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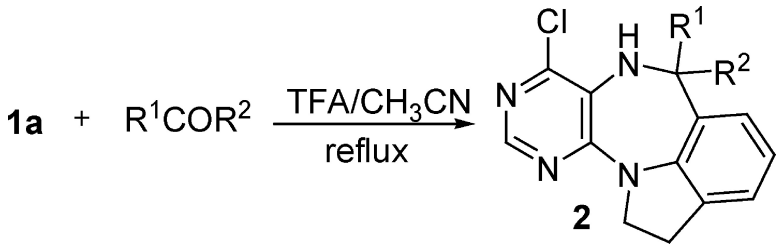

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Design and Synthesis of a Tetracyclic Pyrimidine-Fused Benzodiazepine Library

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Method development for a heterocyclic library which entails novel scaffolds of benzodiazepines fused with various heterocycles, such as pyrimidines, indolines, and tetrahydroquinolines, was accomplished. The new synthetic strategy is based on an electrophilic cyclization reaction involving an iminium intermediate formed by the corresponding aminopyrimidine with a carbonyl compound to give the desired heterocycles in high yields. Subsequent replacement of the chloro group in the resulted structures with a nucleophile, such as boronic acids, amines, alcohols and thiols, led to a library of privileged compounds with up to eight accessible diversity points.

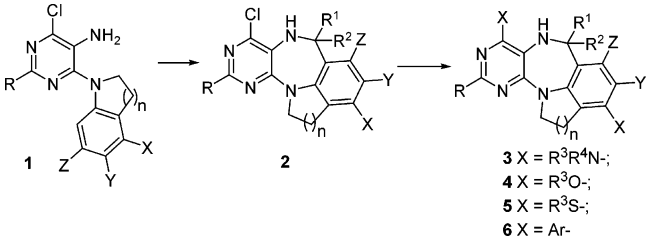
Introduction

Pyrimidine moiety, as a structural component of several key biomolecules, has been employed in design of privileged structures in medicinal chemistry[1] and attracts great attention from organic and medicinal chemists. Various pyrimidine-fused heterocycles, such as purines,[2] pyrrolopyrimidines,[3] pyrazolopyrimidines,[4] pyrimidopyrimidines,[5] imidazopyrimidines,[6] and furopyrimidines,[7] have been studied. It is our ongoing interest to develop new strategies to prepare libraries of novel heterocyclic scaffolds. Consequently, we reported the preparation of libraries of fully substituted purines,[2a,2b] a novel pyrimidine-fused benzodiazepine scaffold,[8] a pyrimidine-fused benzothiazepine scaffold,[9] and a novel indole-fused pteridines scaffold.[10] Recently, the synthesis of pyrimido-[4,5-*b*]-1,4-benzoxazepines, thiazepines, and diazepines[11] and 5,6-dihydro-pyrimido[4,5-*b*]oxazepines[12] were reported by others. As depicted in Scheme 1, an alternative synthetic strategy starting with pyrimidine **1** was envisioned and is based on the notion that saturation of the pyrrole ring of the indole moiety (indoline **1**) would force the cyclization to take place at the phenyl ring to form novel scaffolds of tetracyclic pyrimidine-fused benzodiazepines **2**. Furthermore, the same strategy could be applied to tetrahydroquinolinyl or similar systems, which can be expanded to a library (**3**−**6**) with up to eight diversity points. Herein, the method development toward a tetracyclic pyrimidine-fused benzodiazepine library is reported.

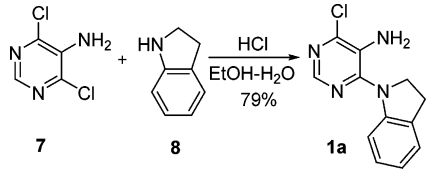
Results and Discussions

To evaluate the feasibility of the strategy shown in Scheme 1, we sought to quickly access two key pyrimidine derivatives (**1a**, $n = 1$ and **1b**, $n = 2$) that would allow us to develop all subsequent reaction conditions. 5-Amino-4-chloro-6-(indolin-1-yl)pyrimidine **1a** ($n = 1$) was readily prepared from commercially available 5-amino-4,6-dichloropyrimidine **7** in good yield according to Scheme 2.[10]

Scheme 1



Scheme 2



To expand the scope of the current methodology, 1,2,3,4-tetrahydroquinoline-substituted pyrimidine **1b** ($n = 2$) was also desired; however, treatment of pyrimidine **7** with 1,2,3,4-tetrahydroquinoline under standard conditions of Scheme 2 failed to give the desired aminopyrimidine **1b**. Therefore, a two-step process was developed for the synthesis of compound **1b** (Scheme 3).[13,14] Nucleophilic substitution of 4,6-dichloro-5-nitropyrimidine **9** by 1,2,3,4-tetrahydroquinoline **10** led to the nitro precursor **11** in good yield, and subsequent reduction of **11** with Fe/NH_4Cl provided the desired starting quinolin-1-ylpyrimidine **1b** in 83% yield.

With both pyrimidine derivatives **1a** and **1b** in hand, we first investigated the cyclization reactions of pyrimidine **1a**. As expected, pyrimidine **1a** reacted with propanaldehyde in refluxing acetonitrile with trifluoroacetic acid (TFA) to give the desired tetracyclic pyrimidobenzodiazepine (**2.1**) in excellent yield (entry 1, Table 1). Moreover, this reaction proceeded to completion in 3 h, which indicated unusually high reactivity of the indolinyl aminopyrimidine system, as

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Scheme 3

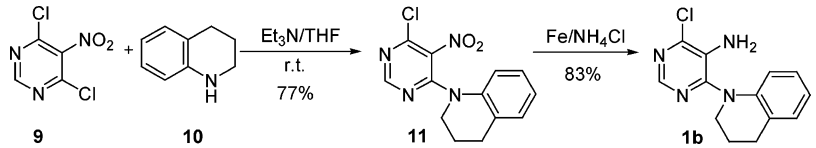
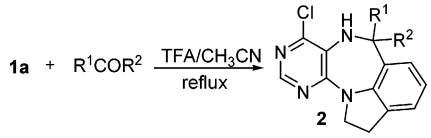


