Novel Structures Derived from 2-[[(2-Pyridyl)methyl]thio]-1*H*-benzimidazole as Anti-*Helicobacter pylori* Agents, Part 1

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2-[[(2-Pyridyl)methyl]thio]-1*H*-benzimidazoles (**2**, sulfides) exhibit antibacterial properties that are selective for *Helicobacter* spp., but they also have an inherent susceptibility to metabolic oxidation to furnish 2-[[(2-pyridyl)methyl]sulfinyl]-1*H*-benzimidazoles (**1**), which act as proton pump inhibitors (PPIs). We have discovered five compounds with retained antibacterial potency and selectivity in which the overall framework of the sulfides **2** could be kept intact while structural modifications were made to remove PPI activity. These compounds, 2-[((2-methyl-3-(2-(2-(2-methoxyethoxy)ethoxy)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (**79**), 2-[((2-methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (**80**), 2-[((2-methyl-3-((2-morpholino)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (**86**), 2-[[[2-methyl-3-[2-(2-methyl-5-nitroimidazol-1-yl)ethylthio]phenyl]methyl]thio]-1*H*-benzimidazole (**88**), and 2-[[[2-methyl-3-[2-(1,2,4-triazol-1-yl)ethylthio]phenyl]methyl]thio]-1*H*-benzimidazole (**89**), had minimum bactericidal concentrations (MBCs) of 0.5, 0.5, 1, 2, and 4 μg/mL, respectively. The reported compounds are bactericidal with MBCs within 1 order of magnitude of MBCs of clinically used antimicrobials such as clarithromycin (0.1 μg/mL) or metronidazole (2−4 μg/mL) but differ from these inasmuch that they have an extremely narrow spectrum activity and appear to be species specific.

Introduction

More than 60% of the world's population is infected with the pathogenic, Gram-negative bacterium *Helicobacter pylori*.[1,2] An infection inevitably leads to gastritis, which in turn may develop into atrophy, and the pathogen has therefore been stated to be carcinogenic to humans by the World Health Organization (WHO). The bacterium is the causative agent of duodenal ulcer relapse as evidenced by numerous clinical trials, and it has been implicated in nonulcer dyspepsia and irritable bowel syndrome although firm relationships regarding these disorders are still lacking. Considering how widespread and common this pathogen is and the rate at which resistance to some of the more common antimicrobials used in *H. pylori* treatments emerges, it is quite clear that the search for new, efficacious, and affordable drugs needs to be intensified.

The antibacterial activity of omeprazole and other proton pump inhibitors (PPIs, **1**, cf. Chart 1) has been studied extensively by several groups.[3−6] It became evident in the course of this work that the corresponding sulfides **2** also exhibited antibacterial properties and that this (antibacterial) effect was selective for *Helicobacter* spp.[7] We therefore studied such sulfides in much more detail and established a quantitative structure−activity relationship (QSAR) in which varying biological activity as measured by minimum bactericidal concentration (MBC) values could be explained by variations in molecular structure.[8] The evaluation of these sulfides in an animal model, however, suggested that their pharmacological properties were not ideal. They displayed an inherent propensity for metabolic oxidation to the corresponding sulfoxides (**1**), that is PPIs, and thus effectively inhibited acid secretion. While acid secretion inhibition is favorable in combination therapies together with antimicrobials,[9,10] it proved counterproductive under our monotherapy conditions.[8] We were, however, still intrigued by the selectivity of the antibacterial activity for *Helicobacter* spp. We therefore thought it worthwhile to study compounds in which the overall framework of the sulfides was kept intact, as illustrated in structure **3**, with the aim of preserving the desired antibacterial profile, while at the same time making structural modifications such that the chemical requirements for PPI activity[11] were no longer met.

We now report on the synthesis and antibacterial profiling of such compounds with the objective of (i) identifying novel chemical entities worthy of optimizing as anti-*Helicobacter* agents while (ii) preserving the desired selective antibacterial activity.

Chemistry

Design Concepts. Inspection of the omeprazole framework **4a** in view of the chemistry behind the conversion[11] of this prodrug to the active species (**4d**) as detailed in Figure 1 immediately suggests three positions for chemical modification. The first is the replacement of the pyridine nitrogen by a methine carbon giving the corresponding phenyl derivative, which effectively would prevent the formation of the

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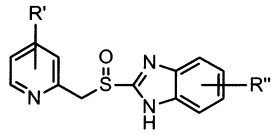
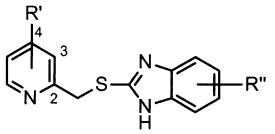
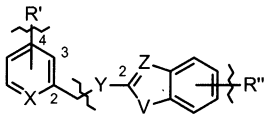
Chart 1. Generic Structure of a PPI (**1**), the Corresponding Sulfide (**2**), and the Compounds (**3**) Investigated in This Study as Possible Novel Anti-*H. pylori* Agents[a]



1



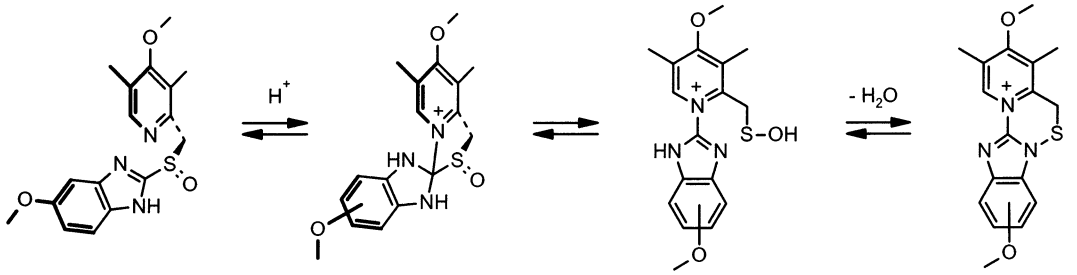
2



X = N, CH
Y = S, O, NH, CH_2
Z = N, CH
V = NH, O, S

3

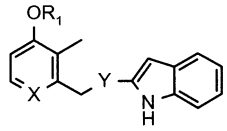
[a] Note that some pertinent positions for substitution in structures **2** and **3** are adequately numbered. The various divisions of compound **3** made for computational chemistry reasons (see text for details) are also indicated in the structure.



4a **4b** **4c** **4d**

Figure 1. Prodrug omeprazole (**4a**) is rapidly converted to the active species **4d** when subjected to acid conditions. Protonation of the benzimidazole moiety renders the 2-carbon susceptible to nucleophilic attack by the pyridine nitrogen furnishing the spiro intermediate **4b**. The spiro intermediate can revert back to starting materials or collapse to the sulfenic acid **4c**, which upon loss of water produces the active species, the sulfenamide **4d**. For a detailed account of this chemistry, check ref 11. Hashed and wedged bonds are not used to picture any stereochemistry but to illustrate bonds pointing away or toward the reader, respectively.

Chart 2. Three Compounds (**5**−**7**) in the Indole Series Out of a Maximum Number of Eight (X = CH or N and Y = S, O, NH, or CH_2) Were Prepared[a]



5 X = CH; Y = CH_2; R_1 = *iso*-Bu
6 X = CH; Y = S; R_1 = *iso*-Bu
7 X = N; Y = S; R_1 = *iso*-Bu

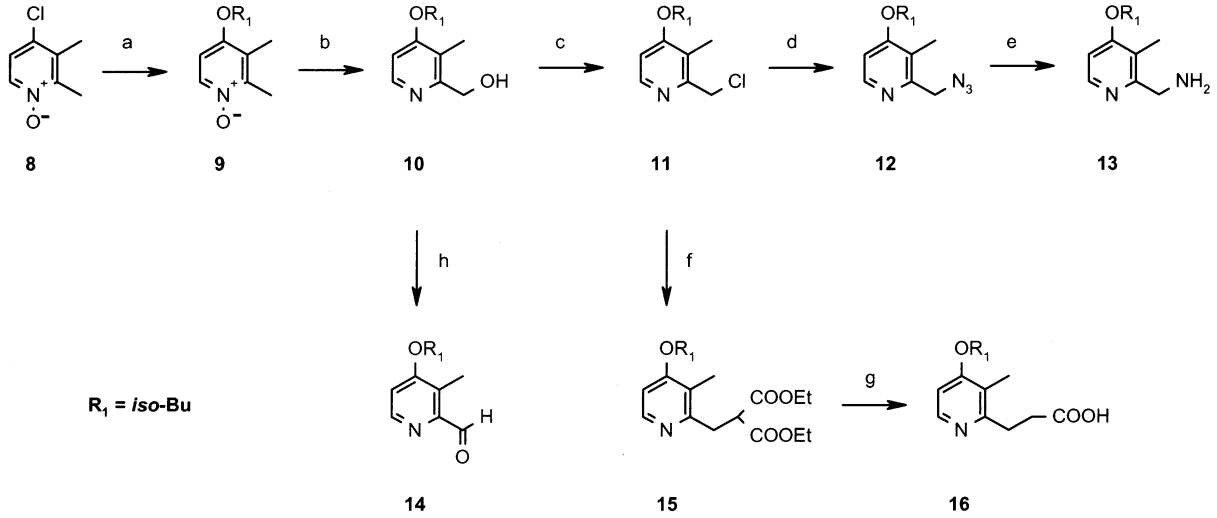
[a] The remaining five indoles were not prepared (see text for details).

spiro intermediate **4b**. The second position for alteration is at the sulfoxide functionality. Substituting -SO- with -O-, -NH-, or -CH_2- would most likely increase the electron density at the two carbon of the benzimidazole moiety such that the spiro intermediate **4b** again could not form. Even if such an intermediate did form, it would be unable to collapse to furnish the sulfenic acid **4c** because the structure lacks the obligate sulfur functionality. The third position for modification is the benzimidazole moiety itself. Substitution by an indole, benzoxazole, benzothiazole, benzofuran, or benzothiophene would remove the required electron relay provided by the original benzimidazole. Allowing for all possible combinations, while disregarding synthetic feasability, this adds up to $2 \times 4 \times 6 = 48$ heterocyclic frameworks to be prepared as shown in structure **3**.

In the indole series, cf. Chart 2, we could have prepared a total of eight compounds (X = CH or N and Y = S, O, NH, or CH_2). We synthesized three such derivatives (**5**−**7**) each of which appeared to be associated with poor stability both when stored as a crystalline solid or kept in a dimethyl sulfoxide (DMSO) solution. A literature survey[12] corroborated to some extent these findings, and we therefore decided against preparing the remaining five compounds in this series. Similarly, the lack of any good precedent in the literature for the preparation of either the 2-amino, the 2-thio, or the 2-oxo-substituted benzofurans and benzothiophenes, respectively, led us to abandon these compounds, too. The two 2-alkyl (Y = CH_2 in **3**)-substituted benzofurans **47** and **48**, however, were prepared, but the corresponding benzothiophenes were not, since (the benzofuran analogues) **47** and **48** were essentially inactive. Finally, as the two 2-oxo-substituted benzimidazoles would in effect constitute *O*-alkyl isoureas, some of which are alkylating agents,[13] they too were excluded. Hence, out of the 48 theoretical core structures **3** that could be prepared, we synthesized and studied 27 different ones. Each of these constituted a unique heterocycle demanding its own, in most instances unprecedented, chemistry.

Findings from our earlier optimization study[8] suggested that the pyridine nucleus, in addition to the heterocyclic moiety at the 2-position, was best substituted with a methyl group at the 3-position and an *iso*-butyloxy group at the 4-position. However, to explore the SAR more broadly and identify structural modifications with unforeseen advantageous properties, we also tested other substituents, especially in the 4-position. Many of these appeared in the patent literature and were claimed to be associated with substantial increases

Scheme 1. Hydroxymethyl Pyridine **10** Was the Common Precursor of Several Building Blocks (**11**, **13**, **14**, and **16**) Each of Which Was Used in Preparing One or Several Target Compounds[a]



[a] The formyl derivative **14** was isolated only as a transient intermediate in the preparation of compound **60**. Reagents: (a) *iso*-Butyl alcohol, NaH. (b) (i) Ac_2O, Δ; (ii) aqueous NaOH. (c) $SOCl_2$. (d) IR 400 N_3 ion exchange resin. (e) $SnCl_2$, PhSH, Et_3N. (f) NaH, diethyl malonate. (g) 6 M HCl, Δ. (h) MnO_2.

in potency. When working with the phenyl series, we aimed at a similar substitution pattern and the same preferred substituents. In other words, the heterocyclic moiety was attached at the 2-position, the methyl group was attached at the 3-position, and the remaining substituent was attached at the 4-position on the phenyl **3** (X = CH). This corresponds to the 2-, 3-, and 4-positions in the pyridine nucleus, respectively. The heterocyclic moieties in the 2-position of **2** and **3** (X = CH), respectively, were in most instances left unsubstituted. Earlier results with the sulfides had indicated that introduction of substituents on the benzimidazole did not afford any immediate advantage with respect to potency.[8] For one set of compounds, however, we did elaborate this end of the molecule with the objective of increasing solubility, cf. structures **80** and **90**−**93**.

Two additional compounds, the nitroimidazole **88** and the triazole **89**, were also prepared. The nitroimidazole moiety of **88** and the 1,2,4-triazole moiety of **89** both have pK_a values around 3. Thus, they would be uncharged at the physiological pH prevailing in the systemic circulation allowing them to penetrate cell membranes readily and enter, for instance, the deep pits in the stomach lining where *H. pylori* is frequently found and could find sanctuary during antimicrobial challenge. Once there, they would become protonated and prevented from reentering the systemic circulation because of the acquired charge. Hence, it is conceivable that these compounds over time would accumulate in the stomach, which in effect would be a means of drug targeting.

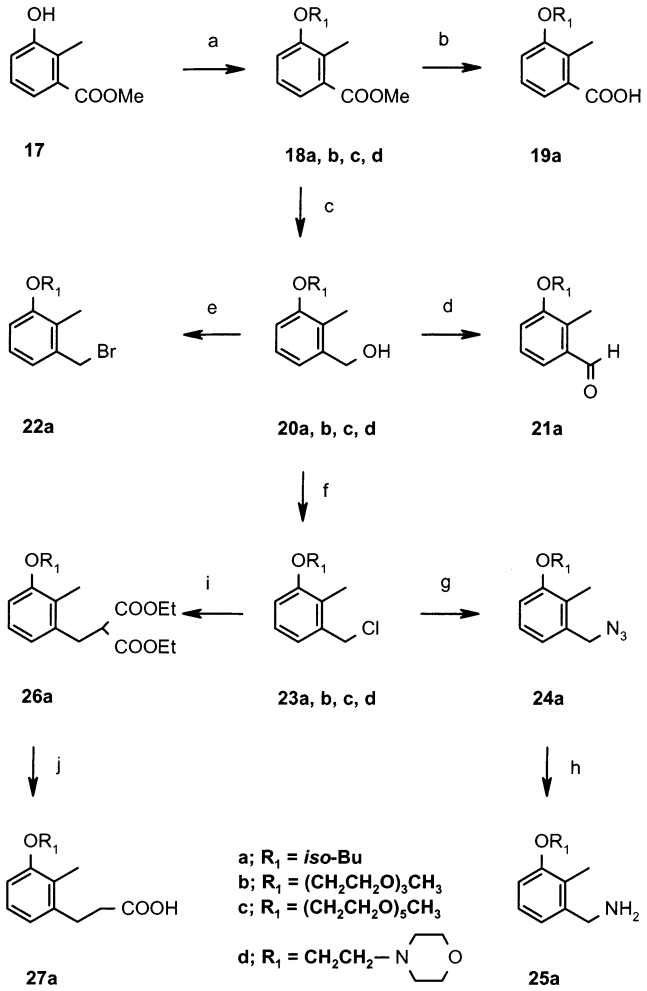
Design Criteria. New core structures that exhibited MBC values within 1 order of magnitude or less of the activity of the parent compound **76** (3 μM) were regarded as hits. A hit was then subjected to limited modifications in order to restore antibacterial activity to 3 μM or less. If this could be achieved, the compound qualified for more elaborate studies.

Computational Chemistry. To identify molecular properties that contributed to the antibacterial activity, we analyzed our data by a number of different QSAR methods. Descriptors were calculated for entire molecules, individual fragments, or discrete substituents as indicated in structure **3**. Quantum chemical descriptors such as highest occupied molecular orbital (HOMO)−lowest unoccupied molecular orbital (LUMO) energies, solvation energies, molecular volume and surface area, moments of inertia, etc. were calculated by the AM1 method implemented in the Spartan program.[14] Two-dimensional (2D) descriptors such as the number of rotatable bonds, number of rings, element counts, clog*P*, cMR, and others were calculated by our in-house developed SELMA software, which is based on the molecular tool kit by Daylight Inc.[15]

Syntheses. As an overall strategy, we tried to use a few common intermediates, e.g., **10**, **18**, and **32**, and divert them into the maximum number of target compounds as late as possible in the syntheses. Hence, the hydroxymethyl pyridine **10**, obtained from **8** in two steps, was converted either to the chloromethyl derivative **11**, the aminomethyl analogue **13**, the 2-formylpyridine **14**, or the propionic acid **16** as outlined in Scheme 1. Similarly, the esters **18** were the common ancestors of the corresponding acid **19a**, the benzyl alcohols **20**, the formyl derivative **21a**, the benzyl bromide **22a**, the benzyl chlorides **23**, the benzylamine **25a**, and the propionic acid **27a** as detailed in Scheme 2. In a like manner, the benzyl alcohols **32** were the precursors of both the benzyl chlorides **33** and the aldehydes **34** as shown in Scheme 3. Each of these building blocks was then used to prepare target compounds as detailed below.

