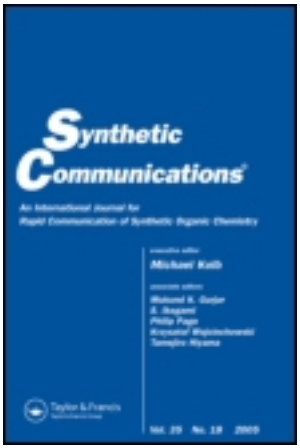

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Synthesis of Novel 1,4-Benzoxazine-2,3-Dicarboximides from Maleic Anhydride and Substituted Aromatic Amines

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Synthesis of Novel 1,4-Benzoxazine-2,3-Dicarboximides from Maleic Anhydride and Substituted Aromatic Amines

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Abstract: A series of novel 1,4-benzoxazine-2,3-dicarboximides starting from maleic anhydride and substituted aromatic amines were synthesized.

Keywords: 1,4-Benzoxazine-2,3-dicarboximide, maleic anhydride, synthesis

INTRODUCTION

Various kinds of 1,4-benzoxazine derivatives show interesting biological activities,[1–5] such as antifungal[6] and antimicrobial[7,8] properties. They are also found in herbicides[9] and dyes.[10] Moreover, a number of 1,4-benzoxazine derivatives are developed as antipyretic, analgesic, anti-inflammatory, and neuroprotective agents.[11–13] Consequently, many efforts have been devoted to the synthesis of them.[2–5,14]

The maleic anhydride is present in several natural products,[15] and it is an important intermediate in the chemical and pharmaceutical industries.[16,17] A variety of methods have been developed for the preparation of some biologically active compounds using maleic anhydride as one of the starting materials.[18,19]

Herein, we report a three-step procedure to synthesize a series of 1,4-benzoxazine-2,3-dicarboximides starting from maleic anhydride and

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substituted aromatic amines in moderate to good yield. Our attempt was to synthesize this novel kind of 1,4-benzoxazine-2,3-dicarboximides and provide more options for pharmaceutical uses.

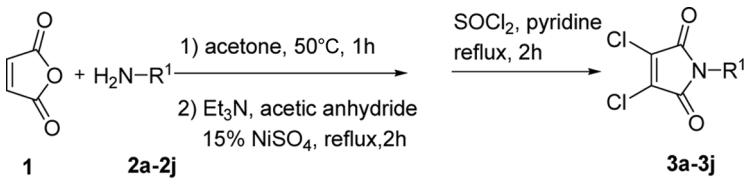
RESULTS AND DISCUSSION

N-Phenyldichloromaleimide derivatives **3** were synthesized according to an improved procedure based on reported methods[20,21] using commercially available maleic anhydride **1** and substituted aromatic amines **2** as the starting materials (Scheme 1). The results are summarized in Table 1.

The condensation reactions of **3** with 2-aminophenol derivatives **4** were studied under different conditions. Initially, reaction of **3a** with **4a** was carried out in methanol or dimethylformamide (DMF) in the presence of CH_3COONa or potassium hydride (KOH).[22–24] However, the reaction was very complex, and we could not isolate the expected product **5a**. After several trials, we found that reaction of **3a** with 2-aminophenol **4a** in ethanol afforded the desired compound **5a** in 71% yield after refluxing for 10 h. Use of dichloromethane as the solvent in the reaction gave **5a** in lower yield (Table 2).

To explore the scope of our method, a variety of *N*-phenyldichloromaleimide derivatives **3** were investigated to react with 2-aminophenol **4a**, 4-chloro-2-amino-phenol **4b**, and 4-*tert*-butyl-2-aminophenol **4c**, respectively, under the optimized reaction condition (Scheme 2).

Most of the *N*-phenyldichloromaleimide derivatives **3** can provide the corresponding products in moderate to good yields. However, reaction of **3** with 4-*tert*-butyl-2-aminophenol **4c** can lead to slightly higher yield than reaction with 2-aminophenol **4a** or 4-chloro-2-aminophenol **4b**. We deduced that the present of the electron-donating group, *tert*-butyl on the benzene ring, may increase the nucleophilicity of **4c**, which makes the attack of the electrophilic *N*-phenyldichloromaleimide **3** easier.



