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

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A parallel chemistry expansion of the 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-phenyl}-sulfanyl)-1-ethanol scaffold (**2**) successfully provided a set of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl carbamates with the generic structure **12**, which displayed potent and selective activities against the gastric pathogen *Helicobacter pylori*. A prototype carbamate **12a** was studied further and found to meet several significant in vitro microbiological criteria required for a novel anti-*H. pylori* agent. The compound displayed low minimal inhibition concentration (MIC) values against a panel of 27 different clinically relevant *H. pylori* strains ($MIC_{90} = 0.25$ μg/mL), including strains resistant to either metronidazole or clarithromycin or both. Additionally, **12a** was almost inactive against a wide range of commensal or pathogenic microorganisms comprising panels of 25 aerobic bacterial strains including two strains of methicillin resistant *Staphylococcus aureus* ($MIC_{90} = >64$ μg/mL) and 18 anaerobic bacterial strains ($MIC_{90} = >64$ μg/mL). The measured rate of resistance development against **12a** was found to be less than 10^{-9}, a clinically acceptable level, and pharmacokinetic studies revealed in vivo exposure levels comparable with those established for antimicrobials currently used in *H. pylori* triple regimen.

Introduction

The microaerophilic bacterium *Helicobacter pylori* has been recognized as the major cause of gastritis, a significant determinant in peptic and duodenal ulcer disease,[1−3] and as an important factor in the development of gastric cancer.[4] Since 1983 when *H. pylori* was first isolated, it has consistently been recovered from the gastric and duodenal mucosae of patients suffering from these medical conditions. The eradication of the bacterium in infected patients has resulted in good healing rates for both active chronic gastritis and duodenal ulcer disease.[5]

Although *H. pylori* is sensitive in vitro to many antibacterials,[6] single therapy regimens have not been very effective in clinical settings. Rather, combination therapies employing bismuth salts or omeprazole or other proton pump inhibitors and two or three antibiotics such as metronidazole, amoxicillin, clarithromycin, or tetracycline have emerged as preferred treatments.[7] While the efficacy of some of these combinations is clinically acceptable, their effectiveness can fall off over time because of the selection of antibiotic resistant strains. Moreover, disrupting the natural population of commensal microorganisms in the gastrointestinal tract sometimes leads to undesired side effects such as diarrhea.

Hence, there are unmet medical needs for novel, efficacious, and selective eradication therapies that minimize resistance problems in both *H. pylori* and also other bacteria and that lack the common gastrointestinal side effects often associated with antibacterials.

In an accompanying paper,[8] we report finding a novel chemical template, 2-[[(phenyl)methyl]thio]-1*H*-benzimidazole **1** (Chart 1), with antimicrobial activity selective for *H. pylori*. The substitution of hydrogen with a sulfur in the 3-position of the phenyl ring of this template proved to be beneficial in improving potency. The tolerance of a larger chemical bulk such as *iso*-Bu, $-(CH_2CH_2O)_3CH_3$, $-(CH_2CH_2O)_5CH_3$, and $-CH_2CH_2$-4-morpholinyl attached to the sulfur suggested that there was potential for further variation in this position.

We explored this possibility and opted for a parallel chemistry approach to quickly map out the scope and limitations. Three out of the four above bulky side chains had the $-CH_2CH_2$Het (Het = O or N) structural motif implicating the ethyl alcohol **2** as a potential starting point for the parallel chemistry effort. The synthesis of this key compound (**8**), with a preferred methyl group[8] in the 2-position of the phenyl ring in place, is shown in Scheme 1. This route immediately suggested an additional two compounds that could lend themselves to a parallel chemistry effort, namely, the acid **9** and the amine **11**, both of which become readily accessible when preparing the alcohol **8**.

The synthesis screen cycle identified the carbamate **12a** (R = Ph in **12**) as a potent compound with many desirable properties. Hence, some additional phenyl carbamate analogues **17** were also prepared in which the right-hand benzimidazole moiety of **12** was substituted with various other heterocycles.

In this paper, we report on the parallel synthesis and the microbiological profiling of several carbamates (**12**) obtained from the alcohol **8**, some amides (**13**) prepared

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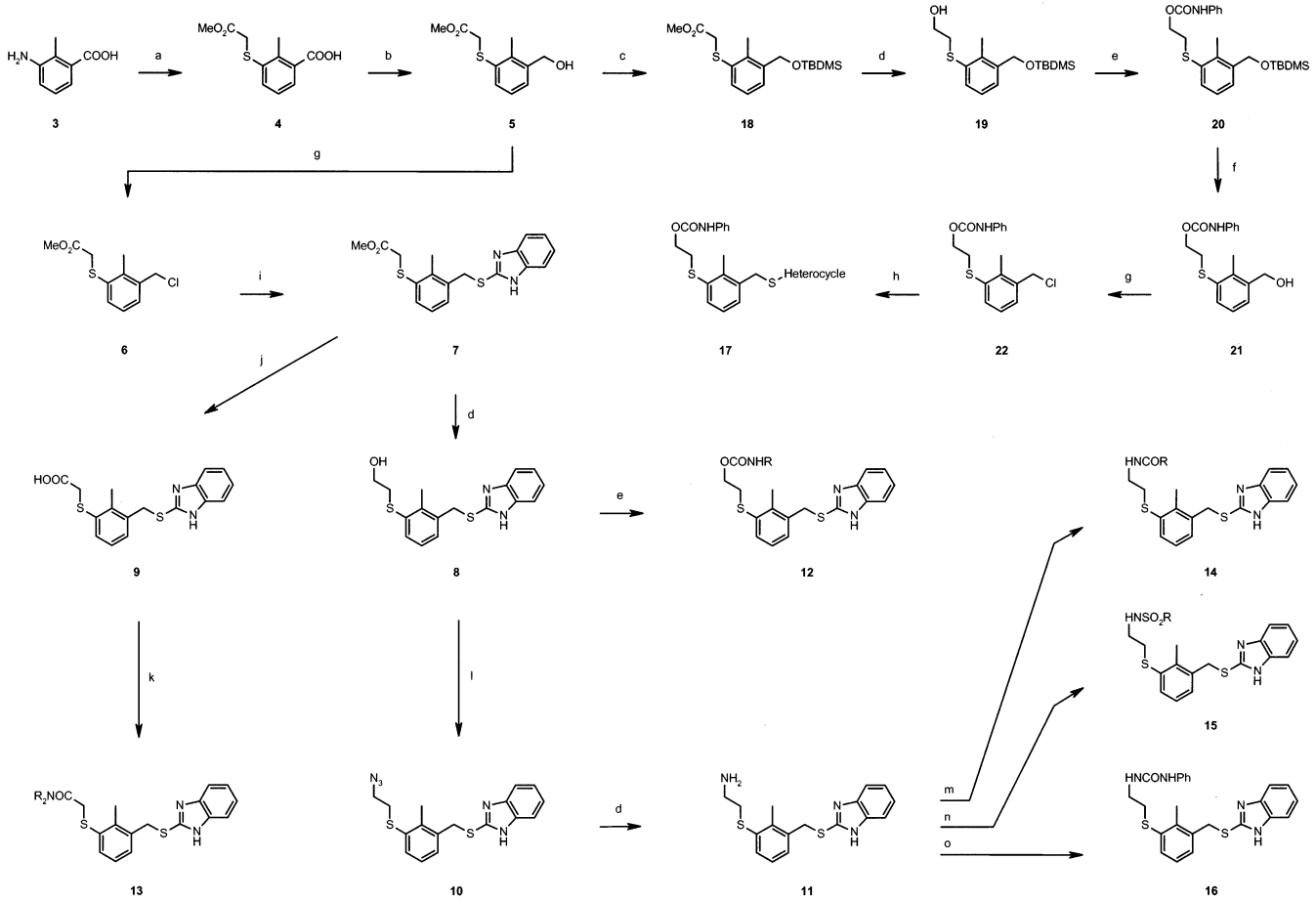
Scheme 1. Synthetic Routes toward Target Compounds **12**−**17**[a]



[a] Reagents: (a) (i) $NaNO_2$, HCl, H_2O, 0 °C; (ii) $HSCH_2CO_2CH_3$, CH_3OH, 60 °C. (b) BH_3·THF, THF, 0 °C. (c) TBDMSCl, imidazole, DMF, 20 °C. (d) LAH, THF, 0 °C. (e) Isocyanate, DMAP (catalytic), THF, 50 °C. (f) Bu_4NF, THF, H_2O, 20 °C. (g) $SOCl_2$, THF, 0−20 °C. (h) Heterocycle-SH, K_2CO_3, DMF, 20 °C. (i) 2-Mercaptobenzimidazole, NaOH, H_2O, CH_3OH, 0−20 °C. (j) LiOH, H_2O, CH_3OH, 20 °C. (k) Amine, HBTU, DMF, 20 °C. (l) PPh_3, NaN_3, CBr_4, 0−20 °C. (m) Acid, DIPEA, HBTU, DMF, 20 °C. (n) Sulfonyl chloride, Et_3N, 1:1 THF: DMF, 20 °C. (o) PhNCO, DMF, 20 °C.

