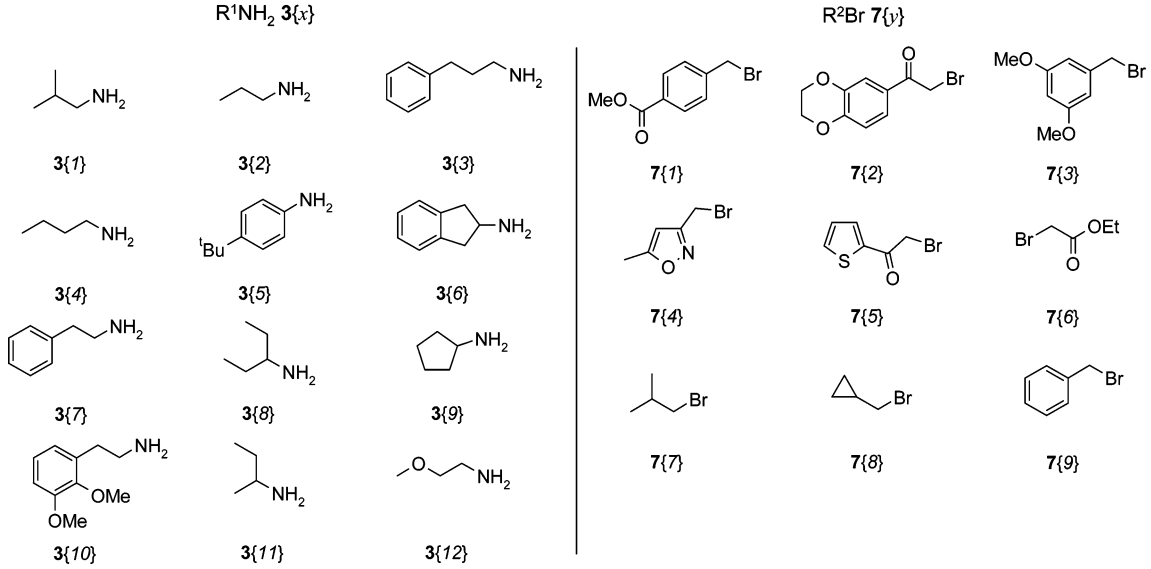
10.1021/cc049832+ CCC: $30.25
Published on Web 02/26/2005

Scheme 1[a]



[a] Reagents and conditions are as follows: (i) R^1NH_2 **3**{*x*}, dimethylformamide (DMF), room temperature (rt); (ii) PS-trisamine, DMF, 50 °C; (iii) H_2(*g*), $Pd(OH)_2$, DMF; (iv) Im_2CS, DMF, rt; (v) Amberlyst H-15, DMF, rt; (vi) R^2Br **7**{*y*}, PS−BEMP, DMF, rt; (vii) triphosgene, $CHCl_3$, rt; (viii) PS-trisamine, $CHCl_3$, 30 °C; (ix) R^2Br **7**{*y*}, PS−BEMP, DMF, $CHCl_3$; and (x) PS-methylthiourea, DMF, $CHCl_3$, 50 °C.

Chart 1. Sets of Amine 3{*x*} and Electrophilic Building Blocks 7{*y*}



intervention. This approach is particularly suitable for the synthesis of compound sets containing 20−200 members, which is a size typically associated with focused library generation. In this study, we target the preparation of 96-member libraries compatible with the use of microtitre plate sample formats.

Results and Discussion

It is important when planning automated syntheses that the synthetic procedures are chosen and optimized with due regard to the capabilities and characteristics (tube sizes, reaction block formats, etc.) of the synthesizer to be used. For this reason, it is helpful to represent the synthesis in the form of a flowchart in which each successive synthesis operation is shown. Moreover, we have found that it is preferable to rehearse chemistries on the robot from the outset, to develop robust protocols in the shortest time. All of the following automated transformations were performed using a Sophas synthesizer,[12] following procedures adapted from our earlier studies. Initially, the chemistry sequence was developed and exemplified by the preparation of a representative 2-alkylthiobenzimidazole **1**{*1,9*} and the corresponding *N,N*′-dialkylbenzimidazolin-2-one **9**{*1,9*}. The individual transformations were each optimized on the robotic synthesizer and then combined to constitute the final multistep flow-through synthesis. In this case, samples of intermediates were fully characterized, to validate the protocols thoroughly. Subsequently, however, the automated library syntheses were performed without isolation or characterization of intermediates. Having developed appropriate synthetic routes, a set of small trial arrays ("rehearsals") were prepared to establish that each of the chosen building blocks performed acceptably under the reaction conditions chosen, before the full combinatorial library syntheses were initiated.

Preparation of Trial Library Compounds 1{*1,9*} and 9{*1,9*}. Our approach to the 2-alkylthiobenzimidazole library **1**{*x,y*}, incorporating two points of diversity derived from a set of amine building blocks **3**{*x*} and a set of electrophilic building blocks **7**{*y*}, respectively (Chart 1), is shown in

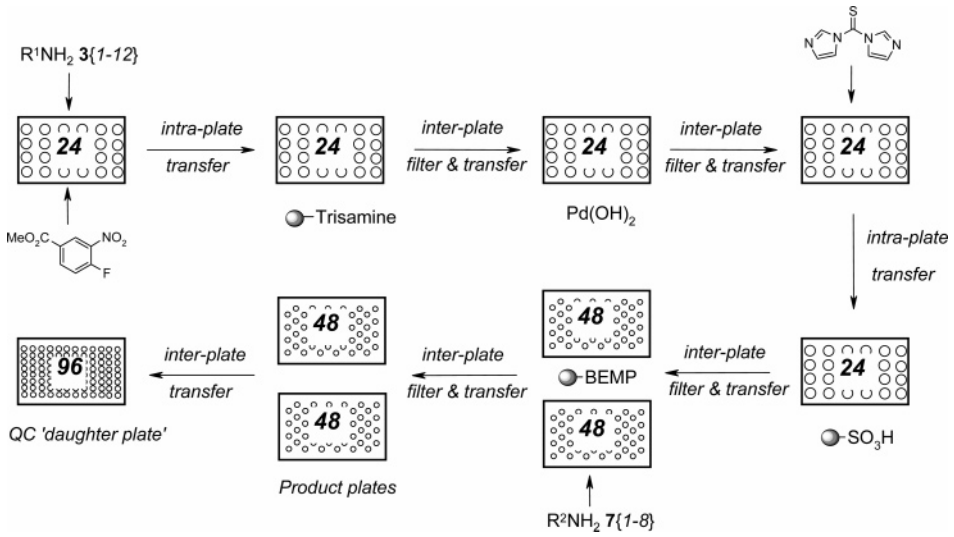


Figure 1. Automated 2-alkylthiobenzimidazole library **1**{*x,y*} synthesis flowchart.

Scheme 1, and the corresponding flowchart is represented in Figure 1. The preparation of the representative example **1**{*1,9*} commences with the S_NAr reaction between a slight excess of methyl 4-fluoro-3-nitrobenzoate (1.1 equiv) and the trial amine **3**{*1*} to afford the nitroaniline **4**{*1*} and was observed to proceed efficiently at ambient temperature in dimethylformamide (DMF).

Although this reaction can be performed satisfactorily in a range of solvents (e.g., $CHCl_3$, EtOH, ^{i}PrOH), DMF was selected as the solvent of choice, to ensure that all intermediates remained in solution throughout the entire synthesis and thereby minimized the risk of blockages in the liquid handling robot. In addition, it is desirable to identify a common solvent in which all the steps in a multistep synthesis can be performed to obviate the need to introduce solvent exchanges protocols. Following scavenging of excess **2** with a polystyrene-supported amino-resin (PS-trisamine,[13] 4.1 mmol/g), the nitroaniline **4**{*1*} was isolated in both high yield (87%) and purity (>98%; ^{1}H NMR). We determined, using a 2-fold excess of PS-trisamine (0.2 equiv.), that the scavenging reaction did not proceed to completion, even at 50 °C. However, the use of a 5-fold excess of the resin (0.5 equiv) ensured that complete scavenging was achieved within 10 h. This in-line scavenging protocol was most conveniently performed by automated transfer of the reaction solutions to separate tubes pre-loaded with PS-trisamine resin within the same 24-position reaction block.

Reduction of the 2-nitroaniline **4**{*1*} to the corresponding *o*-phenylenediamine **5**{*1*} proved to be more problematic. Various combinations of PS-borohydride, and nickel(II) or copper(II) salts, and alternative reductants such as sodium dithionite were evaluated; however, it was not possible to identify a PASP protocol that achieved complete reduction with the desired reproducibility. Catalytic hydrogenolysis, on the other hand, proved to be very reliable, was compatible with DMF as a solvent, and required only a straightforward filtration to isolate the diamine product **5**{*1*}. However, for safety reasons, it was not possible to perform this step on the robot. Therefore, parallel hydrogenolysis was performed by transferring the reaction block to a Greenhouse reactor[14] and carefully purging this with hydrogen. After removal of the palladium hydroxide ($Pd(OH)_2$) catalyst by filtration, the phenylenediamine **5**{*1*} was isolated in 88% yield and excellent purity (>98%; ^{1}H NMR).

The *o*-phenylenediamine **5**{*1*} was converted to the corresponding thiobenzimidazole **6**{*1*} following incubation with a solution of 1,1′-thiocarbonyldiimidazole in DMF at ambient temperature. The resulting reaction solution was automatically transferred to a second tube within the same reaction block containing an excess of the strongly acidic ion-exchange resin Amberlyst H-15 to scavenge any imidazole-containing byproducts. In this way, the thiobenzimidazole **6**{*1*} was obtained in 89% yield and excellent purity (>98%; ^{1}H NMR).

At this stage, the second diversity element was introduced by *S*-alkylation. The observation that acidic heterocycles such as **6**{*1*} are efficiently "captured" by the polystyrene-supported phosphazene base (PS−BEMP) and subsequently undergo an efficient alkylative "release" upon exposure to alkylating agents presented an opportunity for a final in-line purification step.[15] Thus, the thiobenzimidazole **6**{*1*} was briefly incubated with PS−BEMP (2.5 equiv) at ambient temperature for 10 min in DMF before a substoichiometric quantity of benzyl bromide **7**{*9*} (0.8 equiv) was introduced. The resulting suspension was vortexed for 10 h before the supernatant solution was automatically separated by top-filtration and then concentrated to afford the 2-alkylthiobenzimidazole **1**{*1,9*} in 67% overall yield and 98% purity (^{1}H NMR), without the need for any further purification (Table 1).