Scheme 1. **a**, R^1 = phenyl; **b**, R^1 = *p*-F-phenyl; **c**, R^1 = *p*-Cl-phenyl; **d**, R^1 = *p*-CH_3-phenyl; **e**, R^1 = *m*-CH_3-phenyl; **f**, R^1 = *p*-NO_2-phenyl; **g**, R^1 = *m*-NO_2-phenyl; **h**, R^1 = 3,4-dimethoxyphenyl; **i**, R^1 = naphthyl; and **j**, R^1 = benzyl.

Table 1. Synthesis of *N*-phenyldichloromaleimide derivatives **3**

Entry	Substituted aromatic amines **2**	Compound **3**	Yield (%)	MP (°C) (reported)	MP (°C) (found)
1	Aniline **2a**	**3a**	66	204–206[20]	205–206
2	*p*-Fluorobenzenamine **2b**	**3b**	86	161–163[21]	162–164
3	*p*-Chlorobenzenamine **2c**	**3c**	75	214–215[25]	213–215
4	*p*-Toluidine **2d**	**3d**	79	196–198[25]	198–199
5	*m*-Touidine **2e**	**3e**	75	—[a]	147–148
6	*p*-Nitrobenzenamine **2f**	**3f**	88	188–190[21]	193–195
7	*m*-Nitrobenzenamine **2g**	**3g**	86	—[a]	179–180
8	3,4-Dimethoxybenzenamine **2h**	**3h**	61	—[a]	165–167
9	1-Naphthylamine **2i**	**3i**	81	—[a]	199–201
10	Benzylamine **2j**	**3j**	59	109–110[25]	111–112

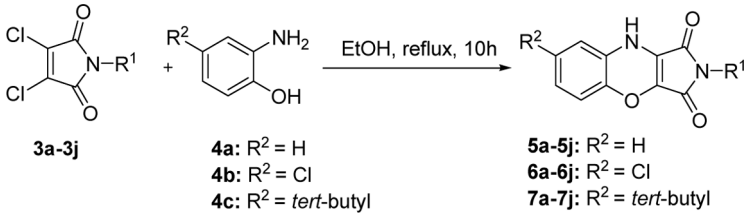
[a]No data available.

In summary, a series of novel 1,4-benzoxazine-2,3-dicarboximides, which may have potential antimicrobial activities, were synthesized starting from maleic anhydride and substituted aromatic amines in moderate

Table 2. Procedure optimization of the cyclization between *N*-phenyldichloromaleimide **3a** and 2-aminophenol **4a**

Entry	Solvent	Catalyst[a]	Temperature[b] (°C)	Time (h)	Yield (%)[c]
1	Methanol	CH_3COONa	60	3	13
2	Methanol	KOH	60	—[d]	—[d]
3	Dimethylformamide (DMF)	CH_3COONa	160	3	—[e]
4	Dimethylformamide (DMF)	KOH	160	—[d]	—[d]
5	Dichloromethane	CH_3COONa	60	3	19
6	Dichloromethane	—	60	2.5	32
7	Ethanol	CH_3COONa	60	2.5	36
8	Ethanol	—	90	2.5	61
9	Ethanol	—	r.t.	24	21
10	Ethanol	—	90	10	71

[a]0.2 eq of KOH or CH_3COONa was used as catalyst.
[b]Refers to temperature of oil baths.
[c]Refers to isolated yield.
[d]The reaction mixture turned to be dark in minutes after KOH was added to the reaction system.
[e]Complex mixtures were observed on TLC, and the desired product was not isolated.



Scheme 2. Synthesis of 1,4-benzoxazine-2,3-dicarboximide derivatives of **5–7**.

to good yield. To the best of our knowledge, this kind of 1,4-benzoxazine-2,3-dicarboximide derivative was synthesized for the first time.

EXPERIMENTAL

Melting points were recorded on a B-540 Buchi melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Bruker instrument at 400 MHz using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as an internal standard. IR spectra were recorded using KBr pellets on a Bruker Vector-22 FTIR spectrophotometer. Mass spectra (MS) and ESI (negative) were recorded on an Esquire-LC-00075 spectrometer. Other regents and solvents are commercially available and used without further purification unless otherwise noted.

