Convenient Synthesis of Benzoxazolone Derivatives by Cross-Coupling of Benzoxazolone Boronates with Aryl Halides

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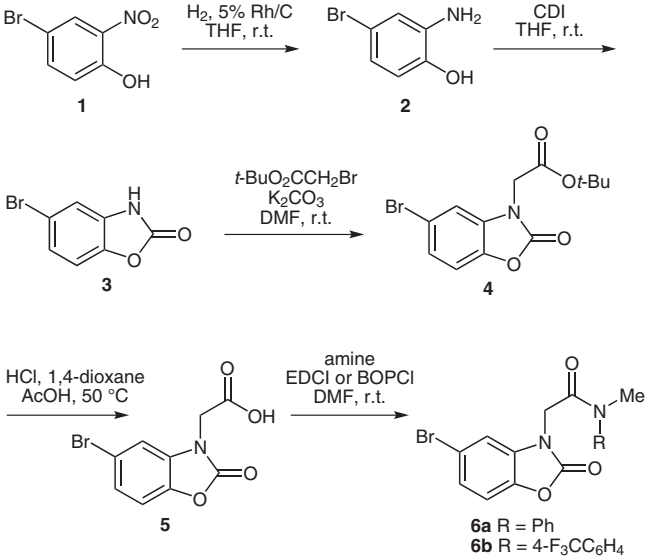
Abstract: Benzoxazolone derivatives with various substituents at the C-5 position were synthesized efficiently via benzoxazolone boronates as the key intermediate. The target compounds were also synthesized from (het)aryl halides in a one-pot process. These methods permitted efficient exploratory syntheses of a series of benzoxazolone derivatives.

Key words: heterocycles, boron, cross-coupling, biaryls, catalysis, arylations

The benzoxazolone scaffold is an important structural motif in a range of medicines.[1–3] We recently reported that benzoxazolone derivatives act as selective ligands for 18-kDa translocator protein (TSPO).[2] Our exploratory studies on benzoxazolone derivatives identified important rules that link substitution at the C-5 position with the pharmacokinetic profiles of these compounds, especially their metabolic stability.[2b] As a result, we needed convenient methods to prepare benzoxazolone derivatives with various substituents in the C-5 position. Although many arylboronate reagents are commercially available, we needed to synthesize (het)arylboronate reagents with multiple substituents or unique substituents as intermediates for a diversity of compounds for bioassay studies. To prepare benzoxazolone derivatives with various substituents at the C-5 position effectively, we needed to synthesize the corresponding benzoxazolone boronates. Although syntheses and applications of benzoxazolone boronates have been described in several patents,[3] no detailed investigation on these compounds has been reported. Here, we present a convenient method for the synthesis of benzoxazolone derivatives with various substituents at the C-5 position via benzoxazolone boronates as key intermediates. The method permits the preparation of several potent TSPO ligands, including a promising compound **8j** with a high TSPO affinity and acceptable metabolic stability (see Table S1 in the Supporting Information).

First, we synthesized a series of 5-bromobenzoxazolone derivatives (Scheme 1). The nitro group in the phenol **1** was reduced chemoselectively by hydrogenation over rhodium on carbon in tetrahydrofuran[4] to give the amine **2**.[5] Carbonylation of **2** with 1,1'-carbonyldiimidazole (CDI) followed by N-alkylation gave the *N*-acetate **4**.[2a,b] Deprotection of **4** with hydrochloric acid gave acid **5**,[2a,b]



Scheme 1 Synthesis of amides **6a** and **6b**

which was condensed with *N*-methylaniline or *N*-methyl-4-(trifluoromethyl)aniline in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), or bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) to afford the corresponding amide derivatives **6a**[2a,b] and **6b**.

Bromobenzoxazolones **4**, **6a**, and **6b** were cross-coupled with bis(pinacolato)diboron under the conditions reported by Miyaura and co-workers[6] to give the corresponding benzoxazolone boronates **7a**–**c** in moderate yield (Table 1). Amide **6a** required a slightly longer reaction time than did ester **4** or amide **6b** (entry 2).