N,N′-Dialkylbenzimidazolin-2-ones **9**{*x,y*} are complementary to 2-alkylthiobenzimidazoles **1**{*x,y*}, in that they can be constructed using similar chemistry and incorporate the same sets of building blocks. However, they are subtly different in that they present side-chain functionalities with different spatial orientations. Our approach to the benzimidazolin-2-one library **9**{*x,y*} is shown in Scheme 1 and utilizes the same *o*-phenylenediamine intermediates **4**{*x*} as those utilized in the 2-alkylthiobenzimidazole synthesis. The trial example **9**{*1,9*} was prepared starting with the phenylenediamine **5**{*1*}, which, upon exposure to triphosgene, was efficiently converted to the benzimidazolone **8**{*1*}. In

Table 1. Isolated Yield and Purity Data for Trial Validation Compounds

compound	yield (%)	purity (%)[a]
	S-Alkylated Series	
4{*1*}	87	>98
5{*1*}	88	>98
6{*1*}	89	>98
1{*1,9*}	98	98
	N-Alkylated Series	
4{*1*}	87	>98
5{*1*}	81	>98
8{*1*}	80	98
9{*1,9*}	83	>98

[a] Purities were determined by ^{1}H NMR and LC/MS (220−330 nm).

this case, other phosgene equivalents (such as 1,1′-carbonyldiimidazole, diethyl carbonate, and bis-(4-nitrophenyl)-carbonate) were determined to be less satisfactory, leading to impure products, with evidence for byproducts resulting from dimerization of the starting *o*-phenylenediamine. However, triphosgene is incompatible with DMF as the reaction solvent. The pragmatic solution was to perform a parallel evaporation after the catalytic hydrogenolysis and change the solvent to chloroform. Chlorinated solvents also ensure good resin swelling, and this helps to ensure efficient quenching of excess triphosgene, following automated intrablock transfer of the reaction solutions to tubes containing PS-trisamine. In this way, the trial compound **8**{*1*} was obtained in 80% yield and >98% purity.

At this stage, the introduction of the second diversity element was investigated, again using benzyl bromide as a representative alkylating agent and PS−BEMP as the polymer-supported base in chloroform. However, in this case, we found that it was not possible to utilize a catch-and-release strategy to effect an in-line product purification. We determined that deprotonation of the benzimidazolin-2-one intermediates **8**{*1*} with PS−BEMP did not form a sufficiently stable immobilized ionic complex to ensure efficient scavenging of any unalkylated benzimidazolin-2-one. This was also found to be the case using DMF as the solvent. Therefore, an alternative strategy was invoked whereby the alkylating agent was used in excess (1.5 equiv) and the crude reaction solutions were separated by automated top-filtration and transferred to new tubes containing PS-thiourea[16] (2.9 mmol/g) to scavenge any unreacted electrophiles. This procedure afforded the trial compound **9**{*1,9*} in 83% yield and >98% purity. The ^{1}H NMR spectra of the trial library members **1**{*1,9*} and **9**{*1,9*} are shown in Figure 2.

Building Block Rehearsal Studies. Prior to committing to a full combinatorial library synthesis, it is advantageous to "rehearse" the building blocks chosen, to establish that they are compatible with—and have sufficient reactivities under—the generic reaction conditions adopted. In this way, the potential for failure, or the isolation of large numbers of compounds with low purities is reduced. Using the previously determined conditions, the S_NAr reaction between the amine set **3**{*1−12*} and methyl 4-fluoro-3-nitrobenzoate **2** was performed in a 24-position block on the top-filtration synthesizer. Following an intrablock transfer, a PS-trisamine scavenge was then performed to remove the slight excess of **2** that was used. In DMF as the solvent, no insolubility difficulties were encountered and all the nitroanilines **4**{*1−12*} were isolated in >98% purity (LC/MS) (Figure 3a). A similar exercise was performed for the set of alkylating agents **7**{*1−8*}. The automated, parallel *S*-alkylation of the representative thiobenzimidazole **6**{*2*} with each alkylating agent **7**{*1−8*} in the presence of PS−BEMP afforded an array of 2-alkylthiobenzimidazoles **1**{*2,1−8*} with purities of 62−96% (see Figure 3b) (LC/MS). Although it is desirable for all products to have purities of >80%, a limited number of products with lower purities (50−80%) that may subsequently be purified by reverse-phase HPLC (RP-HPLC) are acceptable.

However, a different purity profile was obtained when the *N*-alkylation of the corresponding representative benzimidazolin-2-one **8**{*2*} was rehearsed (Figure 4). In this case, two building blocks **7**{*7*} and **7**{*8*} failed to deliver a product that met our minimum purity criteria (>50% purity, according to LC/MS).

Given that both of these building blocks are very volatile, we suspected that evaporation might be responsible for the poor yields and purities of these adducts, although the building block solutions were stored on the robot in septum-protected vials and the *N*-alkylation step was performed in a closed reaction block with excess alkylating agent. However, when these alkylations were repeated in closed reaction vessels away from the synthesizer, even using a

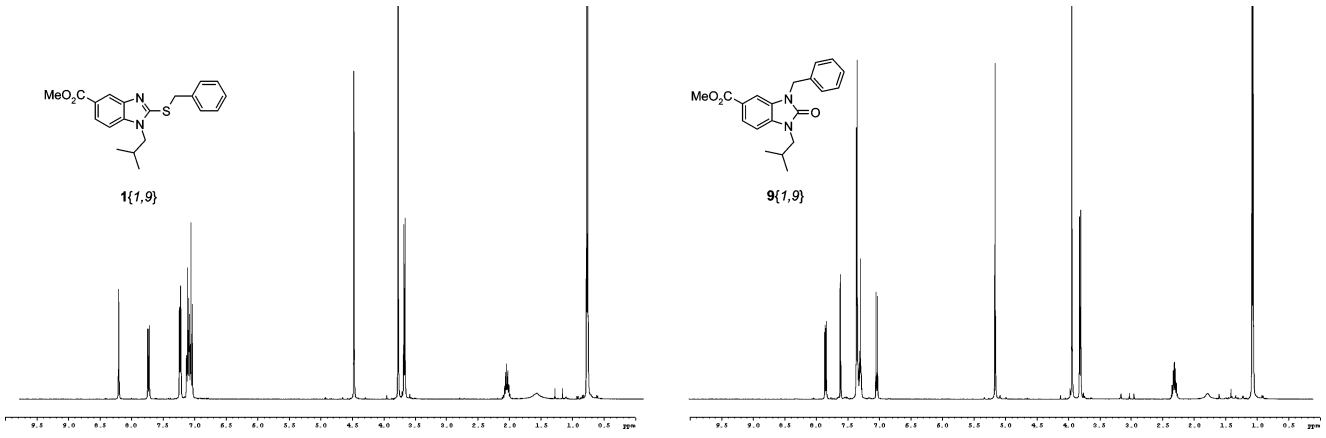


Figure 2. ^{1}H NMR spectra of trial library compounds **1**{*1,9*} and **9**{*1,9*}.

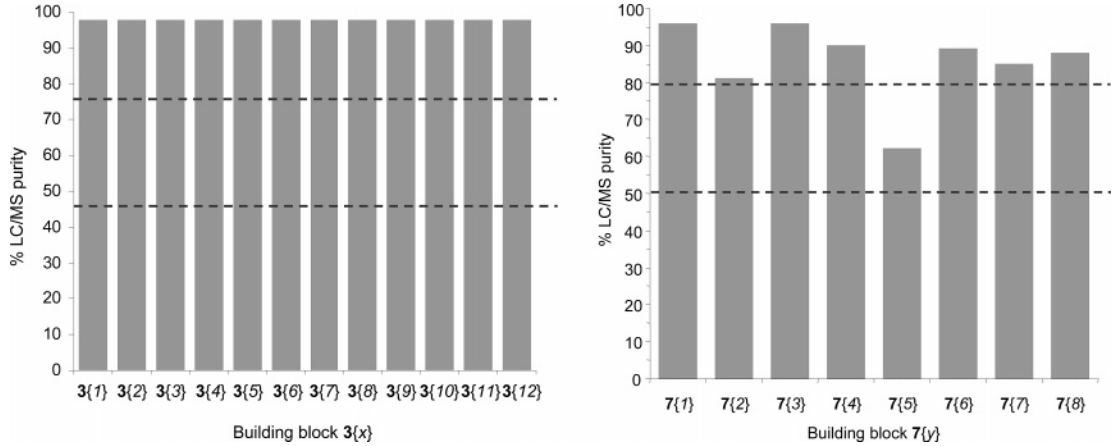


Figure 3. (a). Building block set **3**{*x*} rehearsal targeting the representative 2-nitroaniline library intermediates **4**{*x*}. (b). Building block set **7**{*y*} rehearsal targeting the representative 2-alkylthiobenzimidazoline library members **1**{*2,y*}. Dotted lines show 50% and 80% purity thresholds.

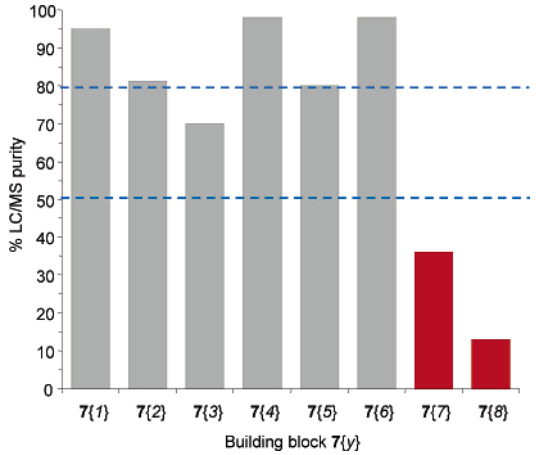


Figure 4. Building block set **7**{*y*} rehearsal targeting the representative *N,N*′-dialkylbenzimidazolin-2-one library members **9**{*2,y*}. Building blocks highlighted in red failed to give products of acceptable purities. Dotted lines show 50% and 80% purity thresholds.

4-fold excess of building blocks **7**{*7*} and **7**{*8*}, an almost identical product purity/yield profile was observed. Importantly, therefore, the poor performance of these particular alkylating agents does not appear to be directly attributable to the use of automation. On this basis, building blocks **7**{*7*} and **7**{*8*} were not used in the preparation of the benzimidazolin-2-one library **9**{*x,y*}.

Preparation of 96-Member 2-Alkylthiobenzimidazole Library 1{*1−12,1−8*} and the 72-Member *N,N*′-Dialkylbenzimidazolin-2-one Library 9{*1−12,1−6*}. The libraries were prepared using the Sophas top-filtration synthesizer, using the reaction conditions developed for the synthesis of the trial compounds **1**{*1,9*} and **9**{*1,9*}. The process is outlined for the 96-member 2-alkylthiobenzimidazole library in Figure 1. The process for the corresponding *N,N*′-dialkylbenzimidazolin-2-one differed only in the addition of a final interplate transfer to allow the final PS-thiourea scavenge of excess alkylating agent. Details of the programs used are given in the Experimental Section.

Although the combinatorial synthesis described is divergent, after incorporation of the set of amine building blocks **3**{*x*}, a linear sequence with several filtration and associated wash steps follows. To avoid excessive dilution of the reaction mixtures, it is important to minimize the volumes of the wash solvents used at each stage. Importantly, the potential for the loss of material through inefficient resin washing can be significantly reduced by the incorporation of thorough vortex mixing in each resin wash step.

Given that the synthesizer can only accommodate a finite number of reaction blocks, to increase throughput, the use of 96-position reaction blocks throughout the library synthesis is desirable, particularly following incorporation of the final set of building blocks. However, we have found that, generally, this is outweighed by the more efficient vortex mixing of the resin suspensions that can be achieved using the larger volume reaction tubes associated with 48-position reaction blocks. However, aliquots of the final product solutions were transferred and diluted in a 96-well microtitre plate in situ to constitute a "daughter plate" and thereby facilitate off-line LC/MS analysis of the library products.

For the 96-member 2-alkylthiobenzimidazole library **1**{*1−12,1−8*}, as shown in Figures 5a and b, 77 of the 96 library members (80%) were obtained in >80% purity (LC/MS). ^{1}H NMR analysis of selected examples confirmed the LC/MS purity profile and established that only *S*-alkylation had occurred. The average isolated yield was 72%, based on the use of a limiting quantity of alkylation in the *S*-alkylation step.