Preparation of 3,4-Dichloro-1-phenyl-1*H*-pyrrole-2,5-dione (3a)

A solution of aniline **2a** (1.9 mL, 20 mmol) in 10 ml acetone was added to a suspension of maleic anhydride **1** (1.96 g, 20 mmol) in 10 ml acetone. After warming it in an oil bath at 55 °C for 1 h, Et_3N (2.5 mL), acetic anhydride (1 mL), and 15% $NiSO_4$ (0.2 mL) were added. After refluxing in 80 °C for another 2 h, the reaction mixture was poured into ice-cold water. The precipitated product was filtered, washed with ice-cold water, and dried under vacuum to give a yellow residue. The obtained residue was dissolved in 15 mL thionyl chloride, then 2 mL pyridine was added dropwise at less than 0 °C over 15 min. The reaction mixture was allowed to stir for additional 15 min at less than 0 °C and 30 min at ambient temperature. Then the reaction mixture was refluxed at 85 °C for 2 h. After removing the solvent under vacuum, the residue of the reaction mixture was reconstituted and diluted with ice-cold water. The resulting mixture was then neutralized (pH about 7.0) using sodium bicarbonate solution and extracted with dichloromethane (3×10 mL). The organic layers were combined, washed with water (2×5 mL), and dried over anhydrous sodium sulfate.

The solvent was removed to give the crude product and then purified by silica-gel column chromatography, eluting with petroleum/ethyl acetate (4:1 v/v) to afford compound **3a** (3.18 g, 66%) as a solid.

In the same manner, compounds **3b–j** were synthesized by reaction of the corresponding substituted aromatic amines **2b–j** with maleic anhydride **1**.

Preparation of 2-Phenyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (5a)

A solution of 3,4-dichloro-1-phenyl-1*H*-pyrrole-2,5-dione **3a** (240 mg, 1 mmol) and 2-aminophenol **4a** (109 mg, 1 mmol) in ethanol (5 mL) was refluxed in an oil bath at 85–95 °C for 10 h. After cooling to room temperature, the solvent was removed under vacuum to give the crude product and then purified by silica-gel column chromatography, eluting with petroleum/ethyl acetate/dichloromethane (8:2:1 v/v/v) to afford compound **5a** (196 mg, 71%) as yellow powder. Mp 201–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (t, 2H, $J = 8.0$ Hz), 7.43–7.37 (m, 3H), 7.28 (dd, 1H, $J = 8.0$ and 1.6 Hz), 6.99 (t, 1H, $J = 8.0$ Hz), 7.00 (t, 1H, $J = 8.0$ Hz), 6.92 (dd, 1H, $J = 8.0$ and 1.6 Hz), 5.45 (s, 1H). IR (KBr): ν (cm^{-1}) 3204, 3035, 1770, 1702, 1678, 1653, 1597, 1502, 1456, 1415, 1299, 1243, 1200. MS (ESI): $m/s = 277$ [M − 1]. Anal. calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.11; H, 3.59; N, 10.02.

In the same manner, compounds **5b–j** were synthesized by reaction of the corresponding *N*-phenyldichloromaleimide derivatives **3b–j** with 2-aminophenol **4a**.

Data

2-(4-Fluorophenyl)-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5b**)

Orange powder, yield 78%, mp 197–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.30 (m, 2H), 7.21–7.14 (m, 3H), 7.07–6.96 (m, 2H), 6.90 (d, 1H, $J = 8.0$ Hz), 6.81 (s, 1H). IR (KBr): ν (cm^{-1}) 3412, 3097, 1768, 1717, 1663, 1601, 1512, 1460, 1402, 1346, 1285, 1234. MS (ESI): $m/s = 295$ [M − 1]. Anal. calcd. for $C_{16}H_9FN_2O_3$: C, 64.87; H, 3.06; N, 9.46. Found: C, 64.79; H, 3.11; N, 9.51.

2-(4-Chlorophenyl)-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5c**)

Yellow powder, yield 70%, mp 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 2H, $J = 9.2$ Hz), 7.38 (d, 2H, $J = 9.2$ Hz), 7.25 (d, 2H,

$J = 7.6$ Hz), 7.16 (t, 1H, $J = 7.2$ Hz), 6.98 (t, 1H, $J = 7.2$ Hz), 6.91 (d, 1H, $J = 7.6$ Hz), 5.56 (s, 1H). IR (KBr): ν (cm^{-1}) 3330, 3112, 3060, 2800, 2385, 1779, 1712, 1646, 1593, 1528, 1496, 1400, 1347, 1280, 1245, 1218. MS (ESI): $m/s = 311$ [M − 1]. Anal. calcd. for $C_{16}H_9ClN_2O_3$: C, 61.45; H, 2.90; N, 8.96. Found: C, 61.34; H, 2.98; N, 8.92.