Table 1. Preparation of Tetracyclic Pyrimidobenzodiazepines (**2.1**−**2.17**)



entry	R^1	R^2	products	time (h)	yield (%)
1	Et	H	**2.1**	3	92
2	*n*Pr	H	**2.2**	3	90
3	Ph	H	**2.3**	4	92
4	*o*-Me−Ph	H	**2.4**	4	97
5	*p*-NO_2−Ph	H	**2.5**	5	96
6	*p*-F-Ph	H	**2.6**	3	90
7	PhCH═CH	H	**2.7**	2	81
8	CH_3CH═CH	H	**2.8**	0.5	83
9	Me	Me	**2.9**	5	95
10	Et	Me	**2.10**	15	92
11	*n*Pr	Me	**2.11**	10	84
12	R^1 R^2 = −$(CH_2)_5$−		**2.12**	5	92
13	Ph	Me	**2.13**	12	87
14	*p*-MeO−Ph	Me	**2.14**	60	62
15	*p*-NO_2−Ph	Me	**2.15**	44	82
16	Ph	Et	**2.16**	65	57
17	Me	COOH	**2.17**	6.5	59

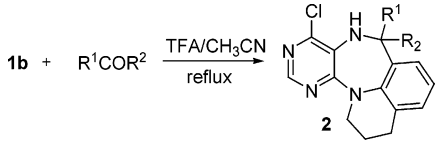
compared to the anilino aminopyrimidine one.[15] The scope of the cyclization was explored with a variety of aldehydes and ketones, and the results are summarized in Table 1.

As evidenced in Table 1, pyrimidine **1a** underwent productive cyclization reactions with a wide range of aldehydes to give the corresponding tetracyclic pyrimidobenzodiazepines (**2.1**−**2.8**) in excellent yields (entries 1−8, Table 1). In a very similar fashion, aliphatic ketones yielded the expected cyclized products in high yields (entries 9−12, Table 1), whereas aromatic ketones tended to react at a slower rate and gave moderate to good yields (entries 13−16). It is noteworthy that various functional groups in the carbonyl compounds, such as nitro, methoxy, and carboxylic acid groups, are tolerated under the current reaction condition.

Similar to indolin-1-ylpyrimidine **1a**, tetrahydroquinolin-1-ylpyrimidine **1b** underwent cyclization reactions with aliphatic and aromatic aldehydes to give the expected tetracyclic pyrimidobenzodiazepines (**2.18**−**2.22**) (entries 1−5, Table 2). Although a nitro group in the carbonyl compound is tolerated (entry 5, Table 2), an olefin group led to much lower yield, which suggested possible side reactions with the olefin group under the current acidic condition. In contrast to pyrimidine **1a**, pyrimidine **1b** reacted with acetone very sluggishly (56 h) and gave low yield of the final product **2.24**. Furthermore, no desired product was isolated from the reaction of pyrimidine **1b** with acetophenone.

Even though pyrimidines **1a** and **1b** reacted similarly with aldehydes to give the tetracyclic pyrimidobenzodiazepines

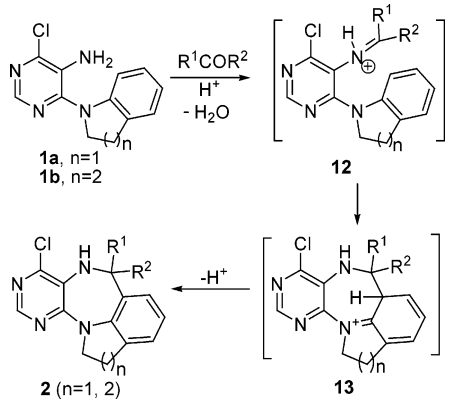
Table 2. Preparation of Tetracyclic Pyrimidobenzodiazepines (**2.18**−**2.25**)



entry	R^1	R^2	products	time (h)	yield (%)
1	Et	H	**2.18**	3.5	97
2	*n*Pr	H	**2.19**	4	95
3	Ph	H	**2.20**	5	96
4	*p*-Me−Ph	H	**2.21**	7	91
5	*p*-NO_2−Ph	H	**2.22**	4	85
6	PhCH═CH	H	**2.23**	10	40
7	Me	Me	**2.24**	56	37
8	Ph	Me	**2.25**	24	*a*

[a] No desired product was isolated.

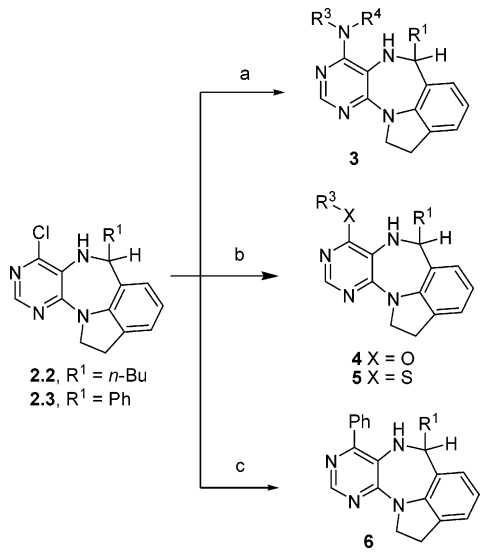
Scheme 4



in high yields within short reaction times, it was interesting to observe that pyrimidine **1b** failed to react with acetophenone under the same conditions. This reactivity difference may be explained on the basis of reaction mechanism. These cyclization reactions are expected to follow a similar pathway as the Pictet−Spengler isoquinoline synthesis,[16] as shown in Scheme 4.

It was proposed that the pyrimidines **1a** or **1b** reacted with an aldehyde or a ketone to form an iminium intermediate **12** under the current acidic condition. The reactive iminium ion **12** underwent an intramolecular electrophilic reaction at the adjacent electron-rich phenyl ring to produce the expected benzodiazepine frame **13**. Elimination of a proton at **13** to regenerate the aromatic phenyl ring led to the final products **2**. Two possible factors were hypothesized to explain the high reactivity of the indolinyl system **1a** toward carbonyl compounds and lack of productive reactions between quinolinylpyrimidine **1b** and ketones. At first, close examination of a molecular model of quinolinylpyrimidine **1b** revealed that the chair conformation of the six-member ring forced one of the R groups of the ketone to bump into the phenyl ring when the iminium ion was approaching. This steric

Scheme 5[a]



[a] Reagents and conditions: (a) R^3NHR^4, *n*-BuOH; (b) R^3XH, NaH, THF; (c) $PhB(OH)_2$, $Pd(OAc)_2$, K_2CO_3, Ph_3P, DME−H_2O.