For the 72-member *N,N*′-dialkylbenzimidazolin-2-one library **9**{*1−12,1−6*}, 58 of the 72 desired compounds (81%) were obtained in >80% purity, according to LC/MS (Figures 6a and b). This was again substantiated by ^{1}H NMR analysis of 20 selected samples, which also confirmed that only *N*-alkylation was obtained in this case. The average isolated yield was 57%.

In both cases, compounds falling below the 80% purity threshold, but with >50% LC/MS purities, were further purified by single-pass autopreparative RP-HPLC to afford additional samples for biological screening.

Conclusions

In conclusion, we have described highly automated multistep polymer-assisted solution phase (PASP) protocols for the synthesis of 2-alkylthiobenzimidazoles and *N,N*′-dialkyl-

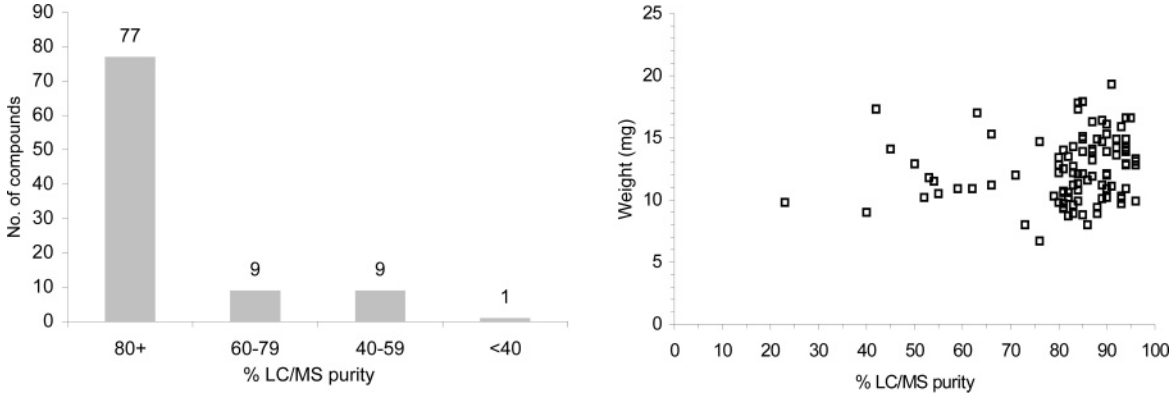


Figure 5. (a) LC/MS purity profile plot for the 2-alkylthiobenzimidazole library **1**{*1*−*12*,*1*−*8*}. (b) Representation of isolated yield plotted against liquid chromatography−mass spectroscopy (LC/MS) purity for the 2-alkylthiobenzimidazoline library **1**{*1*−*12*,*1*−*8*}.

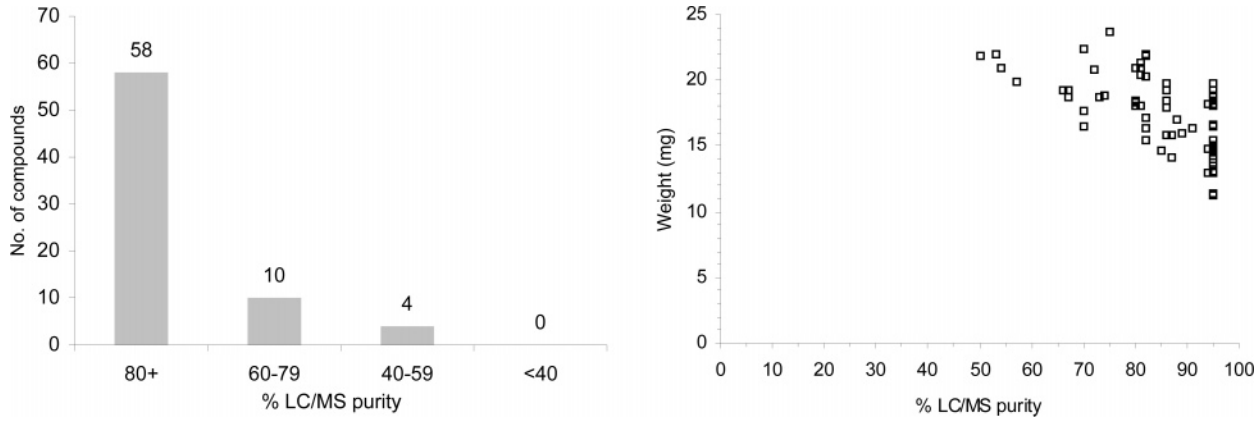


Figure 6. (a) LC/MS purity profile plot for the *N*,*N*′-dialkylbenzimidazolin-2-one library **9**{*1*−*12*,*1*−*6*}. (b) Representation of isolated yield plotted against LC/MS purity for the *N*,*N*′-dialkylbenzimidazolin-2-one library **9**{*1*−*12*,*1*−*6*}.

benzimidazolin-2-ones. These methods have been exemplified by the preparation of a 96-member 2-alkylthiobenzimidazole library **1**{*1*−*12*,*1*−*8*} and a 72-member *N*,*N*′-dialkylbenzimidazolin-2-one library **9**{*1*−*12*,*1*−*6*}, using a single Sophas top-filtration robotic synthesizer that required minimal manual intervention. Building block rehearsals were performed in both cases to establish that the monomers selected were likely to afford library compounds in acceptable yields and purities. In this way, ≥80% of all library members were obtained with ≥80% LC/MS purities and these compounds required no additional purification, prior to primary biological evaluation.

Further studies are ongoing in our laboratory, with the objective of developing fully automated multistep PASP protocols for the preparation of other chemotypes that incorporate in-line purification techniques and thereby avoid the need for routine RP-HPLC purification of the resulting library products.

Experimental Section

General Information. All solvents and reagents were used as supplied, unless noted otherwise. Polymer-supported reagents and scavenger resins were obtained from either Argonaut Technologies or Novabiochem, as appropriate. Analytical high-pressure liquid chromatography (HPLC) was performed under the following conditions: column, Supelcosil ABZ$^+$PLUS 3.3 cm × 4.6 mm, 3 μm; eluent A, water, 0.1% TFA; eluent B, 95% acetonitrile, 5% water, 0.05% TFA; flow rate, 1 mL/min; detection mode, ultraviolet (UV) (diode array: 215, 230, 254 nm); method, gradient 10−95% B in A over 7 min. Retention times (t_R) are reported in terms of minutes at the specified wavelength. Infrared spectra were collected on a Fourier transform infrared (FT-IR) spectroscopy instrument under attenuated total reflectance (ATR). Liquid chromatography−mass spectra (LC/MS) were recorded under electrospray positive and negative ionization, at the following HPLC conditions: column, Supelcosil ABZ$^+$PLUS 3.3 cm × 4.6 mm, 3 μm; eluent A, 10 mM solution of ammonium acetate in water, 0.1% formic acid; eluent B, 95% acetonitrile, 5% water, 0.05% formic acid; flow rate, 3 mL/min; detection mode, UV (diode array: 220−330 nm); method, gradient 0−100% B in A over 3.5 min. High-resolution mass spectra were obtained in either positive or negative electrospray (ESI) ionization mode, using a time-of-flight spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded at 400 and 500 MHz, respectively, for ^{1}H NMR, and at 100, 125, or 175 MHz for ^{13}C NMR (proton decoupled) in the indicated solvent. Chemical shifts (δ) are reported in parts per million (ppm), and the following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, and br = broad. The coupling constant *J*-values are quoted in units of hertz (Hz).

Library Rehearsal of 2-Alkylthiobenzimidazole 1{***x*,*y***}** **Synthesis.** Note: With the exception of catalytic hydrogenolysis, all the following procedures were performed using

a Sophas top-filtration robotic synthesizer to perform all liquid handling and vortexing operations.

Step 1: Synthesis of Nitroaniline ***4****{1}*. A solution of methyl 4-fluoro-3-nitrobenzoate (**2**) (3.5 mL of 0.4 M solution in DMF, 1.3 mmol) was dispensed into an 8-mL vessel in a 24-well reactor block. Isobutylamine (120 μL, 1.2 mmol) was then added to the vessel. The reaction mixture was vortexed at 30 °C for 10 h then transferred by top-filtration to an 8-mL reaction vessel containing PS-trisamine (240 mg, 1.0 mmol). The resin suspensions were heated to 50 °C and vortexed for 18 h. The product solution was then transferred into a new vial, and the solvent was evaporated in vacuo to yield **4**{*1*} as an orange solid (262 mg, 87%). IR ν_{MAX}(cm^{-1}): 3370, 2960, 1712, 1628, 1617; HRMS $C_{12}H_{16}N_2O_4$ requires $(MH)^+$ 253.1180, found 253.1179; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.88 (d, $J = 2$, 1H), 8.45 (brs, 1H), 8.03 (dd, $J = 9$, 2, 1H), 6.85 (d, $J = 9$, 1H), 3.98 (s, 3H), 3.18 (t, $J = 6$, 2H), 2.02 (m, 1H), 1.06 (d, $J = 7$, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 165.7, 147.9, 136.3, 131.1, 129.6, 116.9, 113.5, 52.1, 50.8, 27.9, 20.3. LC/MS: (ESI +ve) *m/z* $(MH)^+$ 253, $t_R = 3.23$ min; HPLC: $t_R = 5.93$ min (>98%; 254 nm).

Step 2: Synthesis of o-Phenylenediamine ***5****{1}*. To a solution of the nitrobenzene **4**{*1*} (150 mg, 0.60 mmol) in DMF (8 mL) was added $Pd(OH)_2$ (20 mg) under an inert atmosphere of nitrogen. The reaction mixture was then placed under a hydrogen atmosphere with stirring for 18 h, during which time the bright yellow color disappeared. The $Pd(OH)_2$ was then removed by filtration and the filtrate was concentrated in vacuo to yield **5**{*1*} as an air-sensitive purple gum (127 mg, 95%). IR ν_{MAX}(cm^{-1}): 3398, 2955, 1688, 1598; HRMS $C_{12}H_{18}N_2O_2$ requires $(MH)^+$ 223.1441, found 223.1440; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58 (dd, $J = 9$, 2, 1H), 7.40 (d, $J = 2$, 1H), 6.57 (d, $J = 9$, 1H), 3.83 (s, 3H), 3.50 (brs, 2H), 2.98 (d, $J = 7$, 2H), 1.93 (m, 1H), 1.01 (d, $J = 7$, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.5, 143.4, 131.7, 124.5, 118.4 (×2), 109.2, 51.6, 51.4, 28.1, 20.5; LC/MS: (ESI +ve) *m/z* 223 $(MH)^+$.