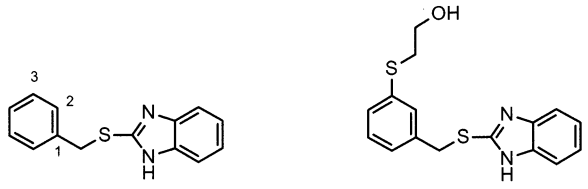
from the acid **9**, and a number of amides (**14**) and sulfonamides (**15**) synthesized from the amine **11**. The synthesis and microbiological evaluation of some additional heterocyclic phenyl carbamates **17** and one follow up phenyl urea compound **16** are also reported. A few select target compounds were studied further and assessed with respect to their pharmacokinetic properties.

Chemistry

Syntheses. The syntheses of the target compounds as outlined in Scheme 1 were typically carried out in parallel arrays on a 0.25−0.5 mmol scale. Crude products after aqueous workup were analyzed by high-performance liquid chromatography (HPLC) and mass spectrometry (MS) and if judged to be of sufficient purity (generally >90%) submitted for biological testing. The objective was to quickly scan the readily accessible structure−activity relationships (SAR) to discover modifications that would justify further focus.

Hence, the alcohol **8** was allowed to react with various isocyanates (Chart 2) to yield the corresponding carbamates by the standard procedure given for compound **12a**. Similarly, amides were prepared by diverting the ester **7** to the acid **9** and coupling it with the appropriate amines (Chart 3) employing HBTU as coupling reagent

Chart 1. Structures of a Novel Chemical Template, 2-[[(Phenyl)methyl]thio]-1*H*-benzimidazole (**1**) with Antimicrobial Activity Selective for the Bacterium *H. pylori* and the Alcohol **2** that Was Chosen as a Starting Point for a Parallel Chemistry Effort



according to the conditions given for target compound **13a**. Reversed amides were prepared by converting the alcohol **8** to the azide **10**, which after reduction furnished amine **11**. This amine was then coupled with carboxylic acids of choice (Chart 4) as exemplified for compound **14**. The sulfonamides were readily formed by reacting amine **11** with a set of sulfonyl chlorides (Chart 5) as illustrated for compound **15**. One follow up urea compound **16** was also prepared by reacting amine **11** with phenyl isocyanate.

Compound **5** became an attractive starting point in the pursuit of heterocyclic derivatives **17**. Protection of the benzyl alcohol with TBDMSCl furnished **18**, which

Chart 2. Isocyanates Used to Prepare the Carbamates **12**

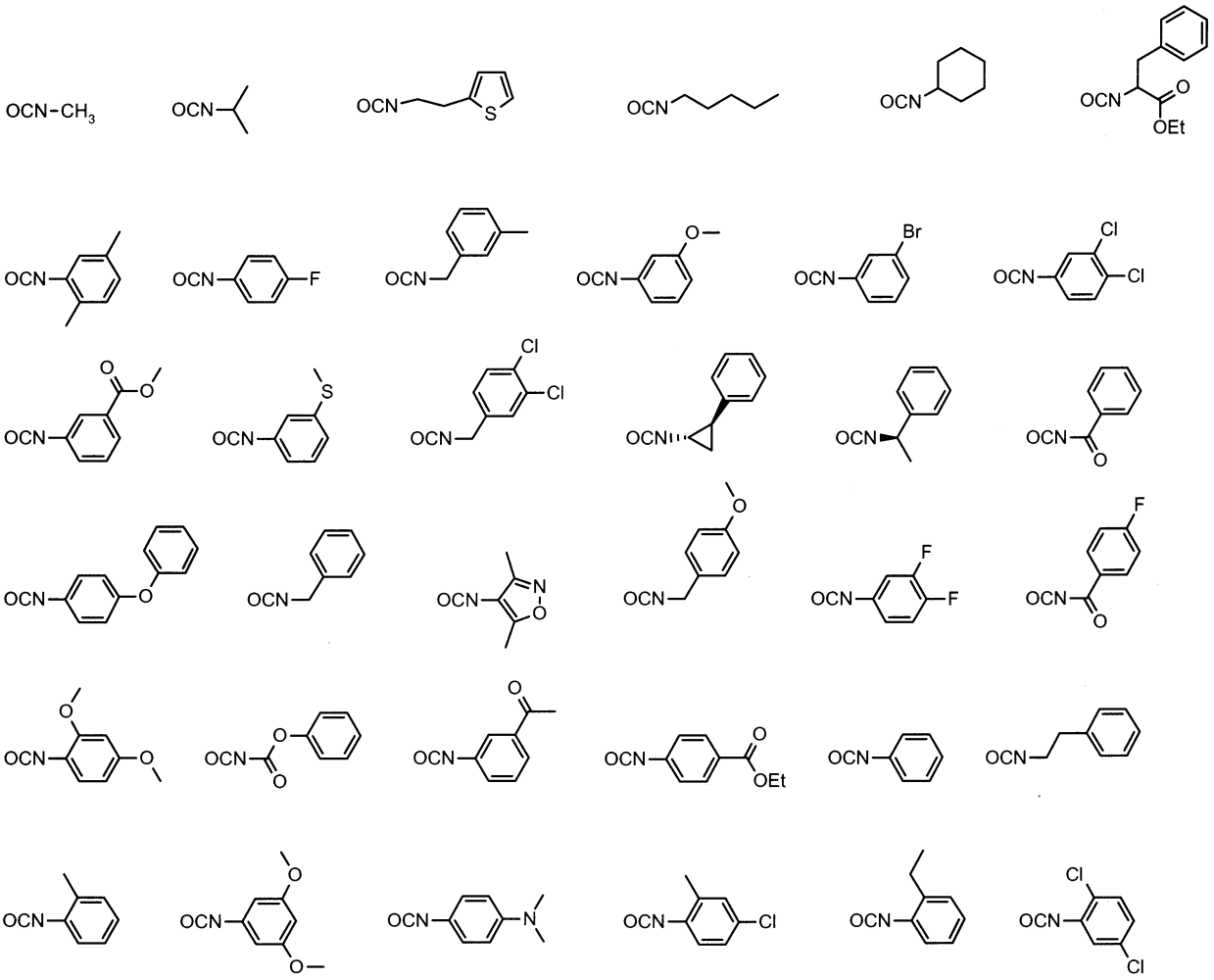
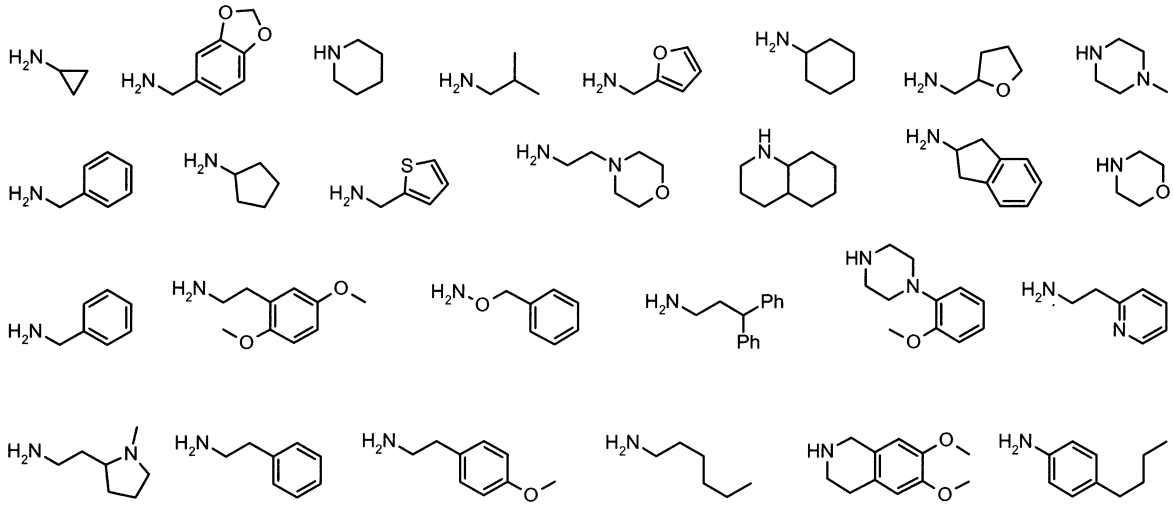