Next, we examined the Suzuki–Miyaura reaction[7] of **7a**–**c** with various (het)aryl bromides in refluxing 1,4-dioxane containing 5 mol% of tetrakis(triphenylphosphine)palladium as a catalyst and potassium carbonate as a base (Table 2). The coupling reaction of amide **7b**[2a] with aryl bromides containing alcohol or amine groups gave moderate yields of the corresponding *N*-aryl derivatives **8a**–**f**[2a] (entries 1–6). Whereas the cross-coupling of amine **6a** with 2-pyridineboronic acid[8] under the above conditions was unsuccessful, the reaction of amide **7b** with 2-bromopyridine gave the desired compound **8g**[2a,b] in 70% yield. A variety of pyridyl bromides containing electron-donating or electron-withdrawing substituents underwent Suzuki–Miyaura coupling (entries 8–12). Products **8h**–**j** have been reported in our patent.[2a]

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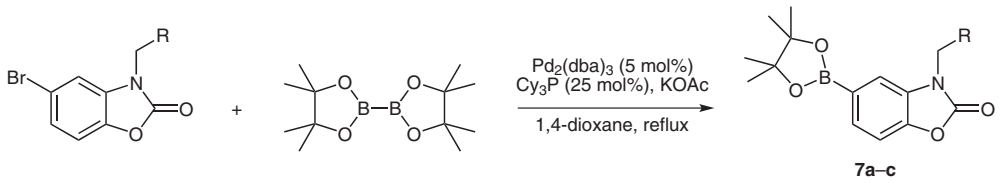
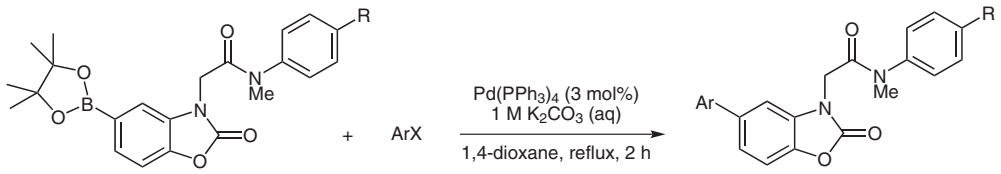
Table 1 Synthesis of Pinacol Arylboronates

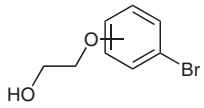
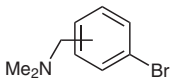
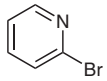
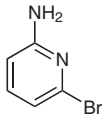
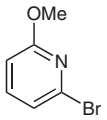
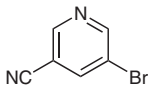
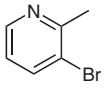


Entry	R	Substrate	Product	Time (h)	Yield[a] (%)
1	CO_2t-Bu	**4**	**7a**	15	78
2	C(O)N(Me)Ph	**6a**	**7b**	28	83
3	C(O)N(Me)-4-$F_3CC_6H_4$	**6b**	**7c**	12	76

[a] Isolated yield.

Table 2 Suzuki–Miyaura Coupling of Benzoxazolone Boronates with Substituted (Het)aryl Bromides