Step 3: Synthesis of 2-Thiobenzimidazole ***6****{1}*. To the *o*-phenylenediamine **5**{*1*} (133 mg, 0.60 mmol) in DMF (2 mL) was added thiocarbonyldiimidazole (1 mL of a 0.72 M solution in DMF). The reaction mixture was vortexed for 10 h at room temperature and then transferred to a new reaction vessel and incubated with Amberlyst H-15 (500 mg) for an additional 10 h. The resin was then drained, the filtrate collected, and the solvent removed in vacuo to yield the 2-thiobenzimidazole **6**{*1*} as a dark solid (141 mg, 89%). IR ν_{MAX}(cm^{-1}): 3230, 2954, 1716, 1691; HRMS $C_{13}H_{16}N_2O_2S$ requires $(MH)^+$ 265.1011, found 265.1008; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.65 (s, 1H), 7.94 (m, 2H), 7.18 (d, $J = 9$, 1H), 4.10 (d, $J = 7$, 2H), 3.93 (s, 3H), 2.45 (m, 1H), 1.00 (d, $J = 7$, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 171.1, 166.6, 136.7, 129.8, 125.2, 111.0, 109.0, 52.3, 51.8, 27.8, 20.2; LC/MS: (ESI +ve) *m/z* 265 $(MH)^+$, $t_R = 3.24$ min; HPLC: $t_R = 5.30$ min (>98%; 254 nm).

Step 4: Synthesis of 2-Alkylthiobenzimidazole ***1****{1,9}*. The 2-thiobenzimidazole **6**{*1*} (13.3 mg, 50 μmol) was dissolved in DMF (0.9 mL). This solution was dispensed into a reaction vessel containing PS−BEMP (65 mg, 150 μmol). The reaction mixture was vortexed for 10 min before a limiting solution of the alkylating agent **7**{*9*} (300 μL of 0.14 M solution in DMF, 42 μmol) was added to the reaction vessel. The reaction mixture was then vortexed for an additional 10 h before the resin was drained and washed. The combined organic washings were evaporated in vacuo to afford the 2-alkylthiobenzimidazole **1**{*1,9*} as a pale pink gum (14.8 mg, 99%). IR ν_{MAX}(cm^{-1}): 2959, 1709, 1432, 1281; HRMS $C_{20}H_{22}N_2O_2S$ requires $(MH)^+$ 355.1480, found 355.1480; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (d, $J = 2$, 1H) 7.92 (dd, $J = 9$, 2, 1H), 7.42 (m, 1H), 7.32−7.22 (m, 5H), 4.63 (s, 2H), 3.93 (s, 3H), 3.83 (d, $J = 8$, 2H), 2.20 (m, 1H), 0.90 (d, $J = 7$, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 167.7, 154.1, 143.0, 139.8, 136.4, 129.1, 128.7, 127.7, 123.9, 123.5, 120.4, 108.7, 52.0, 51.7, 37.2, 29.0, 20.1; LC/MS: (ESI +ve) *m/z* 355 $(MH)^+$, $t_R = 3.75$ min; HPLC: $t_R = 5.89$ min (>98%; 254 nm).

Preparation of 2-Alkylthiobenzimidazole Array 1{*1−12,1−8*}: General Automated Procedure for the 96-Membered Library. *Step 1.* Dispense solutions of methyl 4-fluoro-3-nitrobenzoate **2** (3.5 mL of 0.4 M solution in DMF, 1.3 mmol) and an amine **3**{*1−12*} (1.2 mmol) into 12 8-mL reaction vessels in a 24-position reactor block.

Step 2. Vortex reaction block at 30 °C for 10 h.

Step 3. Perform intrablock transfer of each of the reaction mixtures into new 8-mL reaction vessels containing PS-trisamine (240 mg, 1.0 mmol).

Step 4. Vortex reaction vessels at 50 °C for 18 h.

Step 5. Allow reaction block to cool, then drain resins and wash with DMF (0.5 mL) into new 8-mL vials.

Step 6. Remove reaction block from synthesizer and place it in a Greenhouse reactor block. Add $Pd(OH)_2$ catalyst (20 mg) to each reaction vessel under a nitrogen atmosphere. Purge with hydrogen and stir reactions vigorously at ambient temperature for 18 h.

Step 7. Remove reaction block from Greenhouse. Filter suspensions, to remove catalyst, directly into new 8-mL reaction vessels. Wash with DMF (0.5 mL) and add to filtrates. Replace reaction block on synthesizer.

Step 8. Dispense solution of thiocarbonyldiimidazole (1 mL of 0.8 M solution in DMF, 0.8 mmol) into each of the 12 reaction vessels containing the *o*-phenylenediamines **5**{*1−12*}.

Step 9. Vortex reaction block at 25 °C for 10 h.

Step 10. Perform intrablock transfer of each reaction mixture into new 8-mL reaction vessels containing Amberlyst H-15 resin (500 mg).

Step 11. Vortex reaction block at 25 °C for 10 h.

Step 12. Partition each of the 12 reaction mixtures equally into 8 new reaction vessels (2 × 48 position reactor blocks) containing PS−BEMP (65 mg, 150 μmol).

Step 13. Dilute each reaction vessel with DMF (0.5 mL).

Step 14. Vortex reaction block at 25 °C for 15 min.

Step 15. Dispense solutions of alkylating agents **7**{*1−8*} (300 μL of 0.14 M solution in DMF, 42 μmol, 0.83 equiv) to appropriate reaction vessels.

Step 16. Vortex reaction blocks at 25 °C for 10 h.

Step 17. Drain resins and wash with DMF (0.5 mL) into new vials (2 × 48 blocks).

Step 18. Prepare QC plate; dispense aliquots (60 μL) into 96 well microtitre plate and dilute each well with MeCN (0.9 mL).

Step 19. Remove solvent from bulk samples by parallel centrifugal evaporation in vacuo to afford 2-alkylthiobenzimidazoles **1**{*1*−*12*,*1*−*8*}.

Full characterization for 20 representative examples from the 2-alkylthiobenzimidazole **1**{*1*−*12*,*1*−*8*} array follows; LC/MS data for all 96 members of this array are included in the Supporting Information. Note: Compounds with crude purities <80% were purified by RP-HPLC and, in these cases, yields and purities for the purified samples are given below.

Characterization of Compound 1{*1,8*}. Brown gum (9.3 mg, 70%). IR ν_{MAX}(cm^{-1}): 2960, 1714, 1434, 1298; HRMS $C_{17}H_{22}N_2O_2S$ requires (MH)$^+$ 319.1480, found 319.1472; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.36 (d, J = 2, 1H), 7.91 (dd, J = 9, 2, 1H), 7.23 (d, J = 9, 1H), 3.91 (m, 5H), 3.35 (d, J = 8, 2H), 2.27 (m, 1H), 1.23 (m, 1H), 0.96 (d, J = 7, 6H), 0.63 (m, 2H), 0.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.7, 154.9, 143.0, 139.8, 123.7, 123.3, 120.2, 108.5, 52.0, 51.7, 38.8, 29.0, 20.2, 10.5, 6.0; LC/MS: (ESI +ve) m/z 319 (MH)$^+$, t_R = 3.44 min (81%).

Characterization of Compound 1{*2,2*}. Brown gum (10.6 mg, 59%). IR ν_{MAX}(cm^{-1}): 2958, 1711, 1432, 1288; HRMS $C_{22}H_{22}N_2O_5S$ requires (MH)$^+$ 427.1328, found 427.1339; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (d, J = 2, 1H), 8.02 (dd, J = 9, 2, 1H), 7.63 (m, 2H), 7.33 (d, J = 9, 1H), 6.94 (d, J = 8, 1H), 5.12 (s, 3H), 4.30 (m, 4H), 4.18 (t, J = 7, 2H), 3.94 (s, 3H), 1.92 (m, 2H), 1.01 (t, J = 7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 190.9, 167.0, 153.4, 149.1, 143.6, 139.6, 138.0, 128.6, 125.4, 124.8, 123.1, 119.3, 118.0, 117.6, 109.0, 64.7, 64.0, 52.3, 46.6, 42.0, 22.6, 11.3; LC/MS: (ESI +ve) m/z 427 (MH)$^+$, t_R = 3.32 min (81%).

Characterization of Compound 1{*2,4*}. Brown gum (12.0 mg, 83%). IR ν_{MAX}(cm^{-1}): 2965, 1714, 1435, 1300; HRMS $C_{17}H_{19}N_3O_3S$ requires (MH)$^+$ 346.1225, found 346.1223; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.48 (d, J = 2, 1H), 8.11 (dd, J = 9, 2, 1H), 7.42 (d, J = 9, 1H), 6.08 (s, 1H), 4.73 (s, 2H), 4.20 (t, J = 7, 2H), 3.95 (s, 3H), 2.37 (s, 3H), 1.88 (m, 2H), 0.9 (t, J = 7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 170.8, 166.6, 159.0, 152.3, 137.4, 137.0, 126.6, 125.9, 118.7, 109.7, 101.8, 52.5, 47.0, 27.8, 22.6, 12.3, 11.2; LC/MS: (ESI +ve) m/z 346 (MH)$^+$, t_R = 3.05 min (90%).

Characterization of Compound 1{*3,2*}. Off-white solid (7.8 mg, 37%) (following purification by RP-HPLC). IR ν_{MAX}(cm^{-1}): 2950, 1712, 1672, 1433, 1287; HRMS $C_{28}H_{26}N_2O_5S$ requires (MH)$^+$ 503.1641, found 503.1640; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.41 (d, J = 2, 1H), 7.96 (dd, J = 9, 2, 1H), 7.65−7.60 (m, 2H), 7.33−7.13 (m, 6H), 6.94 (d, J = 8, 1H), 5.08 (s, 2H), 4.34−4.26 (m, 4H), 4.20 (t, J = 7, 2H), 3.93 (s, 3H), 2.73 (t, J = 7, 2H), 2.20 (quin, J = 7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 191.0, 1672, 153.2, 149.0, 143.6, 140.5, 139.9, 138.3, 128.7, 128.2, 126.5, 125.1, 124.6, 123.0, 119.6, 118.0, 117.5, 108.7, 64.7, 64.0, 52.2, 44.3, 41.7, 32.8, 30.3; LC/MS: (ESI +ve) m/z 503 (MH)$^+$, t_R = 3.60 min; HPLC: t_R = 6.15 min (>99%; 254 nm).

Characterization of Compound 1{*4,3*}. Brown gum (12.8 mg, 74%). IR ν_{MAX}(cm^{-1}): 2957, 1711, 1595, 1429, 1296, 1283, 1148; HRMS $C_{22}H_{26}N_2O_4S$ requires (MH)$^+$ 415.1692, found 415.1695; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (d, J = 2, 1H), 7.98 (dd, J = 9, 2, 1H), 7.29 (d, J = 9, 1H), 6.55 (d, J = 2, 2H), 6.30 (t, J = 2, 1H), 4.59 (s, 2H), 4.06 (t, J = 7, 2H), 3.94 (s, 3H), 3.72 (s, 6H), 1.72 (m, 2H), 1.32 (m, 2H), 0.92 (t, J = 7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.2, 160.9, 153.3, 140.9, 138.3, 138.0, 124.8, 124.4, 119.7, 108.8, 107.0, 100.1, 55.3, 52.1, 44.5, 37.6, 31.2, 20.0, 13.5; LC/MS: (ESI +ve) m/z 415 (MH)$^+$, t_R = 3.52 min (90%).