Chart 3. Amines Used to Prepare the Amides **13**



was reduced to the alcohol **19**, which in turn was trapped by phenyl isocyanate to yield the carbamate **20**. Removal of the silyl group with fluoride ion gave the benzyl alcohol **21**, which was activated with $SOCl_2$ to yield the benzyl chloride **22**. Reaction of **22** with the heterocyclic thiolates shown in Chart 6 according to the procedure given for **17a** afforded the desired target compounds.

Microbiology

Bacterial Strains. A panel of 27 *H. pylori* strains was selected based on differences in pathophysiologic history, variations in antibiotic resistance, and diversity in geographical origin, cf. Table 1. Cultures from single colonies containing no more that 5% coccoids were stored at −70 °C in Brucella broth (BBL, Becton Dickinson and Company, Cockeysville, MD) supple-

Chart 4. Carboxylic Acids Used to Prepare the Reversed Amides **14**

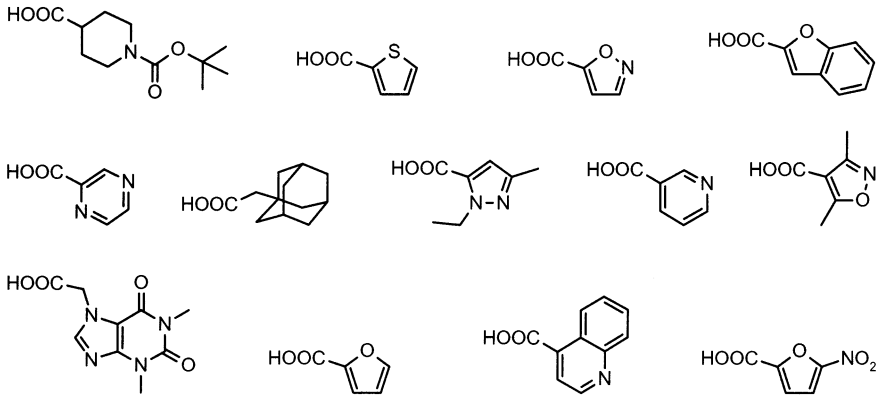


Chart 5. Sulfonyl Chlorides Used to Prepare the Sulfonamides **15**

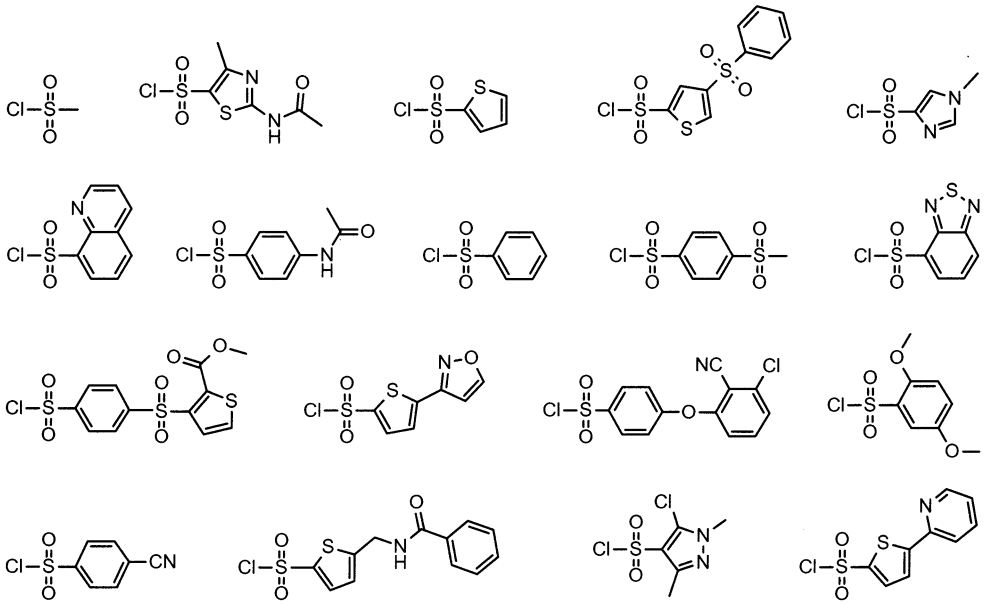
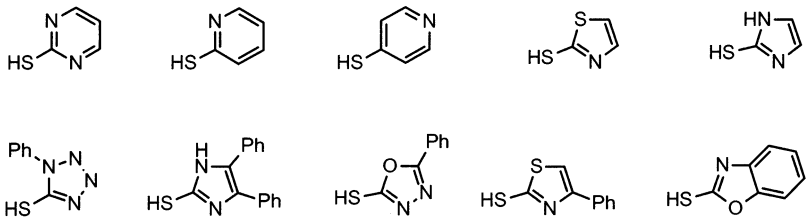


Chart 6. Heterocyclic Thiolates Used to Prepare Target Compounds **17**



mented with 30% glycerol. Frozen cells were grown on Trypticase Soy Agar (Beckton Dickinson and Company) supplemented with 5% sheep blood (BAP, Remel, Lenexa, KS) at 37 °C under microaerophilic conditions (5% O_2, 10% CO_2, and 85% N_2) in a Cellstar Trigas incubator (Queue Systems, Asheville, NC) and transferred to new medium twice prior to testing.

Similarly, panels of 25 aerobic bacterial strains, including two strains of methicillin resistant *Staphylococcus aureus* and 18 anaerobic bacterial strains, representing rather wide ranges of commensal and pathogenic microorganisms, were selected as detailed in Table 2. Aerobic single colonies were grown on Mueller Hinton II Agar (MH, Beckton Dickinson and Company) at 37 °C under aerobic conditions and stored at 4 °C before testing. Anaerobic cultures from single colonies were stored at −70 °C in BBL (Becton Dickinson and Company) supplemented with 30% glycerol. Frozen cells were grown on BAP at 37 °C under anaerobic conditions in an anaerobic/environmental chamber (Sheldon Manufacturing, Inc., Cornelius, OR) and transferred to new medium twice prior to testing.

Antimicrobials. Amoxicillin and metronidazole were purchased from Sigma Chemical Company (St. Louis, MO). Clarithromycin was obtained from Abbott Laboratories (Chicago, IL). Compounds were dissolved in dimethyl sulfoxide (DMSO) at 10 mg/mL and added to the appropriate media to obtain the indicated concentrations in each experiment.

Determination of *H. pylori* Minimal Inhibitory Concentrations (MICs) in the Microdilution Assay. Strains ARHp80, 81, 115, and 206, cf. Table 1, were used in these experiments. Two-fold serial dilutions were prepared in 24 well plates containing a total volume of

Table 1. List of Geographic Origin, Pathophysiologic History, and Resistance Profile of *H. pylori* Strains Used in the Microbiology Studies

strain (ARHp no.)	source[a]	resistance toward
25	Australia, human	metronidazole
32	Australia, human	
37	Sweden	metronidazole
39	Sweden, clinical isolate	
46	U.S.A., duodenal ulcer	
54	U.S.A., duodenal ulcer	metronidazole, clarithromycin
55[b]	U.S.A., duodenal ulcer	clarithromycin
56	Argentina, nonulcer dyspepsia	
65	Argentina, nonulcer dyspepsia	clarithromycin
78	Sweden, mouse	metronidazole
80[b]	Sweden, mouse	metronidazole
81[b]	U.S.A., mouse	
106	U.S.A., duodenitis	metronidazole
115[c]	Sweden, screen strain	
116	Sweden, gastritis	
124	Bangladesh, gastritis	
128	U.K., gastritis	
130	U.K., gastritis	
133	U.K., gastritis	
136	U.S.A., human	
137	U.S.A., human	
143	U.S.A., human	
147	U.S.A., human	metronidazole
206[b,d]	Australia, mouse	
209	Sweden	
211	U.S.A., pig	
212	U.S.A., pig	

[a] The strains are part of our culture collection and come from various clinical sources representing differences in pathopysiologic history, variations in antibiotic resistance, and diversity in geographical origin. [b] Strains used in the microdilution assay. [c] ARHp115 corresponds to strain ATCC 43504 in the accompanying paper, ref 8. [d] Strain used for determining minimum bactericidal concentrations and for studying killing kinetics.