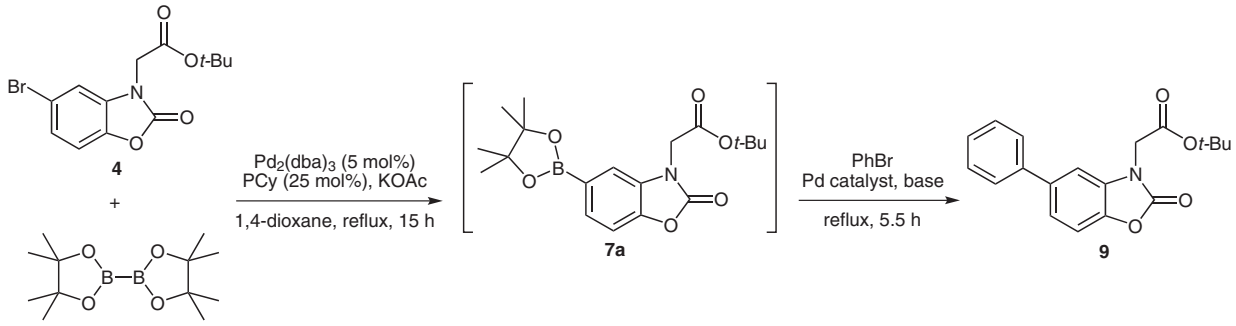


Entry	Ar		Amide	Product	Yield[a] (%)
1		2-	**7b**	**8a**	75
2		3-	**7b**	**8b**	72
3		4-	**7b**	**8c**	54
4		2-	**7b**	**8d**	43
5		3-	**7b**	**8e**	89
6		4-	**7b**	**8f**	70
7			**7b**	**8g**	70
8			**7b**	**8h**	64
9			**7b**	**8i**	68
10			**7b**	**8j**	75
11			**7b**	**8k**	59
12			**7c**	**8l**	62

[a] Isolated yield.

Finally, we examined a one-pot synthesis of the substituted benzoxazolone **9**[2] from ester **4** (Table 3). Benzoxazolone **9** was obtained by cross-coupling of **4** with bis(pinacolato)diboron, followed by coupling with bromobenzene in the presence of potassium carbonate solution (entry 2). The addition of tetrakis(triphenylphosphine)palladium in the second coupling reaction was not advantageous (entry 3). Furthermore, the desired compound **7a**[2a] was not obtained when the cross-coupling reaction of bromo compound **4** with bis(pinacolato)diboron

Table 3 One-Pot Synthesis of Benzoxazolone **9**



Entry	Catalyst	Base	Yield[a] (%)
1	–	–	0
2	–	aq K_2CO_3	26
3	$Pd(PPh_3)_4$ (5 mol%)	aq K_2CO_3	30

[a] Isolated yield.

was conducted in the presence of potassium carbonate instead of potassium acetate, as the use of the former base resulted in recovery of the starting material. We are conducting further optimization studies in attempts to improve the yield of this one-pot process.

In conclusion, we have developed a convenient method for the synthesis of benzoxazolone derivatives with various substituents at the C-5 position by using benzoxazolone boronates as key intermediates. Furthermore, we have developed a one-pot synthesis of the target compounds from the corresponding aryl halides. These methods will permit efficient exploratory syntheses of a series of benzoxazolone derivatives.

Melting points were determined on a Stanford Research Systems OptiMelt MPA100 and are uncorrected. NMR spectra were recorded at r.t. on a JEOL JNM-AL400 FT NMR spectrometer. Chemical shifts are expressed in δ values (ppm) relative to TMS as an internal standard. IR spectra were recorded on a JEOL JIR-SPX60 spectrometer in the ATR mode. High-resolution mass spectra were recorded on Thermo Fisher Scientific LTQ orbitrap Discovery MS equipment. Elemental analyses were performed on a CE Instrument EA1110 and a Yokokawa analytical system IC7000. In general, reagents and solvents were used as received from commercial suppliers without further purification. The progress of reactions was monitored by TLC on Merck silica gel 60 F254 coated glass plates, with visualization by UV radiation (254 nm) or I_2. Flash column chromatography was performed on Merck silica gel 60 (70–230 mesh). All reactions were carried out under N_2 unless otherwise stated.

2-Amino-4-bromophenol (2)

5% Rh/C (5.00 g) was added to a solution of 4-bromo-2-nitrophenol (**1**; 50.7 g, 233 mmol) in THF (500 mL), and the mixture was stirred at r.t. for 11 h under H_2. The mixture was then filtered through Celite, and the filtrate was concentrated to give a brown solid; yield: 43.3 g (99%); mp 133–135 °C.

IR (ATR): 3062, 1497, 1444, 1437, 1279 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.29 (s, 1 H), 6.72 (d, J = 2.4 Hz, 1 H), 6.56 (d, J = 8.3 Hz, 1 H), 6.50 (dd, J = 8.3, 2.4 Hz, 1 H), 4.91 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.3, 138.6, 118.2, 116.1, 115.6, 110.6.