Characterization of Compound 1{*4,4*}. Brown gum (8.9 mg, 59%). IR ν_{MAX}(cm^{-1}): 2962, 1709, 1292; HRMS $C_{18}H_{21}N_3O_3S$ requires (MH)$^+$ 360.1382, found 360.1381; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (d, J = 2, 1H), 8.05 (dd, J = 9, 2, 1H), 7.30 (d, J = 9, 1H), 6.07 (s, 1H), 4.68 (s, 2H), 4.16 (t, J = 7, 2H), 3.94 (s, 3H), 2.36 (s, 3H), 1.79 (m, 2H), 1.37 (m, 2H), 0.95 (t, J = 7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 170.5, 166.9, 159.6, 152.4, 139.4, 137.9, 125.7, 125.1, 119.4, 109.3, 101.8, 52.3, 45.0, 31.3, 27.5, 20.0, 13.6, 12.3; LC/MS: (ESI +ve) m/z 360 (MH)$^+$, t_R = 3.20 min (83%).

Characterization of Compound 1{*5,3*}. Brown gum (15.9 mg, 77%). IR ν_{MAX}(cm^{-1}): 2958, 1713, 1599, 1431, 1297; HRMS $C_{28}H_{30}N_2O_4S$ requires (MH)$^+$ 491.2005, found 491.1999; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.51 (d, J = 2, 1H), 8.02 (dd, J = 9, 2, 1H), 7.59 (d, J = 8, 2H), 7.28 (d, J = 8, 2H), 7.18 (d, J = 9, 1H), 6.51 (d, J = 2, 2H), 6.35 (t, J = 2, 1H), 4.62 (s, 2H), 3.96 (s, 3H), 3.72 (s, 6H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 166.6, 161.0, 154.7, 154.1, 138.2, 137.2, 136.2, 130.2, 127.3, 126.7, 126.3, 126.1, 118.2, 110.3, 107.1, 100.5, 55.4, 52.5, 37.5, 35.1, 31.2; LC/MS: (ESI +ve) m/z 491 (MH)$^+$, t_R = 3.98 min (93%).

Characterization of Compound 1{*5,5*}. Off-white solid (8.7 mg, 45%) (following purification by RP-HPLC). IR ν_{MAX}(cm^{-1}): 2963, 1707, 1656, 1411, 1295; HRMS $C_{25}H_{24}N_2O_3S_2$ requires (MH)$^+$ 465.1307, found 465.1302; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42 (d, J = 2, 1H), 8.00 (dd, J = 4, 2, 1H), 7.92 (dd, J = 9, 2, 1H), 7.72 (dd, J = 5, 2, 1H), 7.58 (d, J = 8, 2H), 7.38 (d, J = 8, 2H), 7.17 (m, 2H), 4.96 (s, 2H), 3.93 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 185.9, 167.3, 153.9, 153.2, 142.0, 141.5, 140.2, 135.1, 133.7, 131.3, 128.5, 127.1, 126.4, 125.0, 124.6, 119.8, 109.5, 52.2, 40.5, 35.0, 31.3; LC/MS: (ESI +ve) m/z 465 (MH)$^+$, t_R = 3.83 min; HPLC: t_R = 6.92 min (>99%; 254 nm).

Characterization of Compound 1{*5,7*}. White solid (7.9 mg, 48%) (following purification by RP-HPLC). IR ν_{MAX}(cm^{-1}): 2961, 1717, 1435, 1295; HRMS $C_{23}H_{28}N_2O_2S$ requires (MH)$^+$ 397.1950, found 397.1950; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.48 (d, J = 2, 1H), 7.98 (dd, J = 9, 2, 1H), 7.62 (d, J = 8, 2H), 7.35 (d, J = 8, 2H), 7.15 (d, J = 9, 1H), 3.95 (s, 3H), 3.36 (d, J = 7, 2H), 2.02 (m, 1H), 1.41 (s, 9H), 1.04 (d, J = 7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 166.9, 156.0, 153.7, 138.8, 138.5, 130.7, 127.3, 126.4, 126.0, 125.5, 118.4, 109.8, 52.3, 40.8, 35.0, 31.2, 28.2, 21.7; LC/MS: (ESI +ve) m/z 397 (MH)$^+$, t_R = 4.05 min; HPLC: t_R = 7.26 min (>99%; 254 nm).

Characterization of Compound 1{*6,2*}. Brown gum (15.1 mg, 72%). IR ν_{MAX}(cm^{-1}): 2929, 1719, 1433, 1284; HRMS $C_{28}H_{24}N_2O_5S$ requires $(MH)^+$ 501.1484, found 501.1485; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.44 (d, $J = 2$, 1H), 7.84 (dd, $J = 9$, 2, 1H), 7.62 (m, 2H), 7.32 (m, 4H), 7.02 (d, $J = 9$, 1H), 6.94 (d, $J = 8$, 1H), 5.60 (m, 1H), 5.12 (s, 2H), 4.30 (m, 4H), 3.91 (s, 3H), 3.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 190.7, 166.8, 153.3, 149.1, 143.7, 139.9, 139.5, 135.8, 128.6, 127.7, 125.5, 124.8 (×2), 123.0, 119.4, 118.0, 117.6, 110.8, 64.8, 64.0, 56.2, 52.3, 42.3, 37.7; LC/MS: (ESI +ve) *m/z* 501 $(MH)^+$, $t_R = 3.61$ min (85%).

Characterization of Compound 1{*6,7*}. Beige solid (3.6 mg, 22%) (following purification by RP-HPLC). IR ν_{MAX}-(cm^{-1}): 2959, 1710, 1432, 1282; HRMS $C_{22}H_{24}N_2O_2S$ requires $(MH)^+$ 381.1637, found 381.1640; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (d, $J = 2$, 1H), 7.76 (dd, $J = 9$, 2, 1H), 7.29 (m, 4H), 6.99 (d, $J = 9$, 1H), 5.40 (m, 1H), 3.90 (s, 3H), 3.53 (m, 4H), 3.36 (d, $J = 7$, 2H), 2.08 (m, 1H), 1.09 (d, $J = 7$, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.5, 154.7, 140.0, 137.4, 127.5, 124.7, 123.9, 123.3, 120.3, 110.0, 55.3, 52.0, 41.4, 37.5, 28.4, 21.9; LC/MS: (ESI +ve) *m/z* 381 $(MH)^+$, $t_R = 3.77$ min; HPLC: $t_R = 6.17$ min (>99%; 254 nm).

Characterization of Compound 1{*9,1*}. Brown gum (14.0 mg, 79%). IR ν_{MAX}(cm^{-1}): 2953, 1716, 1433, 1281; HRMS $C_{23}H_{24}N_2O_4S$ requires $(MH)^+$ 425.1535, found 425.1537; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.48 (d, $J = 2$, 1H), 8.01 (dd, $J = 9$, 2, 1H), 7.97 (d, $J = 8$, 2H), 7.46 (d, $J = 8$, 2H), 7.41 (d, $J = 8$, 1H), 4.86 (m, 1H), 4.72 (s, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.14−1.97 (m, 6H), 1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 166.7, 166.5, 152.5, 140.4, 139.1, 135.5, 130.1, 130.0, 129.2, 125.9, 125.0, 119.3, 111.0, 58.3, 52.4, 52.2, 37.6, 30.1, 25.1; LC/MS: (ESI +ve) *m/z* 425 $(MH)^+$, $t_R = 3.56$ min (94%).

Characterization of Compound 1{*9,3*}. Brown gum (13.3 mg, 74%). IR ν_{MAX}(cm^{-1}): 2951, 1719, 1592, 1434, 1285, 1133; HRMS $C_{23}H_{26}N_2O_4S$ requires $(MH)^+$ 427.1692, found 427.1695; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (d, $J = 2$, 1H), 7.94 (dd, $J = 9$, 2, 1H), 7.33 (d, $J = 8$, 1H), 6.54 (d, $J = 2$, 2H), 6.35 (t, $J = 2$, 1H), 4.84 (m, 1H), 4.60 (s, 2H), 3.94 (s, 3H), 3.72 (s, 6H), 2.18−1.96 (m, 6H), 1.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.0, 161.0, 153.3, 140.5, 137.6, 136.1, 125.1, 124.3, 119.6, 110.6, 107.0, 100.3, 58.0, 55.3, 52.7, 38.2, 30.1, 25.1; LC/MS: (ESI +ve) *m/z* 427 $(MH)^+$, $t_R = 3.58$ min (96%).

Characterization of Compound 1{*9,8*}. Brown gum (10.2 mg, 74%). IR ν_{MAX}(cm^{-1}): 2958, 1703, 1432, 1303; HRMS $C_{18}H_{22}N_2O_2S$ requires $(MH)^+$ 331.1482, found 331.1480; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (d, $J = 2$, 1H), 7.87 (dd, $J = 9$, 2, 1H), 7.32 (d, $J = 9$, 1H), 4.83 (m, 1H), 3.91 (s, 3H), 3.34 (d, $J = 7$, 2H), 2.24−1.97 (m, 6H), 1.79 (m, 2H), 1.24 (m, 1H), 0.64 (m, 2H), 0.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.7, 154.7, 143.9, 137.7, 123.5, 122.9, 120.4, 109.7, 57.3, 52.0, 38.9, 30.0, 25.1, 10.4, 6.0; LC/MS: (ESI +ve) *m/z* 331 $(MH)^+$, $t_R = 3.52$ min (82%).

Characterization of Compound 1{*10,1*}. Brown gum (16.4 mg, 75%). IR ν_{MAX}(cm^{-1}): 2949, 1719, 1702, 1432, 1292; HRMS $C_{28}H_{28}N_2O_6S$ requires $(MH)^+$ 521.1746, found 521.1747; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (d, $J = 2$, 1H), 7.95 (d, $J = 9$, 2H), 7.90 (dd, $J = 8$, 2, 1H), 7.48 (d, $J = 8$, 2H), 7.22 (d, $J = 9$, 1H), 6.87 (t, $J = 8$, 1H), 6.78 (dd, $J = 8$, 2, 1H), 6.50 (dd, $J = 8$, 2, 1H), 4.63 (s, 2H), 4.24 (t, $J = 7$, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.97 (t, $J = 7$, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.6, 166.7, 152.9, 152.7, 147.4, 142.7, 142.0, 139.3, 130.7, 129.9, 129.4, 129.1, 124.2, 124.0, 123.8, 122.3, 120.3, 111.7, 108.5, 60.7, 55.7, 52.1, 52.0, 44.7, 36.4, 30.7; LC/MS: (ESI +ve) *m/z* 521 $(MH)^+$, $t_R = 3.52$ min (89%).

Characterization of Compound 1{*10,2*}. Brown gum (14.9 mg, 65%). IR ν_{MAX}(cm^{-1}): 2944, 1711, 1433, 1299; HRMS $C_{29}H_{28}N_2O_7S$ requires $(MH)^+$ 549.1695, found 549.1692; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (d, $J = 2$, 1H), 7.93 (dd, $J = 9$, 2, 1H), 7.65−7.60 (m, 2H), 7.26 (d, $J = 9$, 1H), 6.95−6.87 (m, 2H), 6.80 (dd, $J = 8$, 2, 1H), 6.61 (dd, $J = 8$, 2, 1H), 5.00 (s, 2H), 4.41 (t, $J = 7$, 2H), 4.34−4.26 (m, 4H), 3.93 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.10 (t, $J = 7$, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 191.1, 167.3, 153.1, 152.8, 149.0, 147.4, 143.6, 140.2, 138.4, 130.4, 128.8, 125.0, 124.5, 124.3, 123.0, 122.3, 119.4, 118.0, 117.5, 112.0, 108.9, 64.7, 64.0, 60.7, 55.8, 52.2, 45.2, 41.8, 30.6; LC/MS: (ESI +ve) *m/z* 549 $(MH)^+$, $t_R = 3.48$ min (88%).