2-(4-Methylphenyl)-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5d**)

Orange yellow powder, yield 72%, mp 212–213°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (d, 2H, $J = 8.8$ Hz), 7.23 (d, 2H, $J = 8.8$ Hz), 7.10 (t, 2 H, $J = 8.0$ Hz), 6.88 (d, 1H, $J = 7.6$ Hz), 6.79 (t, 1H, $J = 7.6$ Hz), 5.58 (s, 1H), 2.39 (s, 3H). IR (KBr): ν (cm^{-1}) 3336, 3098, 2921, 1777, 1712, 1650, 1596, 1518, 1458, 1403, 1351, 1281, 1240, 1214. MS (ESI): $m/s = 291$ [M − l]. Anal. calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.78; H, 4.08; N, 9.49.

2-(3-Methylphenyl)-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5e**)

Yellow powder, yield 67%, mp 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, 1H, $J = 8.0$ Hz), 7.26–7.10 (m, 5H), 6.96 (t, 1H, $J = 7.6$ Hz), 6.89 (d, 1H, $J = 8.0$ Hz), 5.76 (s, 1H), 2.39 (s, 3H). IR (KBr): ν (cm^{-1}) 3342, 3048, 2955, 1770, 1727, 1668, 1600, 1522, 1492, 1460, 1396, 1344, 1291, 1244. MS (ESI): $m/s = 291$ [M − 1]. Anal. calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.76; H, 4.13; N, 9.49.

2-(4-Nitrophenyl)-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5f**)

Yellow powder, yield 71%, mp 205–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, 2H, $J = 9.2$ Hz), 7.77 (d, 2H, $J = 9.2$ Hz), 7.21–6.94 (m, 3H), 6.63 (d, 1H, $J = 9.2$ Hz), 5.63 (s, 1H). IR (KBr): ν (cm^{-1}) 3352, 3126, 3022, 1768, 1735, 1672, 1594, 1516, 1500, 1461, 1420, 1387, 1339, 1248, 1219. MS (ESI): $m/s = 322$ [M − 1]. Anal. calcd. for $C_{16}H_9N_3O_5$: C, 59.45; H, 2.81; N, 13.00. Found: C, 59.41; H, 2.74; N, 12.97.

2-(3-Nitrophenyl)-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5g**)

Yellow powder, yield 66%, mp 192–194°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.22 (d, 1H, $J = 8.0$ Hz), 7.87–7.83 (m, 1H), 7.60 (t, 1H,

$J = 8.4$ Hz), 7.21–7.17 (m, 2H), 7.00 (t, 1H, $J = 8.0$ Hz), 6.92 (d, 1H, $J = 8.8$ Hz), 5.54 (s, 1H). IR (KBr): ν (cm^{-1}) 3326, 3103, 3018, 1768, 1710, 1651, 1601, 1526, 1484, 1449, 1395, 1348, 1303, 1226. MS (ESI): $m/s = 322$ [M − 1]. Anal. calcd. for $C_{16}H_9N_3O_5$: C, 59.45; H, 2.81; N, 13.00. Found: C, 59.36; H, 2.78; N, 12.97.

2-(3,4-Dimethoxyphenyl)-pyrrolo[3,4-*b*][1,4]-benzoxazine-1,3(2*H*,9*H*)-dione (**5h**)

Orange powder, yield 76%, mp 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.13 (m, 2H), 7.03–6.89 (m, 4H), 6.79 (s, 1H), 5.63 (s, 1H), 3.89 (s, 3H), 3.86 (S, 3H). IR (KBr): ν (cm^{-1}) 3394, 3331, 3007, 2967, 2839, 1773, 1720, 1664, 1598, 1514, 1425, 1372, 1335, 1267, 1218. MS (ESI): $m/s = 337$ [M − 1]. Anal. calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 62.86; H, 4.14; N, 8.29.

2-Naphthyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5i**)

Yellow powder, yield 75%, mp 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.95 (m, 2H), 7.71–7.68 (m, 1H), 7.61–7.56 (m, 3H), 7.44 (d, 1H, $J = 7.6$ Hz), 7.17 (t, 2H, $J = 7.6$ Hz), 7.02 (t, 1H, $J = 7.6$ Hz), 6.93 (t, 1H, $J = 8.4$ Hz), 5.78 (s, 1H). IR (KBr): ν (cm^{-1}) 3308, 3051, 1932, 1772, 1707, 1666, 1598, 1510, 1462, 1418, 1380, 1281, 1231. MS (ESI): $m/s = 327$ [M − 1]. Anal. calcd. for $C_{20}H_{12}N_2O_3$: C, 73.16; H, 3.68; N, 8.53. Found: C, 73.09; H, 3.62; N, 8.48.

