Articles

Synthesis of Thia(oxa)zolopyridines and Their Inhibitory Activities for β-Amyloid Fibrillization

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A series of thiazolo[5,4-*b*]pydine and oxazolo[5,4-*b*]pyridine derivatives **1a-o** were designed. These fifteen compounds were evaluated by Aβ42 fibril formation inhibitory assay using thioflavin T as a dye. Thiazolo[5,4-*b*]pyridines **1a-g** showed potent inhibitory activities for Aβ42 fibrillization at IC_{50} of 0.23-4.5 μM. Among them, compounds **1b** and **1k** having methoxy group at C-5 exhibited excellent activities (IC_{50} = 0.23 and 0.50 μM, respectively) than that of Curcumin (IC_{50} = 0.80 μM).

Key Words : Alzheimer's disease, β-Amyloid fibrillization, Thia(oxa)zolopyridines, Binding affinity

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common cause of dementia among elderly people.[1] Fibrillar amyloid-β peptide (Aβ), a pathological hallmark of AD,[2-4] is one of the main components of senile plaques. Formation and accumulation of aggregates of Aβ peptides in the brain are critical factors in the onset of AD.[5,6] Two major Aβ peptides Aβ40 and Aβ42 of different lengths have been derived from amyloid precursor protein (APP).[7,8] Fibrillization of Aβ42 occurs via oligomers and protofibrils more readily than relatively soluble Aβ40.[9,10]

Preventing and reversal of Aβ fibril formation in the brain are currently being targeted as a potential therapeutic approach to AD.[11-13] Recently, several series of inhibitors such as *E,E*-1-iodo-2,5-bis-(3-hydroxycarbonyl-4-methoxy)-styrylbenzene (IMSB),[14,15] (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Curcumin),[16,17] 4-*N*-methylamino-4'-hydroxystilbene (SB-13),[18] and benzofuran analogues[19] have been described, and these compounds were found to inhibit effectively Aβ fibril formation as determined by thioflavin T (ThT) assay. In addition, *N*-methyl-[^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole ([^{11}C]PIB)[20,21] exhibited high affinity for Aβ, good brain entry and clearance.

In an effort to develop a treatment for AD, the structural modification by the introduction of thia(oxa)zolopyridine with an additional binding site instead of benzothiazole nucleus of PIB was designed as shown in Figure 1. We report here the synthesis and evaluation of a series of thia(oxa)zolo[5,4-*b*]pyridine derivatives **1a-o** with potent inhibitory activities for Aβ fibrillization.

Results and Discussion

Chemistry. Thiazolo[5,4-*b*]pyridines **1a-g** and oxazolo-[5,4-*b*]pyridines **1l-o** with *p-N,N*-dimethylaminophenyl group were prepared by the sequence outlined in Scheme 1.

Reduction of nitro group of 3-nitropyridines **2a**, **b** by tin chloride[22] gave the amino compounds **3a**, **b** and subsequent amidation of **3** (**3c-g**: commercially available) with 4-dimethylaminobenzoyl chloride in pyridine afforded the corresponding benzamides **4a-f**, respectively. Conversion of carbonyl group of **4a-f** to thiocarbonyl group with Lawesson's reagent, followed by ring-closure provided the desired thiazolo[5,4-*b*]pyridines **1a-g**.[23] Treatment of **4** with phosphorus pentoxide (for **1l**, **m**) or polyphosphoric acid (for **1n**, **o**) resulted in the corresponding oxazolo[5,4-*b*]pyridines **1l-o**, respectively.[24] Hydroxyl compound **1c** was obtained from methoxy compound **1b** by demethylation using boron tribromide.[25]

