JOURNAL OF combinatorial CHEMISTRY

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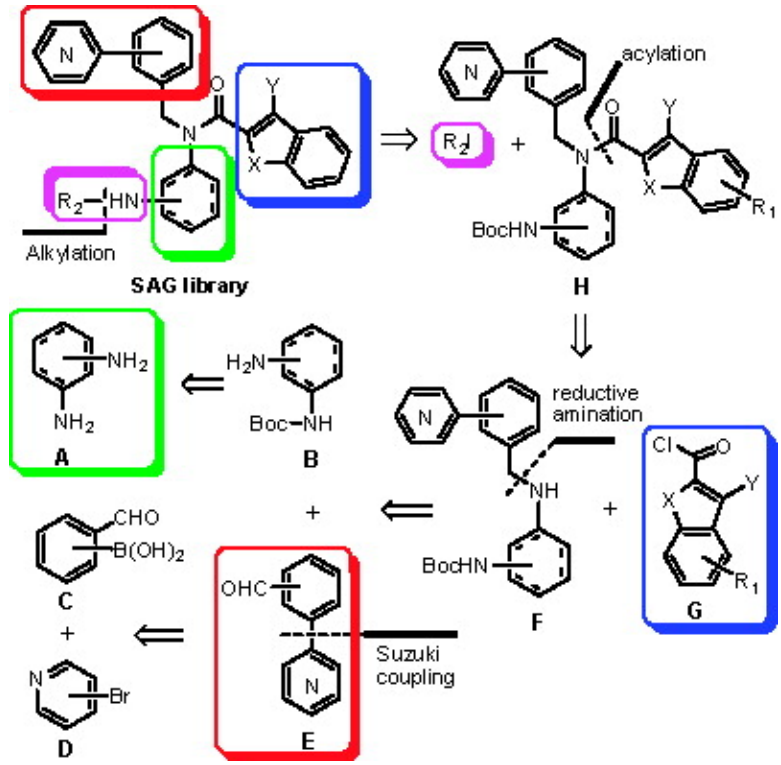
J. Comb. Chem., **2008**, 10 (6), 825-834• DOI: 10.1021/cc800025n • Publication Date (Web): 28 August 2008



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A Concise and Diversity-Oriented Approach to the Synthesis of SAG Derivatives

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Received February 14, 2008

An efficient and rapid solution-phase combinatorial synthesis of the SAG library was developed. The salient features for this library synthesis is the application of carbothioamide-derived palladacycle-catalyzed Suzuki coupling reactions for the parallel synthesis of a series of pyridine-based biaryl aldehydes under aerobic conditions and a direct *N*-alkylation of carbamates using NaH as base in DMF in the presence of catalytic amount of water. The resultant library has been submitted to biological screening to evaluate their potential role in the regulation of Hedgehog pathway.

Introduction

In chemical genetics, the study of interesting biological targets has relied extensively on the use of small molecules.[1] The application of prevalidated scaffolds[2] to investigate specific targets is of high priority because such focused libraries could perturb the function of the targets in a systematic manner, and in return, the generated information could provide enormous instruction for biomedical research.[3] However, synthesis of library with high purity and diversity remains a challenging, yet indispensable step toward the biochemical research. Thus the development of efficient and modular methods to synthesize a large amount of structurally diverse molecular libraries becomes necessary.[4]

Hedgehog (Hh) signaling normally functions to specific embryonic patterns by directing cellular differentiation and proliferation.[5] Mutations in Hh and its downstream signaling molecules are associated with numerous diseases.[6] To date, several small molecules that can regulate Hh signaling pathway have been identified, such as cyclopamine (**1**)[7] and its potent derivative KAAD-cyclopamine (**2**),[8] purmorphamine[9] (**3**), and SAG (**4**)[10] (Figure 1).

Among the molecules listed in Figure 1, SAG (**4**) is particularly attractive because of its exceeding potency to regulate Hh pathway at the concentration of ~3.0 nM, as well as its unique modularity feature for diversity-oriented synthesis. In addition, the structure of SAG also represents a common scaffold exists in a group of pharmacological active substances, such as biarylurea **16**, a potent and orally efficacious MCH-R1 antagonist,[11] and arylpiperazine **17**, a potent and selective agonist of human melanocortin subtype-4-receptor (Figure 2).[12] Thus, SAG could be regarded as a privileged scaffold[13] with a substantial intellectual appeal.

Surprisingly, a synthetic study directed to the diversity-oriented synthesis of SAG has not been reported. Our longstanding interest in the diversity-oriented synthesis and library production promoted us to develop a new approach that requires fewer synthetic steps and low-cost parallel synthesis techniques to synthesize SAG library. Ideally the chemistry should be carried out under aerobic and mild

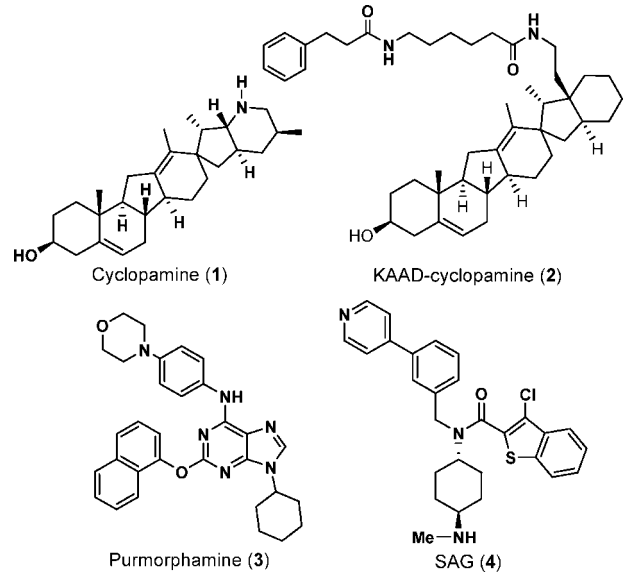

Figure 1. Structures of SAG and its structurally relevant and biologically active molecules.

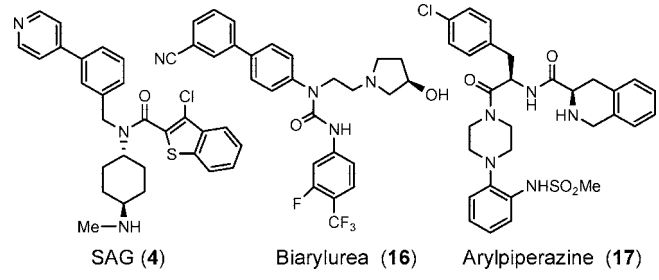

Figure 2. SAG and its structurally relevant and biologically active molecules.

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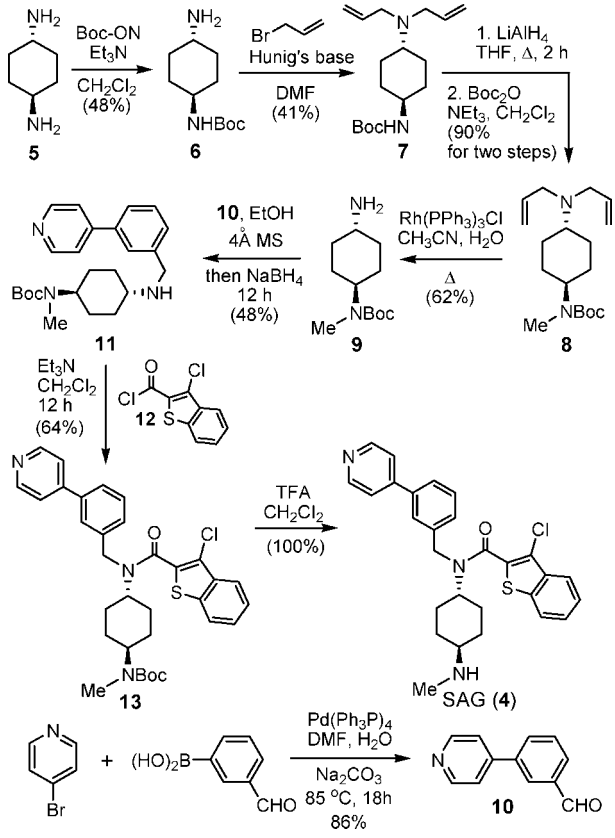
10.1021/cc800025n CCC: $40.75
Published on Web 08/28/2008

Scheme 1. Beachy's Synthesis of SAG **4**



conditions. Herein we report our recent contribution to the development of a concise and robust way to the diversity-oriented synthesis of SAG library.