HRMS (ESI): m/z $[M + H]^+$ calcd for C_6H_7BrNO: 187.9706; found: 187.9704.

5-Bromo-1,3-benzoxazol-2(3*H*)-one (3)

1,1′-Carbonyldiimidazole (46.5 g, 287 mmol) was added to a solution of bromophenol **2** (49.0 g, 261 mmol) in THF (300 mL) at r.t., and the mixture was stirred at r.t. for 2 h. The reaction was then quenched with 2 M aq HCl (700 mL), and the mixture was extracted with EtOAc (2 × 500 mL). The organic layers were combined, washed with brine (500 mL), dried ($NaSO_4$), filtered, and concentrated in vacuo to give a brown solid; yield: 53.2 g (95%); mp 206–208 °C.

IR (ATR): 2359, 1751, 1622, 1473, 1254 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.99 (s, 1 H), 7.27–7.26 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.0, 142.5, 132.0, 124.3, 115.3, 112.4, 111.3.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_7H_3BrNO_2$: 211.9353; found: 211.9350.

***tert*-Butyl [5-Bromo-2-oxo-1,3-benzoxazol-3(2*H*)-yl]acetate (4)**

t-BuO_2CCH_2Br (38.4 mL, 260 mmol) was added to a suspension of benzoxazolone **3** (53.0 g, 248 mmol) and K_2CO_3 (51.3 g, 371 mmol) in DMF (500 mL) cooled in an ice bath. The mixture was warmed to r.t. and stirred for 3 h. H_2O (1000 mL) was added, and the mixture was extracted with 1:1 toluene– EtOAc (2 × 500 mL). The organic layer was separated, washed with H_2O (2 × 500 mL) and brine (500 mL), dried ($NaSO_4$), filtered, and concentrated in vacuo. The residue was triturated with hexane (200 mL) to give a solid that was recovered by filtration and washed with hexane (100 mL) to give a beige solid; yield: 75.2 g (92%); 144–145 °C.

IR (ATR): 1781, 1736, 1608, 1485, 1387 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, J = 8.5, 1.9 Hz, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 7.03 (d, J = 1.9 Hz, 1 H), 4.43 (s, 2 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 154.0, 141.6, 132.1, 125.6, 116.5, 111.7, 111.5, 83.8, 43.9, 28.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{15}BrNO_4$: 328.0179; found: 328.0181.

Anal. Calcd for $C_{13}H_{14}BrNO_4$: C, 47.58; H, 4.30; N, 4.27; Br, 24.35. Found: C, 47.72; H, 4.30; N, 4.32; Br, 24.04.

[5-Bromo-2-oxo-1,3-benzoxazol-3(2*H*)-yl]acetic Acid (5)

4 M HCl in 1,4-dioxane (0.518 mL) was added to a solution of ester **4** (170 mg, 0.518 mmol) in AcOH (1.0 mL). The mixture was stirred at 50 °C for 6.5 h then cooled to r.t. The solvent was removed in vacuo, and the resulting solid was triturated with Et_2O (2.0 mL) to give a white solid; yield: 132 mg (94%); mp 204–206 °C.

IR (ATR): 2953, 1736, 2701, 1483, 1227 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.42 (br s, 1 H), 7.68 (d, *J* = 1.7 Hz, 1 H), 7.37–7.33 (m, 2 H), 4.66 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6, 153.6, 141.1, 132.7, 125.0, 115.8, 112.6, 111.6, 43.1.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_9H_5BrNO_4$: 269.9407; found: 269.9406.

2-[5-Bromo-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (6a)

PhNHMe (4.78 mL, 44.1 mmol), 1-hydroxybenzotriazole (4.97 g, 36.8 mmol), and EDCI·HCl (9.07 g, 47.3 mmol) were added to a solution of acid **5** (10.0 g, 36.8 mmol) in DMF (100 mL) at r.t., and the mixture was stirred at r.t. for 6 h. H_2O (200 mL) was added and the mixture was extracted with 1:1 toluene–EtOAc (2 × 200 mL). The organic layer was separated, washed sequentially with H_2O (2 × 200 mL), 1 M aq HCl (200 mL), and brine (200 mL) then dried ($NaSO_4$) and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography [silica gel, hexane–EtOAc (1: 1)]. The solvent was again removed in vacuo, and the resulting solid was crystallized (*i*-PrOH) to give a white solid; yield: 7.16 g (54%); mp 122–124 °C (*i*-PrOH).