The synthesis of thiazolo[5,4-*b*]pyridines **1h-k** with *p*-

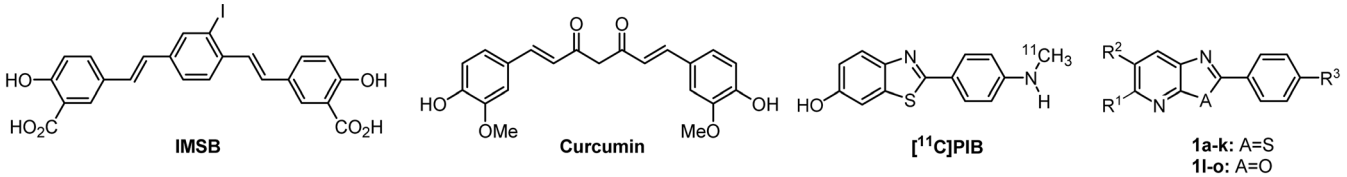
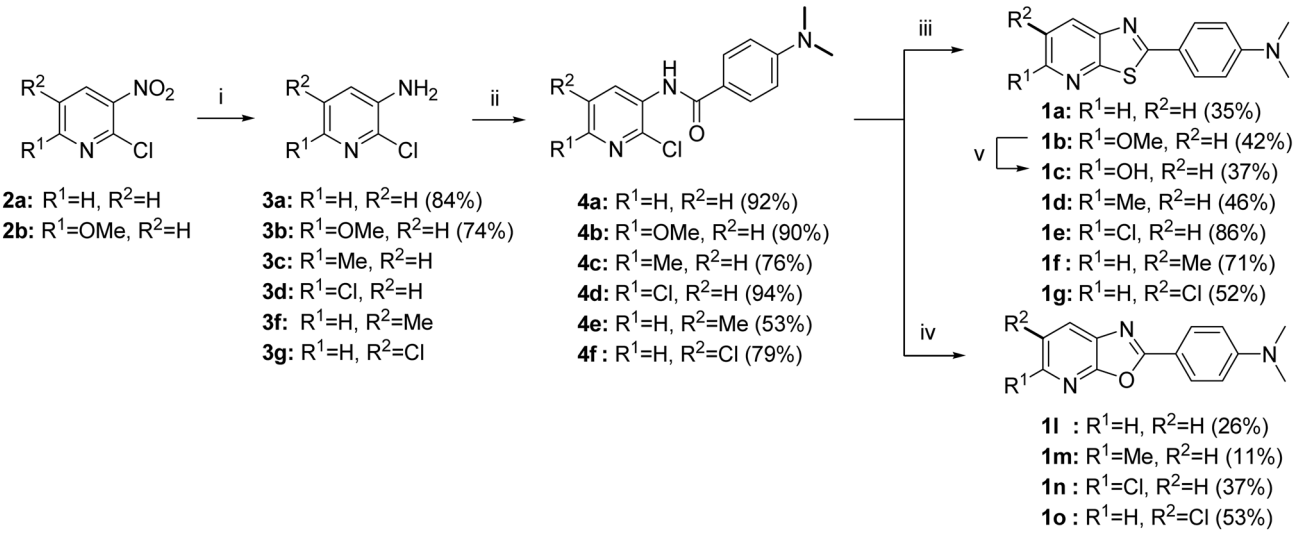
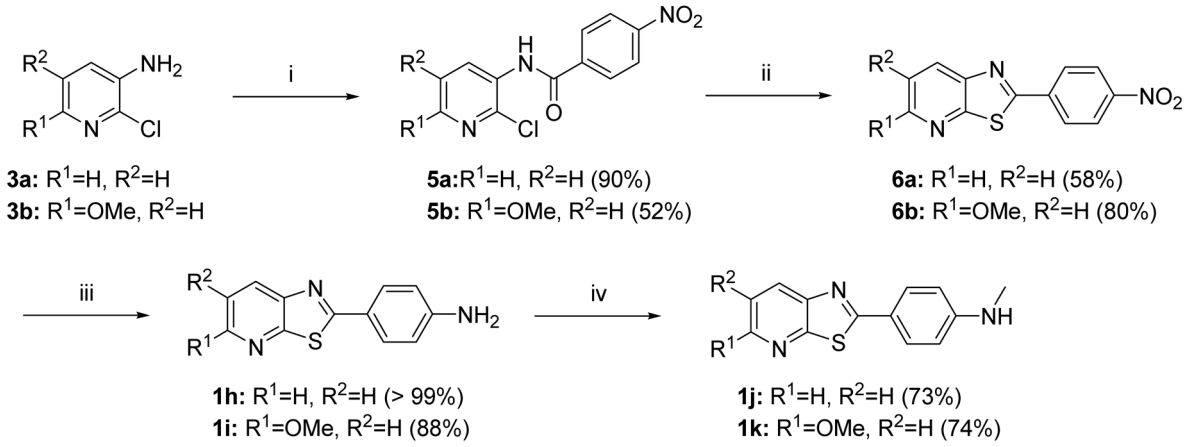