From the propionic acid derivatives **27a** and **16**, target compounds **39**−**44** were prepared via a condensation reaction with the appropriate phenylene diamines, hydroxy anilines, or mercapto anilines, cf. Scheme 4. On occasion, the incipient amides (**36**−**38**) could be isolated, whereas in other instances they immediately collapsed to the desired products (**40**, **43**, and **44**). Target compounds **47** and **48** were both prepared by reacting the acid chlorides **45** and **46**, respectively, with 2-hydroxybenzyl triphenyl phosphonium bromide. The in-

Scheme 2. Esters **18** Were the Common Precursors of Several Building Blocks (**19a**, **20**, **21a**, **22a**, **25a**, and **27a**) Each of Which Was Used in Preparing One or Several Target Compounds[a]



[a] The formyl derivative **21a** was isolated only as a transient intermediate in the preparation of compound **59**. Reagents: (a) K_2CO_3 and the appropriate halide or mesylate. (b) NaOH. (c) $LiAlH_4$. (d) MnO_2. (e) TMSCl, LiBr. (f) $SOCl_2$. (g) IR 400 N_3 ion exchange resin. (h) $SnCl_2$, PhSH, Et_3N. (i) NaH, diethyl malonate. (j) (i) NaOH; (ii) Δ.

termediate esters were then ring-closed by means of a Wittig reaction.

As shown in Scheme 5 target compounds **59**−**67** were obtained either by reacting the appropriate amines (**13** or **25a**) with 2-fluoro benzothiazole (**50**) or 2-chloro benzoxazole (**51**) or by condensing 2-amino benzothiazole (**49**) or 2-amino benzimidazole (**52**) with either a benzoic acid (**19a**) or a formyl derivative (**14**, **21a**, or **34c**). In the latter instance, both the intermediate amide **53** and the imines **54**−**58** had to be reduced to afford the target compounds.

Once the required halides **11**, **23**, and **33** were in hand, target compounds **75**−**93** became readily available upon reaction with the appropriate mercapto derivatives (**68**−**74**), cf. Scheme 6.

Scheme 7, finally, deals with the synthesis of the four target compounds **97**−**100**. Two of these were prepared by a nucleophile (**20a** or **10**) displacing a leaving group ($(CH_3)_2S$ generated in situ from CH_3I and **70**, or F^- in **96**, respectively). The remaining two compounds were obtained by *O*-alkylation of **94** or **95** by **11** or **22a**, respectively, in the presence of Ag_2CO_3.

Microbiology

Bacterial Strains. The *H. pylori* strain used in the antibacterial activity studies was ATCC 43504 from the American Type Culture Collection, Rockville, MD. *Escherichia coli* K-12 and *Staphylococcus aureus* CCUG 1800T, both from the Culture Collection, Department of Clinical Bacteriology, University of Göteborg, Sweden, were used to study antibacterial selectivity. Stock cultures were stored at −70 °C in Brucella broth (Difco; pH 7.0) supplemented with 10% fetal calf serum (FCS) and 20% glycerol. The FCS was inactivated at 56 °C for 30 min prior to use.

Determination of Minimal Inhibitory Concentrations (MICs) and MBCs. Brucella broth (Difco; pH 7.0) supplemented with 10% FCS was preferred for determinations of MICs. Solid medium for determination of MBCs for *Helicobacter* spp. was Columbia blood agar containing 42.5 g/L Columbia Agar Base II and 15 g/L Bacto Agar (both from Oxoid), 7% horse blood, and 1% IsoVitaleX at pH 7.3 ± 0.2 (BBL Microbiology System). *Helicobacter* spp. were grown under microaerophilic conditions (85% N_2, 10% CO_2, and 5% O_2) at 37 °C in an automatic CO_2−O_2 incubator. Other bacteria studied were grown on Luria Agar (Tryptone 10 g/L and yeast extract 5 g/L (Difco), NaCl 5 g/L, and Bacto Agar 15 g/L (Oxoid)) and incubated under aerophilic conditions at 37 °C.

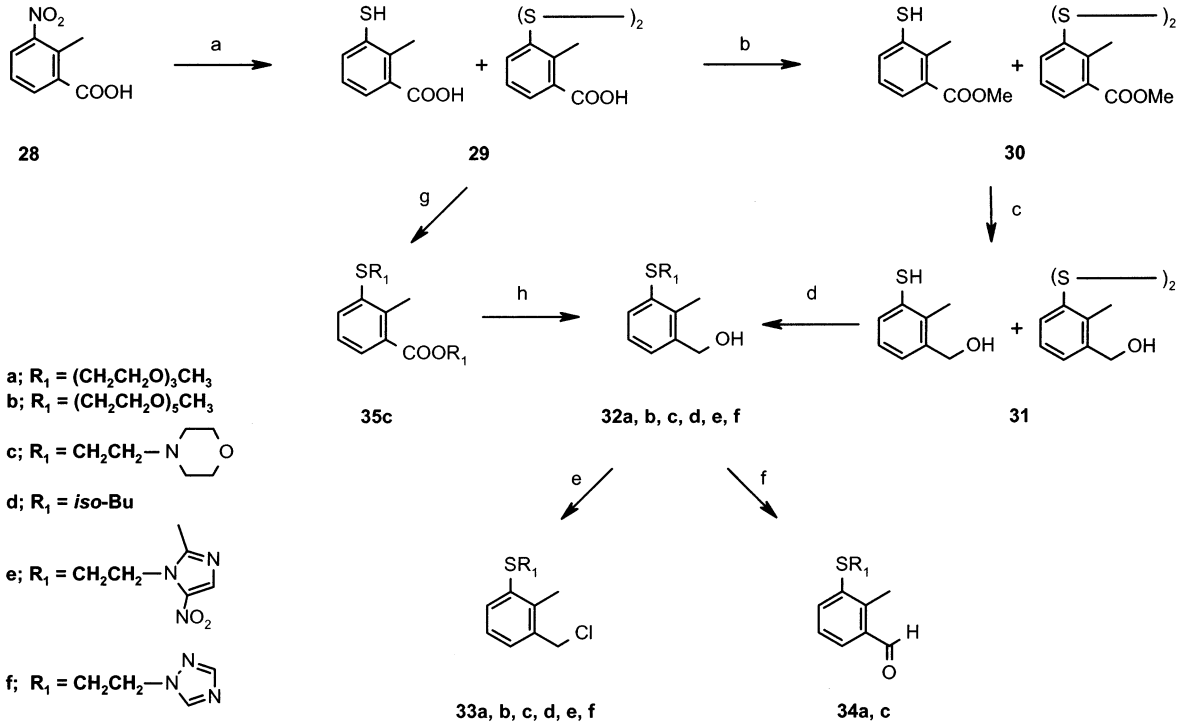
Antibacterial activity was tested by 2-fold serial dilutions of the compounds ranging from 128 to 0.5 μg/mL with an initial cell count of approximately 10^6 CFU/mL. To overcome solubility problems, compounds were dissolved and diluted in DMSO before they were added to the aqueous growth medium. In general, compounds could not be dissolved and diluted in growth medium directly as precipitates frequently formed in the initial (highest concentration) test tube. After the mixtures were incubated for 72 h, MICs were determined by reading the optical density at 560 nm. Then, 10 μL was transferred from each well to a large Columbia blood agar plate (120 mm × 120 mm × 17 mm), which was further incubated for 72 h to determine MBCs. The incubation period on Luria agar for *E. coli* and *S. aureus* was 24 h. Blanks of DMSO, at the concentrations used in the dilutions, did not inhibit bacterial growth. The MIC was defined as the lowest concentration of a given compound completely inhibiting growth whereas the MBC was defined as the lowest concentration of a given compound furnishing less than 10 colonies/spot.

Results

After chemical and other considerations were applied, as detailed above, to the list of tentative core structures to be prepared and evaluated, we decided to pursue 27 of them, cf. entries where $R' = R_1$ in Table 1. Results for an additional 17 entries ($R' \neq R_1$) are also given in Table 1 along with the antibacterial activities of two drugs frequently used in *H. pylori* treatments, namely, amoxicillin and clarithromycin. MICs are not given in Table 1 but were consistently 2-fold lower than the corresponding MBCs.

The three indoles **5**−**7** that were prepared developed colors ranging from pink to blackish green both when

Scheme 3. Benzyl Alcohols **32** Were the Common Precursors of Several Building Blocks (**33** and **34**) Each of Which Was Used in Preparing One or Several Target Compounds[a]



[a] The formyl derivatives **34a** and **34c** and the Ester **35c** were isolated only as a transient intermediates in the preparation of compounds **65**, **67**, and **32c**, respectively. Reagents: (a) (i) Pd/C, H_2; (ii) H^+, $NaNO_2$; (iii) $K^+{}^-SCSOEt$; (iv) aqueous NaOH; (v) H^+. (b) MeOH, H^+. (c) $LiAlH_4$. (d) (i) Ph_3P, H^+; (ii) Et_3N or K_2CO_3 and the appropriate halide or mesylate. (e) $SOCl_2$. (f) MnO_2. (g) K_2CO_3, *N*-(2-chloroethyl)morpholine. (h) $LiAlH_4$.

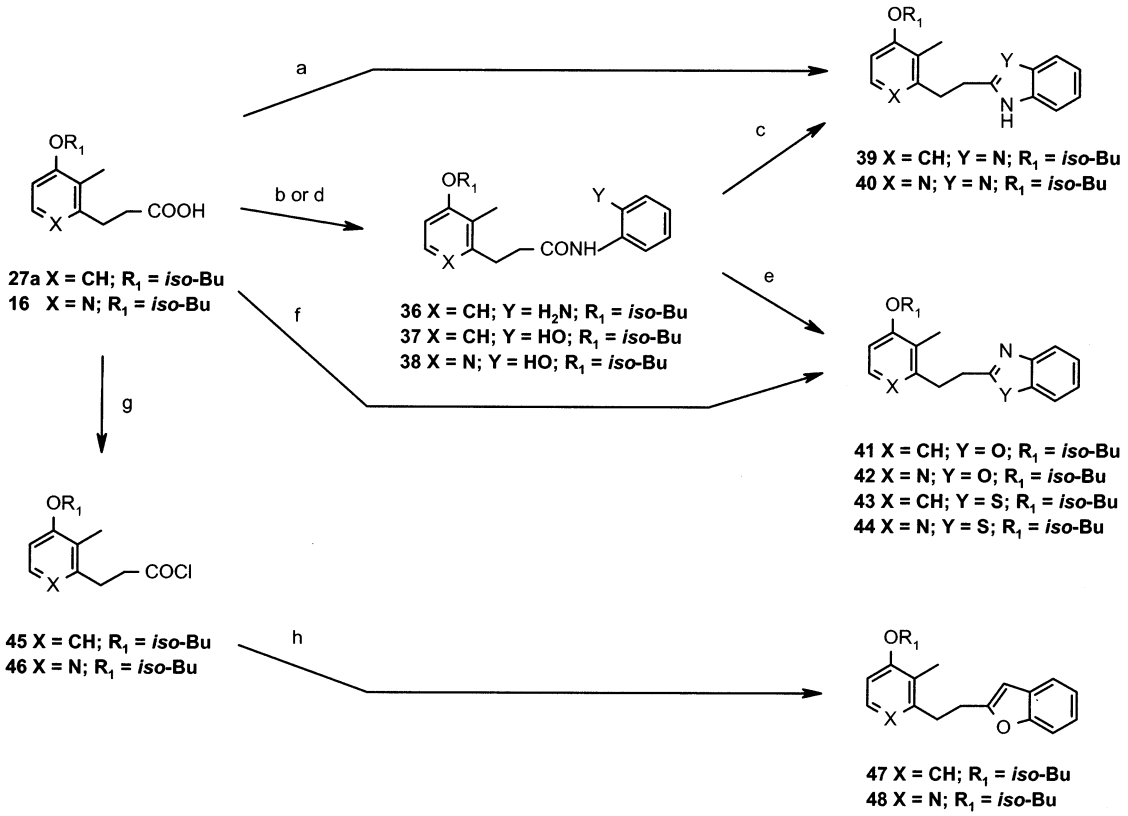
stored as (crystalline) solids or as DMSO solutions. Specifically, compound **6** rapidly decomposed during work up and could only be isolated in low yield after several attempts. Moreover, a DMSO solution of **5** stored at ambient temperature rapidly turned black but high-performance liquid chromatography (HPLC) peak area did not decrease significantly over time, 97.7% at $t = 0$ h to 97.2% at $t = 168$ h. Similarly, compound **7**, although crystalline and thoroughly dried, became tinted within a few hours of storage. The combination of these observations together with literature findings[12] led us to abandon further pursuit of the indoles. MBC values for **5**−**7** were determined to be 52, 98, and 12 μM, respectively, but must be regarded as unreliable.

Inspection of the results for the remaining entries shows that in addition to the parent sulfide **76**, four more compounds tested as actives by our preset criterion of allowing for no more than a 10-fold drop in activity as compared to the parent compound. The four compounds qualifying for limited chemical modifications were the phenethyl benzimidazole **39**, the benzylamino benzimidazole **59**, the (pyridyl)methylamino benzimidazole **60**, and the benzylthio benzimidazole **75**. The synthesis of **39** proved to be the least flexible one with respect to introducing alternative substituents for the *iso*-butyloxy group. Compound **75**, however, was readily amenable to analoging. Therefore, the latter core was preferred for examining alternative substituents and/or functional groups. Of the 17 compounds ($R' \neq R_1$) outside the original design, 14 were variations in the benzylthio benzimidazole series while only two were variations in the amino benzimidazole series.

A comparison of the results for **75** and **87** indicates that a sulfur atom in R′, cf. Table 1, provided a favorable 2-fold increase in potency. This effect is even more pronounced (by some 20-fold) when comparing **85** with **86** demonstrating the 2-(morpholino)ethylthio group to be a beneficial substituent. This substituent is present in **86** (MBC = 2.5 μM), and thus, **86** qualified for further testing. Two other interesting substituents were the tri- and pentaethylene glycol monomethyl ethers as in **77** and **78**, which yielded 2- and 5-fold increases in potency, respectively, as compared to the parent *iso*-butyloxy derivative **75**. Again, substituting the oxygen for a sulfur as in **79** and **80** was beneficial, boosting potency severalfold to 1 μM and qualifying both compounds for additional studies.

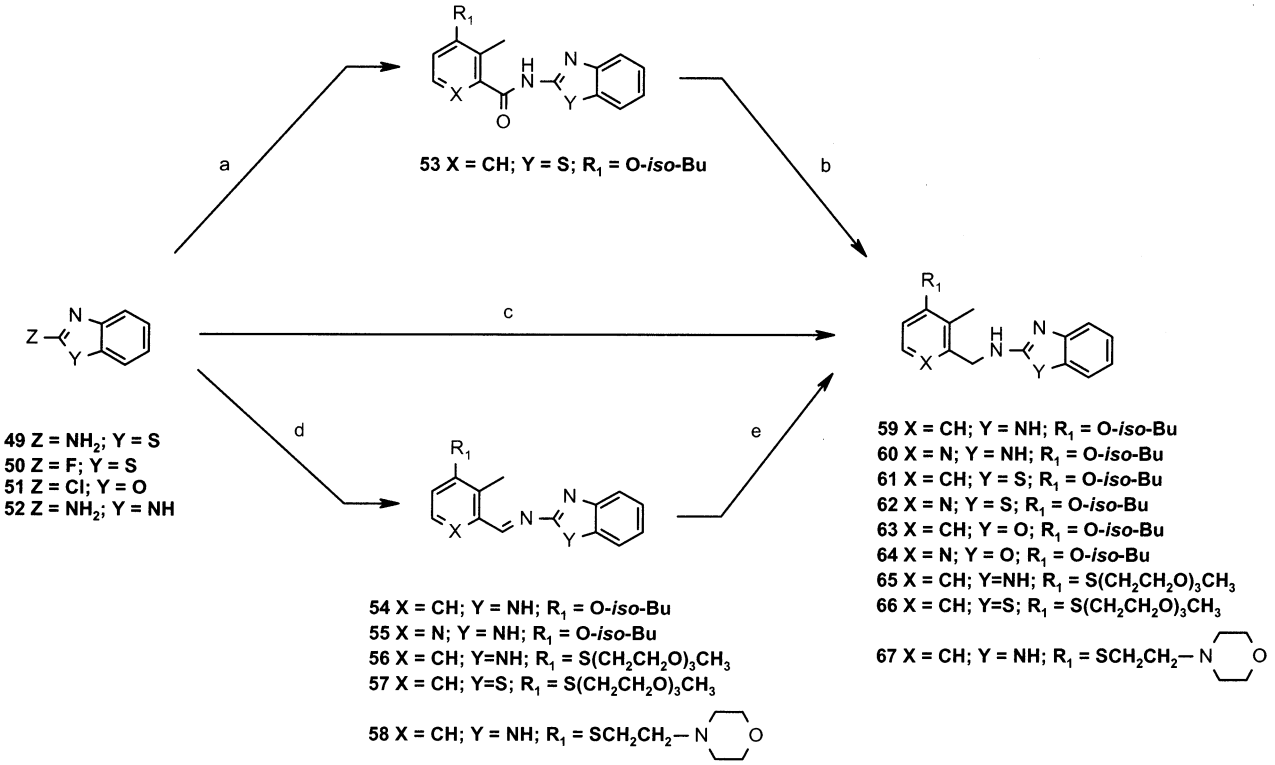
Translating these findings to the benzylamino benzimidazole core **59** was not straightforward as introduction of either the 2-(morpholino)ethylthio substituent, as in **67**, or the thio triethyleneglycol monomethyl ether substituent, as in **65**, resulted in significant losses in potency rather than in expected increases. A further example of the effect of a substituent on one core not immediately transferring to another is the case of compound **65**. Substituting the *iso*-butyloxy group in **59** with the thio triethyleneglycol monomethyl ether residue, as in compound **65**, resulted in a 10-fold loss in potency as discussed above. The same modification in compound **61**, however, furnished more than a 40-fold increase in potency as evidenced by compound **66**. Compounds **90**−**93**, which were prepared to increase solubility, cf. the Microbiology section above, did not provide any obvious advantages over the parent compound **80** in this regard as judged by visual inspection

Scheme 4. Synthesis of Target Compounds **39**−**44**, **47**, and **48**[a]



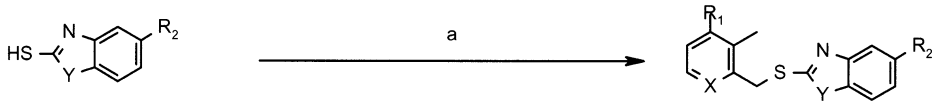
[a] Reagents: (a) Compound **16**, 1,2-diaminobenzene, 6 M HCl. (b) Compound **27a**, 1,2-diaminobenzene, IIDQ. (c) 4 Å molecular sieves, PPTS. (d) 2-Aminophenol, EDC. (e) Compound **37**, hexamethyldisiloxane, P_2O_5 or **38**, methanesulfonic acid, P_2O_5. (f) Compound **27a**, 2-aminothiophenol, methanesulfonic acid, P_2O_5 or **16**, 2-aminothiophenol, 6 M HCl. (g) Oxalyl chloride, DMF. (h) 2-Hydroxy benzyl triphenyl phosphonium bromide, Et_3N.