2-Benzyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**5j**)

Orange red powder, yield 68%, mp 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 2H, $J = 8.0$ Hz), 7.35–7.29 (m, 3H), 7.15 (dd, 1H, $J = 8.0$ and 1.6 Hz), 7.09 (t, 1H, $J = 8.0$ Hz), 6.91 (t, 1H, $J = 8.0$ Hz), 6.93 (dd, 1H, $J = 8.0$ and 0.8 Hz), 5.78 (s, 1H), 4.71 (s, 2H). IR (KBr): ν (cm^{-1}) 3330, 3056, 2962, 2849, 1766, 1709, 1657, 1600, 1520, 1449, 1411, 1345. MS (ESI): $m/s = 291$ [M − 1]. Anal. calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.78; H, 4.18; N, 9.56.

Preparation of 2-Phenyl-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (6a)

A solution of 3,4-dichloro-1-phenyl-1*H*-pyrrole-2,5-dione **3a** (240 mg, 0.1 mmol) and 2-amino-4-chlorophenol **4b** (143 mg, 0.1 mmol) in ethanol

(5 ml) were refluxed in an oil bath at 85–95 °C for 10 h. After cooling to room temperature, the solvent was removed under vacuum to give the crude product, and then purified by silica gel column chromatography eluting with petroleum/ethyl acetate/dichloromethane (6:2:1 v/v/v) to afford compound **6a** (215 mg, 69%) as yellow powder. Mp 209–211°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (t, 2H, $J = 7.6$ Hz), 7.38 (m, 3H), 7.27 (s, 1H), 7.11 (dd, 1H, $J = 8.4$ and 2.0 Hz), 6.84 (d, 1H, $J = 8.4$ Hz), 5.44 (s, 1H). IR (KBr): ν (cm^{-1}) 3202, 3030, 2808, 2712, 1770, 1702, 1677, 1652, 1597, 1501, 1455, 1408, 1298, 1264, 1244. MS (ESI): $m/s = 311$ [M − 1]. Anal. calcd. for $C_{16}H_9ClN_2O_3$: C, 61.45; H, 2.90; N, 8.96. Found: C, 61.37; H, 2.88; N, 9.01.

In the same manner, compounds **6b–j** were synthesized by reaction of the corresponding *N*-phenyldichloromaleimide derivatives **3b–j** with 2-amino-4-chloro-phenol **4b**, respectively.

Data

2-(4-Fluorophenyl)-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6b**)

Yellow powder, yield 73%, mp 199–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.30 (m, 2H), 7.21–7.17 (m, 3H), 6.87 (m, 1H), 6.71 (s, 1H), 6.62 (m, 1H). IR (KBr): ν (cm^{-1}) 3197, 2938, 1769, 1709, 1654, 1603, 1511, 1411, 1236. MS (ESI): $m/s = 329$ [M − 1]. Anal. calcd. for $C_{16}H_8ClFN_2O_3$: C, 58.11; H, 2.44; N, 8.47. Found: C, 58.03; H, 2.41; N, 8.44.

2-(4-Chlorophenyl)-7-choloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6c**)

Orange yellow powder, yield 66%, mp 234–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, $J = 8.8$ Hz), 7.42 (d, 2H, $J = 8.8$ Hz), 7.19–7.16 (m, 2H), 6.90 (d, 1H, $J = 8.8$ Hz), 5.82 (s, 1H). IR (KBr): ν (cm^{-1}) 3332, 3095, 2982, 2815, 1781, 1714, 1651, 1594, 1522, 1495, 1428, 1395, 1276, 1194. MS (ESI): $m/s = 345$ [M − 1]. Anal. calcd. for $C_{16}H_8Cl_2N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.00; H, 3.58; N, 10.03.