hindrance could be avoided when an aldehyde-based iminium ion was approaching, since the hydrogen could be placed over the phenyl ring to alleviate the steric contact. The same steric contact might not be present in indolinylpyrimidine **1a** due to the apparent relative planner structure of the indoline moiety; therefore, both aldehydes and ketones reacted with indolinylpyrimidine **1a** to give the desired products in high yields. Second, indolinylpyrimidine **1a** exhibited unusually high reactivity toward intramolecular cyclizations to the seven-member diazepine frame due to the release of angle strain by the existing indoline ring, as compared to quinolinylpyrimidine **1b**. In the indoline case of **1a**, the outlet angle (126 °) of the [5,6]-bicyclic ring system is close to that (∼129 °) of the forming flat seven-member ring of benzodiazepine, whereas the reduced angle (120 °) in the tetrahydroquinolinyl [6,6]-bicyclic structure **1b** caused more angle strains for formation of the benzodiazepine skeleton. Despite the high reactivity of tetrahydroquinolinylpyrimidine **1b** toward aldehydes, its reaction with ketones was quite similar to those of anilinyl analogues,[15] which demonstrated that it was, indeed, the indolinylpyrimidine system **1a** that was more reactive.

The chloro group in compounds **2** ($n = 1, 2$) presents an excellent opportunity to introduce additional diversity points. Two compounds (**2.2** and **2.3**) were selected as representative examples to examine their reactivity toward various nucleophiles and coupling reactions. As depicted in Scheme 5, compounds **2.2** or **2.3** reacted readily with an amine under either acidic conditions of concentrated aqueous HCl (for *n*-$BuNH_2$, aniline, and morpholine)[17] or in the presence of Et_3N (for pyrrolidine) to give the desired amine-substituted products in moderate to high yields (entries 1−4, Table 3). Other nucleophiles with heteroatoms, such as alcohols and thiols, were also known to react with 6-chloropurines; therefore, their reactions were exemplified with *n*-BuOH, BnSH, and PhSH. Compounds **2.2** or **2.3** reacted with *n*-butanol, benzylthiol, and thiophenol smoothly under basic conditions to give the corresponding *n*-butyloxy-, benzylsulfanyl-, or phenylsulfanyl-substituted pyrimidobenzodiazopines in high yields (entries 5−10, Table 3).[18] Introduction of carbon substitutents to replace the chloro should further expand the scope of the current library; therefore, under nonoptimized Suzuki−Miyaura cross-coupling conditions,[19] compound **2.2** or **2.3** reacted with phenylboronic acid to yield aryl-substituted products (entries 11−12, Table 3) in good yields.

Table 3. Introduction of Final Diversity Points to Compounds **2**

entry	ArCl	nucleophile	product	time	yield (%)
1	2.3	$R^3R^4NH = {}^n$Bu−NH_2	**3a**	3 d	74
2	2.2	R^3R^4NH = Ph−NH_2	**3b**	4.5 d	60
3	2.3	R^3R^4NH = morpholine	**3c**	3 d	90
4	2.2	R^3R^4NH = pyrrolidine	**3d**	3 d	93
5	2.2	$R^3OH = {}^n$Bu−OH	**4a**	30 h	94
6	2.3	$R^3OH = {}^n$Bu−OH	**4b**	33 h	94
7	2.2	R^3SH = Bn−SH	**5a**	7 h	94
8	2.3	R^3SH = Bn−SH	**5b**	7 h	96
9	2.2	R^3SH = Ph−SH	**5c**	9 h	95
10	2.3	R^3SH = Ph−SH	**5d**	7 h	94
11	2.2	NA	**6a**	10 h	53
12	2.3	NA	**6b**	5 h	53

In summary, novel scaffolds of tetracyclic pyrimidobenzodiazepines were prepared on the basis of a new strategy entailing an iminium ion intramolecular cyclization reaction as a key step. The presence of the cyclic indoline or tetrahydroquinoline ring significantly increases the reactivity of the cyclization, as compared to their open anilino analogues, and as a result, this increased reactivity permitted a wide range of aldehydes and ketones to function as productive substrates for the current synthesis. Moreover, the resulting heterocycles possess a highly reactive chloro group on the pyrimidine moiety which allows further introduction of a large variety of new elements via nucleophilic substitution or transition-metal-catalyzed, cross-coupling reaction conditions. These pyrimidine-fused heterocycles as privileged structures could be of interest in searching for novel leads in drug discovery.

Experimental Section

Acetonitrile was treated with calcium hydride and distilled after refluxing for 3 h in a nitrogen atmosphere. All other commercial reagents were used as received without additional purification. Melting point was uncorrected. Mass spectra and HPLC (ELSD) data were recorded on an 1100 LC/MS system (Agilent Technology Corporation). The ^1H and ^{13}C NMR data were obtained on a 300-MHz Varian spectrometer with TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as solvent. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) where noted are quoted in hertz.

1-(6-Chloro-5-nitropyrimidin-4-yl)-1,2,3,4-tetrahydroquinoline (11). To a solution of 4,6-dichloro-5-nitropyrimidine **9** (3.00 g, 15.5 mmol) in anhydrous THF (40 mL) was added dropwise a solution of 1,2,3,4-tetrahydroquinoline **10** (2.07 g, 15.5 mmol) and triethylamine (3.3 mL, 23.3 mmol) in anhydrous THF (20 mL) in an ice bath. After being warmed to room temperature, the reaction mixture was stirred

overnight, then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 1 N HCl (30 mL × 3) and brine (30 mL × 3), and dried over anhydrous $MgSO_4$. Concentration in vacuo and purification by flash chromatography on a silica gel column (petroleum/ EtOAc 10:1, v/v) provided the desired product, 3.46 g (77%), brown solid, mp 130−131 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.14 (td, J = 7.2 Hz, 1.5 Hz, 1H), 7.07 (td, J = 8.1 Hz, 1.8 Hz, 1H), 6.91 (dd, J = 7.5 Hz, 0.9 Hz, 1H), 4.02 (t, J = 6.6 Hz, 2H), 2.79 (t, J = 6.6 Hz, 2H), 2.13−2.04 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 157.1, 154.4, 153.2, 137.5, 132.6, 128.8, 126.4, 126.2, 119.3, 47.2, 26.3, 23.8. ES-MS: 291.0 [M + H] $^+$.