Scheme 5. Synthesis of Target Compounds **59**−**67**[a]



[a] Reagents: (a) Compound **19a**, **49**, EDC, DMAP. (b) $LiAlH_4$. (c) Compound **13**, NaH, and **50**, or **25a**, NaH, and **51**, or **13**, NaH, and **51**. (d) Compound **21a**, K_2CO_3, and **52** or **14**, K_2CO_3, and **52**. (e) $NaCNBH_3$.

Scheme 6. Synthesis of Target Compounds **75**−**93**[a]



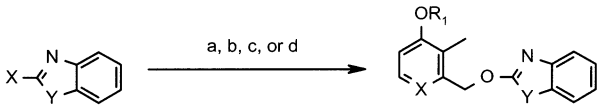
68 Y = NH; R_2 = H
69 Y = S; R_2 = H
70 Y = O; R_2 = H
71 Y = NH; R_2 = COOEt
72 Y = NH; R_2 = COEt
73 Y = NH; R_2 = NH_2
74 Y = NH; R_2 = CH_2OH

75 X = CH; Y = NH; R_1 = O-*iso*-Bu; R_2 = H
76 X = N; Y = NH; R_1 = O-*iso*-Bu; R_2 = H
77 X = CH; Y = NH; R_1 = $O(CH_2CH_2O)_3CH_3$; R_2 = H
78 X = CH; Y = NH; R_1 = $O(CH_2CH_2O)_5CH_3$; R_2 = H
79 X = CH; Y = NH; R_1 = $S(CH_2CH_2O)_3CH_3$; R_2 = H
80 X = CH; Y = NH; R_1 = $S(CH_2CH_2O)_5CH_3$; R_2 = H
81 X = CH; Y = S; R_1 = O-*iso*-Bu; R_2 = H
82 X = N; Y = S; R_1 = O-*iso*-Bu; R_2 = H
83 X = CH; Y = O; R_1 = O-*iso*-Bu; R_2 = H
84 X = N; Y = O; R_1 = O-*iso*-Bu; R_2 = H
85 X = CH; Y = NH; R_1 = OCH_2CH_2—morpholine; R_2 = H
86 X = CH; Y = NH; R_1 = SCH_2CH_2—morpholine; R_2 = H

87 X = CH; Y = NH; R_1 = S-*iso*-Bu; R_2 = H
88 X = CH; Y = NH; R_1 = SCH_2CH_2—(2-nitroimidazole); R_2 = H
89 X = CH; Y = NH; R_1 = SCH_2CH_2—(1,2,4-triazole); R_2 = H
90 X = CH; Y = NH; R_1 = $S(CH_2CH_2O)_5CH_3$; R_2 = COOEt
91 X = CH; Y = NH; R_1 = $S(CH_2CH_2O)_5CH_3$; R_2 = COEt
92 X = CH; Y = NH; R_1 = $S(CH_2CH_2O)_5CH_3$; R_2 = NH_2
93 X = CH; Y = NH; R_1 = $S(CH_2CH_2O)_5CH_3$; R_2 = CH_2OH

[a] Reagents: (a) (i) Compound **11**, **23**, or **33** and aqueous NaOH; (ii) MeOH.

Scheme 7. Synthesis of Target Compounds **97**−**100**[a]



70 X = HS; Y = O
94 X = HO; Y = O
95 X = OH; Y = S
96 X = F; Y = S

97 X = CH; Y = O; R_1 = *iso*-Bu
98 X = N; Y = O; R_1 = *iso*-Bu
99 X = CH; Y = S; R_1 = *iso*-Bu
100 X = N; Y = S; R_1 = *iso*-Bu

[a] Reagents: (a) Compound **70**, MeI, **20a**, and NaH. (b) Compound **94**, Ag_2CO_3, and **11**. (c) Compound **95**, Ag_2CO_3, and **22c**. (d) Compound **10** and NaH.

of (growth medium) stock solutions and were therefore not pursued further.

The results in Table 1 for compounds **88** and **89** show that they did not quite meet the activity criterion of 3 μM for further studies. However, in view of the possible accumulation of these compounds in the stomach, as discussed in the Design Concepts section above, we thought it premature to exclude them at this point. Hence, altogether, five compounds qualified for additional studies, three by virtue of their potency (**79**, **80**, and **86**) and two by virtue of their potential for accumulation at the site of action (**88** and **89**).

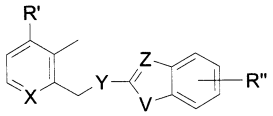
Each compound listed in Table 1 was also tested against *E. coli* and *S. aureus* representing another Gram-negative and a Gram-positive species, respectively (data not shown). With the exception of **60** (MBC = 206 μM (64 μg/mL) against *S. aureus*), no other compound was bactericidal against any of these additional test species. Six of the compounds displayed a minor growth inhibition of both *E. coli* and *S. aureus*. Another seven compounds displayed a similar minor growth inhibition of either *E. coli* or *S. aureus*. In each of these instances, though, the growth inhibition was less than 50% and was only noticeable at the highest concentration tested (128 μg/mL).

Partial least squares analysis using SIMCA on the entire data set and on a subset (the phenyl series) gave models of reasonable quality, $R^2 = 0.74$, $Q^2 = 0.68$ and $R^2 = 0.79$, $Q^2 = 0.70$, respectively. The most important descriptors in both of these models were those describing the size dependence of the R′ substituent such as volume, surface area, and molecular refraction. Increases in these values contributed positively to the MBC potency. Significant descriptors for the right-hand heterocycle were related to electronic properties such as, for instance, HOMO−LUMO energies and electronegativity. Decreases in these values gave decreases in MBC. The model for the entire data set implicated descriptors related to the left-hand aromatic ring as significant, such as, for instance, clog*P* and dipole moment. This analysis indicated that the less lipophilic more polar pyridyl nucleus was preferred over the corresponding phenyl ring. To check that our models were not due to chance, each data set was randomized and reanalyzed several times. Neither of these attempts furnished models with better or even reasonable R^2 or Q^2 and hence supported the notion that our initial models were valid.

Discussion

The advent of bacterial genomics has brought a number of novel targets and structures to the forefront, but none of these have as of yet entered clinical use. With the exception of the oxazolidinones, which were discovered in the late eighties,[16] no truly new original chemical entities exploiting novel bacterial targets have materialized during the past few years. Efforts have until recently primarily focused on chemically modifying existing drugs to alter their spectrum of activity, to improve their pharmacokinetics, or to significantly increase their potency to overcome resistance. An interesting example of the latter is the carbapenem L-786,392, which was designed to provide high affinity binding to the penicillin binding protein PBP2a responsible for resistance in *Staphylococci*.[17] Nevertheless, the emergence and rapid increase in the number of pathogenic bacteria that have acquired resistance to one or more antimicrobials[18,19] have made it quite clear that new drug classes are in demand and that new targets for intervention need to be discovered. This is particularly true for *H. pylori*, which infects more than 60% of the world's population and where the emergence of *H. pylori* strains, which are resistant to the specific antimicrobial agents used for treatment, such as metronidazole[20,21] or clarithromycin,[22] poses ever increasing

Table 1. Compounds Selected and Tested for Anti-*H. pylori* Activity



compd no.	X	Y	Z	V	R′[a]	5-R″	MBC (μg/mL)	MBC (μM)[b]	mp (°C)	microanalysis
5	CH	CH_2	CH	NH	R_1	H	16	52		ND
6	CH	S	CH	NH	R_1	H	32	98		ND
7	N	S	CH	NH	R_1	H	4	12		ND
39	CH	CH_2	N	NH	R_1	H	8	26	108−109	LC
40	N	CH_2	N	NH	R_1	H	32	103	92−94	LC
41	CH	CH_2	N	O	R_1	H	16	52	45	LC
42	N	CH_2	N	O	R_1	H	32	103	63	LC
43	CH	CH_2	N	S	R_1	H	32	98	52	LC
44	N	CH_2	N	S	R_1	H	16	49	oil	LC
47	CH	CH_2	CH	O	R_1	H	128	415	oil	LC
48	N	CH_2	CH	O	R_1	H	16	52	oil[c]	LC
59	CH	NH	N	NH	R_1	H	2	6.5	164−166	LC
60	N	NH	N	NH	R_1	H	8	26	128−129	LC
61	CH	NH	N	S	R_1	H	>128	>392	149−150	LC
62	N	NH	N	S	R_1	H	32	98	130	LC
63	CH	NH	N	O	R_1	H	>128	>412	115	LC
64	N	NH	N	O	R_1	H	32	103	103−104	LC
65	CH	NH	N	NH	R_2	H	32	77	oil	LC
66	CH	NH	N	S	R_2	H	4	9.25	52−54	LC
67	CH	NH	N	NH	R_3	H	32	107	oil	LC
75	CH	S	N	NH	R_1	H	8	19	154−156	LC
76	N	S	N	NH	R_1	H	1	3	d	d
77	CH	S	N	NH	R_4	H	4	9.6	oil	LC
78	CH	S	N	NH	R_5	H	2	3.96	oil	LC
79	CH	S	N	NH	R_2	H	0.5	1.16	oil	$C_{22}H_{28}N_2O_3S_2$[e]
80	CH	S	N	NH	R_6	H	0.5	0.96	oil	$C_{26}H_{36}N_2O_5S_2$[e]
81	CH	S	N	S	R_1	H	>128	>373	oil	LC
82	N	S	N	S	R_1	H	32	93	89−90	LC
83	CH	S	N	O	R_1	H	64	195	oil	LC
84	N	S	N	O	R_1	H	32	81	89−90	LC
85	CH	S	N	NH	R_7	H	16	42	135−136	LC
86	CH	S	N	NH	R_3	H	1	2.5	117−118	$C_{21}H_{25}N_3OS_2$[e]
87	CH	S	N	NH	R_8	H	4	8.76	114−117	LC
88	CH	S	N	NH	R_9	H	2	4.55	149−151	$C_{21}H_{21}N_5O_2S_2 \cdot 3/2H_2O$[e]
89	CH	S	N	NH	R_{10}	H	4	10.48	116−118	$C_{19}H_{19}N_5S_2$[e]
90	CH	S	N	NH	R_6	COOEt	2	3.37	oil	LC
91	CH	S	N	NH	R_6	COEt	2	3.47	glass	LC
92	CH	S	N	NH	R_6	NH_2	8	15	oil[f]	LC
93	CH	S	N	NH	R_6	CH_2OH	8	15	oil	LC
97	CH	O	N	O	R_1	H	32	103	ND	LC
98	N	O	N	O	R_1	H	16	51	ND	LC
99	CH	O	N	S	R_1	H	128	391	oil	LC
100	N	O	N	S	R_1	H	16	49	oil[c]	LC
Am[g]							0.05			
Clari[h]							0.1			

[a] R_1 = O-*iso*-Bu, R_2 = $S(CH_2CH_2O)_3CH_3$, R_3 = $S(CH_2CH_2)$-4-morpholinyl, R_4 = $O(CH_2CH_2O)_3CH_3$, R_5 = $O(CH_2CH_2O)_5CH_3$, R_6 = $S(CH_2CH_2O)_5CH_3$, R_7 = $O(CH_2CH_2)$-4-morpholinyl, R_8 = S-*iso*-Bu, R_9 = $S(CH_2CH_2)$-1-(2-methyl-5-nitro-imidazolyl), and R_{10} = $S(CH_2CH_2)$-1-(1,2,4-triazolyl). [b] Molar units were used in the partial least squares model to account for differences in molecular weight. [c] Solidifies upon prolonged storage. [d] Ref 6. [e] C, H, N, S. [f] Oil that darkens upon prolonged storage. [g] Amoxicillin. [h] Clarithromycin; ND, not determined; LC, purity was determined by two independent LC analyses.

problems. The selective antibacterial activity of the current compounds for *H. pylori* over other Gram-negative and Gram-positive bacteria could suggest that there is a unique target (in *H. pylori*) with which these compounds interact. Accordingly, we believe that the current selection of compounds in fact not only are novel structures but also interact with novel therapeutic target(s).

The studied compounds are bactericidal as opposed to bacteriostatic, and such a property could be crucial for a drug aimed at attacking bacteria in places that are not effectively perfused by the systemic circulation such as the endocardium of the heart or the mucous membrane covering the interior lining of the stomach (or duodenum). Such compartments are hard to reach with antibacterials and accordingly difficult to clear from bacterial infections. Merely suppressing an infection, leaving it for the immune system to clear, might not be adequate. On the contrary, it is our opinion that new anti-*H. pylori* drugs must be bactericidal to become effective in vivo. This is a characteristic of the current compounds.

Introduction of a substituent on one of the nitrogens in the benzimidazole moiety of a PPI **1** offers a fourth possibility for chemical amendment that we refrained from exploring. While such substitution would prevent (complete) conversion of prodrug (**4a**) to active species (**4d**) by blocking the step in which **4c** dehydrates to **4d** (because NH = NR, cf. Figure 1), the sulfenic acid **4c** could still form. Such a species would react indiscrimi-

nately and rapidly with available thiols (furnishing disulfides[23]) rendering it nonspecific in its mode of action. Thiols in various targets (enzymes) as well as thiols in various genera (of bacteria) would be susceptible, and the sought selectivity would be lost at the level of targets as well as species. Hence, neither *N*-substituted analogues of PPIs nor their corresponding *N*-substituted sulfides were considered by us as viable starting points for chemical modifications.

Yet another structural modification that we were discouraged from pursuing was that of oxidizing the sulfoxides **1** to their corresponding sulfones. While this modification would eliminate undesired (PPI) reactivity, earlier unpublished findings from our laboratory had shown that such sulfones generally were quite inactive in our in vitro screens.

The finding that the three most potent compounds (**79**, **80**, and **86**) all belonged to the phenyl series (as opposed to the preferred pyridine series) is explained by the fact that the contribution from the R′ substituent is more significant than the contribution from either of the aromatic rings. The obvious conclusion, however, to prepare the corresponding pyridyl compounds to further increase potency is counterproductive as such a modification would restore the chemical requirements for PPI activity. The incorporation of elongated R′ side chains, such as the oligoethylene glycol moieties, did initially raise some concern. Although the increase in lipophilicity by the addition of an ethylene residue is roughly balanced by the concomitant addition of an oxygen, leaving the overall log*P* unchanged, such modifications may be questionable. Such compounds are detergent-like in both shape and functionality, which could give them a nonspecific lytic or cell membrane-disrupting mode of action. This concern, however, was to some extent mitigated by the finding that these compounds maintained their selectivity for *Helicobacter* spp., which would not be expected if they were acting merely as detergents. Moreover, the widely used household product additive and "nonspecific biocide" trichlosan has recently been shown to have a specific target in *E. coli* lipid biosynthesis.[24]

Irrespective of killing mechanism, a compound must be screened for in vivo efficacy at some stage during development. This is critical in order to determine that drug concentrations sufficient to kill the bacterium are achieved and maintained for appropriate periods of time in the various ecological niches occupied by *H. pylori*. These include the mucous that covers the epithelial cells and fills the gastric pits and also the epithelial cell itself, as *H. pylori* adheres to cell surfaces and can penetrate tight junctions. Such areas are found predominantly, but not exclusively, in the antral region of the stomach close to the pylorus.[25] Other areas with similar physiology where the bacterium has also been detected are in foci of gastric metaplasia in the duodenum. While there are no screens available that allow one to measure concentrations in these compartments readily, the recent developments in infected mouse[26] and rat[27] models could aid in such quests. We believe that such models could become extremely useful when evaluating, for instance, compounds **88** and **89** since it is well-known that *H. pylori* infections induce morphological changes and hence may alter gastric and duodenal physiology. Hence, infected animal models may reflect more appropriately the clinical situation than the corresponding uninfected models. The pharmacological profiling of these compounds in such infected animal models is ongoing and will be reported in due course.

In the current study, we used divergent synthetic routes and flexibility in selecting target compounds. Our syntheses provided the possibility of diverting common precursors, late in the synthesis, into several target compounds, which conserved time. Immediate incorporation of screening results into target compound selection narrowed considerably the number of compounds that we had to prepare to fulfill our screening criteria. This combined approach allowed us to rapidly identify five compounds that satisfied our goal of identifying novel chemical entries, with preserved selective antibacterial properties, worthy of optimizing as anti-*Helicobacter* agents. Each of these compounds constitutes a promising and viable starting point for further development as new therapeutic agents and studies to identify their mode of action are presently in progress.

Experimental Section

General. Chemicals, reagents, and solvents were purchased from any of the major vendors such as Sigma Aldrich, Fluka, Lancaster, Merck, etc. NMR spectra were recorded on 300, 400, or 500 MHz instruments manufactured by Bruker, Switzerland, or Varian, Ca. Mass spectra were recorded on a TRIO-1000 with an electron impact (EI) source, a TRIO 2000 with a static fast atom bombardment (FAB) source, or a VG Platform II with an electrospray (ESI) source. The mass spectrometers were purchased from Micromass, U.K. Compound identity was established by proton and/or carbon NMR and/or EI and/or FAB and/or ESI MS. Compound purity was checked by chromatographic means and/or microanalysis.

