

New Pyrimidine Derivatives possessing ALK Inhibitory Activities

Eun Hye Yang, Jeong In Yun, Muhammad Latif, Hyeon Ji Lee, Chang-Soo Yun, Kwangho Lee, Chi Hoon Park, Sung Yun Cho, Hee Jung Jung, Pilho Kim, Jae Du Ha, and Hyoung Rae Kim*

Korea Research Institute of Chemical Technology, 141 Gajeongro, Yuseong, Daejeon 305-600, Korea

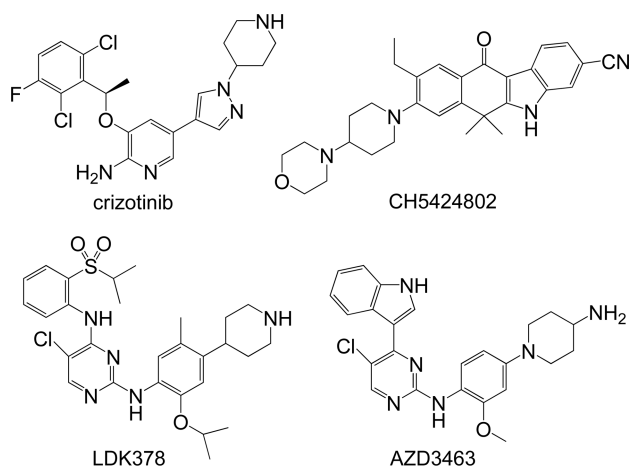
*E-mail: hyungrk@kRICT.re.kr

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Anaplastic lymphoma kinase (ALK), a family of tyrosine kinases has been recently elucidated as a potential target for various cancers due to its implications of tumorigenesis by ALK gene mutations, overexpressions, and amplifications. ALK was first identified in 1994 as a part of nucleophosmin NPM-ALK fusion gene in 60% of anaplastic large-cell lymphoma (ALCL),¹ in late 2007 EML4-ALK fusion gene was found in 3-7% of non-small cell lung cancer,² and a kind of ALK fusion genes are found one by one in various cancers such as DLBCL,³ inflammatory myofibroblastic tumor (IMT),⁴ plasmacytoma,⁵ esophageal cancer,⁶ renal cell carcinoma,⁷ breast cancer,⁸ colon cancer,⁸ and ovarian cancer.⁹ Moreover mutated ALK is much implicated in neuroblastoma¹⁰ and thyroid carcinoma.¹¹ *Crizotinib* (*Xalkori*) was the first small molecule inhibitor which was approved as a treatment of NSCLC including ALK fusion gene by FDA in 2011. *Crizotinib*, a potent inhibitor of both c-Met and ALK tyrosine kinases is a 3-benzyloxy-2-aminopyridine derivative derived from c-Met inhibitors and surprisingly its overall clinical benefit was 87%.¹² Many pharmaceutical companies have been looking forward to finding better ALK inhibitors and among them, CH-5424802 by Chugai Pharm.,¹³ LDK-378 by Novartis/GNF, and AZD-3463 by AstraZeneca are showing excellent progress.

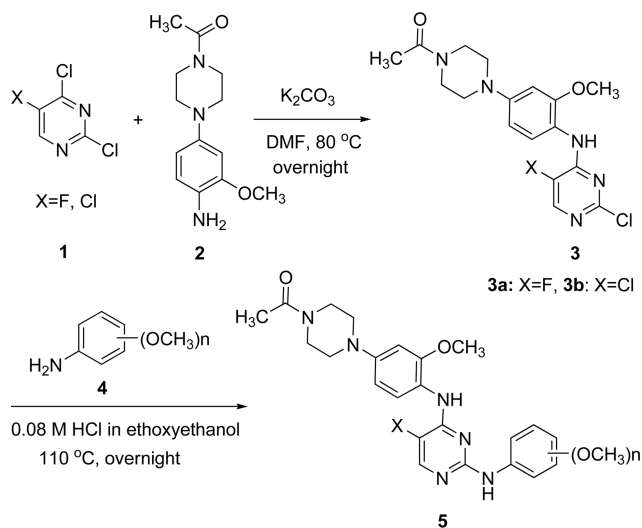
2-Aminopyrimidine derivatives have been massively studied as various kinase inhibitors such as for ALK,¹⁴ EGFR,¹⁵ Aurora kinase,¹⁶ JAK,¹⁷ CK1,¹⁸ LRR2,¹⁹ etc.