4-Chloro-6-(3,4-dihydro-2*H*-quinolin-1-yl)-pyrimidin-5-ylamine (1b). Compound **11** (3.14 g, 10.8 mmol) was dissolved in a mixture of ethanol (40 mL) and water (10 mL). Iron powder (1.82 g, 32.5 mmol) and NH_4Cl (0.34 g, 6.26 mmol) were added, and the mixture was stirred under reflux for 1 h, cooled, and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was extracted with EtOAc, and the organics were washed with saturated $NaHCO_3$ and brine in sequence and dried over anhydrous $MgSO_4$. Concentration in vacuo gave the crude product, which was purified by recrystallization in EtOH to give **1b**, 2.33 g (83%), white solid, mp 115−116 °C. ^{1}H NMR ($CDCl_3$): δ 8.26 (s, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.07 (td, J = 8.1 Hz, 1.5 Hz, 1H), 6.94 (td, J = 7.5 Hz, 1.2 Hz, 1H), 6.39 (d, J = 7.8 Hz, 1H), 3.85 (t, J = 6.0 Hz, 2H), 3.82 (s, br, 2H), 2.89 (t, J = 6.6 Hz, 2H), 2.13−2.05 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 150.4, 146.9, 144.1, 138.7, 129.5, 129.3, 127.7, 126.3, 122.0, 117.1, 47.5, 26.9, 23.5. ES-MS: 261.0 [M + H] $^+$.

General Procedure for the Synthesis of Compounds 2. To a solution of indolin-1-ylpyrimidine **1a** or tetrahydroquinolinylpyrimidine **1b** (0.5 mmol) and an aldehyde (0.6 mmol) or ketone (0.6 mmol) in 3 mL of acetonitrile was added 3 drops of TFA. The mixture was refluxed with stirring until the disappearance of the starting material **1a** or **1b** on TLC. After cooling to room temperature, the solvent was removed in vacuo to give the crude product. Purification by recrystallization or flash chromatography on a silica gel column provided the desired products.

Compound 2.1. 92%, mp 140−142 °C. ^{1}H NMR ($CDCl_3$): δ 8.14 (s, 1H), 7.12−7.10 (m, 1H), 6.91−6.84 (m, 2H), 4.88 (d, J = 5.4 Hz, 1H), 4.50−4.41 (m, 1H), 4.32−4.13 (m, 2H), 3.22−3.11 (m, 2H), 1.63−1.53 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.0, 149.5, 146.3, 140.6, 133.7, 127.7, 126.5, 125.0, 124.3, 121.8, 62.3, 51.1, 30.3, 26.8, 11.3. ES-MS: 287.1 [M + H$^+$].

Compound 2.2. 90%, mp 151−152 °C. ^{1}H NMR ($CDCl_3$): δ 8.15 (s, 1H), 7.11 (dd, J = 6.6 Hz, 0.9 Hz, 1H), 6.90−6.83 (m, 2H), 4.84 (s, br, 1H), 4.50−4.41 (m, 1H), 4.32−4.22 (m, 2H), 3.27−3.06 (m, 2H), 1.63−1.23 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.1, 149.5, 146.3, 140.7, 133.7, 127.8, 126.4, 125.1, 124.3, 121.8, 60.3, 51.1, 39.4, 26.9, 19.7, 13.9. ES-MS: 301.1 [M + H$^+$].

Compound 2.3. 92%, mp 142−144 °C. ^{1}H NMR ($CDCl_3$): δ 8.10 (s, 1H), 7.31−7.21 (m, 3H), 7.17 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.11−7.08 (m, 2H), 6.85 (t, J = 7.8 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.47 (s, 1H), 5.11 (s, br, 1H), 4.43−4.32 (m, 2H), 3.22 (t, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 152.2, 149.7, 146.9, 141.4, 141.2, 133.3, 128.8, 127.9, 127.4, 127.3, 125.6, 125.4, 124.5, 121.5, 63.7, 50.9, 26.7. ES-MS: 335.1 [M + H$^+$].

Compound 2.4. 97%, mp 201−203 °C. ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.20−7.12 (m, 2H), 6.92−6.84 (m, 3H), 6.62 (t, J = 7.5 Hz, 1H), 6.38 (dd, J = 7.2 Hz, 1.5 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H), 5.63 (s, br, 1H), 4.46−4.31 (m, 2H), 3.96 (s, 3H), 3.28−3.20 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 156.8, 152.3, 149.7, 147.2, 142.6, 133.4, 129.5, 129.4, 127.9, 127.6, 126.0, 124.7, 124.5, 122.0, 120.3, 110.4, 59.0, 55.4, 51.2, 27.0. ES-MS: 365.2 [M + H$^+$].

Compound 2.5. 96%, mp 195−196 °C. ^{1}H NMR ($CDCl_3$): δ 8.11 (d, J = 8.7 Hz, 2H), 8.10 (s, 1H), 7.25−7.22 (m, 3H), 6.91 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.62 (d, J = 2.7 Hz, 1H), 5.22 (s, br, 1H), 4.48−4.27 (m, 2H), 3.28−3.21 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 152.2, 150.2, 148.5, 147.4, 147.3, 141.3, 133.7, 128.3, 127.2, 125.1, 124.4, 124.0, 123.7, 121.9, 62.9, 50.9, 26.6. ES-MS: 380.0 [M + H$^+$].

Compound 2.6. 90%, mp 147−148 °C. ^{1}H NMR ($CDCl_3$): δ 8.12 (s, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.08−7.04 (m, 2H), 6.99−6.94 (m, 2H), 6.87 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 5.47 (s, 1H), 5.12 (s, br, 1H), 4.46−4.28 (m, 2H), 3.23 (t, J = 8.1 Hz, 2H). ES-MS: 353.1 [M + H$^+$].

Compound 2.7. 81%, mp 162−163 °C. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 7.25−7.21 (m, 5H), 7.16 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.33−6.18 (m, 2H), 5.06 (t, J = 4.8 Hz, 1H), 4.96 (d, J = 4.2 Hz, 1H), 4.43−4.30 (m, 2H), 3.22−3.16 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 152.0, 149.8, 147.1, 140.8, 135.9, 133.5, 133.1, 129.6, 128.5, 128.0, 126.8, 126.6, 125.3, 125.0, 124.5, 121.7, 61.8, 50.9, 26.7. ES-MS: 361.1 [M + H$^+$].