Chromatography. Analytical HPLC (method A) was run on a LiChrosphere 60 RP-select B (4.0 mm × 125 mm, 5 μm) column using MeCN/0.025 M NaOAc buffer (pH 6.5) as eluent at a flow rate of 0.8 mL/min and detecting at 214−287 nm if nothing else stated. Analytical HPLC (method B) was run on a Phenomenex, Kromasil 5 C8 (4.6 mm × 150 mm, 5 μm) column using MeCN/0.1 M NH_4OAc buffer (pH 7) as eluent at a flow rate of 1 mL/min and detecting at 254 nm if nothing else stated. Analytical HPLC (method C) was run on a Symmetry C8 (3.9 mm × 150 mm, 5 μm) column using a MeCN/phosphate buffer (pH 3.2, $I = 0.05$) gradient (20−80% in 15′ followed by 5′ at 80%) as eluent at a flow rate of 1 mL/min and detecting at 254 nm. Analytical HPLC (method D) was run on a Symmetry C8 (3.9 mm × 150 mm, 5 μm) column using a MeCN/0.1 M NH_4OAc buffer (pH 7) gradient (10−100% in 5′ followed by 2′ at 100%) as eluent at a flow rate of 2 mL/min and detecting at 254 nm. Analytical HPLC (method E) was run on a Supelcosil ABZ+ (4.6 mm × 150 mm, 5 μm) column using a MeCN/0.25 M NH_4OAc buffer/H_2O (75/10/15) as eluent at a flow rate of 1 mL/min and detecting at 275 nm. Analytical HPLC (method F) was run on a Kromasil C8 (3.2 mm × 150 mm, 5 μm) column using a MeCN/0.1 M NH_4OAc buffer (70/30) as eluent at a flow rate of 0.4 mL/min and detecting at 220 nm. Analytical HPLC (method G) was run on a LiChrospher 60 RP-select (4.0 mm × 125 mm, 5 μm) column using a MeCN/phosphate buffer (pH 6.5, $I = 0.025$) gradient (58−70% in 20′) as eluent at a flow rate of 0.8 mL/min and detecting at 280 nm.

Preparative LC was run on Kromasil 7 C8 (7 μm, 50 mm × 250 mm) column using MeCN/0.1 M NH4OAc buffer (pH 7) as eluent at a flow rate of 50 mL/min and detecting at 254−300 nm. Typically, appropriate fractions were combined, the MeCN was removed in vacuo, and the remaining aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated.

Chemistry. 2-[2-(4-*iso*-Butyloxy-3-methyl-phenyl)ethyl]indole (5). Oxalyl chloride (184 mg, 1.45 mmol) was gently added, under inert conditions, to an ice cold solution of **27a** (264 mg, 1.11 mmol) in dry CH_2Cl_2 (6 mL). The resulting mixture was treated with a catalytic amount of dimethylformamide (DMF) and allowed to react at ambient temperature for 3 h. The solvent and excess reagent were evaporated leaving crude **46**, which was immediately dissolved in dry CH_2Cl_2 (4 mL) and treated with 2-aminobenzyl triphenyl phosphonium bromide[28,29] (500 mg, 1.11 mmol). After it was reacted for 3 h at ambient temperature, the solvent was evaporated. The residue was suspended in toluene (8 mL) and reacted with potassium *tert*-butoxide (161.4 mg, 1.44 mmol) for 2 h. An incipient red-orange color changed gradually to beige. A second lot of potassium *tert*-butoxide (85 mg, 0.76 mmol) was added, and the mixture was heated to reflux. Again, an incipient red-orange color gradually changed to beige. The hot solution was filtered, and some silica was added. The filtrate was taken to dryness, and the remaining silica, with the absorbed product, was layered on top of a preconditioned column (EtOAc/heptane/Et_3N; 1/15/0.5%), which was eluted (EtOAc/heptane; 1/15) to furnish 153 mg (44%) of the title compound as a white crystalline solid. Each of the above steps was carried out under an inert atmosphere of nitrogen, and the isolated air sensitive product was stored in a freezer. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 2.12 (septet, 1H), 2.22 (s, 3H), 3.03 (m, 4H), 3.73 (d, 2H), 6.30 (br d, 1H), 6.75 (dd, 2H), 7.10 (m, 3H), 7.32 (m, 1H), 7.53 (d, 1H), 7.78 (br s, 1H). Direct inlet MS (EI) for $C_{21}H_{25}NO$ *m/z* (relative intensity): 307 (M^+, 35). Method E: 97.7% at t_R = 8.3 min.

2-[((3-*iso*-Butyloxy-2-methyl-phenyl)methyl)thio]indole (6). 2-Mercaptoindole (385 mg, 2.58 mmol) and NaOH (210 mg, 5.18 mmol) were dissolved in water (0.5 mL) and added to a solution of **23a** in methanol (6 mL) and reacted for 8 h at ambient temperature. The solvents were evaporated, and the residue was partitioned between CH_2Cl_2 and water. The organic layer was collected, and the aqueous layer was extracted with several additional portions of CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated to furnish a brown-red oil, which was purified on silica (EtOAc; hexane; 8/1) leaving 384 mg (50%) of the title compound as a pale yellow oil. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.04 (d, 6H), 2.1 (sept, 1H), 2.23 (s, 3H), 3.71 (d, 2H), 4.01 (s, 2H), 6.60 (broad d, 2H), 6.74 (d, 1H), 6.98 (t, 1H), 7.07 (m, 1H), 7.15 (m, 1H), 7.22 (d, 1H), 7.53 (d, 1H) 7.78 (broad s, 1H). LC-MS (negative ESI) for $C_{20}H_{23}NOS$ *m/z* (relative intensity): 324 (M-1, 88). Method F: 93.2% at t_R = 21.1 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)thio]indole (7). 2-Mercaptoindole (66 mg, 0.44 mmol) and **11** (85 mg, 0.4 mmol) were dissolved in methanol (2 mL). Sodium hydroxide (0.2 mL, 5 M) was added, and the mixture was allowed to react for 3.5 h in an inert atmosphere of nitrogen. The solvents were evaporated at reduced pressure (1 mm Hg) at 30 °C. Chromatography on silica (CH_2Cl_2/MeOH; 19/1) and subsequent crystallization from CH_2Cl_2/MeCN afforded 59 mg (45%) of the title compound as a white crystalline solid (59 mg, 45%). 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.04 (d, 6H), 2.20 (s, 3H), 3.76 (d, 2H), 4.16 (s, 2H), 6.52 (s, 1H), 6.68 (d, 1H), 7.04 (t, 1H), 7.12 (t, 1H), 7.36 (d, 1H), 7.50 (d, 1H), 8.36 (d, 1H), 10.64 (br s, 1H). Direct inlet MS (EI) for $C_{19}H_{22}N_2OS$ *m/z* (relative intensity): 326.5 (M+, 23). Method G: 99.9% at t_R = 11.4 min.

4-*iso*-Butyloxy-2-hydroxymethyl-3-methyl Pyridine (10). The title compound was prepared from **8** in two steps as described in ref 8.

4-*iso*-Butyloxy-2-chloromethyl-3-methyl Pyridine (11). The title compound was prepared as described in ref 8, method III. FAB-MS (3-nitrobenzyl alcohol) for $C_{11}H_{16}ClNO$ *m/z* (relative intensity): 214 ($M + H^+$, 100).

2-Aminomethyl-4-*iso*-butyloxy-3-methyl Pyridine (13). Compound **11** (0.58 g, 2.71 mmol) was transformed into the corresponding azide **12** according to the method described by Hassner et al.[30] and immediately reduced as described in ref 31. **Caution:** Benzyl azides are known to be explosive and should be handled with care! The material was purified on silica (CH_2Cl_2/CH_2Cl_2 saturated with NH_3; 100/0 to 0/100) leaving 0.35 g (66%) of the title compound as a beige solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.04 (d, 6H), 2.12 (m, 1H), 2.20 (s, 3H), 3.75 (d, 2H), 3.97 (s, 2H), 6.62 (d, 1H), 8.27 (d, 1H).

Diethyl 2-[(4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl]-malonate (15).[32] Diethyl malonate (7.8 mL, 51.2 mmol) was added dropwise to an ice-cold suspension of 60% NaH in oil (2.05 g, 51.2 mmol) in dry tetrahydrofuran (THF, 35 mL) kept under an atmosphere of nitrogen. The resulting mixture was allowed to attain room temperature and stirred until a clear solution was formed. Compound **11** (5.47 g, 25.6 mmol) in dry THF (20 mL) was added dropwise, and the mixture was allowed to react at ambient temperature for 18 h. The solvent was evaporated, and the residue was partitioned between water and Et_2O. The organic layer was washed with water, dried, and concentrated. The product was purified on silica ($PhCH_3$/EtOAc; 6/1 to 4/1) leaving 6.81 g (79%) of the title compound as a colorless oil. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 1.23 (t, 6H), 2.13 (m, 1H), 2.20 (s, 3H), 3.34 (d, 2H), 3.74 (d, 2H), 4.18 (m, 5H), 6.58 (d, 1H), 8.19 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{18}H_{27}NO_5$ *m/z* (relative intensity): 360 ($M + Na^+$, 100), 338 ($M + H^+$, 71), 190 (59). Method B (70% MeCN): 99.6% at t_R = 4.93 min.

3-[(4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl]propionic Acid (16). Compound **15** was dissolved in HCl (6 M, 70 mL) and heated to reflux for 6 h. The mixture was evaporated to dryness, and the residue was recrystallized from MeCN furnishing 5.33 g (79%) of the title compound as a white crystalline solid. 300 MHz ^{1}H NMR (DMSO-d_6): δ 1.04 (d, 6H), 2.12 (m, 1H), 2.24 (s, 3H), 2.,72 (t, 2H), 3.18 (t, 2H), 4.12 (d, 2H), 7.46 (d, 1H), 8.57 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{13}H_{19}NO_3$ *m/z* (relative intensity): 238 ($M + H^+$, 100). Method B (70% MeCN): 99.9% at t_R = 1.51 min.

Methyl 2-Methyl-3-*iso*-butoxy-benzoate (18a). Compound **17**[33] (5.0 g, 33 mmol) was dissolved in 75 mL of MeCN, and anhydrous K_2CO_3 (9.0 g, 66 mmol) was added followed by 1-bromo-2-methylpropane (5.9 g, 43 mmol). The mixture was allowed to react at reflux overnight, cooled, filtered, and taken to dryness. The residue was dissolved in CH_2Cl_2 and washed with diluted NaOH(aq) and brine. The organic layer was collected, dried, and evaporated furnishing 4.3 g (58%) of the title compound, which was used without further purification. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.03 (d, 6H), 2.11 (m, 1H), 2.42 (s, 3H), 3.71 (d, 2H), 3.87 (s, 3H), 6.93 (d, 1H), 7.20 (t, 1H), 7.35 (d, 1H).

Methyl 2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)-ethoxy]benzoate (18b). Compound **17**[33] was *O*-alkylated with the mesylate of triethylene glycol monomethyl ether[34] on a 3.0 mmol scale in 70% yield following the procedure described for **18a**. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.42 (s, 3H), 3.36 (s, 3H), 3.52−3.56 (m, 2H), 3.63−3.65 (m, 2H), 3.65−3.68 (m, 2H), 3.73−3.75 (m, 2H), 3.85−3.87 (m, 2H), 3.86 (s, 3H), 4.10−4.12 (m, 2H), 6.96 (d, 1H), 7.15 (t, 1H), 7.39 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{16}H_{24}O_6$ *m/z* (relative intensity): 313 ($M + H^+$, 10.3). Direct inlet MS (EI) for $C_{16}H_{24}O_6$ *m/z* (relative intensity): 312 (M^+, 7), 281 (6), 147 (13), 103 (31), 91 (12), 59 (100). Method B (80% MeCN): 78.8% at t_R = 2.79 min.

Methyl 2-Methyl-3-[2-(2-(2-(2-(2-methoxyethoxy)ethoxy)-ethoxy)ethoxy)ethoxy]benzoate (18c). Compound **17**[33] was *O*-alkylated with the mesylate of pentaethylene glycol monomethyl ether[35] on a 4.2 mmol scale in 97% yield following the procedure described for **18a**. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.43 (s, 3H), 3.36 (s, 3H), 3.54−3.57 (m, 2H), 3.62−3.68 (m, 12H), 3.73−3.75 (m, 2H), 3.86−3.89 (m, 2H), 3.85−3.87 (m, 2H), 3.88 (s, 3H), 4.11−4.14 (m, 2H), 6.98 (d, 1H), 7.16 (t, 1H), 7.40 (d, 1H).

Methyl 2-Methyl-3-[2-(morpholino)ethoxy]benzoate (18d). Compound **17**[33] (0.5 g, 3 mmol) was dissolved in 7 mL of MeCN, and anhydrous K_2CO_3 (0.91 g, 6.6 mmol) was added followed by 4-(2-chloroethyl)morpholine hydrochloride (0.62 g, 3.3 mmol). The mixture was allowed to react at reflux overnight, cooled, filtered, and taken to dryness, which afforded a quantitative yield (0.84 g) of the title compound, which

was used without further purification. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.44 (s, 3H), 2.61 (m, 4H), 2.86 (t, 2H), 3.74 (m, 4H), 3.90 (s, 3H), 4.13 (t, 2H), 7.00 (t, 1H), 7.20 (d, 1H), 7.42 (d, 1H).

3-*iso*-Butyloxy-2-methylbenzoic Acid (19a). Compound **18a** (1.0 g, 4.5 mmol) was dissolved in 1,2-dimethoxyethane (DME, 5 mL) and treated with NaOH (5 mL, 10% in H_2O) for 2 h at 75 °C. The solvent was evaporated, and the residue was partitioned between water and CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2, acidified with HCl to pH 2, and extracted with EtOAc. The latter organic layer was dried and evaporated to leave 0.89 g (95%) of the title compound as a light yellow solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.07 (d, 6H), 2.13 (m, 6H), 2.55 (s, 3H), 3.74 (d, 2H), 7.0 (d, 1H), 7.20 (t, 1H), 7.58 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{12}H_{16}O_3$ *m*/*z* (relative intensity): 209 ($M + H^+$, 21).

3-*iso*-Butyloxy-2-methylbenzyl Alcohol (20a). A solution of **18a** (10 g, 45 mmol) in THF (40 mL) was gently added to a stirred suspension of $LiAlH_4$ (3.41 g, 90 mmol) in THF (200 mL) under dry and inert conditions and then heated to reflux for 2 h. The reaction was quenched with 2.5 mL of water, 5 mL of 2 M NaOH, and 2.5 mL of water. The mixture was refluxed for another hour and then filtered to remove the solids. The filtrate was evaporated, and the residue was crystallized from heptane (100 mL) affording 8.57 g (98%) of the title compound as light-orange crystals. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 2.12 (m, 1H), 2.25 (s, 3H), 3.72 (d, 2H), 4.70 (d, 2H), 6.79 (d, 1H), 6.96 (d, 1H), 7.15 (t, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{12}H_{18}O_2$ *m*/*z* (relative intensity): 195 ($M + H^+$, 76). Method B (70% MeCN): >95% purity at t_R = 3.78 min.

2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzyl Alcohol (20b). The title compound was prepared on a 2.1 mmol scale in a 51% yield from **18b** according to the procedure given for **20a**. Direct inlet MS (EI) for $C_{15}H_{24}O_5$ *m*/*z* (relative intensity): 284 (M^+, 1), 266 (6), 147 (15), 103 (23), 91 (24), 59 (100).

2-Methyl-3-[2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-ethoxy)ethoxy]benzyl Alcohol (20c). The title compound was prepared on a 4.0 mmol scale in a 49% yield from **18c** according to the procedure given for **20a**. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.12 (s, 3H), 3.38 (s, 3H), 3.51−3.56 (m, 2H), 3.61−3.72 (m, 10H), 3.75−3.79 (m, 2H), 3.85−3.88 (m, 2H), 4.13−4.17 (m, 2H), 4.63−4.66 (s, 2H), 6.81 (d, 1H), 6.98 (d, 1H), 7.16 (t, 1H). Method A (40% MeCN, pH 7): 73.5% at t_R = 2.77 min.

2-Methyl-3-[2-(morpholino)ethoxy]benzyl Alcohol (20d). Crude **18d** (0.84 g, 3.0 mmol) was dissolved in dry THF (2 mL) and added to a suspension of $LiAlH_4$ (0.91 g, 24 mmol) in dry THF (5 mL). The mixture was heated to reflux for 1.5 h, cooled to room temperature, and quenched with aqueous NH_4Cl (5 mL). Solids were removed by filtration and rinsed with THF. The filtrate was evaporated, and the residue was purified on silica gel (MeOH/CH_2Cl_2; 1/19 to 1/10) leaving 1.51 g (90%) of the title compound as light-yellow crystals. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.26 (s, 3H), 2.61−2.67 (m, 4H), 2.83−2.89 (m, 2H), 3.73−3.90 (m, 4H), 4.15−4.21 (m, 2H), 4.73 (s, 2H), 6.84 (m, 1H), 7.02 (m, 1H), 7.19 (m, 1H).

3-*iso*-Butyloxy-2-methylbenzyl Bromide (22a).[36] Chlorotrimethylsilane (1.58 mL, 12.5 mmol) and compound **20a** (0.97 g, 5.0 mmol) were added to a mixture of LiBr (0,87 g, 10.0 mmol) and dry MeCN (10 mL). The reaction was heated to reflux for 18 h and then partitioned between Et_2O and water. The organic layer was washed with 10% Na_2CO_3 and brine. The organic layer was collected, dried, and evaporated. Preparative LC (65% MeCN) furnished 0.83 g (65%) of the title compound as a colorless oil. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 2.12 (m, 1H), 2.29 (s, 3H), 3.72 (d, 2H), 4,53 (s, 2H), 6.79 (d, 1H), 6.92 (d, 1H), 7.11 (t, 1H). Method B (70% MeCN): 99.0% at t_R = 9.6 min.