Table 2. List of Aerobic and Anaerobic Bacteria Used in the Microbiology Studies[a]

aerobes	anaerobes
Aeromonas sobria	*Lactobacillus* sp.
Pseudomonas aeruginosa[b]	*Prevotella melaninogenica*
Enterobacter cloacae[c]	*Prevotella bivia*
Escherichia coli[c]	*Bacteroides ureolyticus*
Klebsiella pneumonia[c]	*Bacteroides thetaiiotaomicron*
Salmonella montevideo	*Bacteroides fragilis*[c]
Salmonella enteritidis	*Bacteroides ovatus*
Serratia marcescens[c]	*Bacteroides vulgatus*
Xanthomonas maltophilia	*Bacteroides caccae*
Enterococcus faecium	*Bilophila wasdworthia*
Enterococcus faecalis	*Fusobacterium mortiferum*[c]
Streptococcus coagulans[c]	*Clostridium difficile*
S. aureus[d]	*Clostridium ramosum*
S. aureus[e]	*Clostridium perfringes*
	Peptostreptococcus micros
	Peptostreptococcus anaerobius

[a] The strains are part of our culture collection and come from different sources representing ranges of commensal and pathogenic microorganisms. [b] Three strains. [c] Two strains. [d] Four strains. [e] MRSA, two strains.

2 mL of BBL supplemented with 5% (v/v) heat-inactivated fetal calf serum (FCS, Intergen, Purchase, NY) per well. Cultures were resuspended in BBL at an OD_{600} of 0.6, and 50 μL of these cultures was inoculated into each well to give a final concentration of 10^7 cells per mL (OD_{600} of less than 0.03, which is the same as that of the noninoculated controls). Plates were then incubated for 2 days, and the amount of growth was recorded at OD_{600} with a plate reader (Molecular Devices, Sunnyvale, CA). MICs were defined as the lowest concentration of antimicrobials resulting in complete inhibition of growth.

Determination of MICs in the Agar Dilution Assay. MICs were determined against a panel of 27 clinical *H. pylori* isolates, 13 aerobic and 16 anaerobic bacterial species on BAP for *H. pylori*, Brucella Agar supplemented with hemin, vitamin K, and 5% laked sheep blood for anaerobes, and Mueller Hinton II Agar for aerobes following NCCLS antimicrobial susceptibility testing methods.[9,10]

Determination of *H. pylori* Minimal Bactericidal Concentrations (MBCs). Strain ARHp206, cf. Table 1, was used in these experiments. Aliquots of culture were taken from the wells in the microdilution assay plates in which no growth had been detected and used to seed BAP. MBCs were determined by visual inspection of the plates and identifying the concentration at which maximum growth inhibition had occurred.

Determination of *H. pylori* Killing Kinetics. Strain ARHp206, cf. Table 1, was used in these experiments. The rates of bacterial killing of compounds at 1 μg/mL against log phase cultures containing 10^6 cells/mL were determined over 24 h. Cultures were placed in a shaking 24 well plate at 37 °C under microaerophilic conditions, and viable counts were quantitatively determined after incubation for 0, 2, 4, 6, and 24 h, respectively.

Determination of *H. pylori* Resistance Rates. Resistance rates were determined after 7 days of incubation in solid medium containing 10 times the MIC of the test compound. Cultures were then resuspended in BBL (OD_{600} of 1, 10^9 cells/mL), serially diluted, and spread on plates with and without the compound. Resistance rates were expressed as the ratio between the number of viable counts on plates with compound and the number of viable counts on plates without compound.

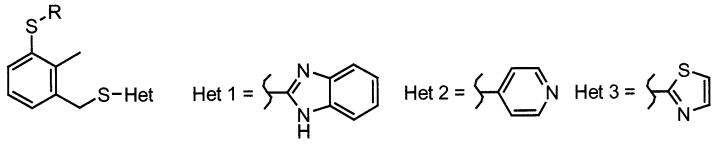
Pharmacokinetic Studies

Compounds were given orally by gavage needle at 30 mg/kg in a vehicle of 85:15 (0.5% aqueous hydroxypropylmethylcellulose:PEG-400) to C57BL/6NTac female mice (6 weeks, 20 g) obtained from Taconic Inc., Germantown, NY. Three mice per time point were bled by cardiac puncture at 15, 30, 60, 120, and 240 min, respectively, after dosing. Blood samples were collected in heparin tubes and centrifuged to yield plasma samples. Aliquots of plasma (50 μL) were diluted with MeCN (150 μL) and centrifuged to remove proteins. The supernatants (20 μL) were analyzed by LC-MS, cf. Experimental Section below, in single ion recording mode to determine plasma concentrations of parent compounds against recorded calibration curves. Lower limits of quantitation were 10−50 ng/mL. LC was run on Luna C8(2) columns (3 μm, 2 mm × 30 mm) obtained from Phenomenex, Torrance, CA, using 0.05% aqueous HCOOH/MeCN as eluent at a flow rate of 1 mL/min with a gradient from 5 to 95% MeCN in 4 min followed by another 1 min at 95% MeCN.

Results

In total, we prepared 36 carbamates **12**, 27 amides **13**, 13 reversed amides **14**, 18 sulfonamides **15**, one urea **16**, and, in addition to **12a**, 10 heterocyclic phenyl

Table 3. Compounds Selected and Tested for Anti-*H. pylori* Activity



compd no.	R	Het no.	MIC (μg/mL) ARHp strain no. 80	81	115[c]	206	MBC (μg/mL)	AUC[a] (ng/mL·h)	C_{max}[a] (ng/mL)	mp (°C)	microanalysis[b]
8	CH_2CH_2OH	1	1	1	1	1	>8	NC	NC	146	$C_{17}H_{18}N_2OS_2$
9	CH_2COOH	1	>16	>16	>16	>16	>8	NC	NC	227	$C_{17}H_{16}N_2O_2S_2 \cdot 1/2H_2O \cdot 1/4EtOAc$
11	$CH_2CH_2NH_2$	1	4	8	4	8	>8	NC	NC	245	$C_{17}H_{19}N_3S_2 \cdot H_2O \cdot 2HCl$
12a	$CH_2CH_2OCONHPh$	1	0.5	0.5	0.5	0.5	1	2074	906	122	$C_{24}H_{23}N_3O_2S_2$
12b	CH_2CH_2OCONH-(3-MeO-Ph)	1	0.25	0.5	0.25	0.5	8	1630	797	58	$C_{25}H_{25}N_3O_3S_2$
12c	CH_2CH_2OCONH-(3,4-di-F-Ph)	1	0.25	0.5	0.25	0.5	8	1127	398	135	$C_{24}H_{21}F_2N_3O_2S_2$
12d	CH_2CH_2OCONH-(4-Me_2N-Ph)	1	0.5	1.0	0.5	1.0	>8	299	331	133	$C_{26}H_{28}N_4O_2S_2$
13a	CH_2CO-(1-piperidinyl)	1	0.25	0.5	0.25	0.5	>8	135	57	140	$C_{22}H_{25}N_3OS_2 \cdot 1/4H_2O$
13b	$CH_2CONHCH_2$-(2-thienyl)	1	0.5	1	0.5	1	8	ND	ND	177	$C_{22}H_{21}N_3OS_3 \cdot 1/4EtOAc$
13c	CH_2CONH-benzyl	1	1	1	1	1	1	ND	ND	156	$C_{24}H_{23}N_3OS_2$
14	CH_2CH_2NHCO-(2-pyrazinyl)	1	0.25	0.5	0.25	0.5	>8	271	471	120	$C_{22}H_{21}N_5OS_2$
15	CH_2CH_2NHSO2-(8-quinolinyl)	1	4	8	4	8	>8	NC	NC	81	$C_{26}H_{24}N_4O_2S_3$
16	$CH_2CH_2NHCONHPh$	1	0.5	0.5	0.5	0.5	8	283	140	174	$C_{24}H_{24}N_4OS_2$
17a	$CH_2CH_2OCONHPh$	2	0.25	0.5	0.25	0.5	8	NC	NC	175	$C_{22}H_{22}N_2O_2S_2$
17b	$CH_2CH_2OCONHPh$	3	0.5	0.5	0.5	0.5	8	99	74	79	$C_{20}H_{20}N_2O_2S_3$
Tet[d]			1	1	1	1		NC	NC		
Met[e]			8	1	1	1		NC	NC		
Am[f]			0.06	0.06	0.06	0.12		NC	NC		
Clari[g]			<0.06	<0.06	<0.06	<0.06		1767	1000		