Compound 2.8. 83%, mp 132−135 °C. ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.13 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 6.93 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 6.88 (t, J = 6.9 Hz, 1H), 5.56−5.37 (m, 2H), 4.83 (d, J = 6.3 Hz, 1H), 4.62 (s, br, 1H), 4.44−4.25 (m, 2H), 3.21−3.14 (m, 2H), 1.62 (dd, J = 6.0 Hz, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.9, 149.4, 146.4, 140.5, 133.2, 131.2, 129.5, 126.4, 125.5, 124.1, 123.9, 121.5, 61.5, 50.7, 26.5, 17.6. ES-MS: 299.1 [M + H$^+$].

Compound 2.9. 95%, mp 117−118 °C. ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.13−7.10 (m, 2H), 6.89 (t, J = 7.2 Hz, 1H), 4.36 (t, J = 8.7 Hz, 2H), 3.17 (t, J = 8.7 Hz, 2H), 1.57 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 152.3, 149.7, 146.7, 140.3, 133.5, 131.7, 125.0, 124.0, 123.1, 121.5, 56.8, 50.7, 30.4, 26.6. ES-MS: 287.1 [M + H$^+$].

Compound 2.10. 92%, mp 86−88 °C. ^{1}H NMR ($CDCl_3$): δ 8.16 (s, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 4.48−4.22 (m, 3H), 3.19−3.12 (m, 2H), 1.85−1.75 (m, 1H), 1.67−1.55 (m, 1H), 1.60 (s, 3H), 0.86 (t, J = 7.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.0, 149.4, 146.1, 140.4, 133.6, 130.7, 124.9, 124.0, 123.9, 121.3, 59.8, 50.7, 34.5, 27.1, 26.6, 8.1. ES-MS: 301.1 [M + H$^+$].

Compound 2.11. 84%, mp 99−101 °C. ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1H), 7.11 (dd, J = 7.2 Hz, 1.2 Hz, 1H),

7.04 (d, J = 8.1 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 4.48−4.23 (m, 3H), 3.20−3.09 (m, 2H), 1.78−1.48 (m, 2H), 1.61 (s, 3H), 1.41−1.18 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.1, 149.5, 146.2, 140.4, 133.7, 130.8, 124.9, 124.0, 123.9, 121.3, 59.7, 50.7, 44.4, 27.7, 26.6, 17.0, 14.2. ES-MS: 315.1 [M + H$^+$].

Compound 2.12. 92%, mp 182−183 °C. ^{1}H NMR ($CDCl_3$): δ 8.12 (s, 1H), 7.10 (t, J = 8.1 Hz, 2H), 6.88 (d, J = 7.8 Hz, 1H), 4.59 (s, br, 1H), 4.34 (td, J = 8.4 Hz, 1.8 Hz, 2H), 3.12 (t, J = 9.0 Hz, 2H), 2.00−1.76 (m, 5H), 1.69−1.49 (m, 4H), 1.33−1.25 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 152.3, 149.1, 145.5, 140.9, 133.6, 133.3, 124.5, 124.0, 121.9, 121.7, 58.2, 50.7, 34.9, 26.6, 25.1, 20.8. ES-MS: 327.1 [M + H$^+$].

Compound 2.13. 87%, mp 188−189 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.30−7.20 (m, 3H), 7.17−7.14 (m, 3H), 6.88−6.80 (m, 2H), 4.76 (s, br, 1H), 4.45−4.36 (m, 1H), 4.23−4.14 (m, 1H), 3.21−3.14 (m, 1H), 1.90 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 152.0, 149.6, 146.5, 145.8, 141.1, 133.4, 130.8, 128.6, 127.6, 126.5, 125.9, 125.5, 124.3, 121.3, 63.6, 50.7, 30.6, 26.7. ES-MS: 349.1 [M + H$^+$].

Compound 2.14. 62%, mp 168−169 °C. ^{1}H NMR ($CDCl_3$): δ 8.07 (s, 1H), 7.14 (d, J = 6.6 Hz, 1H), 7.07 (d, J = 9.0 Hz, 2H), 6.86−6.77 (m, 4H), 4.71 (s, 1H), 4.41−4.34 (m, 1H), 4.25−4.15 (m, 1H), 3.76 (s, 3H), 3.16 (t, J = 8.7 Hz, 2H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 158.8, 152.1, 149.6, 146.3, 141.0, 138.0, 133.4, 131.1, 127.8, 125.9, 125.5, 124.2, 121.2, 113.8, 63.1, 55.1, 50.7, 30.5, 26.7. ES-MS: 379.1 [M + H$^+$].

Compound 2.15. 82%, mp 182−183 °C. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, J = 8.7 Hz, 2H), 8.05 (s, 1H), 7.28−7.21 (m, 3H), 6.95−6.89 (m, 2H), 4.80 (s, 1H), 4.48−4.39 (m, 1H), 4.18−4.07 (m, 1H), 3.23−3.14 (m, 1H), 1.98 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 153.2, 151.7, 149.9, 147.1, 146.5, 141.1, 133.9, 129.1, 127.5, 125.3, 125.0, 124.8, 123.8, 121.7, 63.5, 50.7, 30.9, 26.6. ES-MS: 394.2 [M + H$^+$].

Compound 2.16. 57%, mp 145−147 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.31−7.21 (m, 3H), 7.16−7.14 (m, 3H), 6.83 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 4.86 (s, br, 1H), 4.37−4.17 (m, 2H), 3.15 (t, J = 8.7 Hz, 2H), 2.32−2.12 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 151.4, 149.1, 145.7, 144.5, 141.2, 133.7, 129.3, 128.5, 127.5, 127.1, 126.6, 125.5, 124.2, 120.9, 66.9, 50.7, 34.3, 26.5, 8.5. ES-MS: 363.2 [M + H$^+$].

Compound 2.17. 59%, mp 273 °C (dec). ^{1}H NMR (DMSO-d_6): δ 8.14 (s, 1H), 7.24−7.21 (m, 2H), 6.91 (t, J = 7.2 Hz, 1H), 5.03 (s, 1H), 4.38−4.29 (m, 1H), 4.21−4.11 (m, 1H), 3.21−3.09 (m, 2H), 1.88 (s, 3H). ES-MS: 317.2 [M + H$^+$].