Figure 1. Structures of IMSB, Curcumin, [^{11}C]PIB, and Thia(Oxa)zolopyridines.



Scheme 1. *Reagents and reaction conditions:* (i) $SnCl_2$, EtOH, reflux, 30 min-2 h; (ii) 4-dimethylaminobenzoyl chloride, pyridine, rt, 18 h; (iii) Lawesson's reagent, chlorobenzene, reflux, 3 h; (iv) P_2O_5, hexamethyldisiloxane, 1,2-dichlorobenzene, 140 °C, 2d (for **1l**, **m**) or polyphosphoric acid, dichloromethane, 140 °C, 1d (for **1n**, **o**); (v) BBr_3, dichloromethane, reflux, 12 h.



Scheme 2. *Reagents and reaction conditions:* (i) 4-nitrobenzoyl chloride, pyridine, rt, 18 h; (ii) Lawesson's Reagent, chlorobenzene, reflux, 3 h; (iii) $SnCl_2$, EtOH, reflux, 6-18 h; (iv) $(CH_2O)n$, NaOMe, MeOH, $NaBH_4$, reflux, 5 h.

aminophenyl or *p*-*N*-methylaminophenyl group was outlined in Scheme 2.

Amidation of amino compounds **3a**, **b** and ring-closure of the resulting amides **5a**, **b** were carried out by using procedures analogous to those described above to provide **1a**-**g**. Reduction of nitro group of **6a**, **b** by tin chloride led to the amino compounds **1h**, **i**, which were methylated with paraformaldehyde and sodium borohydride in the presence of sodium methoxide to yield the terminal secondary amines **1j**, **k**.[26]

Biological evaluation. Table 1 shows the *in vitro* inhibitory activities (IC_{50} values) of thia(oxa)zolo[5,4-*b*]pyridines **1a-o** for Aβ42 fibril formation together with those of Curcumin and IMSB as reference compounds.

All the synthesized compounds were evaluated by thioflavin T (ThT) assay[27] as shown in Table 1, twelve compounds showed very good inhibitory activities with IC_{50} of 0.23-4.5 μM. As a whole, thiazolo[5,4-*b*]pyridines **1a-k** displayed better potency for Aβ42 fibril formation than oxazolo[5,4-*b*]pyridines **1l-o**. Especially, compounds **1b** and **1k** with methoxy group at C-5 exhibited excellent inhibitory activities (IC_{50} = 0.23 and 0.50 μM, respectively) compared to Curcumin (IC_{50} = 0.80 μM). Changing methoxy group of **1b** to hydroxyl group of **1c** markedly decreased the activity. In the structure-activity relationship, positional and electronic effects according to R^1 and R^2 substituents did not make any significant difference of inhibitory activity. The variation of amine substituents R^3 did not show a meaningful trend.

In conclusion, a series of thiazolo[5,4-*b*]pyridines based on the structural modification of PIB showed potent inhibitory activities for β-amyloid fibrillization. In particular, compounds **1b** and **1k** exhibited superior inhibitory activities to Curcumin. This preliminary result suggests that these compounds possess a possibility as a treatment for AD.