3-*iso*-Butyloxy-2-methylbenzyl Chloride (23a). Compound **20a** (0.7 g, 3.6 mmol) was dissolved 10 mL of CH_2Cl_2 and treated with $SOCl_2$ (314 μL, 4.32 mmol) for 30 min at ambient temperature. The solvent and excess reagent were evaporated leaving a quantitative yield of the title compound, which was used immediately in the next step. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.03 (d, 6H), 2.10 (m, 1H), 2.29 (s, 3H), 3.70 (d, 2H), 4.60 (s, 2H), 6.79 (d, 1H), 6.90 (d, 1H), 7.10 (t, 1H).

2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethoxy]benzyl Chloride (23b). The title compound was prepared on a 1.1 mmol scale from **20b** according to the procedure given for **23a**. Direct inlet MS (EI) *m*/*z* (relative intensity): 304 (M^++2, 1.7), 302 (M^+, 4.9), 149 (10), 147 (35), 103 (48), 91 (21), 59 (100).

2-Methyl-3-[2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-ethoxy)ethoxy]benzyl Chloride (23c). The title compound was prepared on a 2.0 mmol scale from **20c** according to the procedure given for **23a**. Direct inlet MS (EI) *m*/*z* (relative intensity): 392 (M^++2, 1.7), 390 (M^+, 5.8), 171 (11), 169 (37), 149 (71), 105 (17), 91 (24), 59 (100).

2-Methyl-3-[2-(morpholino)ethoxy]benzyl Chloride Hydrochloride (23d). The title compound was prepared on a 2.9 mmol scale from **20d** according to the procedure given for **23a**. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.16 (s, 3H), 3.07−3.18 (m, 2H), 3.50−3.57 (m, 2H), 3.59−3.66 (m, 2H), 3.96−4.05 (m, 2H), 4.22−4.35 (m, 2H), 4.61 (br s, 4H), 6.88 (d, 1H), 7.03 (d, 1H), 7.18 (t, 1H).

3-*iso*-Butyloxy-2-methylbenzylamine (25a). The title compound was prepared from **23a** (via **24a**) on a 7.72 mmol scale according to the procedure given for **13**. The material was purified on silica (CH_2Cl_2/CH_2Cl_2 saturated with NH_3; 100/0 to 0/100) leaving 1.14 g (76%) of the title compound as a beige solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.03 (d, 6H), 1.38 (br s, 2H), 2.11 (m, 1H), 2.22 (s, 3H), 3.70 (d, 2H), 3.83 (s, 2H), 6.72 (d, 1H), 6.89 (d, 1H), 7.12 (t, 2H). Method B (70% MeCN): 90.0% at t_R = 2.94 min.

Diethyl 2-[3-*iso*-Butoxy-2-methylbenzyl]malonate (26a).[32] The title compound was prepared on an 8.7 mmol scale from **23a** according to the procedure given for **15**. The product was purified on silica (heptane/EtOAc, 15:1) leaving 2.2 g (77%) of **26a** as a colorless oil. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.07 (d, 6H), 1.23 (t, 6H), 2.13 (m, 1H), 2.24 (s, 3H), 3.26 (d, 2H), 3.63 (t, 1H), 3.72 (d, 2H), 4.18 (m, 4H), 6.72 (d, 1H), 6.77 (d, 1H), 7.05 (t, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{28}O_5$ *m*/*z* (relative intensity): 359 ($M + Na^+$, 54), 291 (29), 177 (100). Method B (70% MeCN): 94.5% at t_R = 13.1 min.

3-[(3-*iso*-Butoxy-2-methyl)benzoyl]propionic Acid (27a).[37] Compound **26a** (2.11 g, 6.27 mmol) was dissolved in EtOH−H_2O (4:1, 10 mL) and treated with NaOH (2M, 5 mL) at ambient temperature for 24 h. The mixture was acidified with HCl (6 M), and the solvents were evaporated. The residue was partitioned between Et_2O and HCl (1 M). The organic layer was collected, dried, and evaporated leaving 1.75 g (99%) of the bis-carboxylic acid corresponding to compound **26a** as a white crystalline solid. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.07 (d, 6H), 2.13 (m, 1H), 2.25 (s, 3H), 3.30 (d, 2H), 3.73 (m, 3H), 6.75 (d, 1H), 6.79 (d, 1H), 7.08 (t, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{15}H_{20}O_5$ *m*/*z* (relative intensity): 303 ($M + Na^+$, 84), 281 (38), 280 (76), 177 (92). Method B (70% MeCN): 87.0% at t_R = 1.35 min. A round-bottomed flask charged with neat bis-carboxylic acid (1.62 g, 5.8 mmol) was heated in an oil bath to 130 °C until the evolution of carbon dioxide had ceased (about 2 h) furnishing 1.30 g (95%) of **27a** as a beige crystalline solid. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.08 (d, 6H), 2.13 (m, 1H), 2.23 (s, 3H), 2.66 (t, 2H), 3.00 (t, 2H), 3.73 (d, 2H), 6.74 (d, 1H), 6.79 (d, 1H), 7.10 (t, 1H). Direct inlet MS (EI) for $C_{14}H_{20}O_3$ *m*/*z* (relative intensity): 236 (M^+, 80), 180 (100), 162 (97). Method B (70% MeCN): 91.1% at t_R = 1.54 min.

2-Methyl-3-mercaptobenzoic Acid (29). Compound **28** (20.0 g, 0.11 mole) was hydrogenated and diazotized by standard experimental procedures. The diazonium salt was then transferred to a warm (55 °C) solution of potassium ethylxanthogenate (26.54 g, 0.166 mmol) over a 30 min period while the pH continually was adjusted to 8 with Na_2CO_3. **Caution:** Explosive byproducts may form, see ref 38, and it is recommended that the reaction is done behind protective shields. The mixture was stirred for 30 min, cooled to ambient temperature, and poured onto a mixture of 300 mL of

concentrated HCl and 700 mL of ice water. The precipitate was collected, taken up in water (300 mL), and treated with NaOH (12.0 g, 0.480 mole) at reflux for 20 h. The mixture was poured onto a mixture of 40 mL of concentrated HCl in 300 mL of ice water and extracted with 3 × 500 mL of CH_2Cl_2. The combined organic layers were dried and evaporated furnishing 14.66 g (79%) of the title compound as yellow crystals (which slowly oxidized to the corresponding disulfide upon standing). MHz ^{1}H NMR 500 ($CHCl_3$-*d*): δ 2.48 (s, 3H), 3.29 (s, 1H), 4.61 (broad s, 1H), 7.04 (t, 1H), 7.39 (d, 1H), 7.77 (d, 1H).

2-Methyl-3-mercapto-methylbenzoate (30). Compound **29** (14.7 g, 0.438 mol) was dissolved in 250 mL of MeOH, and a few drops of concentrated H_2SO_4 was added. The mixture was heated to reflux for 48 h and then allowed to cool to ambient temperature before the bulk MeOH was evaporated. The residue was dissolved in Et_2O and washed with 4 × 50 mL of H_2O and 50 mL of brine. The organic layer was collected, dried, and evaporated leaving 14.8 g (93% yield) of the title compound as a viscous yellow oil (which slowly oxidized to the corresponding disulfide upon standing). 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.53 (s, 3H), 3.40 (s, 1H), 3.89 (s, 3H), 7.09 (t, 1H), 7.41 (d, 1H), 7.58 (d, 1H).

2-Methyl-3-mercapto-benzyl Alcohol (31). A solution of **30** (2.0 g, 5.5 mmol) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (1.32 g, 33.2 mmol) in THF (100 mL) under dry and inert conditions. The mixture was heated to reflux for 2 h and then quenched with 2 mL of water, 4 mL of 2 M NaOH, and another 2 mL of water. After it was refluxed for another hour, solids were filtered off and washed with THF. The combined filtrates were evaporated, and the residue was partitioned between 2 M HCl and EtOAc. The organic layer was collected, dried, and evaporated to yield 0.79 g of crude **31** as an oil. According to LC method B (46% MeCN, λ = 226 nm, t_R = 3.6 min), the crude oil contained 80% of the sulfide and 15% of the corresponding disulfide. Another 1.1 g of the disulfide (80% pure by LC) could be isolated by MeOH washings of the solids. The combined sulfide−disulfide mixtures were then reduced as described in the procedure for **32a** furnishing 0.81 g (96%) of the title compound (which slowly oxidized to the corresponding disulfide upon standing). 400 MHz ^{1}H NMR (CH_3OH-d_4): δ 2.38 (s, 3H), 4.60 (s, 2H), 7.10 (t, 1H), 7.29 (d, 1H), 7.43 (d, 1H). 100 MHz ^{13}C NMR (CH_3-OH-d_4): δ 14.4, 62.12, 125.85, 127.38, 129.10, 135.58, 136.05, 140.24. Direct inlet MS (EI) for $C_8H_{10}OS$ *m/z* (relative intensity): 154 (M^+, 100), 137 (51), 136 (92), 135 (53), 121 (38), 92 (37), 91 (90), 77 (43).

2-Methyl-3-(2-(2-(2-methoxyethoxy)ethoxy)ethylthio)-benzyl Alcohol (32a). A mixture of **31** and its disulfide (50 mg, 0.325 mmol monomer) in dioxane/water (4/1) (1 mL) and a small amount of concentrated HCl were reacted with PPh_3 (26 mg, 0.1 mmol) for 1 h at ambient temperature in an inert atmosphere.[39] The solvents were removed, and the residue was taken up in MeCN (1 mL) and reacted with Et_3N (290 mL, 2.08 mmol) and the mesylate of triethylene glycol monomethyl ether[34] (0.30 g, 1.24 mmol) for 3 days at ambient temperature. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was collected, dried, and taken to dryness. The product was purified on silica (pentane/Et_2O; 6/4 to 0/10) furnishing 50 mg (51%) of the title compound as a colorless oil. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.39 (s, 3H), 3.05 (t, 2H), 3.37 (s, 3H), 3.50−3.70 (m, 10H), 4.67 (d, 2H), 7.15 (t, 1H), 7.23 (d, 1H), 7.30 (d, 1H). Method B (70% MeCN, λ = 230 nm): 85.0% at t_R = 3.14 min.

2-Methyl-3-[2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-ethoxy)ethylthio]benzyl Alcohol (32b). The title compound was prepared from **31** (1.07 g, 6.9 mmol) and the mesylate of pentaethylene glycol monomethyl ether[35] (2.29 g, 6.9 mmol) by the same method as that described for **32a**. The crude material was purified by preparative LC (50% MeCN) to give 0.87 g (32%) of the title compound as a colorless oil. 400 MHz $_1$H NMR ($CHCl_3$-*d*): δ 2.42 (s, 3H), 3.08 (t, 2H), 3.38 (s, 3H), 3.54 (q, 2H), 3.56−3.69 (m, 16H), 4.70 (s, 2H), 7.16 (t, 1H), 7.23 (d, 1H), 7.32 (d, 1H). Method B (60% MeCN): 97.0% at t_R = 2.5 min.

2-Methyl-3-[2-(morpholino)ethylthio]benzyl Alcohol (32c). Compound **29** (1.0 g, 5.95 mmol) was dissolved in dry MeCN (15 mL). Potassium carbonate (5.76 g, 41.7 mmol) and *N*-(2-chloroethyl)morpholine (2.77 g, 14.9 mmol) were added and allowed to react at reflux for 16 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (200 mL) and brine (30 mL). The organic layer was dried and evaporated furnishing crude **35c**, which was dissolved in dry THF (5 mL) and added to a suspension of $LiAlH_4$ (0.91 g, 24 mmol) in dry THF (25 mL). The mixture was reacted at reflux for 2 h and then quenched with aqueous NH_4Cl. Solids were filtered off and washed with THF. The combined filtrates were evaporated, and the residue was purified on silica (MeOH/ CH_2Cl_2; 1:19 to 1:10) leaving 1.51 g (90%) of the title compound as a light yellow crystalline material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.37 (s, 3H), 2.38−2.44 (m, 4H), 2.52−2.61 (m, 2H), 2.92−2.98 (m, 2H), 3.59−3.64 (m, 4H), 4.61 (s, 2H), 7.09 (t, 1H), 7.16 (d, 1H), 7.22 (d, 1H).

3-*iso*-Butylthio-2-methylbenzyl Alcohol (32d). The title compound was prepared from **31** (0.43 g, 2.8 mmol) and *iso*-butylbromide (0.45 g, 3.3 mmol) using the same method as that described for **32a**. The crude material was purified on silica (CH_2Cl_2/MeOH; 99/1) leaving 0.29 g (49%) of the title compound as a colorless oil. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 1.87 (m, 1H), 2.41 (s, 3H), 2.76 (d, 2H), 4.71 (d, 2H), 7.13−7.21 (m, 2H), 7.25 (d, 1H). Method B (70% MeCN): 95.0% at t_R = 4.1 min.

2-Methyl-3-[2-(2-methyl-5-nitroimidazol-1-yl)ethylthio]-benzyl Alcohol (32e). A mixture of **31** (1.15 g, 7.47 mmol), 1-(2-chloroethyl)-2-methyl-5-nitroimidazol (1.41 g, 7.44 mmol), and K_2CO_3 (2.4 g, 17.4 mmol) was reacted in an inert atmosphere at reflux for 5 h. The solvent was evaporated, and the residue was partitioned between 400 mL of EtOAc and 100 mL of water. The organic phase was collected and washed with water followed by brine. Some silica was added, and the solvent was carefully removed under reduced pressure. The silica was layered on top of a flash column and eluted with EtOAc. Pure fractions were pooled and taken to dryness. The residue was recrystallized from a few milliliters of EtOH furnishing 730 mg (32%) of crystalline material; mp 110−112 °C. Reprocessing of the mother liquor gave another 560 mg (24%) of product. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.36 (s, 3H), 2.40 (s, 3H), 3.27 (t, 2H), 4.45 (t, 2H), 4.70 (d, 2H), 7.13−7.33 (m, 3H), 7.82 (s, 1H). 75.5 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 14.26, 15.67, 33.05, 45.79, 63.76, 126.47, 126,76, 129.04, 133.11, 133.73, 136.77, 140.16, 150.50. (Two aromatic carbon signals coincide.)

2-Methyl-3-[2-(1,2,4-triazol-1-yl)ethylthio]benzyl Alcohol (32f). 1,2,4-Triazole (13.8 g, 0.2 mol) was added to a solution of Na (4.6 g, 0.2 mol) in 200 mL of 99.5% ethanol and allowed to form a clear solution. 2-Chloroethyl benzenesulfonate[40] (44 g, 0.2 mol) was added, and the mixture was heated to reflux for 15 min and then left at ambient temperature overnight. Sodium benzenesulfonate was filtered off, and the filtrate was concentrated to a syrup, which was redissolved in 200 mL of dichloromethane. A second crop of crystals was filtered off, and the filtrate was evaporated to leave a colorless oil. Vacuum distillation, collecting the fraction between 68 and 78 °C at 0.1 mm Hg, afforded 17 g (65%) of 1-(2-chloroethyl)-1,2,4-triazole.[41] 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 3.62 (t, 2H), 4.23 (t, 2H), 7.71 (s, 1H), 7.97 (s, 1H). 75 MHz ^{13}C NMR: δ 41.6, 50.3, 143.5, 151.6. The triazole (900 mg, 6.8 mmol), **31** (740 mg, 4.4 mmol), and K_2CO_3 (1.8 g, 13 mmol) were heated to reflux for 1 h in 20 mL of MeCN kept under an inert atmosphere. Solids were removed, the filter cake was washed with MeCN, and the combined filtrates were evaporated. Purification on silica (EtOAc) gave 1 g (90%) of an oil that crystallized to a waxy solid. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.34 (s, 3H), 3.27 (t, 2H). 3.56 (broad, 1H) 4.27 (t, 2H), 4.63 (d, 2H), 7.08−7.29 (m, 3H), 7.81 (s, 1H), 7.93 (s, 1H). 75.5 MHz

^{13}C NMR ($CHCl_3$-*d*): δ 15.55, 33.17, 48.69, 63.16, 126.24, 126.54, 129.32, 133.46, 136.81, 140.35, 143.30, 151.88.

2-Methyl-3-[2-(2-(2-methoxyethoxy)ethoxy)ethylthio]-benzyl Chloride (33a). The title compound was prepared on a 0.17 mmol scale from **32a** according to the procedure given for **23a**. Method B (70% MeCN, λ = 226 nm): 90.0% at t_R = 5.79 min.

2-Methyl-3-[2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-ethoxy)ethylthio]benzyl Chloride (33b). The title compound was prepared on a 0.50 mmol scale from **32b** according to the procedure given for **23a**. Method B (60% MeCN): 98.0% at t_R = 5.4 min.

2-Methyl-3-[2-(morpholino)ethylthio]benzyl Chloride Hydrochloride (33c). The title compound was prepared on a 5.2 mmol scale from **32c** according to the procedure given for **23a**. 400 MHz ^{1}H NMR ($CDCl_3$-*d*): δ 2.49 (s, 3H), 2.81−2.92 (m, 2H), 3.12−3.17 (m, 2H), 3.43−3.55 (m, 4H), 3.95−4.01 (m, 2H), 4.23−4.34 (m, 2H), 4.62 (s, 2H), 7.20−7.29 (m, 2H), 7.48 (d, 1H).

3-*iso*-Butylthio-2-methylbenzyl Chloride (33d). The title compound was prepared on a 1.95 mmol scale from **32d** according to the procedure given for **23a**. Method B (70% MeCN): 90.0% t_R = 9.8 min.