Compound 2.18. 97%, colorless syrup. ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H), 7.09 (dd, J = 6.9 Hz, 1.2 Hz, 1H), 7.01−6.94 (m, 2H), 4.50 (s, br, 1H), 4.46−4.39 (m, 1H), 4.15−4.09 (m, 1H), 3.85−3.77 (m, 1H), 2.89 (t, J = 6.9 Hz, 2H), 2.13−1.99 (m, 4H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 150.4, 145.8, 142.6, 141.9, 135.3, 133.0, 131.4, 129.5, 128.3, 123.5, 59.2, 46.1, 26.7, 26.2, 21.4, 11.5. ES-MS: 301.1 [M + H$^+$].

Compound 2.19. 95%, mp 108−110 °C. ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H), 7.09 (dd, J = 6.9 Hz, 2.1 Hz, 1H), 7.01−6.94 (m, 2H), 4.55 (t, J = 8.1 Hz, 1H), 4.12−4.06 (m, 1H), 3.88−3.80 (m, 1H), 2.89 (t, J = 7.5 Hz, 2H), 2.13−1.95 (m, 4H), 1.52−1.35 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 150.5, 145.8, 142.5, 141.9, 135.4, 131.4, 129.5, 128.4, 123.5, 123.4. ES-MS: 315.1 [M + H$^+$].

Compound 2.20. 96%, mp 140−142 °C. ^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.39−7.26 (m, 5H), 7.13 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 5.81 (s, 1H), 3.90−3.82 (m, 1H), 3.66−3.59 (m, 1H), 2.89 (t, J = 7.2 Hz, 2H), 2.11−2.02 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 150.7, 146.3, 142.9, 142.2, 140.3, 135.3, 133.1, 131.8, 130.0, 128.7, 128.3, 127.6, 126.3, 125.3, 123.5, 60.6, 45.8, 26.5, 21.4. ES-MS: 349.2 [M + H$^+$].

Compound 2.21. 91%, colorless syrup. ^{1}H NMR ($CDCl_3$): δ 7.95 (s, 1H), 7.15 (m, 5H), 7.11 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 5.80 (s, 1H), 3.80−3.74 (m, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.35 (s, 3H), 2.08−2.04 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 150.7, 146.3, 142.9, 142.3, 137.3, 137.2, 135.5, 131.7, 129.9, 129.3, 128.4, 126.4, 125.2, 123.5, 60.3, 45.8, 26.5, 21.4, 21.0. ES-MS: 363.2 [M + H$^+$].

Compound 2.22. 85%, mp 245−247 °C. ^{1}H NMR ($CDCl_3$): δ 8.16 (d, J = 8.7 Hz, 2H), 7.96 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 6.3 Hz, 1H), 5.56 (d, J = 5.7 Hz, 1H), 5.19 (d, J = 5.7 Hz, 1H), 4.26−4.19 (m, 1H), 2.90−2.79 (m, 3H), 2.13−1.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 150.5, 148.6, 147.1, 146.6, 143.5, 141.9, 134.1, 132.3, 130.7, 127.0, 126.6, 125.8, 123.9, 123.7, 60.7, 45.5, 26.3, 21.0. ES-MS: 394.1 [M + H$^+$].

Compound 2.23. 40%, mp 114−116 °C. ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H), 7.40−7.23 (m, 5H), 7.13 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.63 (d, J = 2.7 Hz, 2H), 5.34 (t, J = 2.7 Hz, 1H), 4.13−4.05 (m, 1H), 3.88−3.80 (m, 1H), 2.91 (t, J = 6.9 Hz, 2H), 2.15−2.05 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 150.6, 146.2, 136.2, 134.8, 132.4, 131.6, 129.9, 128.6, 128.1, 128.0, 127.9, 126.5, 124.1, 123.7, 59.3, 46.1, 26.6, 21.4. ES-MS: 375.1 [M + H$^+$].

Compound 2.24. 37%, mp 130−132 °C. ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 4.31 (s, br, 1H), 3.99−3.96 (m, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.18−2.10 (m, 2H), 1.79 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 149.7, 145.9, 141.6, 138.1, 132.0, 129.8, 127.4, 123.3, 121.1, 55.6, 46.1, 29.4, 26.7, 21.6. ES-MS: 301.1 [M + H$^+$].

General Procedure for Displacement of the Chloro Group in 2.2 or 2.3 with *n*-BuNH$_2$, Aniline, and Morpholine; Preparation of Compounds 3a, 3b, and 3c. To a solution of compound **2.2** or **2.3** (0.3 mmol) and excess amine (3.0 mmol) in *n*-BuOH (3.0 mL) was added concentrated aqueous HCl (2−3 drops). The mixture was stirred under a nitrogen atmosphere while refluxing until disappearance of **2.2** or **2.3** as monitored by TLC. After cooling of the resulting mixture and concentration in vacuo to dryness, the residue was purified by flash chromatography on silica gel to give the desired product.

Compound 3a. 74%, brown solid, mp 105−107 °C. ^{1}H NMR ($CDCl_3$): δ 8.09 (s, 1H), 7.20−7.15 (m, 3H), 7.12 (t,

J = 4.2 Hz, 1H), 7.08−7.05 (m, 2H), 7.76 (d, J = 4.2 Hz, 2H), 5.85 (t, J = 2.4 Hz, 1H), 5.51 (s, 1H), 4.35−4.29 (m, 2H), 3.30−3.13 (m, 4H), 1.48−1.40 (m, 2H), 1.37−1.23 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 161.4, 157.2, 154.7, 154.6, 142.4, 141.2, 133.1, 128.5, 128.2, 128.0, 127.4, 127.3, 124.0, 120.3, 65.1, 49.6, 40.4, 32.0, 27.1, 20.0, 13.8.

Compound 3b. 60%, pale yellow solid, mp 149−151 °C. ^{1}H NMR ($CDCl_3$): δ 8.40 (s, 1H), 8.32 (s, 1H), 7.68 (dd, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.09 (d, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 6.9 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 4.42−4.33 (m, 1H), 4.30−4.27 (m, 2H), 3.17−3.12 (m, 2H), 2.69 (s, br, 1H), 1.62−1.56 (m, 2H), 1.45−1.38 (m, 2H), 0.88 (t, J = 6.9 Hz, 3H).

Compound 3c. 90%, white solid, mp 158−162 °C. ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H), 7.35−7.25 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 7.11 (d, J = 7.2 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H), 6.58 (d, J = 7.5 Hz, 1H), 5.28 (s, 1H), 4.93 (s, br, 1H), 4.46−4.30 (m, 2H), 3.75−3.65 (m, 4H), 3.19 (t, J = 8.7 Hz, 2H), 3.00−2.93 (m, 2H), 2.87−2.80 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 157.2, 151.7, 150.0, 149.9, 141.8, 132.9, 128.8, 127.8, 127.5, 127.1, 125.8, 124.1, 121.2, 120.5, 66.8, 64.1, 64.0, 50.3, 49.6, 26.8.