IR (ATR): 1772, 1666, 1483, 1377, 1244 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.23 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 7.01 (d, *J* = 1.7 Hz, 1 H), 4.28 (s, 2 H), 3.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 154.2, 141.8, 141.6, 132.6, 130.5, 129.0, 127.2, 125.4, 116.4, 112.0, 111.3, 43.9, 37.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{14}BrN_2O_3$: 361.0182; found: 361.0177.

Anal. Calcd for $C_{16}H_{13}BrN_2O_3$: C, 53.21; H, 3.63; N, 7.76; Br, 22.12. Found: C, 53.15; H, 3.68; N, 7.84; Br, 21.90.

2-[5-Bromo-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-[4-(trifluoromethyl)phenyl]acetamide (6b)

N-methyl-4-(trifluoromethoxy)aniline (1.42 g, 8.11 mmol), BOPCl (2.82 g, 11.1 mmol), and Et_3N (3.10 mL, 22.2 mmol) were added to a solution of acid **5** (2.01 g, 7.39 mmol) in DMF (10 mL) at r.t., and the mixture was stirred at r.t. for 3 h. H_2O (30 mL) was added, and the mixture was extracted with 1:1 toluene–EtOAc (2 × 30 mL). The organic layer was separated, washed sequentially with H_2O (2 × 30 mL) and brine (30 mL), dried ($NaSO_4$), and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography [silica gel, hexane–EtOAc (3: 1)] to give a white solid; yield: 2.60 g (82%); mp 137–139 °C (*i*-PrOH).

IR (ATR): 1794, 1663, 1612, 1485, 1323 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.24 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.03 (s, 1 H), 4.29 (s, 2 H), 3.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 154.1, 145.0, 141.6, 132.4, 127.8 (m), 127.7 (m), 125.6, 124.8, 122.1, 116.5, 112.0, 111.5, 43.9, 37.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{13}BrF_3N_2O_3$: 429.0056; found: 429.0054.

Anal. Calcd for $C_{17}H_{12}BrF_3N_2O_3$: C, 47.57; H, 2.82; N, 6.53; Br, 18.62; F, 13.28. Found: C, 47.58; H, 2.84; N, 6.54; Br, 18.68; F, 13.22.

Pinacol Aryboronates 7a–c; General Procedure

Bis(pinacolato)diboron (1.1 equiv), $Pd_2(dba)_3$ (5 mol%), PCy_3 (25 mol%), and KOAc (1.5 equiv) were added to a suspension of the appropriate 5-bromo-1,3-benzoxazol-2-one in 1,4-dioxane (0.20 M) at r.t. The mixture was stirred at reflux for the appropriate time then cooled to r.t. H_2O was added, and the mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried ($NaSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexane–EtOAc).

***tert*-Butyl [2-Oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazol-3(2*H*)-yl]acetate (7a)**

Prepared from ester **4** (5.00 g, 15.2 mmol) as a white solid; yield: 4.46 g (78%); mp 176–178 °C.

IR (ATR): 1768, 1745, 1458, 1342, 1238 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 1 H), 7.31 (s, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 4.46 (s, 2 H), 1.47 (s, 9 H), 1.35 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 154.4, 145.0, 130.5, 130.1, 113.9, 109.6, 84.1, 83.4, 43.8, 27.9, 24.8.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{19}H_{25}BNO_6$: 374.1780; found: 374.1776.

Anal. Calcd for $C_{19}H_{26}BNO_6$: C, 60.82; H, 6.98; N, 3.73. Found: C, 60.81; H, 7.07; N, 3.73.

***N*-Methyl-2-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazol-3(2*H*)-yl]-*N*-phenylacetamide (7b)**

Prepared from amide **6a** (6.18 g, 17.1 mmol) as a white solid; yield: 5.81 g (83%); mp 163–164 °C.