[a] Compounds were given orally by gavage needle at 30 mg/kg in a vehicle of 85:15 (0.5% aqueous hydroxypropylmethylcellulose:PEG-400) to C57BL/6NTac female mice (6 weeks, 20 g). [b] C, H, N. [c] ARHp115 corresponds to strain ATCC 43504 in the accompanying paper, ref 8. [d] Tetracyclin. [e] Metronidazole. [f] Amoxicillin. [g] Clarithromycin; NC, not checked; ND, not detected.

carbamates **17**. All samples of sufficient purity were subjected to evaluation as growth inhibitors in the microdilution assay. Table 3 contains a summary of results for representative compounds purified to obtain satisfactory analytical data and accurate biological testing results.

In general, we found that a rather large variety of residues could be incorporated into the target molecules while retaining microbiological potency. This was especially true for the sets of carbamates **12** and amides **13** and **14**, where a preference for nonbulky hydrophobic motifs was observed. The sulfonamide analogues **15** displayed poorer potencies as indicated for the quinoline derivative (R = quinoline-8-yl, **15**). Among the analogues tested, the phenyl carbamate **12a** and the benzyl amide **13c** exhibited the most potent bactericidal activities, MBC = 1 μg/mL.

To further assess the viability of selected compounds as drug leads, mice were dosed orally and the plasma concentrations of compounds were monitored over time. The observed areas under the curve (AUC) and maximum plasma concentrations (C_{max}) are shown in Table 3 where applicable. Among the tested compounds, the aryl carbamates gave the best results in this assay. The phenyl carbamate **12a** was chosen as a prototype because of the combination of an MBC of 1 μg/mL and an AUC comparable to that of clarithromycin, an antimicrobial frequently used clinically to control *H. pylori* infections. To explore the effects of structural modifications of **12a**, the syntheses of the phenyl urea analogue **16** and a set of heterocyclic phenyl carbamate variants **17** were undertaken. The results indicate that these modifications yielded compounds with similar microbiological properties but with inferior pharmacokinetic properties. The phenyl carbamate **12a** therefore remained the model compound and was submitted to a more thorough evaluation.

Thus, **12a** was evaluated for its effects on the growth of a variety of clinically important aerobic (13 different bacterial species including two strains of methicillin resistant *S. aureus*) and anaerobic microorganisms (16 different bacterial species), cf. Table 2. No significant growth inhibition effects were observed at concentrations up to 64 μg/mL as evidenced in Figure 1. To further assess the spectrum of activity, **12a** was also screened against a panel of 27 *H. pylori* strains, cf. Table 1. An MIC_{90} of 0.25 μg/mL was observed as illustrated in Figure 1. Hence, a clear antibacterial selectivity for strains of *H. pylori* over both aerobic and anaerobic microorganisms was observed for compound **12a**. The kinetics of *H. pylori* ARHp206 killing of **12a** were evaluated at 1 μg/mL and found to be comparable to that of clarithromycin (Figure 2). Furthermore, the rate of spontaneous resistance development to **12a** in a susceptible (*H. pylori* ARHp206) and a metronidazole resistant (*H. pylori* ARHp80) strain was measured and found to be less than 10^{-9}.

Discussion

Currently preferred *H. pylori* therapies call for a combination of a proton pump inhibitor, e.g., omeprazole,[7] and two antimicrobials. Amoxicillin, clarithromycin, and metronidazole[7,11] are the ones most frequently used. Eradication rates for these therapies typically vary

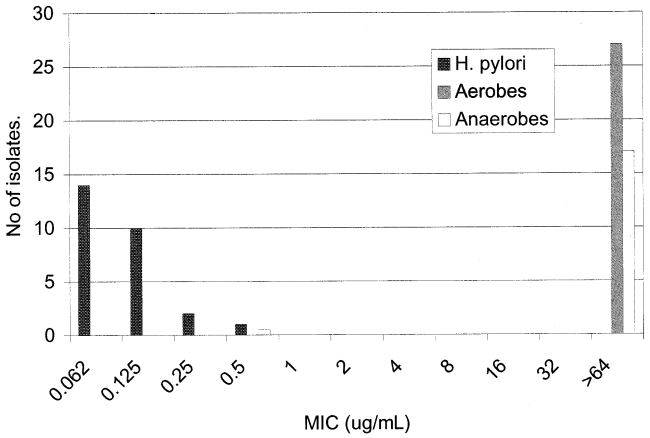


Figure 1. MIC distribution of compound **12a** against panels of 27 *H. pylori* strains (MIC_{90} = 0.25 μg/mL), 25 aerobic bacterial strains (MIC_{90} = >64 μg/mL), and 18 anaerobic bacterial strains (MIC_{90} = >64 μg/mL), cf. Tables 1 and 2 for a list of microorganisms.

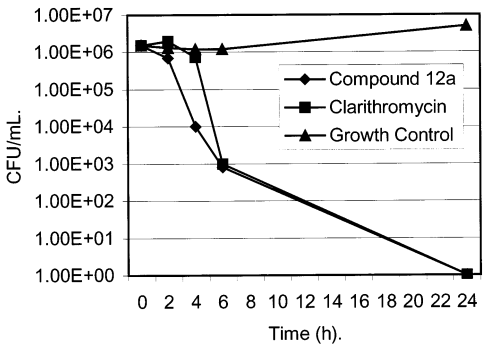


Figure 2. Killing kinetics of compound **12a** and clarithromycin against *H. pylori* strain ARHp206 determined at 1 μg/mL of each compound. No *H. pylori* killing was observed in the absence of compound.

between 80 and 95%,[12−15] depending on which particular *H. pylori* strain(s) are responsible for the infection.[16,17] Infections caused by strains susceptible to amoxicillin, clarithromycin, or metronidazole are generally more easily cured, while those caused by clarithromycin or metronidazole resistant strains are much more difficult to clear. Over the past decade, increased resistance to the antimicrobial components of the triple therapy regimens has been observed,[18,19] and these findings are indeed major drivers for developing novel anti-*H. pylori* agents.

We conclude that the phenyl carbamate **12a** disclosed in this paper does meet several significant in vitro microbiological criteria required for a novel anti-*H. pylori* agent. It displays low MIC values against a rather broad panel of *H. pylori* strains, including strains resistant to either metronidazole or clarithromycin, or both, while it is almost inactive against a rather wide range of commensal or pathogenic microorganisms. The combination of such a selectivity for one species (*H. pylori*) combined with a broad intraspecies antibacterial activity is remarkable and does indeed provide a unique opportunity for exploitation. This is especially true since **12a** displays bactericidal activity and killing rates at equally low concentrations as those of compounds routinely used in the clinic, namely, clarithromycin and amoxicillin.[20] Moreover, pharmacokinetic exposure levels were also in the same order of magnitude as, e.g., clarithromycin with an AUC of 1767 ng/mL·h. Indeed, many of the carbamates studied display AUCs between 1000 and 2000 ng/mL·h. Additionally, the C_{max} observed for **12a** of 0.9 μg/mL was approximately twice the MICs measured for the four *H. pylori* strains used in the microdilution assay (0.5 μg/mL) and was nearly equivalent to the MBC (1 μg/mL).