Characterization of Compound 1{*10,5*}. White solid (8.3 mg, 40%) (following purification by RP-HPLC). IR ν_{MAX}-(cm^{-1}): 2955, 1714, 1674, 1285; HRMS $C_{25}H_{24}N_2O_5S_2$ requires $(MH)^+$ 497.1205, found 497.1202; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.31 (d, $J = 2$, 1H), 7.97 (dd, $J = 4$, 2, 1H), 7.89 (dd, $J = 9$, 2, 1H), 7.70 (dd, $J = 5$, 2, 1H), 7.23 (d, $J = 9$, 1H), 7.15 (dd, $J = 5$, 4, 1H), 6.89 (t, $J = 8$, 1H), 6.80 (dd, $J = 8$, 2, 1H), 6.61 (dd, $J = 8$, 2, 1H), 4.89 (s, 2H), 4.33 (t, $J = 7$, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.06 (t, $J = 7$, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 186.2, 167.7, 152.8, 152.6, 147.5, 142.8, 142.2, 139.6, 134.9, 133.5, 130.8, 128.4, 124.2, 123.9, 123.7, 122.4, 120.3, 111.7, 108.5, 60.7, 55.8, 52.0, 44.8, 40.3, 30.7; LC/MS: (ESI +ve) *m/z* 497 $(MH)^+$, $t_R = 3.41$ min; HPLC: $t_R = 5.68$ min (>99%; 254 nm).

Characterization of Compound 1{*10,6*}. Brown gum (16.1 mg, 84%). IR ν_{MAX}(cm^{-1}): 2936, 1738, 1711, 1298, 1268; HRMS $C_{23}H_{26}N_2O_6S$ requires $(MH)^+$ 459.1590, found 459.1595; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (d, $J = 2$, 1H), 7.89 (dd, $J = 9$, 2, 1H), 7.23 (d, $J = 9$, 1H), 6.90 (t, $J = 8$, 1H), 6.81 (dd, $J = 8$, 2, 1H), 6.62 (dd, $J = 8$, 2, 1H), 4.32 (t, $J = 7$, 2H), 4.22 (m, 4H), 3.92 (s, 3H), 3.86 (s, 6H), 3.06 (t, $J = 7$, 2H), 1.27 (t, $J = 7$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 168.5, 167.7, 152.8, 152.3, 147.4, 142.7, 139.5, 130.8, 124.2, 123.9, 123.7, 122.3, 120.4, 111.7, 108.4, 62.0, 60.7, 55.8, 52.0, 44.8, 34.7, 30.8, 14.1; LC/MS: (ESI +ve) *m/z* 459 $(MH)^+$, $t_R = 3.26$ min (90%).

Characterization of Compound 1{*11,4*}. Brown gum (9.6 mg, 64%). IR ν_{MAX}(cm^{-1}): 2967, 1713, 1432, 1300, 1285; HRMS $C_{18}H_{21}N_3O_3S$ requires $(MH)^+$ 360.1382, found 360.1381; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (d, $J = 2$, 1H), 8.00 (dd, $J = 9$, 2, 1H), 7.50 (d, $J = 9$, 1H), 6.07 (d, $J = 1$, 1H), 4.68 (m, 2H), 4.53 (m, 1H), 3.94 (s, 3H), 2.36 (s, 3H), 2.20−1.90 (m, 2H), 1.63 (d, $J = 7$, 3H), 0.80 (t, $J = 7$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 170.5, 166.8, 159.5, 152.4, 139.6, 136.3, 125.6, 124.8, 119.4, 111.2, 101.8,

56.5, 52.4, 28.0, 27.8, 20.1, 12.2, 11.0; LC/MS: (ESI +ve) *m*/*z* 360 $(MH)^+$, t_R = 3.14 min (83%).

Characterization of Compound 1{*12,5*}. Beige solid (6.7 mg, 41%) (following purification by RP-HPLC). IR ν_{MAX}-(cm^{-1}): 3087, 1716, 1670, 1413, 1283; HRMS $C_{18}H_{18}N_2O_4S_2$ requires $(MH)^+$ 391.0786, found 391.0800; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (d, *J* = 2, 1H), 8.00−7.95 (m, 2H), 7.71 (dd, *J* = 5, 2, 1H), 7.38 (dd, *J* = 9, 1H), 7.15 (dd, *J* = 5, 4, 1H), 4.99 (s, 2H), 4.39 (t, *J* = 5, 2H), 3.93 (s, 3H), 3.72 (t, *J* = 5, 2H), 3.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 185.6, 167.2, 152.9, 141.8, 140.7, 139.1, 135.2, 133.8, 128.6, 125.0, 124.5, 119.7, 109.5, 70.3, 59.2, 52.2, 45.0, 41.0; LC/MS: (ESI +ve) *m*/*z* 391 $(MH)^+$, t_R = 2.95 min; HPLC: t_R = 4.68 min (>99%; 254 nm).

Library Rehearsal of *N,N′*-Dialkylbenzimidazol-2-one 9{*x,y*} Synthesis. *Step 1: Synthesis of Nitroaniline 4{1}.* As defined previously for 2-alkylthiobenzimidazole.

Step 2: Synthesis of o-Phenylenediamine 5{1}. As defined previously for 2-alkylthiobenzimidazole.

Step 3: Synthesis of Benzimidazolin-2-one 8{1}. To a solution of the *o*-phenylenediamine **5**{*1*} **(**150 mg, 0.68 mmol) in chloroform (2 mL) was added triphosgene (1 mL of 0.75 M solution in $CHCl_3$, 0.75 mmol), and the resulting mixture was vortexed for 18 h. The reaction mixture was then transferred by top-filtration into a reaction tube containing PS-trisamine (160 mg, 0.74 mmol) and vortexed at 30 °C for 10 h. The resin was then drained and washed with $CHCl_3$, and the combined filtrates were evaporated in vacuo to yield the benzimidazolin-2-one **8**{*1*} as an off-white solid (134 mg, 80%). IR ν_{MAX}(cm^{-1}): 2955, 1716, 1689; HRMS $C_{13}H_{16}N_2O_3$ requires $(MH)^+$ 249.1239, found 249.1236; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.98 (brs, 1H), 7.84 (dd, *J* = 8, 2, 1H), 7.73 (d, *J* = 2, 1H), 6.99 (d, *J* = 8, 1H), 3.90 (s, 3H), 3.69 (d, *J* = 8, 2H), 2.22 (m, 1H), 0.98 (d, *J* = 7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.0, 155.5, 134.6, 127.3, 124.0, 123.4, 110.5, 107.5, 52.1, 48.5, 27.9, 20.1; LC/MS: (ESI +ve) *m*/*z* 249 $(MH)^+$, t_R = 2.89 min; HPLC: t_R = 4.12 min (>99%; 254 nm).

Step 4: Synthesis of N,N′-Dialkylbenzimidazolin-2-one 9{1,9}. The benzimidazolin-2-one **8**{*1*} (14.9 mg, 60 μmol) in DMF (1 mL) was added to a reaction vessel containing PS−BEMP (70 mg, 150 μmol) and vortexed for 2 min. Benzyl bromide (300 μL of a 0.3 M solution, 90 μmol) was added and the reaction vortexed at 50 °C for an additional 10 h. The reaction mixture was then transferred into a clean reaction vessel that contained PS-methylthiourea (31 mg, 90 μmol) and vortexed at 50 °C for 10 h. The resin was filtered and washed, and the filtrates were evaporated in vacuo to afford the *N,N′*-dialkylbenzimidazolin-2-one **9**{*1,9*} as a colorless gum (16.9 mg, 83%). IR ν_{MAX}(cm^{-1}): 2960, 1699, 1238; HRMS $C_{20}H_{22}N_2O_3$ requires $(MH)^+$ 339.1709, found 339.1710; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (dd, *J* = 8, 2, 1H), 7.57 (d, *J* = 2, 1H), 7.30−7.20 (m, 5H), 6.99 (d, *J* = 8, 1H), 5.09 (s, 2H), 3.86 (s, 3H), 3.73 (d, *J* = 7, 2H), 2.22 (m, 1H), 0.98 (d, *J* = 7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 167.0, 154.8, 136.0, 133.7, 129.0, 128.8, 127.8, 127.4, 123.9, 123.1, 109.2, 107.3, 52.1, 48.9, 44.9, 27.9, 20.1; LC/MS: (ESI +ve) *m*/*z* 339 $(MH)^+$, t_R = 3.46 min; HPLC: t_R = 5.63 min (96%: 254 nm).

Preparation of *N,N′*-Dialkylbenzimidazolin-2-one Array 9{*1−12,1−6*}: General Automated Procedure for the 72-Membered Library. *Step 1.* Dispense solutions of methyl 4-fluoro-3-nitrobenzoate (**2**) (3.5 mL of 0.4 M solution in DMF, 1.3 mmol) and an amine **3**{*1−12*} (1.2 mmol) into 12 8-mL reaction vessels in a 24-position reactor block.

Step 2. Vortex reaction block at 30 °C for 10 h.

Step 3. Perform intrablock transfer of each of the reaction mixtures into new 8-mL reaction vessels containing PS-trisamine (240 mg, 1.0 mmol).

Step 4. Vortex reaction vessels at 50 °C for 18 h.

Step 5. Allow reaction block to cool, then drain resins and wash with DMF (0.5 mL) into new 8-mL vials.

Step 6. Remove reaction block from synthesizer and place in a Greenhouse reactor. Add $Pd(OH)_2$ catalyst (20 mg) to each reaction vessel and replace atmosphere in Greenhouse reactor with H_2 gas at atmospheric pressure for 18 h.

Step 7. Remove reaction block from the Greenhouse reactor. To remove the catalyst, filter suspensions directly into new 8-mL reaction vessels. Wash with DMF (0.5 mL) and add to filtrates. Remove solvent in vacuo and replace reaction block on synthesizer.

Step 8. Dilute each of the reaction vessels with $CHCl_3$ (2 mL).

Step 9. Dispense triphosgene (1 mL of 0.64 M solution in $CHCl_3$) into each reaction vessel.

Step 10. Vortex reaction vessels at 30 °C for 18 h.

Step 11. Perform intrablock transfer of each of the reaction mixtures into new 8-mL reaction vessels containing PS-trisamine (200 mg, 0.80 mmol).

Step 12. Vortex reaction vessels at 30 °C for 10 h.

Step 13. Transfer reaction mixtures into clean 8-mL vessels and add $CHCl_3$ resin washings (1 mL).

Step 14. Divide 75% of each of the 12 reaction mixtures equally into 6 new reaction vessels (2 × 48 position reactor blocks) containing PS−BEMP (65 mg, 150 μmol).

Step 15. Dilute each new reaction vessel with DMF (0.5 mL).

Step 16. Dispense solutions of alkylating agents **7**{*1−6*} (300 μL of 0.20 M solution in DMF, 75 μmol, 1.5 equiv) to appropriate reaction vessels.

Step 17. Vortex reaction blocks at 25 °C for 10 h.

Step 18. Drain resins and wash with DMF (0.5 mL) into new vials (6 mL × 72) containing PS-methylthiourea (35 mg, 100 μmol).

Step 19. Vortex reaction blocks at 25 °C for 10 h.

Step 20. Drain resins and wash with DMF (0.5 mL) into new vials (2 × 48).

Step 21. Prepare QC plate; dispense aliquots (40 μL) into 96 well microtitre plates and dilute each well with MeCN (0.7 mL).