2-(4-Methylphenyl)-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3 (2*H*,9*H*)-dione (**6d**)

Yellow powder, yield 71%, mp 236–238 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (d, 2H, $J = 8.4$ Hz), 7.23 (d, 2H, $J = 8.4$ Hz), 7.19–7.15 (m, 2H),

6.89 (d, 1H, $J = 8.0$ Hz), 5.59 (s, 1H), 2.35 (s, 3H). IR (KBr): ν (cm^{-1}) 3308, 3025, 2923, 1777, 1711, 1652, 1595, 1517, 1495, 1428, 1399, 1275, 1234, 1211. MS (ESI): $m/s = 325$ [M − 1]. Anal. calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.39; H, 3.35; N, 8.55.

2-(3-Methylphenyl)-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3 (2*H*,9*H*)-dione (**6e**)

Orange yellow powder, yield 67%, mp 187–188°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.35 (m, 2H), 7.26–7.10 (m, 2H), 7.09 (d, 1 H, $J = 8.4$ Hz), 7.07–6.96 (m, 1H), 6.85 (d, 1H, $J = 8.4$ Hz), 5.67 (s, 1H), 2.39 (s, 3H). IR (KBr): ν (cm^{-1}) 3204, 2918, 1769, 1702, 1652, 1595, 1519, 1500, 1450, 1406, 1299, 1248, 1199. MS (ESI): $m/s = 325$ [M − 1]. Anal. calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.46; H, 3.33; N, 8.56.

2-(4-Nitrophenyl)-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6f**)

Orange powder, yield 70%, mp 231–233°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, 2H, $J = 9.2$ Hz), 7.76 (d, 2H, $J = 9.2$ Hz), 7.17–6.87 (m, 2H), 6.63 (d, 1H, $J = 9.2$ Hz), 5.75 (s, 1H). IR (KBr): ν (cm^{-1}) 3330, 3081, 1777, 1727, 1670, 1593, 1526, 1425, 1389, 1348, 1275, 1247, 1218. MS (ESI): $m/s = 356$ [M − 1]. Anal. calcd. for $C_{16}H_8ClN_3O_5$: C, 53.72; H, 2.25; N, 11.75. Found: C, 53.68; H, 2.24; N, 11.69.

2-(3-Nitrophenyl)-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6g**)

Yellow powder, yield 64%, mp 208–209°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41–7.49 (m, 4H), 7.22–6.47 (m, 2H), 6.47–6.27 (m, 2H), 6.47–6.27 (m, 1H), 5.65 (s, 1H). IR (KBr): ν (cm^{-1}) 3205, 3024, 1770, 1707, 1676, 1653, 1597, 1540, 1500, 1444, 1405, 1351, 1307, 1263, 1228, 1191. MS (ESI): $m/s = 356$ [M − 1]. Anal. calcd. for $C_{16}H_8ClN_3O_5$: C, 53.72; H, 2.25; N, 11.75. Found: C, 53.67; H, 2.23; N, 11.67.

2-(3,4-Dimethoxyphenyl)-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6h**)

Orange yellow powder, yield 71%, mp 201–203°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 1H, $J = 2.4$ Hz), 7.10 (m, 2H), 6.98 (m, 1H),

6.85–6.83 (d, 1H, $J = 8.4$ Hz), 6.77 (m, 1H), 6.56 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H). IR (KBr): ν (cm^{-1}) 3394, 3331, 3007, 2967, 2839, 1773, 1721, 1665, 1598, 1515, 1443, 1335, 1268, 1187. MS (ESI): $m/s = 371$ [M − 1]. Anal. calcd. for $C_{18}H_{13}ClN_2O_5$: C, 58.00; H, 3.52; N, 7.52. Found: C, 58.01; H, 3.50; N, 7.47.

2-Naphthyl-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6i**)

Yellow powder, yield 72%, mp 222–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.93 (m, 2H), 7.66–7.64 (m, 1H), 7.59–7.52 (m, 3H), 7.43–7.41 (d, $J = 6.8$ Hz, 1H), 7.13–7.09 (m, 2H), 6.85–6.83 (d, $J = 8.0$ Hz, 1H), 5.82 (s, 1H). IR (KBr): ν (cm^{-1}) 3431, 3332, 2925, 2851, 1772, 1710, 1653, 1597, 1526, 1500, 1468, 1417, 1347, 1228. MS (ESI): $m/s = 361$ [M − 1]. Anal. calcd. for $C_{20}H_{11}ClN_2O_3$: C, 66.22; H, 3.06; N, 7.72. Found: C, 66.15; H, 3.09; N, 7.68.