Preparation of Compound 3d. To a solution of compound **2.2** (90 mg, 0.3 mmol) and pyrrolidine (213 mg, 3.0 mmol) in *n*-BuOH (3.0 mL) was added Et_3N (1 mL). The mixture was refluxed with stirrring under a nitrogen atmosphere for 3 days. After cooling to room temperature, the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (petroleum/EtOAc 5:1, v/v) to give the desired product (93.5 mg) as a pale yellow solid, yield 93%, mp 116−118 °C. ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.06 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 4.43−4.22 (m, 2H), 4.17 (t, J = 6.9 Hz, 1H), 3.81−3.73 (m, 2H), 3.64−3.53 (m, 2H), 3.19−3.08 (m, 2H), 1.99−1.84 (m, 4H), 1.41−1.19 (m, 4H), 0.86 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 155.8, 150.8, 150.7, 141.5, 133.1, 129.7, 125.9, 123.5, 120.0, 112.0, 60.5, 50.6, 50.3, 37.6, 26.8, 25.3, 19.3, 14.0.

General Procedure for Displacement of the Chloro Group in 2.2 or 2.3 with *n*-BuOH or $PhCH_2SH$; Preparation of compounds 4a, 4b, 5a, and 5b. To a solution of compound **2.2** or **2.3** (0.3 mmol) in THF (2 mL) was added *n*-BuOH (222 mg, 0.27 mL, 3 mmol) or $PhCH_2SH$ (74.4 mg, 0.07 mL, 0.6 mmol) and then sodium hydride (48 mg, 1.2 mmol). The mixture was warmed to 70 °C with stirring, and the reaction was monitored by TLC until the disappearance of **2.2** or **2.3**. Cold water was added to quench the reaction, followed by extraction with ethyl acetate. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration in vacuo, the crude residue was purified by flash chromatography on silica gel to give the desired product.

Compound 4a. 94%, yellow syrup. ^{1}H NMR ($CDCl_3$): δ 8.10 (s, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.77 (t, J = 7.5 Hz, 1H), 4.63 (s, 1H), 4.45−4.38 (m, 3H), 4.37−4.13 (m, 2H), 3.21−3.05 (m, 2H), 1.82−1.73 (m, 2H), 1.57−1.43 (m, 6H), 1.39−1.22 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.9, 150.3, 148.4, 148.3, 141.2, 132.9, 127.4, 126.3, 123.5, 120.1, 113.1, 66.4, 60.1, 50.0, 39.3, 31.1, 26.7, 19.3, 19.1, 13.7, 13.6.

Compound 4b. 94%, yellow solid, 89−91 °C. ^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.26−7.19 (m, 3H), 7.13−7.06 (m, 3H), 6.79−6.71 (m, 2H), 5.40 (s, 1H), 4.88 (s, br, 1H), 4.38−4.31 (m, 2H), 4.29−4.23 (m, 2H), 3.19 (t, J = 8.1 Hz, 2H), 1.70−1.65 (m, 2H), 1.42−1.34 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.1, 150.9, 149.0, 148.9, 142.5, 142.1, 132.7, 128.4, 127.6, 127.4, 127.3, 124.9, 124.0, 120.1, 114.2, 66.4, 64.1, 50.1, 30.9, 26.8, 19.0, 13.7.

Compound 5a. 94%, yellow syrup. ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 7.38−7.34 (m, 2H), 7.31−7.19 (m, 3H), 7.04 (dt, J = 6.6 Hz, 0.9 Hz, 1H), 6.84−6.76 (m, 2H), 4.54 (d, J = 13.2 Hz, 1H), 4.44 (d, J = 13.5 Hz, 1H), 4.43−4.37 (m, 1H), 430−4.10 (m, 3H), 3.19−3.07 (m, 2H), 1.52−1.15 (m, 4H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C NMR($CDCl_3$): δ 153.1, 150.7, 150.0, 149.9, 140.8, 137.7, 133.1, 128.9, 128.4, 127.9, 127.1, 126.0, 124.8, 123.7, 120.7, 60.1, 50.3, 38.7, 35.4, 26.6, 19.6, 13.7.

Compound 5b. 96%, yellow solid, mp 113−115 °C. ^{1}H NMR ($CDCl_3$): δ 8.27 (s, 1H), 7.30−7.19 (m, 8H), 7.14−7.07 (m, 3H), 6.78 (t, J = 7.5 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.36 (s, 1H), 4.51 (s, br, 1H), 4.41−4.31 (m, 4H), 3.20 (t, J = 9.0 Hz, 2H). ^{13}C NMR($CDCl_3$): δ 154.2, 151.2, 150.6, 150.4, 141.9, 141.5, 137.6, 133.0, 128.9, 128.5, 127.7, 127.3, 127.2, 125.9, 125.7, 124.2, 120.9, 109.7, 64.0, 50.4, 35.3, 26.8.

General Procedure for Displacement of the Chloro Group in 2.2 or 2.3 with Thiophenol; Preparation of Compounds 5c and 5d. To a solution of compound **2.2** or **2.3** (0.3 mmol) and thiophenol (330 mg, 3.0 mmol) in *n*-BuOH (3.0 mL) was added Et_3N (1 mL). The mixture was refluxed with stirrring under a nitrogen atmosphere until the disappearance of **2.2** or **2.3** as monitored by TLC. After cooling to room temperature, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum/EtOAc 5:1, v/v) to give the desired product.

Compound 5c. 95%, yellow syrup. ^{1}H NMR ($CDCl_3$): δ 8.27 (s, 1H), 7.43−7.38 (m, 2H), 7.36−7.28 (m, 3H), 7.09 (d, J = 7.2 Hz, 1H), 6.88−6.81 (m, 2H), 5.03 (s, br, 1H), 4.49−4.41 (m, 1H), 4.33−4.22 (m, 2H), 3.23−3.07 (m, 2H), 1.61−1.51 (m, 2H), 1.49−1.26 (m, 2H), 0.87 (t, J = 6.9 Hz, 3H).

Compound 5d. 94%, yellow syrup. ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H), 7.26−7.05 (m, 11H), 6.80 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 5.41 (s, 1H), 5.31 (s, br, 1H), 4.41−4.28 (m, 2H), 3.19 (t, J = 8.1 Hz, 2H).