Results and Discussion

The synthesis of SAG molecule was accomplished in 8 steps by Beachy and co-workers in 2002[10] (Scheme 1). The key intermediate **9** was synthesized in five steps with 11% overall yield. However, when we tried to repeat this synthesis, we found that the results of the Rh-catalyzed deprotection of allylic groups of substrate **8** was unpredictable, and the synthetic procedure for conversing **7** to **8** via the $LiAlH_4$ reduction was tedious. These difficulties encountered in these reactions promoted us to develop another short and efficient route to access our target molecule SAG and realize its library synthesis.

As highlighted in Figure 3, by starting from compound **6**, we proposed a synthesis of SAG, which includes (i) reductive amination, (ii) acylation, (iii) methylation, and (iv) deprotection.

Clearly, this new strategy would confine protecting group operations and avoid potentially troublesome multistep

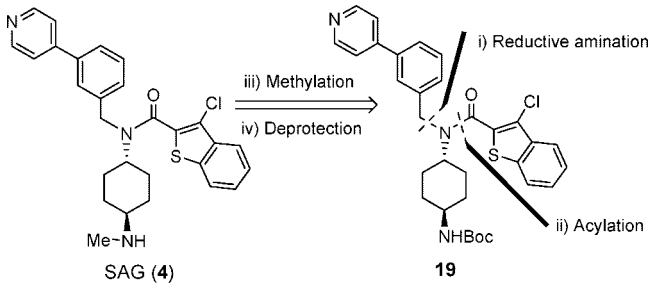
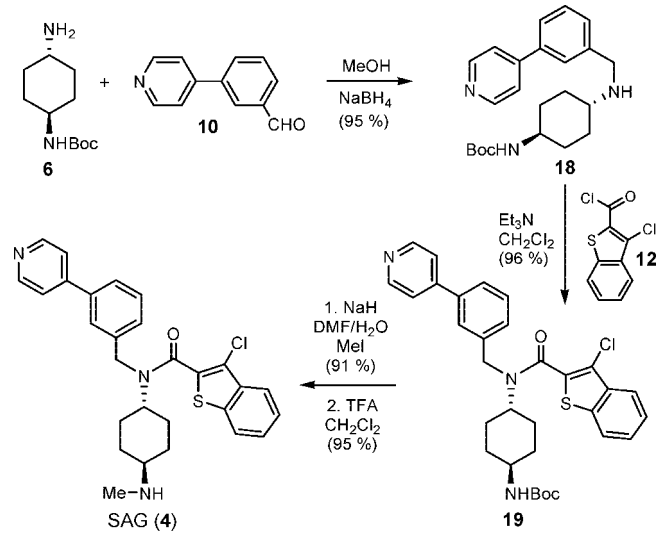


Figure 3. Retrosynthetic analysis.

Scheme 2. Concise Synthesis of SAG (**4**)



synthetic manipulations to synthesize amine **9** in Scheme 1. Furthermore, it would enable a rapid construction of SAG library. Although the proposed direct N-alkylation[14] on carbamate **19** shortened the synthetic route, one potentially competitive side-reaction is the Menschutkin reaction,[15] which might result in the formation of pyridinium salt by N-alkylation on pyridine.

As shown in Scheme 2, the synthesis started with coupling of intermediates **6** and **10** together in methanol in the presence of 4 Å molecular sieves. The resultant imine was then reduced by $NaBH_4$ to give product **18** through a direct reductive amination,[16] as described by Beachy and his co-workers.[10] However, applications of this reaction to the preparation of compound **18** are less satisfactory, providing the product in only ~50% yield. The low yield of compound **18** could be a result of incomplete conversion of the starting materials to their corresponding imine intermediate. Therefore, a variety of reaction conditions were screened, and interestingly, it turned out that full conversion of **6** and **10** to imine could be achieved simply by mixing them in methanol at room temperature for half an hour *without adding any molecular sieves*. This process was evidenced by the observation of the disappearance of a carbonyl peak at 191 ppm and the occurrence of an imine's signal at 158 ppm in a real time ^{13}C NMR study. As a result, compound **18** could be eventually made in 95% yield by addition of $NaBH_4$ to the reaction mixture generated by mixing amine **6** with aldehyde **10** in methanol for 30 min.

With a successful reductive amination procedure, the consequent secondary amine **18** was treated with acyl chloride **12** in CH_2Cl_2 with TEA as the base, the same condition in Scheme 1. To our delight, 96% yield of the desired product **19** was obtained in our case, which indicates that the reaction is highly substrate-dependent.

To complete the synthesis of SAG, we then started to investigate the N-methylation of **19**. Although our proposed methylation is expected to occur predominately under basic conditions, it should be noted that under certain conditions the Menschutkin reaction resulting from addition of alkylating agents to pyridine has been reported.[17] We initially evaluated the methylation reaction by employing the litera-

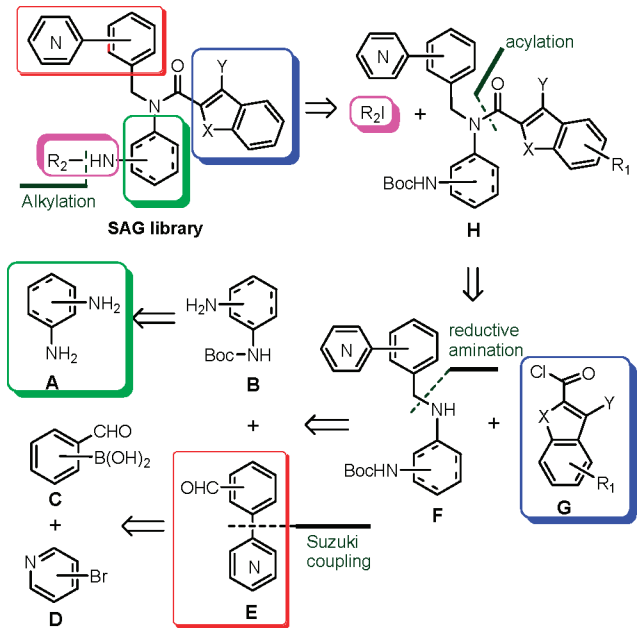


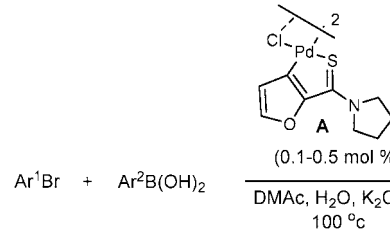
Figure 4. Proposed SAG library synthesis.

ture procedure: compound **19** was first treated with NaH in THF at room temperature under anhydrous conditions; the resultant anion was then reacted with methyl iodide.[18] However, the reaction results were proven to be unpredictable, and in most of the cases, less than 50% yield of the desired product was obtained. To optimize the reaction, we carried out a systematic variation of base, solvent, reaction time, and temperature. We found that the reaction proceeded smoothly in the presence of catalytic amount of water.[19] The desired product was eventually obtained in 91% yield by treatment of substrate **19** with NaH in the presence of catalytic amount of water in DMF at 0 °C for 1 h, followed by reaction with methyl iodide at room temperature for 0.5 h. Thus, our final target SAG was generated in 95% yield by treatment of the methylated product with TFA in CH_2Cl_2.

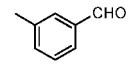
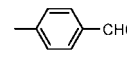
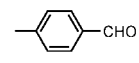
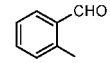
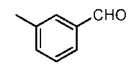
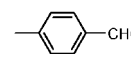
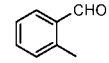
With the short and efficient synthetic approach to make SAG, our next goal was to design a strategy suitable for the diversity-oriented synthesis of SAG library. As shown in Figure 4, the scaffold of SAG could be constructed by combining four distinct modules as highlighted in different colors. The design elements for SAG library included replacing the cyclohexane-1,4-diamine with benzene-1,4-diamine, changing the substitution pattern of the biaryl fragment, varying the isosteric substituents on the benzo[*b*]-thiophene ring, and replacing the methyl group by other alkyl groups. More importantly, our novel synthetic route enables us to introduce different patterns for each fragment at every single step.