Step 22. Remove solvents from bulk samples by parallel centrifugal evaporation in vacuo to afford *N,N′*-dialkylbenzimidazolin-2-one library **9**{*1−12,1−6*}.

Full characterization for 20 representative examples from the *N,N′*-dialkylbenzimidazolin-2-one library **9**{*1−12,1−6*} follows. LC/MS data for all 72 members of the this library are included in the Supporting Information provided.

Characterization of Compound 9{*1,1*}. Off-white solid (18.8 mg, 63%). IR ν_{MAX}(cm^{-1}): 2954, 1702, 1275, 1239; HRMS $C_{22}H_{24}N_2O_5$ requires $(MH)^+$ 397.1763, found 397.1767; ^1H NMR (400 MHz, $CDCl_3$); δ_H 7.98 (d, $J = 8$, 2H), 7.83 (dd, $J = 8$, 2, 1H), 7.52 (d, $J = 2$, 1H), 7.35 (d, $J = 8$, 2H), 7.01 (d, $J = 8$, 2H), 5.14 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.74 (d, $J = 7$, 2H), 2.23 (m, 1H), 0.98 (d, $J = 7$, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 167.3, 167.0, 155.2, 141.4, 134.1, 130.6, 130.2, 129.2, 127.6, 124.5, 123.7, 109.5, 107.8, 52.5, 52.5, 49.3, 45.0, 28.3, 20.5; LC/MS: (ESI +ve) *m/z* 397 $(MH)^+$, $t_R = 3.17$ min (95%).

Characterization of Compound 9{*1,2*}. Cream solid (18.4 mg, 58%). IR ν_{MAX}(cm^{-1}): 2964, 1705, 1680, 1245; HRMS $C_{23}H_{24}N_2O_6$ requires $(MH)^+$ 425.1711, found 425.1713; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.84 (dd, $J = 8$, 2, 1H), 7.57 (m, 2H), 7.46 (d, $J = 2$, 1H), 7.24 (s, 1H), 7.02 (d, $J = 9$, 1H), 6.95 (d, $J = 8$, 1H), 5.25 (s, 2H), 4.31 (m, 4H), 3.86 (s, 3H), 3.74 (d, $J = 7$, 2H), 2.23 (m, 1H), 0.98 (d, $J = 7$, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 189.0, 166.0, 153.9, 147.9, 142.7, 132.9, 128.5, 127.3, 123.1, 122.3, 121.4, 116.7, 116.6, 108.0, 106.5, 63.8, 63.1, 51.0, 48.0, 46.1, 27.0, 19.1; LC/MS: (ESI +ve) *m/z* 425 $(MH)^+$, $t_R = 3.12$ min (86%).

Characterization of Compound 9{*2,1*}. Cream solid (18.4 mg, 64%). IR ν_{MAX}(cm^{-1}): 2952, 1707, 1275, 1234; HRMS $C_{21}H_{22}N_2O_5$ requires $(MH)^+$ 383.1607, found 383.1613; ^1H NMR (400 MHz, $CDCl_3$); δ_H 7.98 (d, $J = 8$, 2H), 7.83 (dd, $J = 8$, 2, 1H), 7.52 (d, $J = 2$, 1H), 7.36 (d, $J = 8$, 2H), 7.02 (d, $J = 8$, 1H), 5.13 (s, 2H), 3.98 (m, 8H), 1.82 (dt, $J = 7$, 2H), 0.98 (t, $J = 7$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 169.6, 169.4, 157.3, 143.7, 136.2, 132.9, 132.5, 131.6, 130.0, 126.9, 126.0, 111.8, 109.9, 54.8, 54.8, 47.3, 45.9, 24.4, 14.0; LC/MS: (ESI +ve) *m/z* 383 $(MH)^+$, $t_R = 3.04$ min (95%).

Characterization of Compound 9{*3,2*}. Cream solid (19.7 mg, 54%). IR ν_{MAX}(cm^{-1}): 2941, 1712, 1676, 1243; HRMS $C_{28}H_{26}N_2O_6$ requires $(MH)^+$ 487.1869, found 487.1865; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (dd, $J = 8$, 2, 1H), 7.58 (m, 2H), 7.46 (d, $J = 2$, 1H), 7.27 (m, 2H), 7.18 (m 3H), 6.94 (m, 2H), 5.23 (s, 2H), 4.31 (m, 4H), 3.96 (t, $J = 7$, 2H), 3.86 (s, 3H), 2.71 (t, $J = 7$, 2H), 2.12 (quin, $J = 7$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 189.5, 166.1, 153.9, 148.4, 143.1, 140.3, 132.8, 129.0, 127.9, 127.8, 127.7, 125.6, 123.6, 122.9, 121.8, 117.2, 117.1, 108.6, 106.6, 64.2, 63.6, 51.5, 46.5, 40.6, 32.4, 29.2; LC/MS: (ESI +ve) *m/z* 487 $(MH)^+$, $t_R = 3.34$ min (86%).

Characterization of Compound 9{*3,5*}. Off-white solid (16.4 mg, 50%). IR ν_{MAX}(cm^{-1}): 2922, 1704, 1667, 1243; HRMS $C_{24}H_{22}N_2O_4S$ requires $(MH)^+$ 435.1378, found 435.1379; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.94 (dd, $J = 4$, 1, 1H), 7.84 (dd, $J = 8$, 2, 1H), 7.73 (dd, $J = 4$, 1, 1H), 7.55 (d, $J = 2$, 1H), 7.26 (m, 2H), 7.19 (m, 4H), 6.92 (d, $J = 8$, 1H), 5.23 (s, 2H), 3.96 (t, $J = 7$, 2H), 3.87 (s, 3H), 2.71 (t, $J = 7$, 2H), 2.13 (quin, $J = 7$, 2H); ^{13}C NMR (175 MHz, $CDCl_3$): δ_c 184.7, 166.9, 154.4, 140.8, 140.8, 134.9, 133.3, 132.8, 12.93, 128.5, 128.5, 128.3, 126.1, 124.3, 123.5, 109.2, 107.2, 52.1, 47.3, 41.1, 32.9, 29.6; LC/MS: (ESI +ve) *m/z* 435 $(MH)^+$, $t_R = 3.28$ min (91%).

Characterization of Compound 9{*3,6*}. Off-white solid (15.0 mg, 51%). IR ν_{MAX}(cm^{-1}): 2940, 1724, 1705, 1249, 1214; HRMS $C_{22}H_{24}N_2O_5$ requires $(MH)^+$ 397.1763, found 397.1767; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (dd, $J = 8$, 2, 1H), 7.56 (d, $J = 2$, 1H), 7.26 (m, 2H), 7.17 (m, 3H), 6.90 (d, $J = 8$, 1H), 4.63 (s, 2H), 4.23 (q, $J = 7$, 2H), 3.94 (t, $J = 7$, 2H), 3.90 (s, 3H), 2.70 (t, $J = 7$, 2H), 2.11 (m, 2H), 1.26 (t, $J = 7$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 167.8, 167.4, 154.7, 141.1, 133.6, 129.4, 128.9, 128.7, 126.5, 124.7, 123.8, 109.3, 107.6, 62.3, 52.5, 42.7, 41.4, 33.3, 30.0, 14.5; LC/MS: (ESI +ve) *m/z* 397 $(MH)^+$, $t_R = 3.19$ min (95%).

Characterization of Compound 9{*4,4*}. Off-white solid (14.0 mg, 54%). IR ν_{MAX}(cm^{-1}): 2956, 1703, 1236; HRMS $C_{18}H_{21}N_3O_4$ requires $(MH)^+$ 344.1610, found 344.1600; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (dd, $J = 8$, 2, 1H), 7.72 (d, $J = 2$, 1H), 7.00 (d, $J = 8$, 1H), 5.94 (s, 1H), 5.10 (s, 2H), 3.90 (m, 5H), 2.34 (s, 3H), 1.74 (m, 2H), 1.39 (m, 2H), 0.95 (t, $J = 7$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 170.9, 167.3, 159.8, 154.6, 133.7, 129.0, 124.7, 123.9, 109.7, 107.6, 101.3, 52.5, 41.7, 37.1, 30.8, 20.4, 14.1, 12.7; LC/MS: (ESI +ve) *m/z* 344 $(MH)^+$, $t_R = 2.97$ min (95%).

Characterization of Compound 9{*5,2*}. Off-white solid (18.3 mg, 49%). IR ν_{MAX}(cm^{-1}): 2959, 1705, 1686, 1251; HRMS $C_{29}H_{28}N_2O_6$ requires $(MH)^+$ 501.2023, found 501.2026. ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (dd, $J = 8$, 2, 1H), 7.62 (m, 2H), 7.54 (m, 3H), 7.45 (m, 2H), 7.10 (d, $J = 9$, 1H), 6.98 (d, $J = 8$, 1H), 5.33 (s, 2H), 4.33 (m, 4H), 3.87 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 188.4, 165.5, 152.3, 149.8, 147.5, 142.3, 132.2, 129.9, 128.1, 125.2, 124.2, 122.8, 122.6, 121.0, 116.3, 116.2, 107.9, 106.9, 63.3, 62.7, 50.6, 45.7, 33.3, 29.9; LC/MS: (ESI +ve) *m/z* 501 $(MH)^+$, $t_R = 3.60$ min (95%).

Characterization of Compound 9{*5,3*}. Off-white gum (14.8 mg, 42%). IR ν_{MAX}(cm^{-1}): 2958, 1706, 1697, 1249; HRMS $C_{28}H_{30}N_2O_5$ requires $(MH)^+$ 475.2233, found 475.2238; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (dd, $J = 8$, 2, 1H), 7.67 (d, $J = 2$, 1H), 7.55 (d, $J = 8$, 2H), 7.48 (d, $J = 8$, 2H), 7.09 (d, $J = 8$, 1H), 6.54 (d, $J = 2$, 2H), 6.36 (t, $J = 2$, 1H), 5.09 (s, 2H), 3.88 (s, 3H), 3.80 (s, 6H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 168.2, 162.5, 155.1, 152.5, 139.4, 134.6, 132.6, 130.5, 127.9, 126.8, 125.4, 125.3, 110.8, 109.5, 107.0, 101.1, 56.7, 53.4, 46.5, 36.1, 32.6; LC/MS: (ESI +ve) *m/z* 475 $(MH)^+$, $t_R = 3.71$ min (94%).

Characterization of Compound 9{*6,1*}. Off-white solid (19.3 mg, 56%). IR ν_{MAX}(cm^{-1}): 2955, 1724, 1699, 1281, 1246; HRMS $C_{27}H_{24}N_2O_5$ requires $(MH)^+$ 457.1763, found 457.1762; ^1H NMR (400 MHz, $CDCl_3$); δ_H 8.00 (d, $J = 8$, 2H), 7.67 (dd, $J = 8$, 2, 1H), 7.54 (d, $J = 2$, 1H), 7.40 (d, $J = 8$, 2H), 7.26 (m, 4H), 6.69 (d, $J = 8$, 1H), 5.56 (m, 1H), 5.15 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.46 (d, $J = 8$, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 167.2, 167.0, 154.6, 141.3, 140.9, 131.9, 130.6, 130.2, 129.5, 127.8, 127.7, 125.1, 124.4, 123.8, 109.6, 109.1, 52.5, 52.5, 52.2, 45.1, 37.1; LC/MS: (ESI +ve) *m/z* 457 $(MH)^+$, $t_R = 3.40$ min (93%).