IR (ATR): 1788, 1668, 1458, 1379, 1342 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.52 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.28 (br s, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 4.32 (s, 2 H), 3.32 (s, 3 H), 1.36 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 154.5, 145.1, 141.9, 131.0, 130.4, 129.9, 128.8, 127.3, 114.0, 109.5, 84.0, 43.7, 37.7, 24.9.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{22}H_{24}BN_2O_5$: 407.1784; found: 407.1775.

Anal. Calcd for $C_{22}H_{25}BN_2O_5$: C, 64.72; H, 6.17; N, 6.86. Found: C, 64.57; H, 6.28; N, 6.72.

***N*-Methyl-2-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazol-3(2*H*)-yl]-*N*-[4-(trifluoromethyl)phenyl]acetamide (7c)**

Prepared from amide **6b** (2.46 g, 5.73 mmol) as a white solid; yield: 2.07 g (76%); mp 156–157 °C.

IR (ATR): 1792, 1655, 1464, 1344, 1321 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.0 Hz, 2 H), 7.61 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.29 (br s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 4.33 (s, 2 H), 3.35 (s, 3 H), 1.35 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 154.4, 145.2, 145.1, 130.8, 130.1, 127.9 (m), 127.6 (m), 114.0, 109.6, 84.1, 43.8, 37.7.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{23}H_{23}BF_3N_2O_5$: 475.1658; found: 475.1661.

Anal. Calcd for $C_{23}H_{24}BF_3N_2O_5$: C, 58.00; H, 5.08; N, 5.88. Found: C, 58.06; H, 5.10; N, 5.93.

Amides 8a–l; General Procedure

$Pd(PPh_3)_4$ (3 mol%) was added to a suspension of the appropriate benzoxazole **7** and (het)aryl bromide (1 equiv) in 1 M aq K_2CO_3 (3 equiv) and 1,4-dioxane (0.15 M) at r.t. The mixture was stirred at reflux for 2 h then cooled to r.t. H_2O was added, and the mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried ($NaSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–EtOAc or $CHCl_3$–MeOH).

2-{5-[2-(2-Hydroxyethoxy)phenyl]-2-oxo-1,3-benzoxazol-3(2*H*)-yl}-*N*-methyl-*N*-phenylacetamide (8a)

Prepared from amide **7b** (55.0 mg, 135 μmol) and 2-(2-bromophenoxy)ethanol (29.3 mg, 135 μmol) as a white solid; yield: 42.6 mg (75%); mp 158–160 °C (*i*-PrOH).

IR (ATR): 1780, 1653, 1485, 1385, 1255 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.43 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.35–7.31 (m, 5 H), 7.23 (d, *J* = 8.3 Hz, 1 H), 7.15 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.07–7.03 (m, 1 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 4.34 (s, 2 H), 4.06 (t, *J* = 4.1 Hz, 2 H), 3.91–3.89 (br m, 2 H), 3.52–3.50 (br m, 1 H), 3.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 155.7, 154.7, 141.9, 141.7, 134.5, 130.8, 130.7, 130.5, 130.2, 129.0, 128.9, 127.2, 123.5, 121.2, 112.4, 111.5, 109.7, 70.4, 61.3, 43.9, 37.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_5$: 419.1601; found: 419.1594.

Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.55; H, 5.35; N, 6.85.

2-{5-[3-(2-Hydroxyethoxy)phenyl]-2-oxo-1,3-benzoxazol-3(2*H*)-yl}-*N*-methyl-*N*-phenylacetamide (8b)

Prepared from amide **7b** (55.0 mg, 135 μmol) and 2-(3-bromophenoxy)ethanol (29.3 mg, 135 μmol) as a white solid; yield: 40.8 mg (72%); mp 145–147 °C (*i*-PrOH).