General Procedure for Displacement of the Chloro Group in 2.2 and 2.3 with $PhB(OH)_2$; Preparation of Compounds 6a and 6b. Compound **3.2** or **3.3** (0.33 mmol) and phenylboronic acid (61 mg, 0.5 mmol) was dissolved in DME (4 mL) under nitrogen atmosphere. Potassium carbonate (138 mg, 1.0 mmol) dissolved in water (4 mL) was added, followed by palladium(II) acetate (0.9 mg, 0.004 mmol) and triphenylphosphine (4.2 mg, 0.016 mmol). The reaction mixture was refluxed with stirring for 6 h. After cooling, the solid was filtered off through a pad of Celite

and washed with ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (5 mL × 3). The combined organic extracts were washed with saturated $NaHCO_3$, water, and brine in sequence; dried with anhydrous $MgSO_4$; concentrated in vacuo; and purified by flash chromatography on silica gel to give the desired product.

Compound 6a. 53%, yellow syrup. ^{1}H NMR ($CDCl_3$): δ 8.46 (s, 1H), 7.55−7.42 (m, 5H), 7.09 (t, J = 4.5 Hz, 1H), 6.80 (d, J = 4.2 Hz, 2H), 4.81 (d, J = 5.4 Hz, 1H), 4.54−4.45 (m, 1H), 4.38−4.28 (m, 1H), 4.05−3.99 (m, 1H), 3.24−3.12 (m, 2H), 1.46 (q, J = 7.8 Hz, 2H), 1.12−0.86 (m, 2H), 0.74 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.0, 151.6, 150.0, 149.9, 141.0, 136.7, 133.3, 128.9, 128.5, 127.3, 125.9, 125.8, 123.9, 120.9, 59.8, 50.8, 38.2, 26.6, 19.2, 13.5.

Compound 6b. 53%, yellow syrup. ^{1}H NMR ($CDCl_3$): δ 8.43 (s, 1H), 7.39−7.35 (m, 3H), 7.27−7.19 (m, 5H), 7.14 (d, J = 7.2 Hz, 1H), 6.97−6.94 (m, 2H), 6.78 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 5.29 (d, J = 3.9 Hz, 1H), 4.78 (d, J = 3.9 Hz, 1H), 4.45 (t, J = 8.7 Hz, 2H), 3.24 (t, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 153.4, 153.1, 151.0, 150.9, 141.7, 141.4, 136.5, 133.1, 128.8, 128.5, 127.8, 127.2, 126.6, 125.7, 124.2, 121.0, 64.6, 50.8, 26.8.

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References and Notes

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(2) (a) Yang, J.; Dang, Q.; Liu, J.; Wei, Z.; Wu, J.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 474. (b) Liu, J.; Dang, Q.; Wei, Z.; Zhang, H.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 627. (c) Lucas, B.; Rosen, N.; Chiosis, G. *J. Comb. Chem.* **2001**, *3*, 518. (d) Ding, S.; Gray, N. S.; Ding, Q.; Wu, X.; Schultz, P. G. *J. Comb. Chem.* **2002**, *4*, 183. (e) Takvorian, A. G.; Combs, A. P. *J. Comb. Chem.* **2004**, *6*, 171. (f) Lucrezia, R. D.; Gilbert, I. H.; Floyd, C. D. *J. Comb. Chem.* **2000**, *2*, 249.
(3) (a) Gangjee, A.; Lin, X.; Queener, S. F. *J. Med. Chem.* **2004**, *47*, 3689. (b) Dang, Q.; Gomez-Galeno, J. E. *J. Org. Chem.* **2002**, *67*, 8703.
(4) (a) Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 568. (b) Selleri, S.; Bruni, F.; Costagli, C.; Costanzo, A.; Guerrini, G.; Ciciani, G.; Gratteri, P.; Bonaccini, C.; Aiello, P. M.; Besnard, F.; Renad, S.; Costa, B.; Martini, C. *J. Med. Chem.* **2003**, *46*, 310.
(5) Thakur, A. J.; Saikia, P.; Prajapati, D.; Sandhu, J. S. *Synlett* **2001**, 1299.
(6) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy. B.; Siekierka, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347.
(7) Gangjee, A.; Zeng, Y.; McGuire, J. J.; Mehraein, F.; Kisliuk, R. L. *J. Med. Chem.* **2004**, *47*, 6893.
(8) Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Bai, X. *Org. Lett.* **2005**, *7*, 1541.
(9) Fu, R.; Xu, X.; Dang, Q.; Bai, X. *J. Org. Chem*. **2005**, *70*, 1081.
(10) Zheng, L.; Xiang, J.; Dang, Q.; Guo, S.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 813.
(11) Duncton, M. A. J.; Smith, L. M., II; Burdzovic-Wizeman, S.; Burns, A.; Liu, H.; Mao, Y.; Wong, W. C.; Kiselyov, A. S. *J. Org. Chem.* **2005**, *70*, 9629.
(12) Xu, Y.-J.; Liu, H.; Pan, W.; Chen, X.; Wong, W. C.; Labelle, M. *Tetrahedron Lett.* **2005**, *46*, 7523.
(13) Norman, M. H.; Chen, N.; Chen, Z.; Fotsch, C.; Hale, C.; Han, N.; Hurt, R.; Jenkins, T.; Kincaid, J.; Liu, L.; Lu, Y.; Moreno, O.; Santora, V. J.; Sonnenberg, J. D.; Karbon, W. *J. Med. Chem*. **2000**, *43*, 4288.
(14) Caron, S.; Vazquez, E. *J. Org. Chem.* **2003**, *68*, 4104.
(15) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *Tetrahedron* **2006**, *62*, 2563.
(16) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(17) Taddei, D.; Slawin, A. M. Z.; Woollins, J. D. W. *Eur. J. Org. Chem.* **2005**, 939.
(18) Lavecchia, G.; Berteina-Raboin, S.; Guillaumet, G. *Tetrahedron Lett.* **2005**, 46, 5851.
(19) (a) Nyerges, M.; Pintér, A.; Virányi, A.; Blaskó, G.; Tõke, L. *Tetrahedron.* **2005**, *61*, 8199. (b) Havelková, M.; Hocek, M.; Cesnek, M.; Dvoøák, D. *Synlett* **1999**, *7*, 1145.

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