Table 1. Inhibitory activities of thia(oxa)zolopyridines **1a-o** for β-amyloid fibrillization

Compds	A	R_1	R_2	R_3	IC_{50} (μM)[a]
1a	S	H	H	NMe_2	2.7
1b	S	MeO	H	NMe_2	0.23
1c	S	HO	H	NMe_2	2.8
1d	S	Me	H	NMe_2	2.6
1e	S	Cl	H	NMe_2	1.1
1f	S	H	Me	NMe_2	2.6
1g	S	H	Cl	NMe_2	4.3
1h	S	H	H	NH_2	1.5
1i	S	MeO	H	NH_2	4.5
1j	S	H	H	NHMe	1.7
1k	S	MeO	H	NHMe	0.50
1l	O	H	H	NMe_2	16
1m	O	Me	H	NMe_2	3.5
1n	O	Cl	H	NMe_2	11
1o	O	H	Cl	NMe_2	15
Curcumin					0.80
IMSB					8.00

[a]ThT assay. IC_{50} was calculated from non-linear redression by *Graphpad Prism* soft-ware.

Experimental

Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR system spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using tetramethylsilane as an internal standard. LC-Mass spectra were determined on a Waters Quattro Micro system. Column chromatography was carried out using silica gel (230-400 mesh). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade.

General procedure for the synthesis of 2-chloropyridin-3-ylamines 3a,b. To a solution of the appropriate 3-nitropyridine compound **2** (2.0 mmol) in ethanol (15 mL) was added tin chloride (10.0 mmol), and the reaction mixture was refluxed for 30 min-2 h. When the reaction was completed, the reaction mixture was treated with 10% $NaHCO_3$. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the compound **3**.

2-Chloropyridin-3-ylamine (3a). Yield 84%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 1.9, 4.3 Hz), 7.10 (dd, 1H, J = 4.3, 7.9 Hz), 7.05 (dd, 1H, J = 1.9, 7.9 Hz), 4.11 (br s, 2H).

6-Methoxy-2-chloropyridin-3-ylamine (3b). Yield 74%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 1H, J = 8.5 Hz), 6.58 (d, 1H, J = 8.5 Hz), 3.89 (s, 3H), 3.69 (br s, 2H).

General procedure for the synthesis of *N*-(2-chloropyridin-3-yl)-4-dimethylaminobenzamides 4a-f. To a solution of the appropriate 3-aminopyridine compound **3** (10.0 mmol) in pyridine (5 mL) was added 4-dimethylaminobenzoyl chloride (10.0 mmol) in pyridine (5 mL), and the reaction mixture was stirred at room temperature for 18 h. When the reaction was completed, the reaction mixture was treated with water. The resulting precipitate was collected by filtration to give the compound **4**.

***N*-(2-Chloropyridin-3-yl)-4-dimethylaminobenzamide (4a).** Yield 92%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (dd, 1H, J = 1.7, 8.2 Hz), 8.34 (br s, 1H), 8.11 (dd, 1H, J = 1.7, 4.7 Hz), 7.82 (d, 2H, J = 9.0 Hz), 7.30 (dd, 1H, J = 4.7, 8.2 Hz), 6.73 (d, 2H, J = 9.0 Hz), 3.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 153.1, 143.1, 139.8, 132.7, 128.8, 128.5, 123.5, 120.0, 111.2, 40.1; MS *m/z* 276 $(M+H)^+$.

6-Methoxy-*N*-(2-chloropyridin-3-yl)-4-dimethylaminobenzamide (4b). Yield 90%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, 1H, J = 9.0 Hz), 8.05 (br s, 1H), 7.82 (d, 2H, J = 9.0 Hz), 6.75 (m, 3H), 3.94 (s, 3H), 3.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 159.0, 152.8, 136.5, 133.4, 128.7, 126.1, 120.8, 111.4, 109.8, 54.1, 40.2.