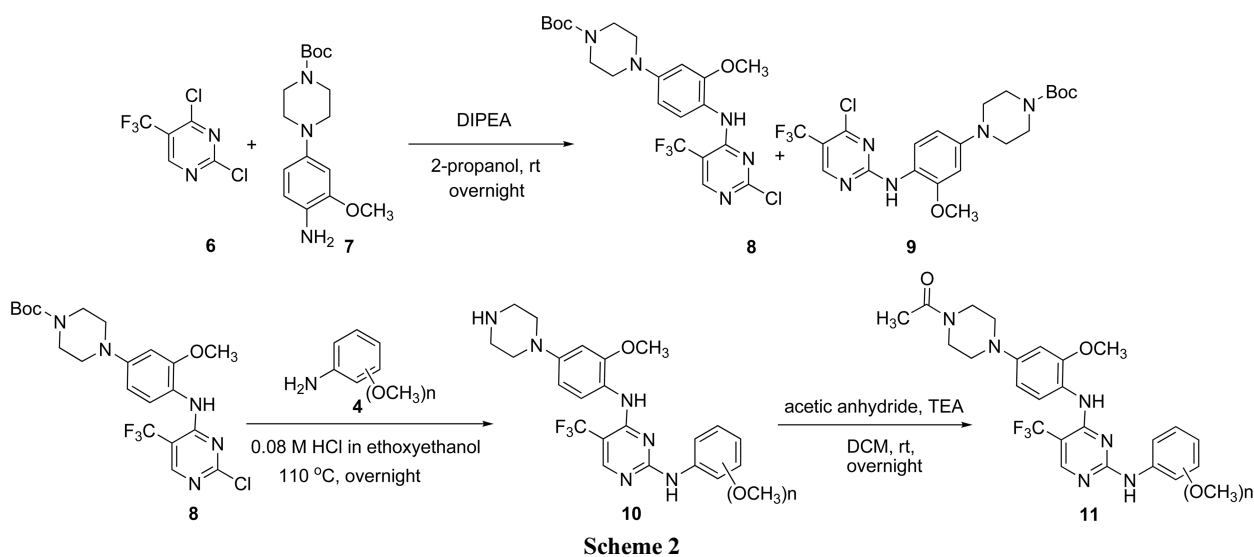
Especially, imatinib and nilotinib for BCR-ABL, dasatinib for BCR-ABL/Src/c-Kit/etc., fostamatinib for Syk, and pazopanib for VEGFR2/PDGFR/c-Kit had approved as new chemical entities by US FDA.

We designed a new series of pyrimidine derivatives to discover a new ALK inhibitor, and among them 4-{4-(piperazin-1-yl)-2-methoxy-phenyl}amino-2-(methoxy-substituted-phenyl)aminopyrimidines were well-matched with crizotinib and LDK378 in docking study. We synthesized those pyrimidine derivatives and evaluated ALK inhibitory activities. 5-Substituted-2,4-dichloropyrimidine **1** (X=F, Cl) was reacted with 4-(*N*-acetylpiperazin-1-yl)-2-methoxyaniline **2** in DMF at 80 °C overnight to predominantly afford 4-substituted-pyrimidine **3** in good yield and it was reacted with various methoxyanilines in 0.08 M HCl solution of ethoxyethanol at 110 °C overnight to afford **5** in moderate to good yields (Scheme 1).