2-Benzyl-7-chloro-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**6j**)

Orange red powder, yield 67%, mp 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.32 (m, 5H), 7.16 (d, 1H, $J = 2.4$ Hz), 7.05 (dd, 1H, $J = 8.4$ and 2.0 Hz), 6.80 (d, 1H, $J = 8.4$ Hz), 5.78 (s, 1H), 4.72 (s, 1H). IR (KBr): ν (cm^{-1}) 3440, 3253, 3051, 2929, 1772, 1707, 1651, 1595, 1502, 1406, 1350, 1281, 1193. MS (ESI): $m/s = 325$ [M − 1]. Anal. calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.47; H, 3.36; N, 8.49.

Preparation of 2-phenyl-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (7a)

A solution of 3,4-dichloro-1-phenyl-1*H*-pyrrole-2,5-dione **3a** (240 mg, 1 mmol) and 2-amino-4-*tert*-butylphenol **4c** (165 mg, 1 mmol) in ethanol (5 ml) were refluxed in an oil bath at 85–95°C for 10 h. After cooling to room temperature, the solvent was removed under vacuum to give the crude product, and then purified by silica gel column chromatography eluting with petroleum/ethyl acetate/dichloromethane (8:2:1 v/v/v) to afford compound **7a** (243 mg, 73%) as orange powder. Mp 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (t, 2H, $J = 8.0$ Hz), 7.42–7.37 (m, 3H), 7.24 (d, 1H, $J = 2.0$ Hz), 7.14 (dd, 1H, $J = 8.0$ Hz), 6.82 (d, 1H, $J = 8.0$ and 2.0 Hz), 5.43 (s, 1H), 1.32 (s, 9H).IR (KBr): ν (cm^{-1}) 3273, 3050, 2953, 2908, 2850, 1778, 1708, 1668, 1645, 1597, 1502, 1405, 1353,

1269, 1212. MS (ESI): $m/s = 333$ [M − 1]. Anal. calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.79; H, 5.39; N, 8.35.

In the same manner, compounds **7b–j** were synthesized by reaction of the corresponding *N*-phenyldichloromaleimide derivatives **3b–j** with 2-amino-4-*tert*-butyl-phenol **4c**, respectively.

Data

2-(4-Fluorophenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7b**)

Orange red powder, yield 84%, mp 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.37 (m, 2H), 7.18–7.15 (m, 4H), 6.82 (d, 1H, $J = 8.4$ Hz), 5.49 (s, 1H), 1.32 (s, 9H). IR (KBr): ν (cm^{-1}) 3283, 2960, 1774, 1712, 1653, 1602, 1513, 1414, 1354, 1231. MS (ESI): $m/s = 351$ [M − 1]. Anal. calcd. for $C_{20}H_{17}FN_2O_3$: C, 68.17; H, 4.86; N, 7.95. Found: C, 68.11; H, 4.82; N, 7.90.

2-(4-Chlorophenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7c**)

Yellow powder, yield 72%, mp 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 2H, $J = 8.8$ Hz), 7.35 (d, 2H, $J = 8.8$ Hz), 7.21 (d, 1H, $J = 2.4$ Hz), 7.12 (dd, 1H, $J = 8.8$ and 2.0 Hz), 6.80 (d, 1H, $J = 8.8$ Hz), 6.2 (s, 1H), 1.31 (s, 9H). IR (KBr): ν (cm^{-1}) 3327, 2961, 2878, 2846, 1785, 1716, 1659, 1600, 1497, 1397, 1211. MS (ESI): $m/s = 367$ [M − 1]. Anal. calcd. for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.09; H, 4.62; N, 7.56.

2-(4-Methylphenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7d**)

Yellow powder, yield 72%, mp 90–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 3H), 7.23 (d, 1H, $J = 2.0$ Hz), 7.13 (dd, 2H, $J = 8.8$ and 2.0 Hz), 6.81 (d, 1H, $J = 8.8$ Hz), 5.44 (s, 1H), 2.40 (s, 3H), 1.32 (s, 9H). IR (KBr): ν (cm^{-1}) 3332, 3050, 2960, 2918, 2856, 1786, 1716, 1659, 1602, 1513, 1401, 1279, 1211. MS (ESI): $m/s = 347$ [M − 1]. Anal. calcd. for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.34; H, 5.76; N, 7.99.