To introduce the biaryl subunit **E** as the first point of diversity, the Pd-catalyzed Suzuki coupling reaction of commercially available arylboronic acids and aryl bromides (see Table 1) was evaluated. Although $Pd(PPh_3)_4$ is frequently used in the Suzuki reaction, most Suzuki couplings need degassed solvents, and the reactions have to be carried out in an inert atmosphere[20] to avoid oxidative Pd-aggregation, which was observed when we tried to synthesize compound **10** under aerobic conditions. Our aim was to construct a small library of SAG as discrete molecules, rather

Table 1. Parallel Synthesis of Biaryl Molecules by Palladacycle **A** Catalyzed Suzuki Coupling Reactions



$Ar^1Br + Ar^2B(OH)_2 \rightarrow Ar^1\text{-}Ar^2$

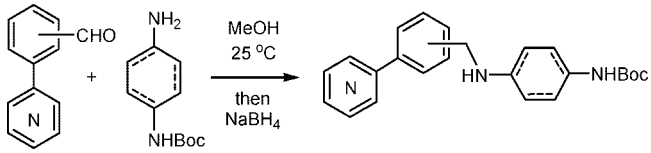
entry	Ar^1	Ar^2	t(h)	Pd(mol %)	product	yield
1			2	0.1	**10a**	86
2			2	0.1	**10b**	83
3			2	0.1	**10c**	79
4			2	0.1	**10d**	90
5			2	0.1	**10e**	91
6			2	0.1	**10f**	89
7			2	0.1	**10g**	87

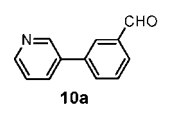
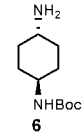
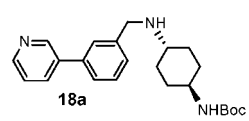
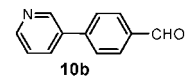
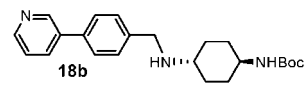
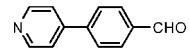
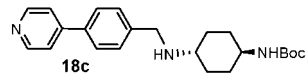
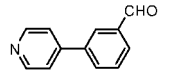
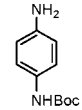
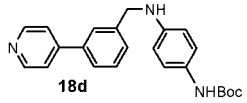
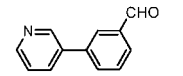
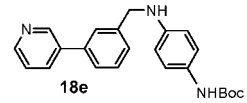
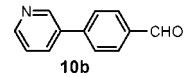
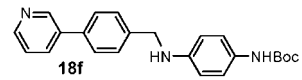
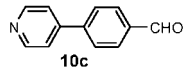
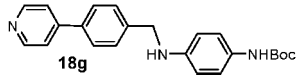
[a] Reaction conditions: Ar^1Br (1 mmol), $Ar^2B(OH)_2$ (1.2 mmol), and K_2CO_3 (2 mmol) in a solution of 25% DMAc water solution (2 mL) at 100 °C. [b] Isolated yield.

than mixture, therefore, the Suzuki reactions which could be carried out in a parallel manner under aerobic conditions would be highly desirable. Our group also developed an air- and moisture-stable carbothioamide-derived palladacycle **A** (Table 1), which could catalyze the Suzuki reaction under aerobic conditions.[21] Thus, our initial experiments were carried out to seek a mild and aerobic reaction condition for the desired Suzuki reactions by utilizing palladacycle **A** as catalyst. After systematic reaction condition optimization, we found out that the reactions could be carried out in air at 100 °C for 2 h with K_2CO_3 as base in the presence of palladacycle **A** as catalyst (1.0 M stock solution in MDAc, less than 0.5 mmol %), and all the reactions gave good results as illustrated in Table 1. It is worthwhile to mention that the stock solution of palladacycle **A** could be stored at room temperature over a month without loss of its catalytic activity.

We then turned our attention to evaluate the reductive amination for the synthesis of secondary amine **18a**−**g** from their corresponding biaryl aldehydes and amines. With regard to the conformational and electronic differencea between cyclohexane-1,4-diamine and benzene-1,4-diamine, the replacement of cyclohexane-1,4-diamine with benzene-1,4-diamine in SAG scaffold may present the formed SAG derivatives with a different stereoelectronic profile, which will be of great interest in the study of their structure−activity relationship. To this end, alkyl amine **6** and aryl amine **6a** were reacted with biaryl aldehydes **10** and **10a**−**c**, respectively, under the optimized conditions described above. To

Table 2. Selective Reductive Amination to Form Secondary Amines



entry	ArCHO	amine	product	yield (%)
1	 **10a**	 **6**	 **18a**	95
2	 **10b**	**6**	 **18b**	93
3	 **10c**	**6**	 **18c**	96
4	 **10**	 **6a**	 **18d**	93
5	 **10a**	**6a**	 **18e**	95
6	 **10b**	**6a**	 **18f**	93
7	 **10c**	**6a**	 **18g**	94

[a] Reaction conditions: ArCHO (3.0 mmol), amine (3.3 mmol) in MeOH for 30 min., then $NaBH_4$ (4.5 mmol) at 25 °C for 10 min. [b] Isolated yield.

our delight, all the selected reactions gave the expected secondary amines **18a**−**g** in excellent yields (Table 2).

With the secondary amines **18a**−**g** in hand, we then started to profile the amide formation by reaction of acyl chlorides **12** and **12a**, **b** with amines **18a**−**d** and **18f**−**g**. Because benzo[*b*]furan can be regarded as benzo[*b*]thiophene isoster, we then decided to make a group of SAG derivatives by displacement of benzo[*b*]thiophene with benzo[*b*]furan. In the event, the secondary amines **18a**−**d** and **18f**−**g** were selected to react with the freshly generated acyl chlorides **12** and **12a**−**b** (derived by the treatment of the corresponding carboxylic acid with distilled thionyl chloride in CH_2Cl_2 at 40 °C for 2 h) in the presence of triethylamine at room temperature for 30 min, and the expected amides **19a**−**h** were formed in good to excellent yields as illustrated in Table 3.

At this point, we focused our attention toward diversifying the *N*-methyl side chain using the direct N-alkylation reaction. To evaluate the generality and robustness of direct N-alkylation of carbamate, we selected methyl-, ethyl-, propyl-, butyl-, and allylic halides in the alkylation reactions.

In the event, five organohalides were reacted with amides **19** and **19h**, individually, and all the reactions gave the desired products in excellent yields of (see Table 4), indicating that our identified reaction conditions are quite general to make structurally diverse alkylated amines. To complete the synthesis, cleavage of the Boc protecting group from SAG scaffold was carried out by treatment of amides **20a**−**e** with TFA in CH_2Cl_2 at 0 °C for 1 h to give the desired products **21a**−**e** in high yields (Table 4).

In conclusion, we have demonstrated a concise and practical approach to the synthesis of SAG. The new synthetic strategy allows modulation of the architecture of SAG by incorporation of four sources of diversity. Thus, the developed strategy opens a rather general access to a broad variety of new SAG type of molecules. The synthesized over 200-member SAG library with high purity (>90%) and good quantities (5−50 mg) is currently under biological investigation and will be reported separately in due course.

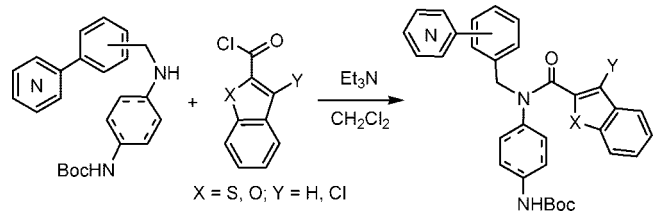
Experimental Section

In this section, we only present the detail for the synthesis of SAG by the new approach, the other information for the syntheses of SAG derivatives is provided in the Supporting Information.