In case of 2,4-dichloro-5-trifluoromethylpyrimidine, reaction of **6** with aniline (**2**) in the presence of base in DMF gave a mixture of 2-substituted and 4-substituted pyrimidines with a trace of 2,4-disubstituted pyrimidine, and the regioisomers could hardly be separated by TLC. Fortunately, **6** reacted with 4-(*N*-Boc-piperazin-1-yl)-2-methoxyaniline **7** in the presence of diisopropylethylamine as a base at room



Scheme 1



temperature in 2-propanol afforded a mixture of **8** and **9** (48% : 30%), and the regioisomers could be nicely separated by silica gel column chromatography. **8** was reacted with various methoxyaniline **4** in 0.08 M HCl solution of ethoxyethanol at 110 °C affording **10** in moderate to good yields. *N*-Acetylation of **10** was performed by acetic anhydride with triethylamine in dichloromethane to give **11** in good yield (Scheme 2).

The regioisomers **8** and **9** could be characterized by ¹H NMR spectra of the reductive dechlorinated products **12** and **13** by Pd/C in the presence of base under H₂ atmosphere. **12** has two different protons at pyrimidine ring which appears at 8.52 ppm and 8.77 ppm as two singlets, while **13** has symmetric two protons at pyrimidine ring which appears at 8.58 ppm as one singlet of two protons.

The synthesized products of **5**, **10**, and **11** were evaluated by ALK inhibition assay and cell proliferation assay against H3122 cell line which was implicated with ALK fusion gene of EML4-ALK. The results are summarized in Table 1. All compounds synthesized showed moderate to good ALK inhibitory activities and also showed anti-proliferative activities against H3122 cell line. Generally, 5-trifluoromethylpyrimidines (**10**, **11**) showed better activities than 5-fluoropyrimidines (**5**) and non-substituted piperazine derivatives of 5-trifluoromethyl-pyrimidines (R=H, **10a-f**) showed better activities than acetyl piperazine derivatives (R=acetyl, **11a-f**). In connection with methoxyphenyl substituents at 2-position of pyrimidines, 2-methoxyphenyl derivatives (**5a**, **10a**, **11a**) and 2,3,4-trimethoxyphenyl derivatives (**5f**, **10f**, **11f**) showed good results in enzyme and cell-based assays. 2-Methoxy group is thought to be related to the increase of ALK inhibitory activity and 5-methoxy group with 2- or 3-methoxy group hinders the activities (**5c**, **5d**, **5e**, **10d**, **10e**, **11d**, **11e**). The standard compound, crizotinib exhibited IC₅₀ value of 0.010 μM in ALK enzyme assay and IC₅₀ value of 0.092 μM in cell-based assay of our own and **10f** showed 2.5-fold better activity in enzyme and cell-based assays than crizotinib. **10f** also showed good inhibitory activity against ALK L1196M enzyme, the important point mutation of

Table 1. Results of ALK inhibition assay and cell proliferation assay (H3122 cell line)

Compd #	X	R	Ar	ALK IC ₅₀ (μM)	H3122 IC ₅₀ (μM)
crizotinib				0.010 ^a	0.092 ^a
5a	F	CH ₃ CO	2-methoxyphenyl	0.055	2.7
5b	F	CH ₃ CO	3-methoxyphenyl	0.051	0.63
5c	F	CH ₃ CO	2,5-dimethoxyphenyl	0.70	>10
5d	F	CH ₃ CO	3,5-dimethoxyphenyl	0.10	5.6
5e	F	CH ₃ CO	3,4,5-trimethoxyphenyl	0.32	6.9
5f	Cl	CH ₃ CO	2,3,4-trimethoxyphenyl	0.054	0.38
10a	CF ₃	H	2-methoxyphenyl	0.015	0.14
10b	CF ₃	H	3-methoxyphenyl	0.025	0.76
10c	CF ₃	H	4-methoxyphenyl	0.017	0.80
10d	CF ₃	H	2,5-dimethoxyphenyl	0.081	2.3
10e	CF ₃	H	3,4,5-trimethoxyphenyl	0.15	1.1
10f	CF ₃	H	2,3,4-trimethoxyphenyl	0.004	0.034
11a	CF ₃	CH ₃ CO	2-methoxyphenyl	0.032	0.51
11b	CF ₃	CH ₃ CO	3-methoxyphenyl	0.21	5.6
11c	CF ₃	CH ₃ CO	4-methoxyphenyl	0.10	1.9
11d	CF ₃	CH ₃ CO	2,5-dimethoxyphenyl	0.26	7.2
11e	CF ₃	CH ₃ CO	3,4,5-trimethoxyphenyl	0.23	8.3
11f	CF ₃	CH ₃ CO	2,3,4-trimethoxyphenyl	0.025	0.47

^aThe IC₅₀ values were estimated at KRICT.

crizotinib-resistant ALK (IC₅₀ = 0.094 μM, IC₅₀ of crizotinib = 0.22 mM).