6-Methyl-*N*-(2-chloropyridin-3-yl)-4-dimethylaminobenzamide (4c). Yield 76%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, 1H, J = 8.2 Hz), 8.25 (br s, 1H), 7.82 (d, 2H, J = 9.0 Hz), 7.15 (d, 1H. J = 8.2 Hz), 6.74 (d, 2H, J = 9.0 Hz), 3.08 (s, 6H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 153.0, 152.7, 138.8, 130.0, 129.3, 128.8, 122.8, 120.3, 111.2, 40.1, 23.4; MS *m/z* 290 $(M+H)^+$.

6-Chloro-*N*-(2-chloropyridin-3-yl)-4-dimethylaminobenzamide (4d). Yield 94%; ivory solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, 1H, J = 8.6 Hz), 8.26 (br s, 1H), 7.80 (d, 2H, J = 8.9 Hz), 7.31 (d, 1H, J = 8.6 Hz), 6.73 (d, 2H, J = 8.9 Hz), 3.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 153.2, 142.6, 138.0, 131.9, 130.9, 128.9, 123.8, 119.6, 111.2, 40.1; MS *m/z* 310 $(M+H)^+$.

5-Methyl-*N*-(2-chloropyridin-3-yl)-4-dimethylaminobenzamide (4e). Yield 53%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, 1H, J = 1.9 Hz), 8.29 (br s, 1H), 7.93 (d, 1H, J = 1.9 Hz), 7.82 (d, 2H, J = 9.0 Hz), 6.74 (d, 2H, J = 9.0 Hz), 3.09 (s, 6H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 153.0, 143.4, 137.1, 133.7, 131.9, 129.1, 128.8, 120.1, 111.2, 40.1, 18.1; MS *m/z* 290 $(M+H)^+$.

5-Chloro-*N*-(2-chloropyridin-3-yl)-4-dimethylaminobenzamide (4f). Yield 79%; ivory solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (d, 1H, J = 2.4 Hz), 8.31 (br s, 1H), 8.06 (d, 1H, J = 2.4 Hz), 7.80 (d, 2H, J = 9.0 Hz), 6.73 (d, 2H, J = 9.0 Hz), 3.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 153.2, 141.2, 137.3, 133.1, 131.6, 128.9, 127.8, 119.4, 111.2, 40.0; MS *m/z* 310 $(M+H)^+$.

General procedure for the synthesis of 2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridines 1a, b, d-g. To a solution of the appropriate benzamide compound **4** (0.5 mmol) in chlorobenzene (3-5 mL) was added Lawesson's reagent (0.3 mmol), and the reaction mixture was refluxed for 3 h. After cooling, the reaction mixture was neutralized with 1 N sodium hydroxide and treated with dichloromethane and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue

was purified by silica gel column chromatography to give the title compound.

2-(4-Dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1a). Yield 35%; brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, 1H, J = 1.5, 4.7 Hz), 8.18 (dd, 1H, J = 1.5, 8.2 Hz), 7.98 (d, 2H, J = 9.0 Hz), 7.38 (dd, 1H, J = 4.7, 8.2 Hz), 6.77 (d, 2H, J = 9.0 Hz), 3.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 158.4, 152.5, 147.7, 145.7, 129.0, 128.6, 121.1, 111.6, 40.1.

5-Methoxy-2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1b). Yield 42%; yellow solid; mp 202.0-203.0 °C; IR (KBr): 3431, 1718, 1495, 1360, 1287, 1262, 1178, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, 1H, J = 2.1 Hz), 8.12 (d, 1H, J = 2.1 Hz), 7.94 (d, 2H, J = 8.9 Hz), 6.74 (d, 2H, J = 8.9 Hz), 3.95 (s, 3H), 3.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 156.0, 152.7, 148.2, 144.4, 129.7, 129.2, 128.0, 120.8, 111.8, 40.2; MS *m/z* 286 $(M+H)^+$.

5-Methyl-2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1d). Yield 46%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 8.3 Hz), 7.96 (d, 2H, J = 9.0 Hz), 7.23 (d, 1H, J = 8.3 Hz), 6.76 (d, 2H, J = 9.0 Hz), 3.08 (s, 6H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 157.7, 155.1, 152.4, 145.6, 128.8, 121.3, 121.2, 111.6, 40.2, 24.3; MS *m/z* 270 $(M+H)^+$.