Preparation of (4-Amino-cyclohexyl)-carbamic Acid *tert*-Butyl Ester (6). A solution of Boc_2O (1.0 g, 4.6 mmol) in methanol (25 mL) was slowly added to *trans*-1, 4-diaminocyclohexane (1.0 g, 8.8 mmol) in methanol (100 mL), and the reaction mixture was stirred at room temperature for 1 h. After filtration, the filtrate was concentrated under vacuum to ~5 mL, and then cooled to −20 °C. The crystallized product was collected. The filtrate was resubmitted to the same reaction condition. After the second cycle, the desired product **6** was obtained in 56% yield (1.05 g). IR (cm^{-1}): 3365, 2933, 1686, 1520. ^1H NMR (300 MHz, $CDCl_3$): δ 4.90−5.02 (br, 1H), 3.30−3.42 (br, 1H), 2.58−2.66 (m, 1H), 1.92−2.00 (br, 2H), 1.85−1.97 (m, 4H), 1.43 (s, 9H), 1.10−1.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 77.9, 48.7, 48.0, 34.2, 34.1, 31.0, 30.9, 27.3. MS (EI) calcd for $C_{11}H_{22}N_2O_2$ (M^+) 214; found 214.

Preparation of 3-Pyridin-4-yl-benzaldehyde (10). To a solution of 4-bromopyridine hydrochloride (533.4 mg, 2.7 mmol) in water (4.0 mL) and toluene (4.8 mL) was added slowly a solution of Na_2CO_3 (714 mg, 6.7 mmol) in water (7.0 mL) at room temperature. The solution was then mixed with 3-formylbenzeneboronic acid (431 mg, 2.9 mmol), $Pd(PPh_3)_4$ (100 mg, 0.086 mmol). The reaction mixture was stirred at 85 °C for 24 h, and then cooled to room temperature. The reaction was worked up by extraction of the mixture with CH_2Cl_2 (4 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography (silica gel, petroleum ether/EtOAc = 1/4) to give product **10** (420 mg) in 85% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 10.1 (s, 1H), 8.72−8.74 (m, 2H), 8.17 (s, 1H), 7.90−7.99 (m, 2H), 7.69 (t, J = 11.4 Hz, 1 H), 7.57 (d, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ191.5, 150.3, 146.5, 138.8, 136.8, 132.5, 130.1, 129.6, 127.5, 121.3. HRMS (ESI) calcd for $C_{12}H_9NO$ ($M + H^+$) 184.07569; found 184.07538.

Table 3. Amide Bond Formation



entry	amine	acyl chloride	product	yield (%)
1	**18a**	**12**	**19a**	96
2	**18b**	**12a**	**19b**	93
3	**18a**	**12a**	**19c**	94
4	**18c**	**12a**	**19d**	93
5	**18d**	**12**	**19e**	96
6	**18f**	**12a**	**19f**	95
7	**18g**	**12a**	**19g**	97
8	**18g**	**12b**	**19h**	95

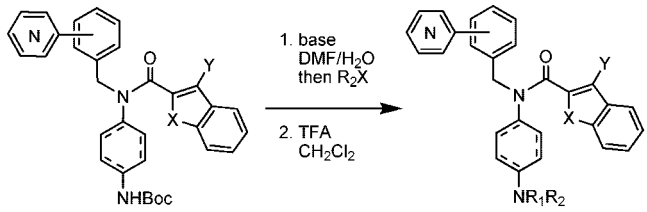
[a] Reaction conditions: amine (1.0 mmol), acycl chloride (1.1 mmol), and Et_3N (2.0 mmol) in CH_2Cl_2 at 25 °C for 30min. [b] Isolated yield.

Preparation of [4-(3-Pyridine-4-yl-benzylamino)-cyclohexyl]-carbamic Acid *tert*-Butyl Ester (18). To a solution of 3-pyridinyl benzaldehyde (**10**) (205 mg, 1.1 mmol) in methanol (20 mL) was added *N*-Boc-1,4-diaminocyclohexane (**6**) (300 mg, 1.4 mmol), and the mixture was stirred at room temperature for 30 min. To this solution was added $NaBH_4$ (0.5 g, 13.2 mmol) in portions at 0 °C, and the reaction mixture was stirred at room temperature overnight. The reaction was worked up by addition of saturated aqueous Na_2CO_3 (2 mL), and the mixture was then extracted with chloroform (3 × 6 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (CH_2Cl_2/MeOH = 10/1) to give **18** (398 mg) in 95% yield.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, J = 8.1 Hz, 2H), 7.39−7.61 (m, 6H), 4.30−4.50 (br, 1H), 3.88(s, 2H), 3.30−3.50 (br, 1H), 2.40−2.60 (m, 1H), 1.90−2.10 (m, 4H), 1.70−1.90(br, 1H), 1.44 (s, 9H), 1.06− 1.40(m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 150.0, 148.3, 141.5, 138.1, 129.1 128.7, 126.6, 125.5, 121.6, 79.0, 55.6, 51.0, 49.4, 31.9, 28.3. HRMS (ESI) calcd for $C_{23}H_{31}N_3O_2$ ($M + H^+$) 382.24890; found 382.24896.

Preparation of {4-[(3-Chloro-benzo[*b*]thiophene-2-carbonyl)-(3-pyridin-4-yl-benzyl)-amino]-cyclohexyl}-Carbamic Acid *tert*-Butyl Ester (19). To a solution of **18** (410 mg, 1.1 mmol) and Et_3N (280 μL, 2.0 mmol) in CH_2Cl_2 (10 mL) was added 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride **12** (278 mg, 1.2 mmol), and the reaction mixture was stirred at room temperature for 0.5 h. The solvent was removed, and the residue was purified by a flash chromatography on silica gel (acetone/PE = 5:1) to give the desired product **19** (587 mg) in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (br, 2H), 7.20−8.20 (m, 10H), 3.70−5.00 (m, 4H), 3.20−3.40 (br, 1H), 1.75−2.20 (m, 4H), 1.42−1.75 (br, 2H), 1.38 (s, 9H), 0.90−1.30 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 163.7, 155.1, 150.2, 148.1, 147.7, 139.2, 138.4, 137.2, 135.6, 130.0, 129.3, 127.6, 126.5, 126.2, 125.5, 122.7, 122.5, 121.6, 119.0, 79.2, 58.7, 48.5, 45.1, 32.1, 30.5, 29.7, 29.3, 28.3. HRMS(EI) calcd for $C_{32}H_{34}ClN_3O_3S$ (M^+) 575.2009; found 575.2018.

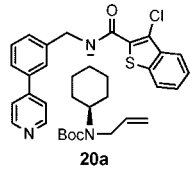
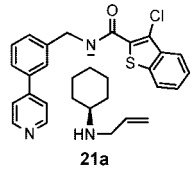
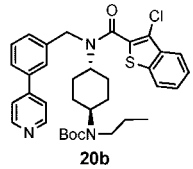
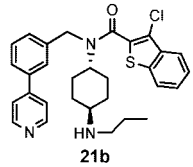
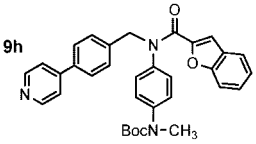
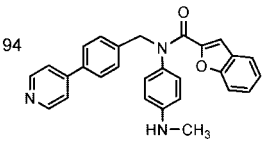
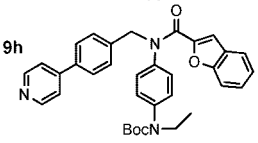
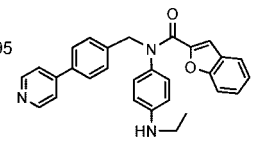
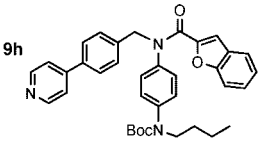
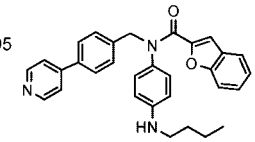
Preparation of 3-Chloro-benzo[*b*]thiophene-2-carboxylic Acid (4-Methylamino-cyclohexyl)-(3-pyridin-4-yl-benzyl) Amide (SAG). To a solution of compound **19** (61 mg, 0.1 mmol) in DMF (6.0 mL) was added water (2 μL),