Moreover, *H. pylori* exhibits an acceptable rate of spontaneous resistance development against **12a**. In addition, strains that already are metronidazole or clarithromycin resistant do not show increased resistance rates. This finding suggests that preexisting resistance found in *H. pylori* in the clinical setting could be overcome by new chemical entities belonging to, e.g., the **12a** carbamate family.

The entire biologically relevant chemical diversity space[21] might not have been fully probed or explored in this study. Accordingly, we believe that a second round of highly focused SAR work around the carbamate family, applying appropriate property filters, scoring functions, and experimental design algorithms,[21] would indeed identify compounds that meet additional criteria such as metabolic stability and in vivo efficacy and tolerability.

To conclude, a parallel chemistry expansion of the 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]phenyl}-sulfanyl)-1-ethanol scaffold (**2**) successfully rendered a set of carbamates with the generic structure **12**, which displayed potent and selective activity against the gastric pathogen *H. pylori*. The measured rate of resistance development against **12a** was found to be less than 10^{-9}, a clinically acceptable level, and pharmacokinetic studies revealed in vivo exposure levels comparable with those established for antimicrobials currently used in *H. pylori* triple regimen. Further elaboration of the carbamate family **12** to exploit its unusual selective anti-*H. pylori* activity is therefore justified.

Experimental Section

General. Chemicals, reagents, and solvents were purchased from any of the major vendors if nothing else is stated or referenced. NMR spectra were recorded on a 500 MHz instrument manufactured by Bruker, Switzerland. Mass spectra were recorded on a VG Platform II equipped with an electrospray (ESI) source, both purchased from Micromass, U.K. Compound purity was checked by chromatographic means and/or microanalysis.

Chromatography. Preparative HPLC was run on ODS-AQ columns (5 μm, 30 mm × 250 mm) obtained from YMC Inc., Wilmington, NC, using MeCN/0.1 M NH_4OAc buffer (pH 7) as eluent at a flow rate of 30 mL/min with gradient from 10 to 100% MeCN in 20 min, followed by another 10 min at 100% MeCN.

Chemistry. Methyl 2-{[3-(Hydroxymethyl)-2-methylphenyl]sulfanyl}acetate (5). An ice cold solution of 3-amino-2-methylbenzoic acid (**3**), (11.3 g, 75 mmol) in H_2O (100 mL) was treated with concentrated HCl (15 mL), and $NaNO_2$ (5.5 g, 80 mmol) in H_2O (40 mL) was added over 30 min. The incipient diazonium salt was kept at 0 °C and over 40 min added to a solution of methyl thioglycolate (8.48 g, 80 mmol) in methanol (50 mL) kept at 60 °C. During the addition, the pH of the reaction medium was kept in the range of 5−6 by very carefully adding saturated Na_2CO_3. After the end of addition, the reaction was heated at 60−70 °C for an additional 45 min. The mixture was cooled to 0 °C, and the pH was adjusted to approximately 1 with concentrated HCl and extracted with EtOAc. The organic layer was collected, dried over Na_2SO_4, filtered, and evaporated to leave 17.4 g of crude

3-[(2-methoxy-2-oxoethyl)sulfanyl]-2-methylbenzoic acid (**4**). The acid was dissolved in tetrahydrofuran (THF, 120 mL) and cooled on an ice bath. 1 M Borane−THF solution (130 mL, 130 mmol) was added, and the mixture was allowed to react for 1 h. The reaction was quenched with ice water and extracted with EtOAc. The organic layer was collected, dried over Na_2SO_4, evaporated, and purified on silica gel (CH_2Cl_2/EtOAc, 20/1) to give 5 g (22%) of the target compound. ^{1}H NMR ($CHCl_3$-*d*): δ 2.45 (s, 3H), 3.62 (s, 2H), 3.71 (s, 3H), 4.72 (s, 2H), 7.18 (t, J = 7.8 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H).

Methyl 2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetate (7). Compound **5** (4.4 g, 19 mmol) was dissolved in methylene chloride (220 mL), treated with thionyl chloride (5 mL, 68 mmol), and allowed to react at ambient temperature for 4 h. The solvents were evaporated to yield 4.3 g of crude methyl 2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}acetate (**6**) as a slightly brown oil. The chloride **6** was dissolved in methanol (50 mL) and mixed with an ice cold solution of 2-mercaptobenzimidazole (2.69 g, 18 mmol) dissolved in a mixture of water (10 mL), methanol (30 mL), and NaOH (0.71 g, 18 mmol). The methanolic solution was allowed to react at ambient temperature for 6 h and then taken to dryness. The residue was partitioned between CH_2Cl_2 (600 mL) and 5% Na_2CO_3 (300 mL). The organic layer was collected, dried over Na_2SO_4, and evaporated to give 4.2 g (62%) of the target compound as a light yellow solid. ^{1}H NMR ($CHCl_3$-*d*): δ 2.49 (s, 3H), 3.60 (s, 2H), 3.75 (s, 3H), 4.54 (s, 2H), 7.00 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.24−7.28 (m, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.57 (bm, 2H). MS (ESI) for $C_{18}H_{18}N_2O_2S_2$ *m/z* (relative intensity): 359 (M + H, 100).

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol (8). Compound **7** (5.7 g, 16 mmol) was dissolved in THF (100 mL) and cooled on a ice-bath. LAH (0.5 g, 13 mmol) was added portion wise over 5 min. After it reacted for 30 min, the reaction was carefully quenched with sodium sulfate decahydrate. Filtration and evaporation afforded 4.1 g (78%) of the target copmound; mp 146 °C. ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H), 3.03 (t, J = 6.8 Hz, 2H), 3.60 (t, J = 6.8 Hz, 2H), 4.63 (s, 2H), 7.13−7.16 (m, 3H), 7.26−7.30 (m, 2H), 7.48 (bm, 2H). MS (ESI) for $C_{17}H_{18}N_2OS_2$ *m/z* (relative intensity): 331 (M + H, 100). Anal. ($C_{17}H_{18}N_2OS_2$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)acetic Acid (9). Compound **7** (0.68 g, 1.9 mmol) was dissolved in MeOH (14 mL) and allowed to react with LiOH (0.25 g, 10 mmol) dissolved in H_2O (2 mL) for 1 h. The solvents were evaporated, and the residue was partitioned between 5% Na_2CO_3 (100 mL) and ethyl acetate (100 mL). The aqueous layer was collected, and the pH was adjusted to about 4 with 4 M HCl and extracted with a 2:1 EtOAc/THF mixture. The combined organic layers were dried over $MgSO_4$ and evaporated to 0.5 g (76%) of the title compound as a white solid; mp 227 °C. ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H), 3.8 (s, 2H), 4.6 (s, 2H), 7.1−7.15 (m, 3H), 7.22 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.47 (bs, 2H). MS (ESI) for $C_{17}H_{16}N_2O_2S_2$ *m/z* (relative intensity): 345 (M + H, 100). Anal. ($C_{17}H_{16}N_2O_2S_2 \cdot 1/2H_2O \cdot 1/4EtOAc$) C, H, N.

2-({3-[(2-Azidoethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole (10). A mixture of **9** (0.165 g, 0.5 mmol), triphenylphosphine (0.184 g, 0.7 mmol), and sodium azide (0.13 g, 2 mmol) in dimethylformamide (DMF, 4 mL) was stirred on an ice bath. Carbon tetrabromide (0.25 g, 0.75 mmol) was added, and the reaction was allowed to proceed for 18 h. Methylene chloride (20 mL) was added, the resulting suspension was filtered, and the solids were rinsed with CH_2Cl_2. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated. Purification on silica gel (EtOAc/hexane, 1/5) gave 85 mg (48%) of the title compound. ^{1}H NMR ($CHCl_3$-*d*): δ 2.49 (s, 3H), 3.05 (t, J = 7 Hz, 2H), 3.45 (t, J = 7 Hz, 2H), 4.61 (s, 2H), 7.07 (t, J = 7.7 Hz, 1H), 7.21−7.26 (m, 3H), 7.29 (d, J = 8.4 Hz, 1H), 7.55 (bm, 2H). MS (ESI) for $C_{17}H_{17}N_5S_2$ *m/z* (relative intensity): 356 (M + H, 100).