Experimental

Synthesis of 3a and 3b.

3a: A mixture of 4-(*N*-acetyl piperazine-1-yl)-2-methoxy-

aniline **2** (0.996 g, 4.0 mmol), 2,4-dichloro-5-fluoropyrimidine **1** (0.862 g, 5.2 mmol) and K_2CO_3 (0.718 g, 5.2 mmol) in DMF (6 mL) was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was poured into cold water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (DCM/*i*-PrOH, 10/1) to give **3** (1.033 g) in 68% yield. 1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J = 8.8 Hz, 1H), 8.00 (s, 1H), 7.52 (s, 1H), 6.62-6.47 (m, 2H), 3.92 (s, 3H), 3.79 (dd, J = 4.6, 9.3 Hz, 2H), 3.64 (dd, J = 4.4, 8.8 Hz, 2H), 3.21-3.12 (m, 4H), 2.15 (s, 3H).

3b: 94% yield; 1H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, J = 8.7 Hz, 1H), 8.13 (s, 1H), 7.88 (s, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.54 (s, 1H), 3.93 (s, 3H), 3.79 (t, J = 4.7 Hz, 2H), 3.64 (t, J = 4.7 Hz, 2H), 3.21-3.11 (m, 4H), 2.15 (s, 3H).

Synthesis of 5a-5f.

5a: A mixture of **3** (0.100 g, 0.26 mmol), 2-methoxyaniline (0.029 mL, 0.26 mmol) in a solution of 0.08 M HCl in ethoxyethanol (2.9 mL) was stirred at 110 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then the concentrate was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude mixture was purified by flash column chromatography on silica gel (DCM/*i*-PrOH, 10/1) to give **5a** (0.090 g) in 74% yield. 1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J = 9.1 Hz, 1H), 8.10-7.92 (m, 1H), 7.53-7.45 (m, 1H), 7.29 (s, 1H), 7.00-6.84 (m, 2H), 6.56 (s, 2H), 3.90 (d, J = 4.9 Hz, 6H), 3.79 (d, J = 4.53 Hz, 2H), 3.64 (d, J = 4.4 Hz, 2H), 3.20-3.10 (m, 4H), 2.15 (s, 3H); LCMS (*m/e*) 467.14 ($M+1$) $^+$.

5b: 80% yield; 1H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.29 (s, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.64-6.52 (m, 3H), 3.91 (s, 3H), 3.84-3.73 (m, 5H), 3.68-3.60 (m, 2H), 3.20-3.08 (m, 4H), 3.15 (s, 3H); LCMS (*m/e*) 467.14 ($M+1$) $^+$.

5c: 78% yield; 1H NMR ($CDCl_3$, 300 MHz) δ 8.34 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.24 (s, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.71-6.54 (m, 2H), 6.50-6.41 (m, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.82-3.77 (m, 2H), 3.72 (s, 3H), 3.69-3.62 (m, 2H), 3.21-3.11 (m, 4H), 2.16 (s, 3H); LCMS (*m/e*) 497.02 ($M+1$) $^+$.

5d: 72% yield; 1H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.05 (s, 1H), 6.79 (s, 2H), 6.57-6.50 (m, 3H), 6.16 (s, 1H), 3.90 (s, 3H), 3.82-3.71 (m, 8H), 3.68-3.60 (m, 2H), 3.20-3.08 (m, 4H), 2.15 (s, 3H); LCMS (*m/e*) 497.08 ($M+1$) $^+$.

5e: 70% yield; 1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 3.2 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 6.81 (s, 2H), 6.53 (d, J = 2.1 Hz, 1H), 6.46 (dd, J = 2.1, 8.8 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.82-3.73 (m, 8H), 3.58-3.16 (m, 2H), 3.15-3.06 (m, 4H), 2.15 (s, 3H); LCMS (*m/e*) 527.04 ($M+1$) $^+$.