Table 4. Synthesis of SAG and Its Derivatives



X = O, S; Y = H, Cl

A: R_1 = Boc; R_2 = CH_3, C_2H_5, C_3H_5, C_3H_7, C_4H_9
B: R_1 = H, R_2 = CH_3, C_2H_5, C_3H_5, C_3H_7, C_4H_9

entry	starting material	product **A**	yield (%)[a]	product **B**	yield (%)[b]
1	**19**	 **20a**	94	 **21a**	94
2	**19**	 **20b**	96	 **21b**	94
3	**19h**	 **20c**	94	 **21c**	90
4	**19h**	 **20d**	95	 **21d**	93
5	**19h**	 **20e**	95	 **21e**	94

[a] Isolated yield with semipreparative HPLC performed on a Agilent 1100 series machine with a XDB-C18 (250 × 9.4 mm) column (100% CH_3CN, 3 mL/min). [b] Isolated yield with a flash chromatography on silica gel.

followed by addition of NaH (~60 mg, 60% suspension in mineral oil), and the reaction mixture was stirred at 0 °C for 1 h. To this solution was added MeI (15 uL), and the resultant mixture was stirred at room temperature for 5 h. The reaction was worked up by addition of saturated solution of $NaHCO_3$ (10 mL) extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by semipreparative HPLC (94 × 250 XDB C18 column (100% CH_3CN, 3 mL/min) to give the methylated product **20** (57 mg) in 91% yield. ^{1}H NMR (300 MHz, DMSO, T = 333 K): δ 8.63 (d, J = 9.1 Hz, 2H), 8.04−8.22 (m, 1H), 7.84−7.89 (m, 1H), 7.46−7.69 (m, 8H), 4.80 (s, 2H), 3.80−4.18 (br, 1H), 3.60−3.66 (br, 1H), 2.57 (s, 3H), 1.79−1.90 (m, 4H), 1.33−1.55 (m, 2H), 1.33 (s, 9H), 1.26−1.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, 323 K): δ 163.6, 155.9, 150.2, 147.8, 139.2, 138.4, 137.2, 135.6, 130.0, 29.3, 127.5, 126.5, 125.4, 122.7, 122.5, 121.6, 118.7, 79.4, 58.7, 52.6, 45.0, 30.8, 29.4, 28.6, 28.3.

To a solution of **20** in CH_2Cl_2 (1.0 mL) was added trifluoroacetic acid (1.0 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was worked up by addition of a saturated solution of Na_2CO_3 (2 mL) and then extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were finally dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (CH_2Cl_2/acetone/TEA = 40/10/1) to give SAG (45 mg) in 95% yield. ^{1}H NMR (300 MHz, DMSO): δ 8.64 (d, J = 6.0 Hz, 2H), 8.07 (d, J = 7.5 Hz, 1H), 7.85−7.88 (m, 1H), 7.47−7.70 (m, 8H), 4.78 (s, 2H), 3.70−3.90 (br, 1H), 2.20 (s, 3H), 1.85−1.89 (m, 2H), 1.60−1.80 (m, 4H), 0.8−1.0 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 163.7, 150.3, 148.0, 139.3, 138.5, 137.3, 135.7, 129.3, 127.6, 126.5, 125.8, 125.6, 125.5, 122.7, 122.5, 121.6, 119.0, 59.0, 57.4, 45.8, 3.4, 31.8, 29.8. HRMS (EI) calcd for $C_{28}H_{28}ClN_3OS$ (M+) 489.1642; found 489.1651.

General Procedure for Preparation of 18a−18g. To a solution of pyridinyl benzaldehyde (**10a−c**) (1.0 mmol) in methanol (15 mL) was added **6−6a** (1.1 mmol), and the mixture was stirred at room temperature for 30 min. To this solution was added $NaBH_4$ (100 mg, 2.5 mmol) in portion at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was worked up by addition of a saturated aqueous Na_2CO_3 (2 mL); the mixture was then extracted with chloroform (3 × 6 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (CH_2Cl_2/MeOH = 10/1) to give compound **18a−18g**.

Preparation of of [4-(3-Pyridin-3-yl-benzylamino)-cyclohexyl]-carbamic Acid *tert*-Butyl Ester (18a). Product **18a** (361 mg) was obtained in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (d, J = 2.1 Hz, 1H), 8.56 (d, J = 4.5 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.31−7.44 (m, 4H), 4.30−4.40 (br, 1H), 3.86 (s, 2H), 3.30−3.50 (br, 1H), 2.40−2.56 (m, 1H), 1.92−2.08 (m, 4H), 1.42 (s, 9H), 1.09−1.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 155.1, 148.3, 148.1, 140.7, 137.9, 136.4, 134.3, 129.1, 127.9, 126.9, 125.8, 123.4, 79.0, 55.5, 50.8, 49.3, 31.8, 31.6, 28.3. MS (EI) calcd for $C_{23}H_{31}N_3O_2$ (M^+) 381; found 381.

Preparation of [4-(4-Pyridin-3-yl-benzylamino)-cyclohexyl]-carbamic Acid *tert*-Butyl Ester (18b). Product **18b** (358 mg) was obtained in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81−8.82 (m, 1H), 8.55 (dd, J_1 = 4.5, J_2 = 1.5, 1H), 7.82−7.86 (m, 1H), 7.52 (dd, J_1 = 6.3, J_2 = 1.8, 2H), 7.31−7.44 (m, 3H), 4.30−4.40 (br, 1H), 3.83 (s, 2H), 3.65−3.78 (br, 1H), 3.30−3.50 (br, 1H), 2.40−2.56 (m, 1H), 1.92−2.08 (m, 4H), 1.54−1.68 (br, 1H), 1.41 (s, 9H), 1.08−1.30 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 155.2, 148.2, 148.1, 140.6, 136.3 134.1, 128.7, 127.1, 123.4, 79.0, 55.4, 50.6, 49.4, 31.9, 28.3. MS (EI) calcd for $C_{23}H_{31}N_3O_2$ (M^+) 381; found 381.

Preparation of [4-(4-Pyridin-4-yl-benzylamino)-cyclohexyl]-carbamic Acid *tert*-Butyl Ester (18c). Product **18c** (365 mg) was obtained in 96% yield. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.62 (d, J = 5.4 Hz, 2H), 7.31−7.60 (m, 6H), 4.30−4.40 (br, 1H), 3.84 (s, 2H), 3.34−3.46 (br, 1H), 2.40−2.58 (m, 1H), 1.92−2.08 (m, 4H), 1.50−1.64 (br, 1H), 1.42 (s, 9H), 1.03−1.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 150.1, 148.0, 141.7, 136.7, 128.8, 127.0, 121.5, 79.1, 58.3, 55.5, 50.7, 49.5, 31.9, 28.4. MS (EI) calcd for $C_{23}H_{31}N_3O_2$ (M^+) 381; found 381.

Preparation of [4-(3-Pyridin-4-yl-benzylamino)-phenyl]-carbamic Acid *tert*-Butyl Ester (18d). Product **18d** (348 mg) was obtained in 93% yield. ^{1}H NMR (300 MHz, CDCl3): δ 8.63 (d, J = 6.0 Hz, 2H), 7.66 (s, 1H), 7.44−7.53 (m, 3H), 7.44 (d, J = 4.8 Hz, 2H), 7.19 (d, J = 7.5 Hz, 2H), 6.59 (d, J = 8.7 Hz, 2H), 4.37 (s, 2H), 1.49 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 150.0, 148.0, 144.1, 140.6, 138.2, 129.2, 129.0, 128.0, 125.8, 125.6, 121.5, 121.0, 113.2, 79.7, 48.3, 28.2. MS (EI) calcd for $C_{23}H_{25}N_3O_2$ (M^+) 375; found 375.