5-Chloro-2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1e). Yield 86%; yellow solid; mp 243.0-244.0 °C; IR (KBr): 3436, 1604, 1471, 1426, 1372, 1189, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1H, J = 8.5 Hz), 7.93 (d, 2H, J = 8.9 Hz), 7.36 (d, 1H, J = 8.5 Hz), 6.75 (d, 2H, J = 8.9 Hz), 3.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 157.4, 152.5, 146.6(2C), 130.7, 129.0, 121.8, 120.8, 40.2; MS *m/z* 290 $(M+H)^+$.

6-Methyl-2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1f). Yield 71%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.96 (s, 1H), 7.95 (d, 2H, J = 8.6 Hz), 6.75 (d, 2H, J = 8.6 Hz), 3.09 (s, 6H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 154.8, 152.5, 147.7, 146.4, 131.2, 129.2, 129.0, 121.1, 111.7, 40.2, 18.5; MS *m/z* 270 $(M+H)^+$.

6-Chloro-2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1g). Yield 52%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, 1H, J = 2.1 Hz), 8.12 (d, 1H, J = 2.1 Hz), 7.94 (d, 2H, J = 8.9 Hz), 6.74 (d, 2H, J = 8.9 Hz), 3.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 156.0, 152.7, 148.2, 144.4, 129.7, 129.2, 128.0, 120.8, 111.8, 40.2; MS *m/z* 286 $(M+H)^+$.

5-Hydroxy-2-(4-dimethylaminophenyl)thiazolo[5,4-*b*]pyridine (1c). To a solution of **1b** (29 mg, 0.1 mmol) in dichloromethane (2 mL) was added tribromoborane (1 mL, 1 M BBr_3 in dichloromethane, 1.0 mmol) at 0 °C, and the reaction mixture was refluxed for 12 h. After cooling, the reaction mixture was neutralized with 1 N sodium hydroxide and treated with dichloromethane and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **1c** (10 mg, 37%): yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.41 (s, 1H), 8.06 (d, 1H, J = 8.8 Hz), 7.77 (d, 2H, J = 8.7 Hz), 7.23 (d, 1H, J = 8.8 Hz), 6.77 (d, 2H, J = 8.7 Hz), 3.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 156.2, 153.0, 148.3, 144.9, 130.3, 129.7, 128.4, 121.0, 111.9.

General procedure for the synthesis of 2-(4-dimethylaminophenyl)oxazolo[5,4-*b*]pyridines 1l-o. To a solution of diphosphorus pentoxide (439 mg, 1.5 mmol) and hexamethyldisiloxane (1.3 mL, 6.0 mmol) in 1,2-dichlorobenzene (3 mL) was added the appropriate benzamide compound **4** (0.5 mmol) at 140 °C, and the reaction mixture was stirred for 2 d. When the reaction was completed, the reaction mixture was treated with 10% $NaHCO_3$. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (for **1l**, **m**). Polyphosphoric acid (2.0 g) was added to the appropriate benzamide compound **4** (0.5 mmol) at 140 °C, and the reaction mixture was stirred for 1 d. When the reaction was completed, the reaction mixture was neutralized with 1 N NaOH. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound (for **1n**, **o**).

2-(4-Dimethylaminophenyl)oxazolo[5,4-*b*]pyridine (1l). Yield 26%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, 1H, J = 1.4, 5.0 Hz), 8.15 (d, 2H, J = 9.0 Hz), 7.96 (dd, 1H, J = 1.4, 7.8 Hz), 7.15 (dd, 1H, J = 5.0, 7.8 Hz), 6.79 (d, 2H, J = 9.0 Hz), 3.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 159.8, 152.6, 143.2, 134.4, 129.5, 126.9, 120.7, 113.8, 112.1, 40.4; MS *m/z* 240 $(M+H)^+$.