5f: 75% yield; 1H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, J =

8.6 Hz, 1H), 8.02 (s, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.56 (s, 1H), 6.62-6.52 (m, 2H), 3.92 (d, J = 2.8 Hz, 6H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82-3.79 (m, 2H), 3.66-3.63 (m, 2H), 3.19-3.12 (m, 4H), 2.15 (s, 3H); LCMS (*m/e*) 543.05 ($M+H$) $^+$.

Synthesis of 8 and 9. To a solution of 4-(*N*-Boc-piperazine-1-yl)-2-methoxyaniline **7** (7.10 g, 23.0 mmol) and *N,N*-diisopropylethylamine (4.80 mL, 27.6 mmol) in 2-propanol (46 mL) was added 2,4-dichloro-5-(trifluoromethyl)pyrimidine **6** (3.10 mL, 23.0 mmol). The solution was stirred at room temperature overnight and concentrated under reduced pressure. The concentrate was extracted with EtOAc and washed twice with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (*n*-Hexane/EtOAc, 5/1) to give **8** (5.45 g, 48%) and **9** (3.37 g, 30%). **8**: 1H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H), 8.22 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 6.57 (d, J = 8.8 Hz, 1H), 6.53 (s, 1H), 3.90 (s, 3H), 3.59 (s, 4H), 3.13 (s, 4H), 1.49 (s, 9H); **9**: 1H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 3.88 (s, 3H), 3.59 (s, 4H), 3.11 (s, 4H), 1.48 (s, 9H).

Synthesis of 10a-10f. The same procedure was applied as the synthesis of **5a**.

10a: 69% yield; 1H NMR (CD_3OD , 300 MHz) δ 8.27 (s, 2H), 8.05 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.32 (s, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 7.2 Hz, 2H), 6.54 (d, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.20-3.17 (m, 4H), 3.11-3.08 (m, 4H); LCMS (*m/e*) 475.19 ($M+1$) $^+$.

10b: 62% yield; 1H NMR (CD_3OD , 300 MHz) δ 8.27 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.19 (t, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.54-6.49 (m, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 3.19-3.16 (m, 4H), 3.12-3.09 (m, 4H); LCMS (*m/e*) 475.19 ($M+1$) $^+$.

10c: 68% yield; 1H NMR (CD_3OD , 300 MHz) δ 8.23 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 3H), 7.03 (s, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.53 (s, 1H), 6.45 (d, J = 8.7 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.16-3.13 (m, 4H), 3.08-3.05 (m, 4H); LCMS (*m/e*) 475.26 ($M+1$) $^+$.

10d: 71% yield; 1H NMR (CD_3OD , 300 MHz) δ 8.29 (s, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.04 (s, 1H), 7.70 (s, 1H), 7.39 (s, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.59-6.48 (m, 4H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 3.21-3.18 (m, 4H), 3.12-3.09 (m, 4H); LCMS (*m/e*) 505.14 ($M+1$) $^+$.

10e: 75% yield; 1H NMR (CD_3OD , 300 MHz) δ 8.27 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.29 (s, 1H), 6.79 (s, 2H), 6.52 (s, 1H), 6.44 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.74 (s, 6H), 3.13-3.11 (m, 4H), 3.08-3.06 (m, 4H); LCMS (*m/e*) 535.29 ($M+1$) $^+$.

10f: 75% yield; 1H NMR (CD_3OD , 300 MHz) δ 8.26 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.47 (s, 1H), 7.35 (s, 1H), 6.57-6.51 (m, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.19-3.17 (m, 4H), 3.11-3.09 (m, 4H); LCMS (*m/e*) 535.29 ($M+1$) $^+$.

Synthesis of 11a-11f.