Preparation of [4-(3-Pyridin-3-yl-benzylamino)-phenyl]-carbamic Acid *tert*-Butyl Ester (18e). Product **18e** (356 mg) was obtained in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (d, J = 1.5 Hz, 1H), 8.60 (dd, J_1 = 4.8 Hz, J_2 = 1.5 Hz, 1H), 7.85−7.89 (m, 1H), 7.48 (s, 1H), 7.42−7.47 (m, 4H), 7.17 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 8.7 Hz, 2H), 6.30−6.42 (br, 1H), 4.22 (s, 2H), 4.39−4.41 (br, 1H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 148.3, 148.2, 144.2, 140.5, 137.9, 136.3, 134.3, 129.2, 129.1, 127.1, 126.0, 125.9, 125.8, 123.4, 121.0, 113.2, 113.1, 79.6, 67.8, 48.4, 28.3, 25.5. MS (EI) calcd for $C_{23}H_{25}N_3O_2$ (M^+) 375; found 375.

Preparation of [4-(4-Pyridin-3-yl-benzylamino)-phenyl]-Carbamic Acid *tert*-Butyl Ester (18f). Product 18f (348 mg) was obtained in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86−8.87 (m, 1H), 8.60−8.63 (m, 1H), 7.86−7.91 (m, 1H), 7.40−7.60 (m, 5H), 7.30−7.40 (m, 2H), 7.18 (d, J = 13.2 Hz, 2H), 6.62 (d, J = 13.2 Hz, 2H), 6.31−6.42 (br, 1H), 4.40 (s, 2 h), 3.95−4.10 (br, 1H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 148.3, 148.1, 144.3, 139.6, 136.5, 136.3, 134.2, 128.9, 128.0, 127.2, 123.5, 121.2, 113.2, 79.8, 48.1, 28.3. MS (EI) calcd for $C_{23}H_{25}N_3O_2$ (M^+) 375; found 375.

Preparation of [4-(4-Pyridin-3-yl-benzylamino)-phenyl]-carbamic Acid *tert*-Butyl Ester (18g). Product **18g** (352 mg) was obtained in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62−8.65 (m, 2H), 7.43−7.61(m, 6H), 7.13 (d, J = 13.5 Hz, 2H), 6.57 (d, J = 13.2 Hz, 2H), 6.13−6.27 (br, 1H), 3.92−4.02 (br, 1H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 150.3, 148.0, 144.2, 140.7, 137.0, 128.9, 128.0, 127.2, 121.5, 121.2, 113.3, 80.0, 48.2, 28.4. MS (EI) calcd for $C_{23}H_{25}N_3O_2$ (M^+) 375; found 375.

General Procedure for Preparation of 19a−19h. To a solution of substrate **18a−18g** (1.0 mmol) and Et_3N (280 μL, 2.0 mmol) in CH_2Cl_2 (10 mL) were added the corresponding acyl chlorides **12** and **12a−12b** (1.1 mmol, prepared by reaction of the individual acid with $SOCl_2$), and the mixture was stirred at room temperature for 0.5 h. The reaction was worked up by removal of solvent, and the residue was purified by a flash chromatography on silica gel (acetone/PE = 5/1) to give the products **19a−19h**.

Preparation of {4-[(3-Chloro-benzo[*b*]thiophene-2-carbonyl)-(4-pyridin-3-yl-benzyl)-amino]-cyclohexyl}-carbamic Acid *tert*-Butyl Ester (19a). Product **19a** (552 mg) was obtained in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.83 (d, J = 1.8 Hz, 1H), 8.57 (dd, J_1 =7.2 Hz, J_2 = 2.4 Hz, 1H), 8.04−8.10 (m, 1H), 7.95−8.00 (m, 1H), 7.84−7.87 (m, 1H), 7.50−7. 60 (m, 4H), 7.40−7. 50 (m, 3H), 6.16 (d, J = 11.4 Hz, 1H), 4.79 (s, 2H), 3.75−3.86 (br, 1H), 3.14−3.21 (m, 1H), 1.71−1.81 (m, 6H), 1.33 (s, 9H), 1.08−1.30 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.5, 155.0, 148.4, 148.1, 138.9, 138.0, 137.1, 135.5, 134.3, 129.2, 126.5, 125.4, 123.4, 122.6, 122.3, 118.9, 79.1, 58.2, 48.7, 44.5 32.1, 30.3, 28.2. HRMS (EI) calcd for $C_{32}H_{34}ClN_3O_3S$ [M^+] 575.2009; found 575.2018.

Preparation of {4-[(Benzo[*b*]thiophene-2-carbonyl)-(4-pyridin-3-yl-benzyl)-amino]-cyclohexyl}-carbamic Acid *tert*-Butyl Ester (19b). Product **19b** (503 mg) was obtained in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (d, J = 3.0 Hz, 1H), 8.58 (dd, J_1 = 6.6 Hz, J_2 = 2.1 Hz, 1H), 7.60−7.86 (m, 3H), 7.32−7.60 (m,8H), 4.81 (s, 2H), 4.35−4.57 (br, 1H), 4.20−4.30 (br, 1H), 3.20−3.41 (br, 1H), 2.00−2.04 (m, 2H), 1.86−1.89 (m, 2H), 1.50−1.80 (m, 2H), 1.40 (s, 9H), 1.13−1.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 155.1, 148.4, 148.1, 140.1, 138.7, 138.6, 136.7, 134.1, 127.5, 127.3, 125.7, 124.7, 124.6, 123.5, 122.2, 79.2, 57.2, 48.6, 32.3, 29.8, 28.3. HRMS (EI) calcd for $C_{32}H_{35}N_3O_3S$ 541.2399; found 541.2398.

Preparation of {4-[(Benzo[*b*]thiophene-2-carbonyl)-(3-pyridin-3-yl-benzyl)-amino]-cyclohexyl}-carbamic Acid *tert*-Butyl Ester (19c). Product **19c** (508 mg) was obtained in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.60 (d, J = 3.0 Hz, 1H), 7.75−7.86 (m, 3H), 7.34−7.50 (m, 8H), 4.83 (s, 2H), 4.38−4.52 (br, 1H), 4.22−4.38 (br, 1H), 3.20−3.41 (br, 1H), 2.00−2.04 (m, 2H), 1.68−1.89 (m, 2H), 1.54−1.64 (m, 2H), 1.41 (s, 9H), 1.16−1.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 155.0, 148.4, 148.3, 148.1, 140.0, 138.6, 137.4, 136.3, 134.4, 129.3, 127.4, 127.3, 126.0, 125.4, 125.1, 124.6, 123.5, 122.2, 79.2, 58.0, 48.6, 32.3, 29.6, 29.5, 28.3. HRMS (EI) calcd for $C_{32}H_{35}N_3O_3S$ [M^+] 541.2399; found 541.2392.

Preparation of {4-[(Benzo[*b*]thiophene-2-carbonyl)-(4-pyridin-4-yl-benzyl)-amino]-cyclohexyl}-carbamic Acid *tert*-Butyl Ester (19d). Product **19d** (503 mg) was obtained in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64−8.85 (br, 2H), 7.70−7.87 (m, 2H), 7.30−7.68 (m, 9H), 4.85 (s, 2H), 4.26−4.41 (br, 1H), 3.30−3.51 (br, 1H), 2.03−2.07 (m, 2H), 1.88−1.92 (m, 2H), 1.56−1.81 (m, 2H), 1.44 (s, 9H), 1.15−1.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 155.0, 150.1, 147.7, 139.3, 137.1, 136.7, 135.5, 130.0, 127.6, 127.0, 125.4, 122.6, 122.4, 121.4, 119.0, 79.1, 58.7, 48.5, 44.8, 32.0, 29.1, 28.2. HRMS (EI) calcd for $C_{32}H_{35}N_3O_3S$ [M^+] 541.2399; found 541.2398.