2-Methyl-3-[2-(2-methyl-5-nitroimidazol-1-yl)ethylthio]-benzyl Chloride (33e). The title compound was prepared on a 1.8 mmol scale from **32e** according to the procedure given for **23a**. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.46 (s, 3H), 2.47 (s, 3H), 3.32 (t, 2H), 4.51 (t, 2H), 4.60 (s, 2H), 7.13−7.36 (m, 3H), 7.93 (s, 1H). 75.5 MHz ^{13}C NMR ($CDCl_3$): δ 13.26, 15.75, 32.66, 44.81, 45.91, 126.59, 128.91, 129.04, 129.78, 133.94, 137.01, 137.70, 149.59.

2-Methyl-3-[2-(1,2,4-triazol-1-yl)ethylthio]benzyl Chloride (33f). The title compound was prepared on a 0.4 mmol scale from **32f** according to the procedure given for **23a** and immediately used in the next step without further characterization.

2-[2-(3-*iso*-Butoxy-2-methylphenyl)ethyl]-1*H*-benzimidazol (39). 1,2-Diaminobenzene (151 mg, 1.40 mmol) and 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (462 mg, 1.52 mmol) were added to a solution of **27a** (300 mg, 1.27 mmol) in CH_2Cl_2 (3 mL) and reacted at ambient temperature for 12 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and 5% $NaHCO_3$. The organic layer was collected, dried, and evaporated. The residue was purified by preparative LC (55% MeCN) leaving 180 mg (43%) of **36** as a beige crystalline solid. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.04 (d, 6H), 2.08 (m, 1H), 2.21 (s, 3H), 2.57 (t, 2H), 3.02 (t, 2H), 3.72 (d, 2H), 6.70 (m, 3H), 6.77 (d, 1H), 7.03 (m, 3H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): 11.27, 19.30, 28.41, 29.39, 37.40, 74.46, 109.21, 117.72, 119.21, 121.06, 123.98, 124.80, 125.51, 126.17, 127.06, 139.95, 140.77, 157.34, 171.18. FAB-MS (3-nitrobenzyl alcohol) for $C_{20}H_{26}N_2O_2$ *m/z* (relative intensity): 327 (M + H$^+$, 100). Method B (70% MeCN): 96.9% at t_R = 7.38 min.

Pyridinium *p*-toluenesulfonate (304 mg, 1.2 mmol) was added to a mixture of **36** (132 mg, 0.40 mmol) in 1,2-dichloroethane (2 mL) and reacted in an inert atmosphere over molecular sieves (4 Å) for 20 h at reflux. The mixture was filtered, and the filtrate was partitioned between CH_2Cl_2 and saturated citric acid. The organic layer was washed with water, dried, and evaporated. The material was purified on silica ($PhCH_3$/EtOAc; 3/1) leaving 99 mg (81%) of the title compound as a beige crystalline solid. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.07 (d, 6H), 2.13 (m, 1H), 2.16 (s, 3H), 3.23 (s, 4H), 3.71 (d, 2H), 6.71 (m, 2H), 7.03 (t, 1H), 7.25 (m, 2H), 7.58 (broad s, 2H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): 11.12, 19.31, 28.41, 30.09, 32.11, 74.45, 109.27, 120.89, 122.18, 124.80, 126.22, 139.79, 154.46, 157.29. FAB-MS (3-nitrobenzyl alcohol) for $C_{20}H_{24}N_2O$ *m/z* (relative intensity): 309 (M + H$^+$, 100). Method A (58% MeCN, λ = 270 nm): 94.6% at t_R = 8.3 min. Method C: 98% at t_R = 9.11 min.

2-[2-(4-*iso*-Butoxy-3-methyl-2-pyridyl)ethyl]-1*H*-benzimidazol (40). A mixture of **16** (200 mg, 0.84 mmol) and 1,2-diaminobenzene (150 mg, 1.38 mmol) in HCl (1.5 mL, 6 M) was refluxed for 20 h. The mixture was carefully neutralized with aqueous 10% NaOH and then partitioned between CH_2Cl_2 and aqueous 5% $NaHCO_3$. The organic layer was collected, dried, and evaporated. Purification on silica (CH_2Cl_2/MeOH, 96/4) afforded 260 mg (99%) of the title compound as a beige crystalline solid. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.05 (d, 6H), 2.15 (m, 1H), 2.21 (s, 3H), 3.30 (m, 2H), 3.42 (t, 2H), 3.77 (d, 2H), 6.68 (d, 1H), 7.18 (m, 2H), 7.55 (broad s, 2H), 8.35 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{23}N_3O$ *m/z* (relative intensity): 310 (M + H$^+$, 100). Method A (58% MeCN, λ = 280 nm): 99.0% at t_R = 9.8 min. Method B (50% MeCN): 96.9% at t_R = 6.75 min.

2-[2-(3-*iso*-Butoxy-2-methylphenyl)ethyl]benzoxazole (41).[42] 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (421 mg, 2.2 mmol) and 2-aminophenol (203 mg, 1.86 mmol) were added to a solution of **27a** (400 mg, 1.7 mmol) in MeCN (5 mL) and reacted at ambient temperature for 18 h. The solvent was evaporated, and the residue partitioned between CH_2Cl_2 and saturated citric acid. The organic layer was collected, dried, and evaporated. Purification on silica (hexane/EtOAc; 5/1) afforded 393 mg (71%) of compound **37** as a white crystalline solid. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.05 (d, 6H), 2.10 (m, 1H), 2.19 (s, 3H), 2.64 (t, 2H), 3.04 (t, 2H), 3.71 (d, 2H), 6.74 (m, 2H), 6.80 (t, 1H), 6.85 (d, 1H), 6.97 (d, 1H), 7.08 (m, 2H), 7.46 (broad s, 1H), 8.80 (broad s, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): 11.29, 19.33, 28.43, 29.30, 37.55, 74.51, 109.45, 119.62, 120.37, 120.97, 122.12, 124.80, 125.47, 126.38, 127.08, 139.32, 148.57, 157.43, 172.75. FAB-MS (3-nitrobenzyl alcohol) for $C_{20}H_{25}NO_3$ *m/z* (relative intensity): 328 (M + H$^+$, 50), 219 (100). Method B (60% MeCN): 92.0% at t_R = 11.12 min.

Hexamethyldisiloxane (1.63 mL, 7.6 mmol) was added to a solution of P_2O_5 (0.95 g, 6.7 mmol) in dry 1,2-dichloroethane (3.5 mL) under an inert atmosphere and then heated to reflux for 10 min. Compound **37** dissolved in 1,2-dichloroethane (3.5 mL) was added and allowed to react for 3 h at reflux. The mixture was poured onto ice water and extracted with CH_2Cl_2. The organic layer was collected, dried, and evaporated. Purification on silica (hexane/EtOAc; 15/1) afforded 200 mg (63%) of compound **41** as a colorless oil. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.05 (d, 6H), 2.11 (m, 1H), 2.27 (s, 3H), 3.10 (m, 4H), 3.87 (d, 2H), 6.72 (d, 1H), 6.82(d, 1H), 7.07 (t, 1H), 7.30 (m, 2H), 7.50 (m, 1H), 7.70 (m, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): 11.23, 19.34, 28.47, 29.51, 30.71, 74.53, 109.41, 110.29, 119.41, 120.84, 124.12, 124.54, 124.86, 126.26, 139.53, 141.30, 150.79, 157.37, 166.44. FAB-MS (3-nitrobenzyl alcohol) for $C_{20}H_{23}NO_2$ *m/z* (relative intensity): 310 (M + H$^+$, 100). Method A (70% MeCN): 94.4% at t_R = 8.8 min. Method C: 91% at t_R = 18.16 min.

2-[2-(4-*iso*-Butoxy-3-methyl-2-pyridyl)ethyl]benzoxazole (42).[43,44] Compound **38** was prepared on a 0.84 mmol scale in 90% yield from **16** according to the procedure given for **37** in the experimental of **41** above. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.04 (d, 6H), 2.13 (m, 1H), 2.20 (s, 3H), 2.92 (t, 2H), 3.10 (t, 2H), 3.76 (d, 2H), 6.46 (d, 1H), 6.78 (t, 1H), 6.92 (d, 1H), 7.00 (t, 1H), 7.24 (d, 1H), 8.25 (d, 1H), 10.25 (broad s, 1H). 100 MHz ^{13}C NMR ($CHCl_3$-*d*): 10.36, 19.13, 28.16, 30.11, 35.04, 74.52, 105.29, 118.44, 119.71, 120.68, 121.64, 125.96, 126.56, 146.57, 148.58, 158.16, 163.83, 172.90. FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{24}N_2O_3$ *m/z* (relative intensity): 329 (M + H$^+$, 90), 220 (50). Method A (40−70% MeCN, λ = 280 nm): 93.6% at t_R = 14.1 min. Method B (60% MeCN): 98.0% at t_R = 5.32 min.

Compound **38** (249 mg, 0.76 mmol) was added to a solution of P_2O_5/CH_3SO_3H (1/10, w/w, 2.2 g) and stirred at ambient temperature for 1 h and then at 70 °C for 10 h. The reaction was quenched with 5% $NaHCO_3$ and then partitioned between 10% NaOH and CH_2Cl_2. The organic layer was dried, filtered, and evaporated. Purification on silica (heptane/EtOAc; 1/1) afforded 30 mg (13%) of the title compound **42** as a yellow crystalline solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.04 (d, 6H), 2.13 (m, 1H), 2.21 (s, 3H), 3.40 (m, 4H), 3.77 (d, 2H), 6.63 (d, 1H), 7.30 (m, 2H), 7.48 (m, 1H), 7.68 (m, 1H), 8.27 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{22}N_2O_2$ *m/z* (relative

intensity): 311 (M + H^+, 100). Method A (70% MeCN, λ = 245 nm): 98.8% at t_R = 7.8 min. Method D: 93% at t_R = 3.95 min.

2-[2-(3-*iso*-Butoxy-2-methylphenyl)ethyl]benzothiazole (43).[43,44] 2-Aminothiophenol (79 mg, 0.63 mmol) and **27a** (100 mg, 0.43 mmol), in that order, were added to a solution of P_2O_5/CH_3SO_3H (1/10, w/w, 1 g) reacted at room temperature for 1 h and at 70 °C for 10 h. The reaction was quenched with 5% $NaHCO_3$ and then partitioned between 10% NaOH and CH_2Cl_2. The organic layer was dried, filtered, and evaporated. Purification on silica (heptane/EtOAc; 15/1) afforded 78 mg (56%) of compound **43** as a slightly yellow oil. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.06 (d, 6H), 2.13 (m, 1H), 2.26 (s, 3H), 3.21 (t, 2H), 3.36 (t, 2H), 3.72 (d, 2H), 6.73 (d, 1H), 6.84 (d, 1H), 7.11 (t, 1H), 7.36 (t, 1H), 7.47 (t, 1H), 7.85 (d,1H), 8.02 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{20}H_{23}NOS$ *m/z* (relative intensity): 326 (M + H^+, 100). Method A (70% MeCN, λ = 245 nm): 99.9% at t_R = 7.0 min. Method D: 98% at t_R = 4.92 min.

2-[2-(4-*iso*-Butoxy-3-methyl-2-pyridyl)ethyl]benzothiazole (44). A mixture of **16** (100 mg, 0.42 mmol) and 2-aminothiophenol (116 mg, 0.96 mmol) was heated to reflux in HCl (1 mL, 6 M) for 20 h. The mixture was carefully neutralized with 10% NaOH and then partitioned between CH_2Cl_2 and 5% $NaHCO_3$. The organic layer was collected, dried, and evaporated. Purification on silica (CH_2Cl_2/MeOH; 98/2) afforded 41 mg (30%) of the title compound as a yellow oil. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.08 (d, 6H), 2.17 (m, 1H), 2.24 (s, 3H), 3.40 (t, 2H), 3.64 (t, 2H), 3.80 (d, 2H), 6.68 (d, 1H), 7.38 (t, 1H), 7.49 (t, 1H), 7.88 (d, 1H), 8.03 (d, 1H), 8.35 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{22}N_2OS$ *m/z* (relative intensity): 327 (M + H^+, 100). Method A (70% MeCN, λ = 280 nm): 97.8% at t_R = 8.6 min. Method C: 97% at t_R = 8.09 min.

2-[2-(3-*iso*-Butoxy-2-methylphenyl)ethyl]benzofuran (47). Oxalyl chloride (519 mg, 4.09 mmol) and a catalytic amount of DMF was added to **27a** (485 mg, 2.05 mmol) dissolved in dry CH_2Cl_2 (15 mL) and reacted at ambient temperature in an inert atmosphere for 2 h. The mixture was taken to dryness, and the crude acid chloride **45** was dissolved in dry toluene (25 mL) and reacted with Et_3N (626 mg, 6.18 mmol) and 2-hydroxybenzyl triphenyl phosphonium bromide[45,46] (921 mg, 2.05 mmol) at reflux for 8 h. Precipitated materials were filtered off and washed several times with Et_2O. The combined filtrates were evaporated, and the residue was filtered through a short plug of silica. Preparative LC (74% MeCN) afforded 84 mg (13%) of the title compound as a yellow oil. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.06 (d, 6H), 2.13 (m, 1H), 2.25 (s, 3H), 3.02 (m, 2H), 3.07 (m, 2H), 3.73 (d, 2H), 6.41 (s, 1H), 6.73 (d, 1H), 6.80 (d, 1H), 7.08 (t, 1H), 7.19 (t, 1H), 7.23 (t, 1H), 7.45 (d, 1H), 7.49 (d, 1H). 150 MHz ^{13}C NMR ($CHCl_3$-*d*): 11.23, 19.37, 28.50, 29.43, 31.86, 74.54, 102.11, 109.17, 110.75, 120.27, 120.99, 121.00, 122.42, 123.20, 124.84, 126.08, 128.92, 140.37, 154.67, 157.33, 158.73. Direct inlet MS (EI) for $C_{21}H_{24}O_2$ *m/z* (relative intensity): 308 (M^+, 25), 177 (40), 131 (100). Method A (75% MeCN, λ = 245 nm): 99.8% at t_R =11.7 min. Method B (89% MeCN): 97.6% at t_R = 5.77 min.

2-[2-(4-*iso*-Butoxy-3-methyl-2-pyridyl)ethyl]benzofuran (48). The title compound was prepared on a 0.42 mmol scale starting from **16** according to the procedure for **47**. Preparative HPLC (56% MeCN) afforded 60 mg (15%) of the title compound as a yellow oil. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): 1.03 (d, 6H), 2.10 (m, 1H), 2.13 (s, 3H), 3.18 (m, 4H), 3.67 (d, 2H), 6.37 (s, 1H), 6.56 (d, 1H), 7.17 (m, 2H), 7.37 (d, 1H), 7.41 (d, 1H), 8.27 (d, 1H). 125 MHz ^{13}C NMR ($CHCl_3$-*d*): 10.43, 19.14, 27.61, 28.15, 33.26, 74.21, 102.10, 104.64, 110.68, 119.91, 120.21, 122.31, 123.07, 128.93, 147.54, 154.63, 158.79, 158.86, 163.26. FAB-MS (3-nitrobenzyl alcohol) for $C_{20}H_{24}NO_2$ *m/z* (relative intensity): 310 (M + H^+, 25). Method A (70% MeCN, λ = 245 nm): 94.3% at t_R = 11.4 min. Method C: 92% at t_R = 9.18 min.

2-[(3-*iso*-Butyloxy-2-methylphenyl)methylamino]-1*H*-benzimidazole (59). Activated MnO_2 (12 g, 139 mmol) and **20a** (1.0 g, 5.15 mmol) were mixed in CH_2Cl_2 (4 mL) and reacted in an inert atmosphere at ambient temperature for 45 min. The mixture was filtered through Celite, and the filtrate was taken to dryness leaving 0.87 g (88%) of **21a** as a yellow oil. Method B (70% MeCN): 99.0% at t_R = 6.09 min. The aldehyde **21a** was mixed with **52** (0.60 g, 4.53 mmol) and K_2CO_3 (1.25 g, 9.05 mmol) in MeOH (5 mL) and reacted at ambient temperature for 27 h. Solids were removed, and the filtrate was evaporated leaving the imine **54** as an orange oil. FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{21}N_3O$ *m/z* (relative intensity): 308 (M + H^+, 100). The imine **54** was dissolved in MeOH (5 mL) and reacted with small portions of $NaCNBH_3$ (0.81 g, 12.9 mmol) at 0 °C.[47] After it reacted for 2 h, the bulk of the solvent was removed and the residue was partitioned between H_2O (pH 9) and EtOAc. The organic layer was dried and evaporated, and the resulting red oil was crystallized from MeOH/EtOAC/Et_2O (0.5/1/8.5) affording the title compound 0.64 g (40%) as beige crystals. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.03 (d, 6H), 2.10 (m, 1H), 2.20 (s, 3H), 3.70 (d, 2H), 4.55 (s, 2H), 4.98 (br s, 1H), 6.77 (d, 1H), 6.91 (d, 1H), 7.03 (m, 2H), 7.09 (t, 1H), 7.26 (m, 2H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{23}N_3O$ *m/z* (relative intensity): 310 (M + H^+, 100). Method A (58% MeCN, λ = 284 nm): 100% at t_R = 7.5 min. Method B (70% MeCN): 99.0% at t_R = 3.69 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)amino]-1*H*-benzimidazole (60). The title compound was prepared on a 2.56 mmol scale in 41% yield following the procedure for **59**. Required building blocks were **10** (to give **14**) and **52**. Precipitation from MeOH/Et_2O afforded crystalline material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.07 (d, 6H), 2.15 (m, 1H), 2.30 (s, 3H), 3.79 (d, 2H), 4.67 (s, 2H), 6.75 (d, 1H), 7.22 (dd, 2H), 7.34 (dd, 2H), 8.29 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{18}H_{22}N_4O$ *m/z* (relative intensity): 311 (M + H^+, 56). Method A (52−70% MeCN, λ = 285 nm): 100% at t_R = 10.9 min. Method B (70% MeCN): 99% at t_R = 3.21 min.