11a: To a solution of **10a** (0.023 g, 0.049 mmol) in CH_2Cl_2 (1 mL) was added triethylamine (10 mL, 0.070 mmol) and acetic anhydride (7 mL, 0.074 mmol) at 0 °C. The reaction

mixture was stirred overnight at room temperature. The reaction mixture was dissolved in EtOAc, and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel (DCM/MeOH, 10/1) to give **11a** (0.013 g) in 53% yield. ¹H NMR (CD₃OD, 300 MHz) δ 8.28 (s, 2H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 1H), 7.36 (s, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.90-6.83 (m, 2H), 6.54 (d, *J* = 7.2 Hz, 2H), 3.88 (s, 6H), 3.81 (t, *J* = 4.9 Hz, 2H), 3.66 (t, *J* = 4.9 Hz, 2H), 3.20-3.14 (m, 4H), 2.16 (s, 3H); LCMS (*m/e*) 517.28 (M+1)⁺.

11b: 52% yield; ¹H NMR (CD₃OD, 300 MHz) δ 8.27 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.45 (s, 1H), 7.29 (s, 1H), 7.20 (t, *J* = 8.2 Hz, 2H), 7.05 (t, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.54-6.48 (m, 2H), 3.89 (s, 3H), 3.80 (t, *J* = 4.9 Hz, 2H), 3.73 (s, 3H), 3.65 (t, *J* = 4.9 Hz, 2H), 3.16-3.12 (m, 4H), 2.16 (s, 3H); LCMS (*m/e*) 517.21 (M+1)⁺.

11c: 60% yield; ¹H NMR (CD₃OD, 300 MHz) δ 8.24 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.46 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.07 (s, 1H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.53 (s, 1H), 6.44 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.79 (t, *J* = 4.9 Hz, 2H), 3.64 (t, *J* = 4.9 Hz, 2H), 3.17-3.11 (m, 4H), 2.15 (s, 3H); LCMS (*m/e*) 517.21 (M+1)⁺.

11d: 50% yield; ¹H NMR (300 MHz, CD₃OD) δ 8.29 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.03 (s, 1H), 7.72 (s, 1H), 7.41 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.59-6.49 (m, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82-3.78 (m, 2H), 3.64 (s, 5H), 3.19-3.13 (m, 4H), 2.16 (s, 3H); LCMS (*m/e*) 547.24 (M+1)⁺.

11e: 60% yield; ¹H NMR (CD₃OD, 300 MHz) δ 8.27 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 6.78 (s, 2H), 6.51 (s, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.79-3.76 (m, 2H), 3.74 (s, 6H), 3.64-3.61 (m, 2H), 3.14-3.09 (m, 4H), 2.15 (s, 3H); LCMS (*m/e*) 577.19 (M+1)⁺.

11f: 54% yield; ¹H NMR (CD₃OD, 300 MHz) δ 8.27 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.50 (s, 1H), 7.40 (s, 1H), 6.58-6.50 (m, 4H), 3.93 (s, 3H), 3.89 (s, 6H), 3.86 (s, 3H), 3.83-3.79 (m, 2H), 3.67-3.64 (m, 2H), 3.18-3.13 (m, 4H), 2.16 (s, 3H); LCMS (*m/e*) 577.26 (M+1)⁺.

The reductive dechlorination of **8** and **9**.

12: To a solution of **8** (0.030 g, 0.062 mmol) in MeOH (1 mL) (through which N₂ had been passed for 5 min), 10% Pd/C catalyst and K₂CO₃ (10% Pd/C:K₂CO₃ = 2:1) was added. The reaction mixture was stirred under an H₂ atmosphere for 30 min at room temperature. The catalyst was removed by filtration through a pad of Celite and the solvent was removed under reduced pressure to give **12** (0.0205 g) in 73% yield. ¹H NMR (CDCl₃, 300 MHz) δ (s, 1H), 8.51 (s, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.54 (s, 1H), 3.89 (s, 3H), 3.59 (t, *J* = 4.2 Hz, 4H), 3.12 (t, *J* = 4.2 Hz, 4H), 1.48 (s, 9H).

13: 79% yield; ¹H NMR (CDCl₃, 300 MHz) δ (s, 2H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.78 (s, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.55 (s, 1H), 3.89 (s, 3H), 3.59 (s, 4H), 3.12 (s, 4H), 1.49 (s, 9H).

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