Synthesis of {4-[(Chloro-benzo[*b*]thiophene-2-carbonyl)-(3-pyridin-4-yl-benzyl)-amino]-phenyl}-carbamic Acid *tert*-Butyl Ester (19e). Product **19e** (546 mg) was obtained in 96% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.61−8.80 (br, 2H), 7.63−7.70 (m, 6H), 7.33−7.56 (m, 4H), 6.97−7.24 (m, 4H), 5.16 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0, 152.4, 149.2, 148.7, 138.2, 137.7, 137.6, 135.3,

130.3, 129.6, 129.4, 128.1, 127.2, 126.4, 126.2, 125.6, 125.0, 122.5, 122.1, 120.6, 119.7, 80.5, 53.7, 28.0. HRMS (EI) calcd for $C_{32}H_{28}ClN_3O_3S$ [M^+] 569.1539; found 569.1532.

Preparation of {4-[(3-Chloro-benzo[*b*]thiophene-2-carbonyl)-(4-pyridin-3-yl-benzyl)-amino]-phenyl}-carbamic Acid *tert*-Butyl Ester (19f). Product **19f** (540 mg) was obtained in 95% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.55 (d, $J' = 3.6$ Hz, 1H), 7.83 (m, 1H), 7.21−7.72 (m, 12H), 6.99 (d, $J' = 8.6$ Hz, 2H), 5.13 (s, 2H), 1.41 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): 162.9, 152.5, 147.9, 147.6, 138.3, 137.5, 136.6, 136.5, 136.0, 135.3, 135.2, 134.3, 130.4, 129.2, 128.0, 127.0, 126.2, 124.9, 123.5, 122.4, 122.3, 120.5, 118.3, 80.3, 53.4, 28.0. HRMS (EI) calcd for $C_{32}H_{28}ClN_3O_3S$ [M^+] 569. 1539; found 569.1523.

Preparation of {4-[(Benzo[*b*]thiophene-2-carbonyl)-(4-pyridin-4-yl-benzyl)-amino]-phenyl}-carbamic Acid *tert*-Butyl Ester (19g). Product **19g** (518 mg) was obtained in 97% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.60−8.79 (br, 2H), 7.30−7.78 (m, 10H), 7.18 (d, $J' = 5.8$ Hz, 2H), 6.99 (d, $J' = 5.8$ Hz, 2H), 6.49 (s, 1H), 5.14 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0, 152.4, 150.0, 149.9, 147.9, 138.2, 137.7, 137.6, 137.1, 135.5, 135.3, 130.4, 129.4, 128.7, 128.3, 128.1, 127.6, 127.2, 127.1, 126.4, 125.5, 125.0, 123.8, 122.7, 122.5, 122.4, 121.5, 120.7, 118.3, 80.6, 53.5, 28.1. HRMS (EI) calcd for $C_{32}H_{29}N_3O_3S$ [M^+] 535.1929; found 535.1933.

Preparation of {4-[(Benzofuran-2-carbonyl)-(4-pyridin-4-yl-benzyl)-amino]-phenyl}-carbamic Acid *tert*-Butyl Ester (19h). Product **19h** (493 mg) was obtained in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, $J = 5.7$ Hz, 2H), 7.05−7.56 (m, 12H), 7.00−7.05 (m, 2H), 6.15 (s, 1H), 5.10 (s, 2H), 1.49 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 159.9, 154.3, 152.6, 150.0, 147.8, 147.4, 138.9, 137.8, 137.0, 136.2, 129.7, 128.8, 126.9, 126.8, 126.6, 123.2, 122.3, 121.4, 118.8, 112.5, 111.8, 80.6, 54.0, 28.2. HRMS (EI) calcd for $C_{32}H_{29}N_3O_3S$ 535.1929, found 535.1933.

General Procedure for Preparation of 21a−21e. To a solution of compound **19*x*** (0.1 mmol) in DMF (6.0 mL) was added water (2 μL), followed by addition of NaH (~60 mg, 60% suspension in mineral oil), and the mixture was stirred at 0 °C for 1 h. To this solution was added organohalides at 0 °C, and the mixture was stirred at room temperature for 5 h. The reaction was worked up by addition of a saturated solution of $NaHCO_3$ (10 mL); the mixture was first extracted with Et_2O (3 × 20 mL), and the combined extract was then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by semipreparative HPLC (96 × 250 XDB C18 column (100% CH_3CN, 3 mL/min) to give the methylated product **20*x***, which was dissolved in CH_2Cl_2 (1.0 mL). Trifluoroacetic acid (1.0 mL) was added at 0 °C, and the mixture was stirred at room temperature for 4 h. The reaction was worked up by addition of a saturated solution of Na_2CO_3 (2 mL); the mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (CH_2Cl_2/acetone/TEA = 40/10/1) to give compound **21*x***.

Preparation of 3-Chloro-benzo[*b*]thiophene-2-carboxylic Acid (4-Allylamino-cyclohexyl)-(3-pyridin-4-yl-benzyl)-amide (21a). Compound **19** (57 mg, 0.10 mmol) was treated with 3-bromoprop-1-ene (25 μL) (25 μL) according to the general protocol to afford **20a** (58 mg) in 94% yield. ^{1}H NMR (300 MHz, DMSO-d_6, $T = 353$K): δ 8.64 (d, $J =$ 4.5 Hz, 2H), 8.08 (d, $J = 7.5$ Hz, 1H), 7.87 (d, $J = 7.5$ Hz, 1H), 7.40−7.70 (m, 8H), 5.64−5.73 (m, 1H), 4.96−5.05 (m, 2H), 4.80 (s, 2H), 3.80−3.92 (br, 1H), 3.60−3.65 (m, 2H), 3.48−3.56 (br, 1H), 1.70−1.86 (br, 4H) 1.40−1.70 (b, 4H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 155.1, 150.2, 147.9, 139.2, 138.5, 137.3, 135.9, 135.7, 130.4, 129.2, 127.6, 126.4, 125.8, 125.6, 125.4, 122.7, 122.6, 122.5, 122.4, 121.5, 119.0, 115.2, 79.5, 54.4, 45.7, 36.2, 29.7, 28.3. HRMS(ESI) calcd for $C_{35}H_{39}ClN_3O_3S$ (M + H^+) 616.2395; found 616.2388.

Compound **20a** (58 mg) was treated with TFA as described in the general procedure to give product **21a** (45 mg) in 94% yield. ^{1}H NMR (300 MHz, d6-DMSO, $T = 353$K): δ 8.65 (d, $J = 6.0$ Hz, 2H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.86−7.90 (m, 1H), 7.40−7.80 (m, 8H), 5.74−5.83 (m, 1H), 5.11 (d, J = 17.4 Hz, 1H), 4.99 (d, $J = 10.2$ Hz, 1H), 4.79 (s, 2H), 3.74−3.90 (br, 1H), 3.07−3.14 (m, 2H), 2.35−2.50 (m, 2H), 1.82−1.94 (m, 2H), 1.62−1.81 (m, 4H), 0.89−0.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 163.5, 150.1, 147.9, 139.1, 138.3, 137.1, 136.4, 135.5, 129.1, 127.5, 126.4, 125.6, 125.5, 122.5, 122.3, 121.4, 118.8, 115.8, 58.8, 54.8, 49.2, 45.3, 32.0, 30.0. HRMS (ESI) calcd for $C_{30}H_{31}ClN_3OS$(M + H^+) 516.1871, found 516.1861.

Preparation of 3-Chloro-benzo[*b*]thiophene-2-carboxylic Acid (4-Propylamino-cyclohexyl)-(3-pyridin-4-yl-benzyl)-amide (21b). Compound **19** (57 mg, 0.10 mmol) was treated with 1-iodopropane (25 uL) according to the general protocol to afford **20b** (59 mg) in 96% yield. ^{1}H NMR (300 MHz, d6-DMSO, $T = 353$K): δ 8.64 (dd, $J_1 = 4.5$ Hz, $J_2 =$ 1.5 Hz, 2H), 8.07 (d, $J = 7.5$ Hz, 1H), 7.85−7.88 (m, 1H), 7.48−7.61 (m, 8H), 4.80 (s, 2H), 3.80−3.93 (br, 1H), 3.30−3.50 (br, 1H), 2.84−2.96 (m, 2H), 1.70−1.86 (m, 4H), 1.51−1.70 (m, 4H), 1.27−1.42 (m, 2H), 1.27 (s, 9H), 0.72−0.77 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, $T = 328$K): δ 163.6, 155.3, 150.2, 139.3, 139.2, 137.3, 135.7, 130.6, 129.2, 127.6, 126.4, 125.6, 125.4, 122.7, 122.5, 121.5, 119.0, 79.2, 54.6, 54.5, 45.5, 30.9, 28.4, 23.6, 11.2. HRMS (ESI) calcd for $C_{35}H_{41}ClN_3O_3S$ (M + H^+) 618.2551; found 618.2503.