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethylamine (11). Compound **10**, 2-({3-[(2-azidoethyl)sulfanyl]-2-methylbenzyl}sulfanyl)-1*H*-benzimidazole (0.42 g, 1.2 mmol), was added to an ice cold suspension of LAH (0.3 g, 7.9 mmol) in THF (10 mL). After 45 min, the reaction was carefully quenched with sodium sulfate decahydrate and filtered. The filtrate was evaporated, and the residue was dissolved in EtOAc and washed with 1 N HCl. The aqueous layer was collected, washed with EtOAc, and evaporated to give a white solid. The solid was dried in vacuo, dissolved in MeOH, and reprecipitated with Et_2O to yield 253 mg (58%) of the target compound a white powder; mp 245 °C. ^{1}H NMR (H_2O-d_2): δ 2.5 (s, 3H), 3.13 (t, J = 6.3 Hz, 2H), 3.18 (t, J = 6.3 Hz, 2H), 4.62 (s, 2H), 7.08 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.56 (m, 2H), 7.68 (m, 2H). MS (ESI) for $C_{17}H_{19}N_3S_2$ *m/z* (relative intensity): 330 (M + H, 100). Anal. ($C_{17}H_{19}N_3S_2 \cdot H_2O \cdot 2HCl$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl Phenylcarbamate (12a). A solution of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-ethanol (100 mg, 0.3 mmol) and phenyl isocyanate (35 mg, 0.3 mmol) in DMF (2 mL) was allowed to react for 18 h at ambient temperature. The mixture was concentrated in vacuo and purified by reversed phase LC to yield 60 mg (44%) of the target compound as a white solid; mp 122 °C. ^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H), 3.27 (t, J = 6.6 Hz, 2H), 4.25 (t, J = 6.6 Hz, 2H), 4.62 (s, 2H), 7.00 (bt, 1H), 7.14−7.18 (m, 2H), 7.27−7.31 (m, 4H), 7.38−7.40 (m, 2H), 7.48 (m, 2H), 7.56 (m, 1H), 9.75 (s, 1H). MS (ESI) for $C_{24}H_{23}N_3O_2S_2$ *m/z* (relative intensity): 450 (M + H, 100). Anal. ($C_{24}H_{23}N_3O_2S_2$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3-Methoxyphenylcarbamate (12b). White solid; mp 54−58 °C. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H), 3.18 (t, J = 6.5 Hz, 2H), 3.27 (s, 3H), 4.16 (t, J = 6.5 Hz, 2H), 4.53 (s, 2H), 6.50 (dd, J = 8.2, 2.3 Hz, 1H), 6.96 (bd, 1H), 7.05−7.12 (m, 5H), 7.21 (d, J = 7.4 Hz, 1H), 7.30 (m, 2H), 7.48 (bm, 1H), 9.66 (s, 1H). MS (ESI) for $C_{25}H_{25}N_3O_3S_2$ *m/z* (relative intensity): 480 (M + H, 100). Anal. ($C_{25}H_{25}N_3O_3S_2$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 3,4-Difluorophenylcarbamate (12c). White solid; mp 135 °C. ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H), 3.19 (t, J = 6.5 Hz, 2H), 4.17 (t, J = 6.5 Hz, 2H), 4.53 (s, 2H), 7.05−7.49 (m, 10H), 9.92 (s, 1H). MS (ESI) for $C_{24}H_{21}F_2N_3O_2S_2$ *m/z* (relative intensity): 486 (M + H, 100). Anal. ($C_{24}H_{21}F_2N_3O_2S_2$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl 4-(Dimethylamino)phenylcarbamate (12d). White solid; mp 133 °C. ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H), 2.75 (s, 6H), 3.16 (t, J = 6.6 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 4.54 (s, 2H), 6.60 (d, J = 9.0 Hz, 2H), 7.04−7.09 (m, 3H), 7.18−7.22 (m, 3H), 7.30 (d, J = 7.7 Hz, 2H), 7.47 (bs, 1H), 9.28 (s, 1H). MS (ESI) for $C_{26}H_{28}N_4O_2S_2$ *m/z* (relative intensity): 493 (M + H, 100). Anal. ($C_{26}H_{28}N_4O_2S_2$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-1-(1-piperidinyl)-1-ethanone (13a). A mixture of **9** (100 mg, 0.29 mmol), piperidine (30 mg, 0.32 mmol), and HBTU (120 mg, 0.32 mmol) was dissolved in DMF (2 mL) and allowed to react for 18 h. The mixture was taken up in EtOAc and washed with 5% $NaHC0_3$ and brine. The organic layer was collected, dried over $MgSO_4$, and evaporated to furnish 110 mg (92%) of the title compound; mp 140 °C. ^{1}H NMR (DMSO-d_6): δ 1.20 (bm, 2H), 1.29 (bm, 2H), 1.35 (bm, 2H), 2.20 (s, 3H), 3.20 (s, bm, 4H), 3.69 (s, 2H), 4.39 (s, 2H), 6.90−6.94 (bm, 3H), 7.05 (d, J = 7.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 7.25 (bm, 2H). MS (ESI) for $C_{22}H_{25}N_3OS_2$ *m/z* (relative intensity): 412 (M + H, 100). Anal. ($C_{22}H_{25}N_3OS_2 \cdot 1/4H_2O$) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-(2-thienylmethyl)acetamide (13b). White solid; mp 177 °C. MS (ESI) for $C_{22}H_{21}N_3OS_3$ *m/z* (relative intensity): 440 (M + H, 100). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H), 3.73 (s, 2H), 4.49 (d, J = 5.8 Hz, 2H), 4.66 (s,

2H), 6.98 (m, 2H), 7.14−7.20 (m, 3H), 7.30 (m, 2H), 7.43 (m, 2H), 7.60 (m, 1H), 8.80 (t, J = 5.8 Hz, 1H). Anal. ($C_{22}H_{21}N_3OS_3$·1/4EtOAc) C, H, N.

2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)-*N*-benzylacetamide (13c). White solid; mp 156 °C. ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H), 3.72 (s, 2H), 4.28 (d, J = 5.9 Hz, 2H), 4.62 (s, 2H), 7.09−7.23 (m, 10H), 7.38 (bs, 1H), 7.56 (bs, 1H), 8.65 (t, J = 5.9 Hz, 1H), 12.61 (s, 1H). MS (ESI) for $C_{24}H_{23}N_3OS_2$ m/z (relative intensity): 434 (M + H, 100). Anal. ($C_{24}H_{23}N_3OS_2$) C, H, N.

***N*-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-2-pyrazinecarboxamide (14).** A mixture of **11** (658 mg, 2 mmol), 2-pyrazinecarboxylic acid (248 mg, 2 mmol), DIPEA (1 mL, 5.7 mmol), and HBTU (829 mg, 2.2 mmol) in DMF (8 mL) was allowed to react overnight. The mixture was diluted with EtOAc (200 mL) and washed with water (2 × 100 mL) and brine. The organic layer was dried over $MgSO_4$ and taken to dryness. The residue was purified by reversed phase LC to furnish 600 mg (69%) of the title compound as a white solid; mp 120 °C. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 3.17 (t, J = 6.5 Hz, 2H), 3.54 (dt, J = 6.5, 1.4 Hz, 2H), 4.61 (s, 2H), 7.14−7.55 (m, 7H), 8.75 (s, 1H), 8.89 (s, 1H), 9.21 (bs, 1H). MS (ESI) for $C_{22}H_{21}N_5OS_2$ m/z (relative intensity): 436 (M + H, 100). Anal. ($C_{22}H_{21}N_5OS_2$) C, H, N.

***N*-[2-({3-[(1*H*-Benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-8-quinolinesulfonamide (15).** A solution of **11** (100 mg, 0.3 mmol) dissolved in THF/DMF (1:1, 2 mL) was allowed to react with 8-quinolinesulfonyl chloride (70 mg, 0.3 mmol) and triethylamine (70 mg, 0.3 mmol) for 2 h. The mixture was taken to dryness, and the residue was purified by reversed phase preparative LC to give 95 mg (61%) of the target compound as a white powder; mp 81 °C. ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H), 2.93 (t, J = 6.3 Hz, 2H), 3.04 (t, J = 6.3 Hz, 2H), 4.57 (s, 2H), 7.01 (m, 2H), 7.15 (m, 2H), 7.22 (m, 1H), 7.38 (m, 1H), 7.48 (bt, 1H), 7.56 (m, 1H), 7.71−7.77 (m, 2H), 8.30 (dt, J = 8.5, 1.5 Hz, 2H), 8.55 (dd, J = 8.5, 1.5 Hz, 1H), 9.05 (m, 1H), 12.58 (s, 1H). MS (ESI) for $C_{26}H_{24}N_4O_2S_3$ m/z (relative intensity): 521 (M + H, 100). Anal. ($C_{26}H_{24}N_4O_2S_3$) C, H, N.