Characterization of Compound 9{*6,2*}. Off-white solid (22.0 mg, 61%). IR ν_{MAX}(cm^{-1}): 2943, 1699, 1685, 1241; HRMS $C_{28}H_{24}N_2O_6$ requires $(MH)^+$ 485.1713, found 485.1712; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (dd, $J =$

8, 2, 1H), 7.59 (m, 2H), 7.47 (d, $J = 2$, 1H), 7.25 (m, 4H), 6.98 (d, $J = 8$, 1H), 6.70 (d, $J = 8$, 1H), 5.53 (quin, $J = 9$, 1H), 5.27 (s, 2H), 4.33 (m, 4H), 3.83 (s, 3H), 3.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 188.4, 165.5, 152.8, 147.5, 142.2, 139.2, 130.2, 128.3, 126.8, 125.7, 123.2, 122.4, 121.8, 120.9, 116.2, 116.2, 107.7, 107.2, 63.3, 62.6, 50.5, 50.4, 45.6, 35.2; LC/MS: (ESI +ve) *m/z* 485 $(MH)^+$, $t_R = 3.35$ min (82%).

Characterization of Compound 9{*6,6*}. Off-white solid (14.9 mg, 55%). IR $\nu_{MAX}(cm^{-1})$: 2953, 1709, 1696, 1254, 1230; HRMS $C_{22}H_{22}N_2O_5$ requires $(MH)^+$ 395.1607, found 395.1603; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (dd, $J =$ 8, 2, 1H), 7.57 (d, $J = 2$, 1H), 7.26 (m, 4H), 6.69 (d, $J = 8$, 1H), 5.51 (m, 1H), 4.66 (s, 2H), 4.25 (q, $J = 7$, 2H), 3.88 (s, 3H), 3.45 (d, $J = 9$, 4H), 1.29 (t, $J = 8$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 167.9, 167.3, 154.4, 140.9, 132.0, 129.6, 127.6, 125.0, 124.5, 123.8, 109.4, 109.2, 62.3, 52.5, 52.2, 42.8, 37.0, 14.5; LC/MS: (ESI +ve) *m/z* 395 $(MH)^+$, $t_R = 3.18$ min (95%).

Characterization of Compound 9{*7,1*}. Off-white solid (18.2 mg, 55%). IR $\nu_{MAX}(cm^{-1})$: 2957, 1708, 1278, 1240; HRMS $C_{26}H_{24}N_2O_5$ requires $(MH)^+$ 445.1763, found 445.1765; ^{1}H NMR (400 MHz, $CDCl_3$); δ_H 7.98 (d, $J = 8$, 2H), 7.77 (dd, $J = 8$, 2, 1H), 7.48 (d, $J = 2$, 1H), 7.31−7.14 (m, 7H), 6.48 (d, $J = 8$, 1H), 5.10 (s, 2H), 4.18 (t, $J =$ 7, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.08 (t, $J = 7$, 2H); ^{13}C NMR (175 MHz, $CDCl_3$): δ_c 166.9, 166.7, 154.3, 140.9, 137.7, 133.2, 130.2, 129.8, 128.9, 128.7, 128.7, 127.2, 126.9, 124.1, 123.4, 109.1, 107.2, 52.2, 52.1, 44.5, 43.0, 34.5; LC/MS: (ESI +ve) *m/z* 445 $(MH)^+$, $t_R = 3.23$ min (94%).

Characterization of Compound 9{*7,2*}. Off-white solid (19.3 mg, 55%). IR $\nu_{MAX}(cm^{-1})$: 2934, 1703, 1677, 1251; HRMS $C_{27}H_{24}N_2O_6$ requires $(MH)^+$ 473.1713, found 473.1713; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 (dd, $J =$ 8, 2, 1H), 7.58 (m, 2H), 7.45 (d, $J = 2$, 1H), 7.25 (m, 2H), 7.20 (m, 3H), 6.97 (d, $J = 8$, 1H), 6.78 (d, $J = 8$, 1H), 5.24 (s, 2H), 4.32 (m, 4H), 4.14 (t, $J = 7$, 2H), 3.85 (s, 3H), 3.06 (t, $J = 7$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 188.7, 165.8, 153.2, 147.7, 142.5, 136.8, 132.2, 128.1, 127.7, 127.5, 127.1, 125.6, 122.9, 122.1, 121.2, 116.5, 116.4, 107.8, 105.9, 63.6, 62.9, 50.8, 45.8, 42.1, 33.5; LC/MS: (ESI +ve) *m/z* 473 $(MH)^+$, $t_R = 3.23$ min (86%).

Characterization of Compound 9{*7,4*}. Off-white solid (13.8 mg, 47%). IR $\nu_{MAX}(cm^{-1})$: 2937, 1702, 1236; HRMS $C_{22}H_{21}N_3O_4$ requires $(MH)^+$ 392.1610, found 392.1609; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (dd, $J = 8$, 2, 1H), 7.70 (d, $J = 2$, 1H), 7.26−7.13 (m, 5H), 6.82 (d, $J = 8$, 1H), 5.83 (s, 1H), 5.08 (s, 2H), 4.14 (t, $J = 7$, 2H), 3.89 (s, 3H), 3.05 (t, $J = 7$, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 170.9, 167.3, 159.8, 154.4, 138.1, 133.4, 129.2, 129.1, 128.8, 127.2, 124.7, 124.0, 109.7, 107.5, 101.3, 52.5, 43.4, 37.1, 34.9, 12.7; LC/MS: (ESI +ve) *m/z* 392 $(MH)^+$, $t_R = 3.05$ min (95%).

Characterization of Compound 9{*7,5*}. Off-white solid (15.9 mg, 50%). IR $\nu_{MAX}(cm^{-1})$: 2932, 1703, 1668, 1238; HRMS $C_{23}H_{20}N_2O_4S$ requires $(MH)^+$ 421.1226, found 421.1222; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.94 (dd, $J =$ 8, 1, 1H), 7.75 (m, 2H), 7.53 (d, $J = 2$, 1H), 7.27−7.16 (m, 6H), 6.78 (d, $J = 8$, 1H), 5.23 (s, 2H), 4.14 (t, $J = 7$, 2H), 3.86 (s, 3H), 3.06 (t, $J = 7$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 184.0, 166.3, 153.6, 140.1, 137.2, 134.2, 132.6, 132.1, 128.5, 128.2, 128.0, 127.8, 126.1, 123.5, 122.7, 108.5, 106.5, 51.4, 46.6, 42.6, 34.0; LC/MS: (ESI +ve) *m/z* 421 $(MH)^+$, $t_R = 3.17$ min (86%).

Characterization of Compound 9{*7,6*}. Off-white solid (14.8 mg, 52%). IR $\nu_{MAX}(cm^{-1})$: 2953, 1739, 1706, 1254, 1223; HRMS $C_{21}H_{22}N_2O_5$ requires $(MH)^+$ 383.1607, found 383.1605; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (dd, $J =$ 8, 2, 1H), 7.56 (d, $J = 2$, 1H), 7.26 (m, 2H), 7.19 (m, 3H), 6.77 (d, $J = 8$, 1H), 4.65 (s, 2H), 4.25 (q, $J = 7$, 2H), 4.13 (t, $J = 7$, 2H), 3.90 (s, 3H), 3.05 (t, $J = 7$, 2H), 1.29 (t, $J =$ 7, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ_c 167.4, 167.0, 154.1, 137.9, 133.3, 128.8, 128.8, 128.7, 126.8, 124.2, 123.3, 108.8, 107.2, 61.9, 52.1, 43.2, 42.3, 34.7, 14.1; LC/MS: (ESI +ve) *m/z* 383 $(MH)^+$, $t_R = 3.04$ min (95%).

Characterization of Compound 9{*8,4*}. Off-white solid (14.8 mg, 55%). IR $\nu_{MAX}(cm^{-1})$: 2965, 1699, 1239; HRMS $C_{19}H_{23}N_3O_4$ requires $(MH)^+$ 358.1767, found 358.1762; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (dd, $J = 8$, 2, 1H), 7.72 (d, $J = 2$, 1H), 7.10 (d, $J = 8$, 1H), 5.89 (s, 1H), 5.11 (s, 2H), 4.23 (m, 1H), 3.88 (s, 3H), 2.34 (s, 3H), 2.04 (m, 2H), 1.86 (m, 2H), 0.83 (t, $J = 7$, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 170.9, 167.3, 160.0, 155.0, 133.0, 129.0, 124.5, 123.6, 109.7, 108.8, 101.1, 58.6, 52.5, 37.1, 26.0, 12.7, 11.5; LC/MS: (ESI +ve) *m/z* 358 $(MH)^+$, $t_R = 3.03$ min (95%).

Characterization of Compound 9{*8,6*}. Off-white solid (16.6 mg, 64%). IR $\nu_{MAX}(cm^{-1})$: 2967, 1750, 1701, 1242, 1197; HRMS $C_{18}H_{24}N_2O_5$ requires $(MH)^+$ 349.1763, found 349.1752; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (dd, $J =$ 8, 2, 1H), 7.56 (d, $J = 2$, 1H), 7.11 (d, $J = 8$, 1H), 4.64 (s, 2H), 4.20 (m, 3H), 3.90 (s, 3H), 2.05 (m, 2H), 1.86 (m, 2H), 1.23 (t, $J = 7$, 3H), 0.84 (t, $J = 7$, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 167.1, 166.7, 154.4, 132.5, 128.8, 123.7. 122.7, 108.4, 108.1, 61.5, 57.9, 51.8, 42.0, 25.3, 13.7, 10.7; LC/MS: (ESI +ve) *m/z* 349 $(MH)^+$, $t_R = 2.99$ min (95%).

Characterization of Compound 9{*11,4*}. Off-white solid (13.1 mg, 51%). IR $\nu_{MAX}(cm^{-1})$: 2972, 1702, 1694, 1247; HRMS $C_{18}H_{21}N_3O_4$ requires $(MH)^+$ 344.1610, found 344.1604; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (dd, $J =$ 8, 2, 1H), 7.72 (d, $J = 2$, 1H), 7.12 (d, $J = 8$, 1H), 5.93 (s, 1H), 5.10 (s, 2H), 4.46 (m, 1H), 3.90 (s, 3H), 2.35 (s, 3H), 2.11−1.80 (m, 2H), 1.53 (d, $J = 7$, 3H), 0.85 (t, $J = 8$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 168.6, 165.0, 157.6, 152.2, 130.5, 126.8, 122.2, 121.3, 107.4, 106.5, 99.0, 50.2, 49.8, 34.8, 25.3, 16.6, 10.4, 9.3; LC/MS: (ESI +ve) *m/z* 344 $(MH)^+$, $t_R = 2.90$ min (95%).

Acknowledgment. We thank GlaxoSmithKline for their generous financial support of this work.

Supporting Information Available. Copies of ^{1}H NMR and ^{13}C NMR spectra for 20 representative library members, together with tabulated yield and purity data for the 96-member 2-alkylthiobenzimidazole library **1**{*1−12,1−8*} and the 72-member *N,N′*-dialkylbenzimidazolin-2-one library **9**{*1−12,1−6*}. Photographs of the instrumentation used in this study. (PDF.) This information is available free of charge via the Internet at http://pubs.acs.org.

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CC049832+