Compound **20b** (59 mg) was treated with TFA as described in the general procedure to give product **21b** (46 mg) in 94% yield. ^{1}H NMR (300 MHz, DMSO-d_6, $T =$ 353K): δ 8.65 (dd, $J_1 = 4.5$ Hz, $J_2 = 1.2$ Hz, 2H), 8.08 (d, $J = 7.5$ Hz, 1H), 7.87 (m, 1H), 7.44−7.69 (m, 8H), 4.79 (s, 2H), 3.74−3.90 (br, 1H), 2.48−2.57 (m, 2H), 1.88−1.95 (m, 2H), 1.67−1.77 (m, 4H), 1.34−1.43 (m, 2H), 0.91−1.10 (br, 2H), 0.83 (t, $J = 4.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, $T = 328$K): 163.7, 150.2, 147.9, 139.1, 138.5, 137.2, 135.6, 129.3, 127.6, 126.5, 125.6, 125.5, 122.6, 122.5, 121.5, 119.1, 58.4, 55.6, 48.0, 45.3, 30.7, 29.6, 21.9, 11.4. HRMS (ESI) calcd for $C_{30}H_{33}ClN_3OS$ (M + H^+) 518.2027; found 518.1992.

Preparation of Benzofuran-2-carboxylic Acid (4-Methylamino-phenyl)-(3-pyridin-4-yl-benzyl)-amide (21c). Compound **19h** (52 mg, 0.1 mmol) was treated with MeI (15 uL) according to the general protocol to afford **20c** (51 mg) in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$, $T = 353$K): δ 8.65 (d, $J = 8.4$ Hz, 2H), 7.06−7.61 (m, 14H), 6.30 (s, 1H), 5.14 (s, 2H), 3.28 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 154.4, 154.3, 150.3, 150.2, 147.7, 147.6, 143.7, 138.8, 137.8, 137.2, 129.6, 128.2, 127.1, 127.0, 126.8, 126.7, 126.1, 123.3, 122.3, 121.4, 112.6, 111.8, 80.7, 53.9, 37.1, 28.2. HRMS (ESI) calcd for $C_{33}H_{32}N_3O_4$ ($M + H^+$) 534.2387; found 534.2376.

Compound **20c** (51 mg) was treated with TFA as described in the general procedure to give **21c** (36 mg) in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, $J = 4.5$ Hz, 2H), 7.15−7.60 (m, 10H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.54−6.57 (m, 2H), 6.00 (s, 1H), 5.10 (s, 2H), 3.95−4.05 (br, 1H), 2.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 154.4, 150.2, 149.2, 147.9, 147.8, 138.3, 137.1, 131.3, 129.9, 129.2, 127.2, 126.9, 126.5, 123.1, 122.4, 121.5, 112.7, 112.2, 111.9, 54.2, 30.6. HRMS (ESI) calcd for $C_{28}H_{24}N_3O_2$ ($M + H^+$) 434.1863; found 434.1854.

Preparation of Benzofuran-2-carboxylic Acid (4-Ethylamino-phenyl)-(3-pyridin-4-yl-benzyl)-amide (21d). Compound **19h** (52 mg, 0.1 mmol) was treated with iodoethane (25 uL) according to the general protocol to afford **20d** (51 mg) in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, $J = 4.8$ Hz, 2H), 7.08−7.60 (m, 14H), 6.34 (s, 1H), 5.16 (s, 2H), 3.70 (q, $J = 6.9$ Hz, 2H), 1.44 (s, 9H),1.16 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 154.4, 154.1, 150.2, 147.7, 142.3, 139.5, 137.8, 137.3, 129.6, 128.4, 127.8, 127.0, 126.7, 123.3, 122.2, 121.5, 112.6, 111.8, 80.4, 53.9, 44.6, 28.3, 13.8. HRMS (EI) calcd for $C_{34}H_{34}N_3O_4$ ($M + H^+$) 548.2544; found 548.2534.

Compound **20d** (51 mg) was treated with TFA as described in the general procedure to give **21d** (39 mg) in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, $J = 3.6$ Hz, 2H), 7.68(d, $J = 6.0$ Hz, 2H), 7.61(d, $J = 8.1$ Hz, 2H), 7.50(d, $J = 8.1$ Hz, 2H), 7.43(d, $J = 5.7$ Hz, 2H), 7.28−7.33 (m, 1H), 7.12 −7.19 (m, 1H), 6.88 (dd, $J_1 = 6.6$ Hz, $J_2 = 1.8$ Hz, 2H), 6.54 (dd, $J_1 = 6.6$ Hz, $J_2 = 1.8$ Hz, 2H), 6.17 (s, 1H), 5.09 (s, 2H), 3.16 (q, $J = 7.2$ Hz, 2H), 1.26 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 154.5, 151.3, 148.4, 148.0, 147.0, 139.8, 135.8, 131.5, 130.1, 129.2, 127.2, 126.5, 123.1, 122.3, 113.1, 112.3, 111.9, 54.3, 38.5, 14.6. HRMS (EI) calcd for $C_{29}H_{26}N_3O_2$ ($M + H^+$) 448.2019; found 448.2011.

Preparation of Benzofuran-2-carboxylic acid (4-butylamino-phenyl)-(3-pyridin-4-yl-benzyl)-amide (21e). Compound **19h** (52 mg, 0.11 mmol) was treated with 1-iodobutane (40 uL) according to the general protocol to give **20e** (55 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, $J = 4.2$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.45−7.49 (m, 4H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.36 (s, 1H), 7.30 (d, $J = 12.8$ Hz, 1H), 7.19 (dd, $J_1 = 8.4$ Hz, $J_2 = 6.8$ Hz, 3H), 7.09 (d, $J = 8.4$ Hz, 2H), 6.35 (s, 1H), 5.15 (s, 2H), 3.65 (t, $J = 7.2$ Hz, 2H), 1.48−1.53 (m, 2H), 1.44 (s, 9H), 1.29−1.34 (m, 2H), 0.86−0.93 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 154.4, 154.2, 150.2, 147.7, 142.5, 139.4, 137.8, 137.2, 129.6, 128.3, 127.8, 127.0, 126.8, 126.7, 123.3, 122.2, 121.4, 112.6, 111.8, 80.3, 53.9, 49.4, 30.5, 28.2, 19.8, 13.7. HRMS (EI) calcd for $C_{36}H_{38}N_3O_4$ ($M + H^+$) 576.2857; found 576.2856.

Compound **20e** (55 mg) was treated with TFA as described in the general procedure to give **21e** (42 mg) in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (dd, $J_1 = 4.5$ Hz, $J_2 = 1.5$ Hz, 2H), 7.10−7.60 (m, 10H), 6.88(d, $J = 8.7$ Hz, 2H), 6.55(d, $J = 8.7$ Hz, 2H), 6.01(s, 1H), 5.09 (s, 2H), 3.80−3.94 (br, 2H), 3.01−3.18(br, 2H), 1.63 (t, $J = 7.2$ Hz, 2H), 1.40−1.48(m, 2H), 0.97 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 154.3, 150.2, 148.4, 147.7, 138.3, 137.0, 131.0, 129.8, 128.2, 127.1, 126.8, 126.5, 123.1, 122.3, 121.4, 113.0, 112.9, 112.2, 111.9, 54.2, 43.5, 31.4, 20.2, 13.9. HRMS (ESI) calcd for $C_{31}H_{30}N_3O_2$ ($M + H^+$) 476.2333; found 476.2319.

Acknowledgment. We gratefully acknowledge financial support of this work by the National Science Foundation of China (Grants 20672004 and 20521202).

Supporting Information Available. Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for the known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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