***N*-[2-({3-[(1*H*-benzimidazol-2-ylsulfanyl)methyl]-2-methylphenyl}sulfanyl)ethyl]-*N*′-phenylurea (16).** A soultion of **11** (100 mg, 0.3 mmol) dissolved in DMF (2 mL) and phenyl isocyanate (36 mg, 0.3 mmol) was allowed to react at ambient temperature overnight. The solvent was evaporated, and the residue was purified by reversed phase preparative LC furnishing 85 mg (63%) of the target compound as a white powder; mp 174 °C. ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H), 2.98 (t, J = 6.6 Hz, 2H), 3.22 (dt, J = 6.6, 5.9 Hz, 2H), 4.54 (s, 2H), 6.39 (t, J = 5.9 Hz, 1H), 6.91 (t, J = 7.3 Hz, 1H), 7.13−7.17 (m, 3H), 7.22−7.28 (m, 3H), 7.37−7.41 (m, 4H), 7.56 (m, 1H), 8.62 (s, 1H); 12.61 (s, 1H). MS (ESI) for $C_{24}H_{24}N_4OS_2$ m/z (relative intensity): 449 (M + H, 100). Anal. ($C_{24}H_{24}N_4OS_2$) C, H, N.

2-({2-Methyl-3-[(4-pyridinylsulfanyl)methyl]phenyl}sulfanyl)ethyl phenylcarbamate (17a). A vigorously stirred solution of of 2-{[3-(chloromethyl)-2-methylphenyl]sulfanyl}-ethyl phenylcarbamate (**22**) (135 mg, 0.4 mmol) in DMF (2 mL) was treated with 4-thiopyridine (65 mg, 0.59 mmol) and K_2CO_3 (65 mg, 0.59 mmol) and allowed to react at ambient temperature for 1.5 h. The mixture was diluted to 25 mL with EtOAc, washed with H_2O (15 mL), 2 × 1 N KOH (15 mL), and brine (15 mL). The organic layer was collected, dried over $MgSO_4$, and taken to dryness leaving a thick oil. Purification on silica gel (EtOAc/hexane, 1/9 to 3/7) furnished 130 mg (79%) of the target compound as a waxy solid; mp 175 °C. ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H), 3.28 (t, J = 6.5 Hz, 2H), 4.25 (t, J = 6.5 Hz, 2H), 4.40 (s, 2H), 7.01 (t, J = 7.3 Hz, 1H), 7.20−7.49 (m, 9H), 8.40 (d, J = 4.5 Hz, 2H), 9.75 (bs, 1H). MS (ESI) for $C_{22}H_{22}N_2O_2S_2$ m/z (relative intensity): 411 (M + H, 100). Anal. ($C_{22}H_{22}N_2O_2S_2$) C, H, N.

2-({2-Methyl-3-[(1,3-thiazol-2-ylsulfanyl)methyl]phenyl}sulfanyl)ethyl Phenylcarbamate (17b). White solid; mp 79 °C. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 3.26 (t, J = 6.5 Hz, 2H), 4.25 (t, J = 6.5 Hz, 2H), 4.53 (s, 2H), 7.01 (t, J = 7.3 Hz, 1H), 7.17−7.46 (m, 7H), 7.70 (d, J = 3.3 Hz, 1H), 7.79 (d, J = 3.3 Hz, 1H), 9.74 (bs, 1H). MS (ESI) for $C_{20}H_{20}N_2O_2S_3$ m/z (relative intensity): 417 (M + H, 100). Anal. ($C_{20}H_{20}N_2O_2S_3$) C, H, N.

Methyl 2-{[3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}acetate (18). A mixture of **5** (9.8 g, 43 mmol), imidazole (5 g, 74 mmol) and TBDMSCl (8 g, 53 mmol) in DMF (15 mL) was allowed to react at ambient temperature for 45 min. The mixture was taken up in EtOAc and washed with 1 N HCl, H_2O, and brine. The organic layer was collected, dried over $MgSO_4$, and evaporated leaving 14 g (95%) of the target compound as a yellow liquid. ^{1}H NMR ($CHCl_3$-d): δ 0.11 (s, 6H), 0.97 (s, 9H), 2.39 (s, 3H), 3.62 (s, 2H), 3.72 (s, 2H), 4.72 (s, 2H), 7.20 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H).

2-{[3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}-1-ethanol (19). LAH (2 g, 53 mmol) was slowly added to a stirred ice cold solution of **18** (14 g, 41 mmol) in THF (50 mL) and allowed to react for 30 min. The reaction was quenched with H_2O (2 mL) and 4 M NaOH (1 mL). The mixture was filtered, and the solids were rinsed with THF. The filtrate was taken up in EtOAc and washed with 1 N HCl and brine. The organic layer was collected, dried over $MgSO_4$, and evaporated to leave 11 g (86%) of title compound as a yellow liquid. ^{1}H NMR ($CHCl_3$-d): δ 0.12 (s, 6H), 0.97 (s, 9H), 2.40 (s, 3H), 3.09 (t, J = 6.0 Hz, 2H), 3.75 (t, J = 6.0 Hz, 2H), 4.72 (s, 2H), 7.19 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H).

2-{[3-(Hydroxymethyl)-2-methylphenyl]sulfanyl}-ethyl phenylcarbamate (21). A mixture of **19** (11 g, 35 mmol), phenyl isocyanate (6.58 g, 55 mmol), and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) in THF (10 mL) was allowed to react for 2 h at 50 °C. The mixture was taken up in EtOAc and washed with 1 N HCl and brine. The organic layer was collected, dried over $MgSO_4$, and evaporated to afford crude 2-{[3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]sulfanyl}ethyl phenylcarbamate **20**. ^{1}H NMR ($CHCl_3$-d): δ 0.13 (s, 6H), 0.95 (s, 9H), 2.40 (s, 3H), 3.17 (t, J = 6.6 Hz, 2H), 4.34 (t, J = 6.6 Hz, 2H), 4.72 (s, 2H), 6.54 (bs, 1H), 7.11−7.41 (m, 8H). The crude carbamate was dissolved in THF (10 mL) and allowed to react with 75% aqueous tetrabutylammonium fluoride (17 mL, 47 mmol) at ambient temperature for 1 h. The mixture was taken up in 1 N HCl and extracted with EtOAc. The organic layer was collected, washed with brine, and dried over $MgSO_4$. Purification was done on silica gel (EtOAc/hexane, 1/9 to 3/7). An oily yellowish solid was obtained, which was triturated with hexane, collected on a sintered glass frit, and rinsed with hexane to yield 4.43 g (40%) of the target compound as a white powder. ^{1}H NMR ($CHCl_3$-d): δ 2.48 (s, 3H), 3.19 (t, J = 6.7 Hz, 2H), 4.35 (t, J = 6.7 Hz, 2H), 4.72 (s, 2H), 6.55 (bs, 1H), 7.09−7.36 (m, 8H).

2-{[3-(Chloromethyl)-2-methylphenyl]sulfanyl}ethyl Phenylcarbamate (22). An ice cold solution of **21** (0.5 g, 1.6 mmol) in THF (3 mL) was treated with $SOCl_2$ (1 mL, 14 mmol) and allowed to react at ambient temperature for 45 min. Evaporation of the solvent and trituration of the residue with hexane gave 525 mg (98%) of the title compound as an off-white solid. ^{1}H NMR ($CHCl_3$-d): δ 2.54 (s, 3H), 3.20 (t, J = 6.6 Hz, 2H), 4.35 (t, J = 6.6 Hz, 2H), 4.63 (s, 2H), 6.52 (bs, 1H), 7.10−7.37 (m, 8H).

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