2-[((3-*iso*-Butyloxy-2-methylphenyl)methyl)amino]benzothiazole (61). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.07 g, 5.56 mmol), 4-(*N*,*N*-dimethylamino)-pyridine (1.05 g, 8.56 mmol), **19a** (0.89 g, 4.28 mmol), and **49** (0.70 g, 4.71 mmol) were mixed in MeCN (30 mL) and reacted at ambient temperature for 17 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and 0.5 M HCl. The organic layer was collected, washed with brine, dried, and evaporated. Preparative LC (70% MeCN) afforded 0.81 g (56%) of the amide **53** as a beige solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 0.99 (d, 6H), 2.03 (m, 1H), 2.32 (s, 3H), 3.60 (d, 2H), 6.84 (t, 1H), 6.86 (t, 1H), 7.07−7.17 (m, 3H), 7.25 (t, 1H), 7.78 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{20}N_2O_2S$ *m/z* (relative intensity): 341 (M + H^+, 100). Method A (60% MeCN, λ = 285 nm): 94.0% at t_R = 9.40 min). Method B (70% MeCN): 99.0% at t_R = 6.28 min.

Compound **53** (0.5 g, 1.47 mmol) dissolved in THF (2 mL) was added to a suspension of $LiAlH_4$ (61 mg, 1.6 mmol) in THF (6 mL) and reacted under dry conditions an inert atmosphere at ambient temperature for 12 h. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, water (1 mL), 2 M NaOH (2 mL), and water (3 mL). The solids were filtered off, the filtrate was evaporated, and the residue was recrystallized from MeCN affording 0.47 g (97%) of the title compound as white crystals. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 2.13 (m, 1H), 2.27 (s, 3H), 3.73 (d, 2H), 4.63 (s, 2H), 6.81 (d, 1H), 6.95 (d, 1H), 7.09 (t, 1H), 7.14 (t, 1H), 7.30 (t, 1H), 7.58 (d, 1H), 7.60 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{19}H_{22}N_2OS$ *m/z* (relative intensity): 327 (M + H^+, 100). Method A (60% MeCN, λ = 270 nm): 95.0% at t_R = 11.5 min. Method B (70% MeCN): 94.0% at t_R = 8.36 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)amino]-benzothiazole (62). Compound **13** (30 mg, 0.15 mmol) in dry THF (1 mL) was added to a suspension of NaH (6 mg, 14 mmol) in dry THF (0.5 mL) kept in an inert atmosphere. 2-Fluorobenzthizole **50** (25 μL, 0.22 mmol) was added slowly (**Caution:** The reaction is strongly exotermic) and was allowed to react at ambient temperature for 20 h. The reaction was quenched with water and then extracted with CH_2Cl_2. The organic layer was evaporated, and the residue was purified

by preparative LC (60% MeCN) to give 10 mg (20%) of the title compound. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.06 (d, 6H), 2.15 (m, 1H), 2.22 (s, 3H), 3.78 (d, 2H), 4.72 (s, 2H), 6.71 (d, 1H), 7.00−7.63 (m, 4H), 8.23 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{18}H_{21}N_3OS$ *m/z* (relative intensity): 328 ($M + H^+$, 100). Method A (70% MeCN): 96.0% at $t_R = 5.96$ min. Method D: 93% at $t_R = 3.97$ min.

2-((3-*iso*-Butyloxy-2-methylphenyl)methylamino)benzoxazole (63). Compound **25a** (180 mg, 0.87 mmol) dissolved in dry DMF (1 mL) was added to a suspension of NaH (38 mg, 0.87 mmol) in dry THF (1 mL) kept in an inert atmosphere. After 2 min, 2-chlorobenzoxazole **51** (66μL, 0.59 mmol) was added slowly and allowed to react for 1.5 h at ambient temperature. The reaction was quenched with water (1 mL). Volatile solvents were removed in vacuo, and the residue was purified by preparative LC (50−70% MeCN) affording 77 mg (29%) of the title compound as a white solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 2.13 (m, 1H), 2.28 (s, 3H), 3.73 (d, 2H), 4.66 (s, 2H), 5.30 (broad s, 1H), 6.82 (d, 1H), 6.95 (d, 1H), 7.03 (t, 1H), 7.14 (t, 1H), 7.17 (t, 1H), 7.25 (d, 1H), 7.36 (d, 1H). LC-MS (ESI) for $C_{19}H_{22}N_2O_2$ *m/z* (relative intensity): 311 ($M + H^+$, 14). Method A (58% MeCN, $\lambda = 244$ nm): 99.0% at $t_R = 12.8$ min. Method D: 98% at $t_R = 4.23$ min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)amino]-benzoxazole (64). The title compound was prepared on a 0.51 mmol scale in 11% yield starting from compound **13** according to the procedure given for **63**. Purification by preparative LC (60% MeCN) furnished the title compound as a white solid. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.07 (d, 6H), 2.10 (m, 1H), 2.20 (s, 3H), 3.78 (d, 2H), 4.67 (d, 2H), 6.71 (d, 1H), 7.03 (t, 1H), 7.10 (broad s, 1H), 7.15 (t, 1H), 7.27 (d, 1H), 7.42 (d, 1H), 8.29 (d, 1H). LC-MS (ESI) for $C_{18}H_{21}N_3O_2$ *m/z* (relative intensity): 312 ($M + H^+$, 54), 256 (100), 239 (11). Method A (58% MeCN, $\lambda = 241$ nm): 98.0% at $t_R = 6.0$ min. Method B (70% MeCN): 99.0% at $t_R = 5.39$ min.

2-[(3-[2-(2-(2-Methoxyethoxy)ethoxy)ethylthio]-2-methylphenyl)methylamino]-1*H*-benzimidazole (65). The title compound was prepared on a 0.47 mmol scale in 70% yield following the procedure for **59**. Required building blocks were **32a** (to give **34a**) and **52**. Preparative LC (46% CH_3CN) furnished the title compound as a white solid. 500 MHz ^{1}H NMR ($CHCl_3$-d_1): δ 2.04 (s, 3H), 2.92 (t, 2H), 3.33 (s, 3H), 3.56 (m, 2H), 3.62 (m,4H), 3.67 (m, 4H), 4.31 (s, 2H), 6.98 (t, 1H), 7.06 (d, 1H), 7.09 (dd, 2H), 7.14 (d, 1H), 7.18 (dd, 2H). 100 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 15.93, 33.25, 46.03, 58.91, 69.92, 69.97, 70.34, 70.47, 71.75, 126.21, 126.90, 130.03, 136.04, 137.18, 137.46, 154.92. FAB-MS (glycerol) for $C_{22}H_{29}N_3O_3S$ *m/z* (relative intensity): 416 ($M + H^+$, 100). Method A (40−70% MeCN, $\lambda = 285$ nm): 98% at $t_R = 9.5$ min. Method C: 97% at $t_R = 6.53$ min.

2-[(3-[2-(2-(2-Methoxyethoxy)ethoxy)ethylthio]-2-methylphenyl)methylamino]-1*H*-benzothiazole (66). The title compound was prepared on a 0.65 mmol scale in 53% yield following the procedure for **59**. Required building blocks were **32a** (to give **34a**) and **49**. Preparative LC (50% MeCN) afforded 186 mg of enriched material, which was further purified on silica (EtOAc/heptane containing 2% *iso*-PrOH); overall yield, 0.15 g (53%). 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.41 (s, 3H), 3.07 (t, 2H), 3.35 (s, 3H), 3.51 (m, 2H), 3.60 (m, 6H), 3.64 (t, 2H), 4.61 (s, 2H), 7.07 (dt, 1H), 7.12 (t, 1H), 7.18 (d, 1H), 7.27 (dt, 1H), 7.31 (d, 1H), 7.52 (d, 1H), 7.55 (dd, 1H). 100 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 16.11, 32.95, 49.64, 59.04, 69.69, 70.47, 70.63, 71.97, 117.66, 121.54, 124.54, 126.05, 126.81, 128.12, 129.22, 132.51, 137.74, 143.96, 169.09. LC-MS (APcI) for $C_{22}H_{28}N_2O_3S_2$ *m/z* (relative intensity): 433 ($M + H^+$, 100). Method A (40−70% MeCN): 99% at $t_R =$ min. Method C: 100% at $t_R = 12.06$ min.

2-[(3-[2-(Morpholino)ethylthio]-2-methylphenyl)methylamino]-1*H*-benzimidazole (67). The title compound was prepared on a 0.69 mmol scale in 15% yield following the procedure for **59**. Required building blocks were **32c** (to give **34c**) and **52**. The product was purified first on silica (Et_2O/MeOH/Et_3N; 17/2/1) and then by preparative LC (33% MeCN, $\lambda = 285$ nm). 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.38 (s 3H), 2.48 (m 4H), 2.63 (m, 2H), 3.01 (m, 2H), 4.58 (s, 3H), 7.05 (m, 2H), 7.12 (t, 1H), 7.18 (d, 1H), 7.27 (m, 2H). FAB-MS (3-nitrobenzyl alcohol) for $C_{21}H_{26}N_4OS$ *m/z* (relative intensity): 383 ($M + H^+$, 100). Method C: 96.3% at $t_R = 2.37$ min. Method D: 94% at $t_R = 2.31$ min.

2-[((3-*iso*-Butyloxy-2-methylphenyl)methyl)thio]-1*H*-benzimidazole (75). Compound **68** (0.39 g, 2.58 mmol), suspended in 6 mL of MeOH, was treated with 2 M NaOH (2.58 mL, 5.16 mmol) and allowed to form a solution. Compound **23a** (0.5 g, 2.35 mmol) was added and reacted for 18 h at ambient temperature. The solvents were evaporated, and the residue was partitioned between water and CH_2Cl_2 (4 × 25 mL). The organic layers were combined, dried, and evaporated. Purification on silica (CH_2Cl_2/MeOH; 99/1) afforded 355 mg (46%) of desired material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.03 (d, 6H), 2.10 (m, 1H), 2.29 (s, 3H), 3.70 (d, 2H), 4.56 (s, 2H), 6.75 (d, 1H), 6.90 (d, 1H), 7.05 (t, 1H), 7.20 (t, 1H), 7.21 (t, 1H), 7.29 (d, 1H), 7.70 (d, 1H). Method A (70% MeCN, $\lambda =$ 286 nm): 98.0% at $t_R = 9.8$ min. Method D: 94% at $t_R = 4.06$ min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)thio]-1*H*-benzimidazole (76). The title compound was prepared as described in ref 8.

2-[((2-Methyl-3-(2-(2-(2-methoxyethoxy)ethoxy)-ethoxy)phenyl)methyl)thio]-1*H*-benzimidazole (77). The title compound was prepared from **68** (0.18 g, 1.18 mmol) and **23b** (0.33 g, 1.08 mmol) by the method described for **75**. Preparative LC (40% MeCN) afforded 115 mg (26%) of the desired material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.22 (s, 3H), 3.46 (s, 3H), 3.50−3.55 (m, 2H), 3.61−3.68 (m, 4H), 3.70−3.74 (m, 2H), 3.79−3.85 (m, 2H), 4.01−4.07 (m, 2H), 4.49 (br s, 2H), 6.70 (d, 1H), 6.84 (d, 1H), 6.97 (t, 1H), 7.13−7.19 (m, 2H), 7.42−7.55 (m, 2H). FAB-MS (3-nitrobenzyl alcohol) for $C_{22}H_{28}N_2O_4S$ *m/z* (relative intensity): 439 ($M + Na^+$, 53), 417 ($M + H^+$, 43). Direct inlet MS (EI) for $C_{22}H_{28}N_2O_4S$ *m/z* (relative intensity): 416 (M^+, 5), 270 (56), 149 (71), 105 (49), 91 (50). Method A (gradient 40−70% MeCN, $\lambda = 286$ nm): 98.0% at $t_R = 9.7$ min. Method B (40% MeCN): 97.0% at $t_R = 6.2$ min.

2-[((2-Methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)-ethoxy)ethoxy)ethoxy)phenyl)methyl)thio]-1*H*-benzimidazole (78). The title compound was prepared from **68** (0.33 g, 2.19 mmol) and **23c** (0.78 g, 1.99 mmol) by the method described for **75**. Preparative HPLC (44% MeCN) afforded 0.57 g (57%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.25 (s, 3H), 3.33 (s, 3H), 3.49−3.53 (m, 2H), 3.57−3.64 (m, 12H), 3.67−3.71 (m, 2H), 3.80−3.84 (m, 2H), 4.05−4.09 (m, 2H), 4.53 (broad s, 2H), 6.72 (d, 1H), 6.88 (d, 1H), 7.00 (t, 1H) 7.12−7.22 (m, 2H), 7.30 (d, 1H), 7.68 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{21}H_{26}N_4OS$ *m/z* (relative intensity): 527 ($M + Na^+$, 93), 505 ($M + H^+$, 9). Method A (gradient 40−70%, $\lambda = 286$ nm): 99.0% at $t_R = 8.2$ min. Method B (40% MeCN): 99.0% at $t_R = 5.7$ min.

2-[((2-Methyl-3-(2-(2-(2-methoxyethoxy)ethoxy)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (79). The title compound was prepared from **68** (0.33 g, 2.16 mmol) and **33a** (0.58 g, 1.80 mmol) by the method described for **75**. Preparative HPLC (60% MeCN) afforded 0.47 g (60%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.43 (s, 3H), 3.02 (t, 2H), 3.35 (s, 3H), 3.52−3.55 (m, 2H), 3.56−3.68 (m, 8H), 4.55 (s, 2H), 7.01 (t, 1H), 7.12 (d, 1H), 7.19−7.23 (m, 2H), 7.25 (d, 1H), 7.50−7.55 (m, 2H). Method A (gradient 40−70% MeCN, $\lambda = 287$ nm): 96.0% at $t_R = 11.5$ min. Anal. ($C_{22}H_{28}N_2O_3S_2$) C, H, N, S.

2-[((2-Methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)-ethoxy)ethoxy)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (80). The title compound was prepared from **68** (85 mg, 0.56 mmol) and **33b** (208 mg, 0.51 mmol) by the method described for **75**. Preparative HPLC (50% MeCN) afforded 103 mg (35%) of the desired material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.44 (s, 3H), 3.02 (t, 2H), 3.34 (s, 3H), 3.49−3.58 (m, 2H), 3.58−3.64 (m, 16H), 4.56 (s, 2H), 7.00 (t, 1H), 7.14 (d, 1H), 7.16−7.22 (m, 2H), 7.24 (d, 1H), 7.30−7.70 (broad s, 2H). 100 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 16.24, 33.01, 36.13, 58.89, 69.68, 70.23, 70.40, 70.49, 71.82, 122.13, 126.18, 128.26,

128.92, 135.33, 136.28, 137.08, 149.69. LC-MS (ESI) for $C_{26}H_{36}N_2O_5S_2$ *m/z* (relative intensity): 543 (M + Na^+, 100), 521 (M + H^+, 80). Method A (gradient 40−70% MeCN, λ = 287 nm): 98.5% at t_R = 10.3 min. Method B (60% MeCN): 99.0% at t_R = 3.8 min. Anal. ($C_{26}H_{36}N_2O_5S_2$) C, H, N, S.

2-[((3-*iso*-Butyloxy-2-methylphenyl)methyl)thio]benzothiazole (81). The title compound was prepared from **69** (0.43 g, 2.58 mmol) and **23a** (0.50 g, 2.35 mmol) by the method described for **75**. Purification on silica (CH_2Cl_2/MeOH; 99/1) afforded 0.64 g (79%) of the desired material. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 3H), 1.06 (d, 3H), 2.15 (m, 1H), 2.34 (s, 3H), 3.73 (d, 2H), 4.65 (s, 2H), 6.79 (d, 1H), 7.02 (d, 1H), 7.11 (t, 1H), 7.31 (t, 1H), 7.44 (t, 1H), 7.77 (d, 1H), 7.92 (d, 1H). Method A (70%, λ = 281 nm): 99.0% at t_R = 10.9 min. Method C: 98% at t_R = 9.38 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)thio]benzothiazole (82). The title compound was prepared from **69** (0.40 g, 2.39 mmol) and **11** (0.57 g, 2.63 mmol) by the method described for **75**. The residue was crystallized from Et_2O affording 0.46 g (56%) of the desired material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.06 (d, 6H), 2.15 (m, 1H), 2.35 (s, 3H), 3.78 (d, 2H), 4.80 (s, 2H), 6.65 (d, 1H), 7.28 (t, 1H), 7.42 (t, 1H), 7.78 (d, 1H), 7.95 (d, 1H), 8.30 (d, 1H). Method A (70% MeCN, λ = 280 nm): 99.0% at t_R = 7.9 min. Method C: 96% at t_R = 13.36 min.