5-Methyl-2-(4-dimethylaminophenyl)oxazolo[5,4-*b*]pyridine (1m). Yield 11%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 2H, J = 9.0 Hz), 7.83 (d, 1H, J = 7.9 Hz), 7.13 (d, 1H, J = 7.9 Hz), 6.78 (d, 2H, J = 9.0 Hz), 3.11 (s, 6H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 159.5, 152.8, 152.7, 132.0, 129.2, 126.9, 120.1, 113.5, 111.6, 40.1, 24.1; MS *m/z* 254 $(M+H)^+$.

5-Chloro-2-(4-dimethylaminophenyl)oxazolo[5,4-*b*]pyridine (1n). Yield 37%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, J = 9.0 Hz), 7.89 (d, 1H, J = 8.1 Hz), 7.31 (d, 1H, J = 8.1 Hz), 6.81 (d, 2H, J = 9.0 Hz), 3.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 158.6, 152.8, 144.4, 133.6, 129.5, 128.7, 120.9, 113.1, 111.9, 40.3; MS *m/z* 274 $(M+H)^+$.

6-Chloro-2-(4-dimethylaminophenyl)oxazolo[5,4-*b*]pyridine (1o). Yield 53%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.00 (d, 2H, J = 9.0 Hz), 7.54 (s, 1H), 6.86 (d, 2H, J = 9.0 Hz), 3.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 158.4, 153.6, 141.5, 135.7, 129.7, 128.0, 127.1, 112.2, 111.8, 40.4; MS *m/z* 278 $(M+H)^+$.

General procedure for the synthesis of *N*-(2-chloropyridin-3-yl)-4-nitrobenzamides 5a, b. To a solution of the appropriate 3-aminopyridine compound **3** (10.0 mmol) in pyridine (25 mL) was added 4-nitrobenzoyl chloride (10.0 mmol) in pyridine (5 mL), and the reaction mixture was stirred at room temperature for 18 h. When the reaction was completed, the reaction mixture was treated with water. The resulting precipitate was collected by filtration to give the

compound **5**.

***N*-(2-Chloropyridin-3-yl)-4-nitrobenzamide (5a).** Yield 90%; ivory solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (dd, 1H, J = 1.7, 8.2 Hz), 8.44 (br s, 1H), 8.40 (d, 2H, J = 8.8 Hz), 8.21 (dd, 1H, J = 1.7, 4.7 Hz), 8.10 (d, 2H, J = 8.8 Hz), 7.36 (dd, 1H, J = 4.7, 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 150.2, 144.7, 140.4, 139.3, 131.5, 129.2, 128.4, 124.3, 123.6; MS *m/z* 228 $(M+H)^+$.

6-Methoxy-*N*-(2-chloropyridin-3-yl)-4-nitrobenzamide (5b). Yield 52%; ivory solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, 1H, J = 8.8 Hz), 8.38 (d, 2H, J = 8.7 Hz), 8.14 (br s, 1H), 8.09 (d, 2H, J = 8.7 Hz), 6.79 (d, 1H, J = 8.8 Hz), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 160.0, 150.0, 139.6, 137.4, 133.7, 128.3, 124.7, 110.1, 54.3; MS *m/z* 272 $(M+H)^+$.

General procedure for the synthesis of 2-(4-nitrophenyl)thiazolo[5,4-*b*]pyridines 6a, b. To a solution of the appropriate benzamide compound **5** (2.0 mmol) in chlorobenzene (12-15 mL) was added Lawesson's reagent (1.2 mmol), and the reaction mixture was refluxed for 3 h. After cooling, the reaction mixture was neutralized with 1 N sodium hydroxide and treated with dichloromethane and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the compound **6**.

2-(4-Nitrophenyl)thiazolo[5,4-*b*]pyridine (6a). Yield 58%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (dd, 1H, J = 1.5, 4.6 Hz), 8.37 (m, 3H), 8.30 (d, 2H, J = 8.9 Hz), 7.52 (dd, 1H, J = 4.6, 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 158.6, 149.4, 148.1, 147.2, 138.9, 130.9, 128.4, 124.4, 122.0; MS *m/z* 258 $(M+H)^+$.