2-(3-methylphenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7e**)

Orange powder, yield 73%, mp 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, 1H, $J = 8.0$ Hz), 7.23–7.14 (m, 5H), 6.81 (d, 1H, $J = 8.8$ Hz), 5.51 (s, 1H), 2.39 (s, 3H), 1.32 (s, 9H). IR (KBr): ν (cm^{-1}) 3389, 3333, 3028, 2958, 2912, 2853, 1782, 1719, 1650, 1602, 1500, 1436, 1395, 1276, 1238. MS (ESI): $m/s = 347$ [M − 1]. Anal. calcd. for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.37; H, 5.72; N, 8.07.

2-(4-Nitrophenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7f**)

Orange powder, yield 83%, mp 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 2H, $J = 9.2$ Hz), 7.76 (d, 2H, $J = 9.2$ Hz), 7.24–7.17 (m, 2H), 6.83 (d, 1H, $J = 8.4$ Hz), 5.33 (s, 1H), 1.32 (s, 9H). IR (KBr): ν (cm^{-1}) 3394, 3100, 2961, 2916, 2857, 1782, 1718, 1649, 1600, 1533, 1501, 1399, 1348, 1219. MS (ESI): $m/s = 378$ [M − 1]. Anal. calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.28; H, 4.49; N, 11.06.

2-(3-Nitrophenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7g**)

Yellow powder, yield 73%, mp 191–193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, 1H, $J = 2$ Hz), 8.21 (d, 1H, $J = 7.6$ Hz), 7.85 (d, 1H, $J = 8.0$ Hz), 7.64 (t, 1H, $J = 8.0$ Hz), 7.24 (m, 1H), 7.16 (d, 1H, $J = 8.4$ Hz), 6.84 (d, 1H, $J = 8.0$ Hz), 5.66 (s, 1H), 1.32 (s, 9H). IR (KBr): ν (cm^{-1}) 3458, 332, 3098, 2964, 2865, 1788, 1773, 1725, 1662, 1602, 1504, 1399, 1340, 1214. MS (ESI): $m/s = 378$ [M − 1]. Anal. calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.36; H, 4.49; N, 11.07.

2-(3,4-Dimethoxyphenyl)-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7h**)

Light brown powder, yield 83%, mp 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.21 (m, 2H), 7.12 (dd, 1H, $J = 8.4$ and 1.6 Hz), 6.94 (d, 1H, $J = 2.0$ Hz), 6.78 (t, 2H, $J = 8.4$ Hz), 5.99 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 1.31 (s, 9H). IR (KBr): ν (cm^{-1}) 3444, 2960, 1770, 1719, 1658, 1603, 1513, 1452, 1333, 1262. MS (ESI): $m/s = 393$ [M − 1]. Anal. calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.96; H, 5.62; N, 7.08.

2-Naphthyl-7-*tert*-butyl-pyrrolo[3,4-*b*] [1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7i**)

Orange powder, yield 81%, mp 98–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, 1H, $J = 8.4$ Hz), 7.91–7.89 (m, 1H), 7.68–7.66 (m, 1H), 7.54–7.50 (m, 3H), 7.39 (d, 1H, $J = 7.6$ Hz), 7.24 (m, 1H), 7.02 (dd, 1H, $J = 8.4$ and 1.6 Hz), 6.45 (d, 1H, $J = 8.4$ Hz), 6.27 (s, 1H), 1.32 (s, 9H). IR (KBr): ν (cm^{-1}) 3440, 3333, 3058, 2959, 2849, 1788, 1717, 1657, 1601, 1506, 1412, 1373, 1373, 275, 1227. MS (ESI): $m/s = 383$ [M − 1]. Anal. calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.91; H, 5.22; N, 7.27.

2-Benzyl-7-*tert*-butyl-pyrrolo[3,4-*b*][1,4]benzoxazine-1,3(2*H*,9*H*)-dione (**7j**)

Yellow powder, yield 72%, mp 141–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 2H, $J = 7.2$ Hz), 7.35–7.29 (m, 3H), 7.15 (s, 1H), 7.10 (d, 1H, $J = 8.4$ Hz), 6.79 (d, 1H, $J = 8.4$ Hz), 5.45 (s, 1H), 4.72 (s, 2H), 1.29 (s, 9H). IR (KBr): ν (cm^{-1}) 3282, 3060, 2956, 2912, 2867, 1768, 1706, 1649, 1600, 1508, 1437, 1352, 1225. MS (ESI): $m/s = 347$ [M − 1]. Anal. calcd. for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.35; H, 5.72; N, 8.04.

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