2-[((3-*iso*-Butyloxy-2-methyl-1-phenyl)methyl)thio]benzoxazole (83). Compound **70** (195 mg, 1.29 mmol) was added to a solution of 55% NaH (60 mg, 2.4 mmol) in dry DMF (5 mL) and reacted for 0.5 h at ambient temperature. Compound **23a** (250 mg, 1.17 mmol) was added, and the mixture was stirred at room temperature for 0.5 h and then heated to 70 °C for 18 h. The reaction was quenched with H_2O and then with CH_2Cl_2. The organic layer was dried and evaporated, and the resulting oil was chromatographed on silica (CH_2Cl_2/MeOH; 9/1) leaving 155 mg (41%) of the desired material. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.10 (d, 6H), 2.16 (m, 1H), 2.39 (s, 3H), 3.76 (d, 2H), 4.66 (s, 2H), 6.83 (d, 1H), 7.07 (d, 1H), 7.15 (t, 1H), 7.28 (t, 1H), 7.32 (t, 1H), 7.47 (d, 1H), 7.68 (d, 1H). Method A (70% MeCN, λ = 280 nm): 98.0% at t_R = 10.2 min. Method D: 98% at t_R = 5.04 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)thio]benzoxazole (84). The title compound was prepared from **70** (294 mg, 1.95 mmol) and **11** (375 mg, 1.95 mmol) by the method described for **75** with the exception that EtOH was used as solvent instead of MeOH. Purification on silica ($PhCH_3$/EtOAc; 6/1) afforded 319 mg (64%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.06 (d, 6H), 2.18 (m, 1H), 2.35 (s, 3H), 3.80 (d, 2H), 4.80 (s, 2H), 6.73 (d, 1H), 7.25 (t, 1H), 7.28 (t, 1H), 7.45 (d, 1H),7.65 (d, 1H), 8.34 (d, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 10.75, 19.14, 28.15, 37.12, 74.43, 105.81, 109.88, 118.36, 120.83, 123.79, 124.18, 141.97, 148.00, 151.85, 153.46, 163.44, 165.23. FAB-MS (3-nitrobenzyl alcohol) for $C_{18}H_{20}N_2O_2S$ *m/z* (relative intensity): 329 (M + H^+, 100). Method A (70% MeCN, λ = 244 nm): 99.0% at t_R= 5.7 min. Method D: 98% at t_R = 4.36 min.

2-[((2-Methyl-3-((2-morpholino)ethoxy)phenyl)methyl)thio]-1*H*-benzimidazole (85). The title compound was prepared from **68** (0.25 g, 1.65 mmol) and **23d** (0.40 g, 1.50 mmol) by the method described for **75**. Crystallization from EtOAc afforded 0.30 g (52%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.30 (s, 3H), 2.65 (m, 4H), 2.87 (m, 2H), 3.75 (m, 4H), 4.13 (m, 2H), 4.60 (s, 2H), 6.80 (d, 1H), 6.97 (d, 1H), 7.09 (t, 1H), 7.19−7.30 (m, 2H), 7.33 (d, 1H), 7.74 (d, 1H). Method A (gradient 40−70% MeCN, λ = 286 nm): 98.0% at t_R = 10.6 min. Method D: 98% at t_R = 2.87 min.

2-[((2-Methyl-3-((2-morpholino)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (86). The title compound was prepared from **68** (56 mg, 0.37 mmol) and **33c** (100 mg, 0.34 mmol) by the method described for **75**. Purification on silica (EtOAc) afforded 54 mg (40%) of the desired material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.50 (s, 7H), 2.68 (m, 2H), 3.03 (m, 2H), 3.72 (m, 4H), 4.61 (s, 2H), 7.08 (t, 1H), 7.18 (d, 1H), 7.20−7.28 (m, 2H), 7.35 (d, 1H), 7.75 (d, 1H). FAB-MS (3-nitrobenzyl alcohol) for $C_{21}H_{25}N_3OS_2$ *m/z* (relative intensity): 400 (M + H^+, 100). TOF-MS: exact mass calcd for $C_{21}H_{25}N_3OS_2$ (M + H^+), 400.1517; found, 400.1516. Method A (58% MeCN, λ = 287 nm): 99.0% at t_R = 5.0 min. Anal. ($C_{21}H_{25}N_3OS_2$) H, N; C: calcd, 63.12; found, 62.66.

2-[((3-*iso*-Butylthio-2-methylphenyl)methyl)thio]-1*H*-benzimidazole (87). The title compound was prepared from **68** (221 mg, 1.47 mmol) and **33d** (307 mg, 1.34 mmol) by the method described for **75**. Preparative LC (65% MeCN) afforded 163 mg (36%) of the desired material. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.06 (d, 6H), 1.89 (h, 1H), 2.47 (s, 3H), 2.76 (d, 2H), 4.59 (s, 2H), 7.06 (t, 1H), 7.15 (d, 1H), 7.19−7.24 (m, 3H), 7.52 (bs, 2H). LC-MS (ESI) for $C_{19}H_{22}N_2S_2$ *m/z* (relative intensity): 343 (M + H^+, 30). Method A (gradient 58−70% MeCN, λ = 288 nm): 99.0% at t_R = 9.2 min. Method B (70% MeCN): 99.0% at t_R = 6.0 min.

2-[[[2-Methyl-3-[2-(2-methyl-5-nitroimidazol-1-yl)ethylthio]phenyl]methyl]thio]-1*H*-benzimidazole (88). A solution of **33e** (586 mg, 1.8 mmol) in 10 mL of MeCN was reacted with **68** (300 mg, 2 mmol) and K_2CO_3 (1 g, 7.2 mmol) in an inert atmosphere for 2 h at reflux. The organic layer was evaporated, and the residue was treated with 50 mL of water. The solid material was collected and recrystallized from 25 mL of MeCN affording 440 mg (55%) of crystalline title compound. 300 MHz ^{1}H NMR (CH_3OH-d_4): δ 2.26 (s, 3H), 2.43 (s, 3H), 3.29 (t, 2H), 4.40 (t, 2H), 4.49 (s, 2H), 4.89 (broad, >3H exchangeable hydrogens), 7.02 (t, 1H), 7.09−7.19 (m, 3H), 7.29 (d, 1H), 7.36−7.49 (m, 2H) 7.79 (s, 1H). 75.5 MHz ^{13}C NMR (CH_3OH-d_4): δ 13.94, 16.52, 33.54, 36.99, 46.63, 123.52, 127.61, 129.83, 130.18, 132.69, 136.05, 137.17, 138.37, 139.89, 150.83, 152.24. Anal. ($C_{21}H_{21}N_5O_2S_2 \cdot 3/2H_2O$) C, H, N, S.

2-[[[2-Methyl-3-[2-(1,2,4-triazol-1-yl)ethylthio]phenyl]methyl]thio]-1*H*-benzimidazole (89). A solution of **33f** (107 mg, 0.4 mmol) in 10 mL of MeCN was reacted with **68** (150 mg, 1 mmol) and K_2CO_3 (1 g, 7.25 mmol) in an inert atmosphere for 1 h at reflux. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was collected, dried, and evaporated. Purification on silica (EtOAc/*iso*-PrOH; 95/5) afforded 100 mg (65%) of the title compound. 300 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.37 (s, 3H), 3.28 (t, 2H), 4.30 (t, 2H), 4.43 (s, 2H), 6.86−7.00 (m, 2H), 7.10−7.22 (m, 3H), 7.32−7.72 (broad, 2H), 7.87 (s, 1H), 7.91 (s, 1H). 75.5 MHz^{13}C NMR ($CHCl_3$-*d*): δ 16.25, 33.05, 36,70, 49.24, 122.23, 126.25, 128.73, 129.41, 133.92, 136.12, 137.38, 143.23, 149.06, 151.74. Anal. ($C_{19}H_{19}N_5S_2$) C, H, N, S.

5-Ethoxycarbonyl-2-[((2-methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethylthio)phenyl)methyl)thio]]-1*H*-benzimidazole (90). The title compound was prepared from **71** (225 mg, 1.00 mmol), prepared by the standard procedure described in ref 48, and **33b** (375 mg, 0.92 mmol) by the method described for **75**. Preparative LC (50% MeCN) afforded 128 mg (22%). 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.41 (t, 3H), 2.45 (s, 3H), 3.02 (t, 2H), 3.32 (s, 3H), 3.49−3.58 (m, 7H), 3.58−3.63 (m, 11H), 4.39 (q, 2H), 4.61 (s, 2H), 7.03 (t, 1H), 7.19 (d, 1H), 7.26 (d, 1H), 7.50 (d, 1H), 7.93 (t, 1H), 8.20 (s, 1H), 10.79 (d, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 14.36, 16.28, 33.00, 35.79, 58.89, 60.86, 69.66, 70.21, 70.39, 70.45, 70.49, 71.79, 109.00, 112.21, 117.37, 120.00, 123.55, 124.00, 124.32, 126.20, 128.32, 129.04, 136.34, 137.11, 138.99, 216.60. LC-MS (ESI) for $C_{29}H_{40}N_2O_7S_2$ *m/z* (relative intensity): 615 (M + Na^+, 10), 593 (M + H^+, 100). Method A (gradient 40−70% MeCN, λ = 226 nm): 99.0% at t_R = 13.2 min. Method B (60% MeCN): 99.0% at t_R = 4.5 min.

2-[((2-Methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethylthio)phenyl)methyl)thio]-5-(propyl-1-one)-1*H*-benzimidazole (91). The title compound was prepared from **72** (146 mg, 0.71 mmol), prepared by the standard procedure described in ref 48, and **33b** (260 mg, 0.64 mmol) by the method described for **75**. Preparative LC (50% MeCN) afforded 200 mg (49%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.25 (t, 3H), 2.44 (s, 3H), 3.01 (t, 1H), 3.06 (q, 1H), 3.32 (s, 3H), 3.49−3.58 (m, 4H), 3.58−3.62 (m, 17H), 4.61 (s, 2H), 7.03 (t, 1H), 7.19 (d, 1H), 7.25 (d, 1H), 7.53 (d, 1H), 7.88 (d of d, 1H), 8.19 (s, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 8.57, 16.23, 31.75, 32.91, 35.74, 58.86, 69.62,

70.20, 70.36, 70.43, 70.45, 71.76, 122.59, 126.22, 128.24, 128.87, 131.32, 134.91, 136.40, 137.01, 200.79. LC-MS (ESI) for $C_{29}H_{40}N_2O_6S_2$ *m/z* (relative intensity): 599 ($M + Na^+$, 100), 577 ($M + H^+$, 60). Method A (gradient 40−70% MeCN, λ = 230 nm): 99.4% at t_R = 11.2 min. Method B (60% MeCN): 99.0% at t_R = 4.0 min.

5-Amino-2-[((2-methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)-ethoxy)ethoxy)ethoxy)ethylthio)phenyl)methyl)thio]-1*H*-benzimidazole (92). The title compound was prepared from **73** (117 mg, 0.71 mmol) and **33b** (260 mg, 0.64 mmol) by the method described for **75**. Preparative LC (50% MeCN) afforded 230 mg (67%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.40 (s, 3H), 3.00 (t, 2H), 3.33 (s, 3H), 3.51 (m, 2H), 3.54−3.62 (m, 17H), 4.46 (s, 2H), 6.57 (d of d, 1H), 6.72 (s, 1H), 6.98 (t, 1H), 7.07 (d, 1H), 7.21 (d, 1H), 7.32 (d, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 16.11, 32.86, 36.51, 58.85, 69.59, 70.17, 70.33, 70.42, 71.76, 112.04, 126.12, 128.13, 128.60, 135.49, 136.15, 136.88, 142.24, 144.96, 147.39. LC-MS (ESI) for $C_{26}H_{37}N_3O_5S_2$ *m/z* (relative intensity): 558 ($M + Na^+$, 100), 536 ($M + H^+$, 30). Method A (gradient 40−70% MeCN, λ = 310 nm): 97.0% at t_R = 5.0 min. Method B (60% MeCN): 98.0% at t_R = 2.4 min.

5-Hydroxymethyl-2-[((2-methyl-3-(2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)ethylthio)phenyl)-methyl)thio]-1*H*-benzimidazole (93). The title compound was prepared from **74**[48] (128 mg, 0.71 mmol) and **33b** (260 mg, 0.64 mmol) by the method described for **75**. Preparative LC (50% MeCN) afforded 200 mg (57%) of the desired material. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 2.38 (s, 3H), 2.98 (t, 2H), 3.32 (s, 3H), 3.48−3.57 (m, 4H), 3.57−3.61 (m, 16H), 4.50 (s, 2H), 4.71 (s, 2H), 6.96 (t, 1H), 7.08 (d, 1H), 7.12 (d, 1H), 7.19 (d, 1H), 7.30−7.70 (broad s, 2H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 16.15, 32.86, 36.03, 58.87, 65.34, 69.60, 70.17, 70.33, 70.41, 71.77, 126.16, 128.18, 128.70, 135.21, 136.21, 136.94, 144.95, 150.10. LC-MS (ESI) for $C_{27}H_{38}N_2O_6S_2$ *m/z* (relative intensity): 573 ($M + Na^+$, 100), 551 ($M + H^+$, 30). Method A (gradient 40−70% MeCN, λ = 310 nm): 95.0% at t_R = 4.5 min. Method B (60% MeCN): 99.0% at t_R = 2.3 min.

2-[((3-*iso*-Butyloxy-2-methylphenyl)methyl)oxy]benzoxazole (97). The method of Yamato et al.[49] was applied for the preparation of the title compound. Thus, **70** (0.42 g, 2.7 mmol), **20a** (1.55 g, 7.95 mmol), and MeI (1.13 g, 7.95 mmol) were dissolved in dry THF (20 mL) and cooled to to 0 °C after which 55% NaH (0.46 g, 10.6 mmol) was added. After it was reacted for 3 h at ambient temperature, the mixture was poured onto ice water. The THF was evaporated, and the residual aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried, and evaporated. The remaining oil was heated to 300 °C for 3 h and then worked up by preparative LC (80% MeCN) affording 300 mg (36%) of the title compound as a colorless oil. 400 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.07 (d, 6H), 2.14 (m, 1H), 2.33 (s, 3H), 3.75 (d, 2H), 5.61 (s, 2H), 6.88 (d, 1H), 7.09 (d, 1H), 7.18 (t, 1H) 7.19 (t, 1H), 7.26 (t, 1H), 7.36 (t, 1H), 7.53 (d, 1H). Method A (70% MeCN, λ = 225 nm): 99.0% at t_R = 9.8 min. Method B (80% MeCN): 99.0% at t_R = 6.1 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)oxy]benzoxazole (98). The method of Streeting et al.[50] was applied for the preparation of the title compound. Thus, **94** (0.18 g, 1.32 mmol) and Ag_2CO_3 (0.37 g, 1.35 mmol) were added to a solution of **11** (0.34 g, 1.35 mmol) in dry toluene (5 mL). The mixture was heated to 110 °C in an inert atmosphere in the dark. After 4 h, the mixture was cooled to ambient temperature and diluted with toluene (20 mL) and filtered through Hyflo Supercel filter aid. The filtrate was concentrated and partitioned between CH_2Cl_2 (40 mL) and 2 M NaOH (25 mL). The organic layer was collected, washed with 2 M NaOH (25 mL) and water (25 mL), dried, and evaporated. Preparative LC (60% MeCN) afforded 126 mg (31%) of the title compound as a colorless oil. 600 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.05 (d, 6H), 2.12 (m, 1H), 2.31 (s, 3H), 3.79 (d, 2H), 5.70 (s, 2H), 6.75 (d, 1H), 7.18 (t, 1H), 7.25 (q, 1H), 7.35 (d, 1H), 7.52 (d, 1H), 8.38 (d, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-*d*): δ 10.37, 19.13, 28.13, 72.89, 74.46, 98.26, 106.67, 109.72, 118.04, 122.25, 122.78, 124.15, 141.09, 148.20, 148.57, 152.14, 163.45, 163.66. LC-MS (ESI) for $C_{18}H_{20}N_2O_3$ *m/z* (relative intensity): 313 ($M + H^+$, 50), 256 (20), 154 (50), 136 (100). Method A (70% MeCN, λ = 225 nm): 96.0% at t_R = 5.0 min. Method B (70% MeCN): 98.0% at t_R = 5.4 min.

2-[((3-*iso*-Butyloxy-2-methylphenyl)methyl)oxy]benzothiazole (99). The title compound was prepared on a 1.32 mmol scale starting from **95** and **22a** according to the procedure given for **98**. Preparative LC (70% MeCN) afforded 70 mg (16%) of the desired material as a colorless oil. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.08 (d, 6H), 2.15 (m, 1H), 2.32 (s, 3H), 3.75 (d, 2H), 5.63 (s, 2H), 6.88 (d, 1H), 7.07 (d, 1H), 7.19 (t, 1H), 7.24 (t, 1H), 7.39 (t, 1H), 7.65 (d, 1H), 7.74 (d, 1H). Method A (70% MeCN, λ = 214 nm): 99.0% at t_R = 13.0 min. Method B (70% MeCN): 99.0% at t_R = 7.9 min.

2-[((4-*iso*-Butyloxy-3-methyl-2-pyridyl)methyl)oxy]benzothiazole (100). Compound **10** (100 mg, 0.51 mmol) was added to a suspension of 55% NaH (90 mg, 2.0 mmol) in dry THF (6 mL). The mixture was stirred at ambient temperature for 0.5 h, and then, **96** (78 mg, 0.51 mmol) was added and allowed to react for 1 h. The THF was evaporated, and the residue was partitioned between CH_2Cl_2 (40 mL) and water (25 mL). The organic layer was dried and evaporated. Preparative LC (70% MeCN) afforded 91 mg (54%) of the title compound as a yellow oil. 500 MHz ^{1}H NMR ($CHCl_3$-*d*): δ 1.06 (d, 6H), 2.14 (m, 1H), 2.30 (s, 3H), 3.78 (d, 2H), 5.72 (s, 2H), 6.74 (d, 1H), 7.22 (t, 1H), 7.37 (t, 1H), 7.63 (d, 1H), 7.72 (d, 1H), 8.36 (d, 1H). 126 MHz ^{13}C NMR ($CHCl_3$-d_1): δ 10.43, 19.12, 28.13, 72.89, 74.40, 106.52, 120.87, 121.21, 122.33, 123.48, 125.87, 132.13, 148.16, 149.20, 153.02, 163.61, 172.54. LC-MS (ESI) for $C_{18}H_{20}N_2O_2S$ *m/z* (relative intensity): 329 ($M + H^+$, 100), 273 (25), 219 (35). Method A (70% MeCN, λ = 215 nm): 99.0% at t_R = 8.1 min. Method B (70% MeCN): 98.0% at t_R = 6.5 min.

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(35) The mesylate was prepared by standard literature methods furnishing the product as a colorless oil. FAB-MS (3-nitrobenzyl alcohol) for $C_{12}H_{26}O_8S$ *m/z* (relative intensity): 331 ($M + H^+$, 34).
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