5-Methoxy-2-(4-nitrophenyl)thiazolo[5,4-*b*]pyridine (6b). Yield 80%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 2H, J = 9.0 Hz), 8.20 (m, 3H), 6.93 (d, 1H, J = 8.8 Hz), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 161.2, 148.8, 142.8, 139.4, 133.2, 127.7, 124.4, 111.4, 54.3.

General procedure for the synthesis of 2-(4-aminophenyl)thiazolo[5,4-*b*]pyridines 1h, i. To a solution of the appropriate nitrophenyl compound **6** (1.0 mmol) in ethanol (10 mL) was added tin chloride (5.0 mmol), and the reaction mixture was refluxed for 6-18 h. When the reaction was completed, the reaction mixture was treated with 10% $NaHCO_3$. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound.

2-(4-Aminophenyl)thiazolo[5,4-*b*]pyridine (1h). Yield > 99%; yellow solid; mp 236.5-238.0 °C; IR (KBr): 3320, 3201, 1604, 1471, 1439, 1296, 1217, 1177 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, 1H, J = 1.3, 4.7 Hz), 8.18 (dd, 1H, J = 1.3, 8.2 Hz), 7.90 (d, 2H, J = 8.5 Hz), 7.38 (dd, 1H, J = 4.7, 8.2 Hz), 6.75 (d, 2H, J = 8.5 Hz), 4.11 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 158.3, 149.8, 147.5, 146.1, 129.3, 129.0, 123.7, 121.2, 114.8; MS *m/z* 228 $(M+H)^+$.

5-Methoxy-2-(4-aminophenyl)thiazolo[5,4-*b*]pyridine (1i). Yield 88%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.6 Hz), 6.82 (d, 1H, J = 8.8 Hz), 6.74 (d, 2H, J = 8.6 Hz), 4.40 (s, 3H), 4.12 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 161.9, 154.8, 149.1, 142.7, 131.9, 128.7, 124.2, 114.8, 109.8, 54.1.

General procedure for the synthesis of 2-(4-methylaminophenyl)thiazolo[5,4-*b*]pyridines 1j, k. To a solution of the appropriate aminophenyl compound **6** (0.2 mmol) and paraformaldehyde (0.3-0.8 mmol) in methanol (3 mL) was added 25 wt% NaOMe in methanol (0.6-0.8 mmol) at 0 °C. After being stirred at reflux for 2 h, sodium borohydride (0.6-0.8 mmol) was slowly added and the reaction mixture was further refluxed for 3 h. When the reaction was completed, the reaction mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the title compound.

2-(4-Methylaminophenyl)thiazolo[5,4-*b*]pyridine (1j). Yield 73%; yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, 1H, J = 1.4, 4.7 Hz), 8.17 (dd, 1H, J = 1.4, 8.2 Hz), 7.94 (d, 2H, J = 8.8 Hz), 7.37 (dd, 1H, J = 4.7, 8.2 Hz), 6.67 (d, 2H, J = 8.8 Hz), 4.21 (br s, 1H), 2.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 158.3, 152.0, 147.6, 145.9, 129.3, 128.7, 122.3, 121.2, 112.0, 30.3.

5-Methoxy-2-(4-methylaminophenyl)thiazolo[5,4-*b*]pyridine (1k). Yield 74%; yellow solid; mp 227.0-228.0 °C; IR (KBr): 3306, 1608, 1463, 1373, 1265, 1181 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H, J = 8.8 Hz), 7.86 (d, 2H, J = 8.6 Hz), 6.81 (d, 1H, J = 8.8 Hz), 6.65 (d, 2H, J = 8.6 Hz), 4.11 (br s, 1H), 4.01 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 161.8, 154.8, 151.4, 142.8, 131.7, 128.6, 122.8, 112.1, 109.7, 54.1, 30.3; MS *m/z* 272 $(M+H)^+$.

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