IR (ATR): 1782, 1662, 1597, 1587, 1485 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.37–7.35 (m, 3 H), 7.29 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 1 H), 7.16–7.12 (m, 1 H), 7.11–7.08 (m, 1 H), 7.03 (d, *J* = 1.7 Hz, 1 H), 6.92 (dd, *J* = 7.8, 2.2 Hz, 1 H), 4.35 (s, 2 H), 4.16 (t, *J* = 4.5 Hz, 2 H), 4.02–4.00 (m, 2 H), 3.32 (s, 3 H), 2.06 (t, *J* = 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 159.0, 154.8, 142.5, 142.3, 142.0, 137.6, 131.7, 130.5, 129.9, 128.9, 127.3, 121.8, 120.3, 114.1, 113.2, 110.1, 107.6, 69.3, 61.5, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_5$: 419.1601; found: 419.1595.

Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.51; H, 5.36; N, 6.71.

2-{5-[4-(2-Hydroxyethoxy)phenyl]-2-oxo-1,3-benzoxazol-3(2*H*)-yl}-*N*-methyl-*N*-phenylacetamide (8c)

Prepared from amide **7b** (55.0 mg, 135 μmol) and 2-(4-bromophenoxy)ethanol (29.3 mg, 135 μmol) as a white solid; yield: 30.5 mg (54%); mp 175–177 °C (*i*-PrOH).

IR (ATR): 1774, 1674, 1597, 1489, 1383 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.48–7.42 (m, 3 H), 7.34 (d, *J* = 7.1 Hz, 2 H), 7.26–7.19 (m, 2 H), 7.02–6.97 (m, 3 H), 4.35 (s, 2 H), 4.14 (t, *J* = 4.5 Hz, 2 H), 4.04–3.97 (m, 2 H), 3.32 (s, 3 H), 2.04 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 158.3, 154.8, 142.0, 141.9, 137.5, 133.9, 131.7, 130.5, 128.9, 128.5, 127.2, 121.4, 114.9, 110.1, 107.2, 69.3, 61.5, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_5$: 419.1601; found: 419.1596.

Anal. Calcd for $C_{24}H_{22}N_2O_5 \cdot 0.25\ H_2O$: C, 68.15; H, 5.36; N, 6.62. Found: C, 68.24; H, 5.35; N, 6.57.

2-[5-{2-[(Dimethylamino)methyl]phenyl}-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (8d)

Prepared from **7b** (150 mg, 367 μmol) and 2-$BrC_6H_4NMe_2$ (78.7 mg, 367 μmol) as a brown solid; yield: 66.0 mg (43%); mp 106–107 °C.

IR (ATR): 1782, 1697, 1684, 653, 1558 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.46 (m, 3 H), 7.43 (dd, *J* = 6.8, 6.8 Hz, 1 H), 7.38–7.29 (m, 4 H), 7.28–7.24 (m, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.11 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.09–7.06 (m, 1 H), 4.32 (s, 2 H), 3.29 (s, 3 H), 3.27 (s, 2 H), 2.18 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 154.9, 142.0, 141.8, 141.8, 137.5, 136.4, 130.9, 130.4, 130.4, 130.3, 128.8, 127.4, 127.3, 126.9, 124.0, 110.1, 109.4, 61.2, 45.3, 43.8, 37.8.

HRMS (ESI): *m/z* calcd for $C_{25}H_{26}N_3O_3$: 416.1969; found: 416.1958.

Anal. Calcd for $C_{25}H_{25}N_3O_3 \cdot 0.25\ H_2O$: C, 71.49; H, 6.12; N, 10.01. Found: C, 71.64; H, 6.18; N, 10.26.

2-[5-{3-[(Dimethylamino)methyl]phenyl}-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (8e)

Prepared from **7b** (150 mg, 367 μmol) and 3-$BrC_6H_4NMe_2$ (78.7 mg, 367 μmol) as a white solid; yield: 136 mg (89%); mp 146–148 °C.

IR (ATR): 1778, 1662, 1595, 1487, 1383 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1 H), 7.52 (dd, *J* = 7.5, 7.5 Hz, 2 H), 7.45 (dd, *J* = 7.5. 7.5 Hz, 2 H), 7.43–7.37 (m, 3 H), 7.33–7.28 (m, 2 H), 7.23 (d, *J* = 8.3 Hz, 1 H), 7.15 (s, 1 H), 4.37 (s, 2 H), 3.59 (s, 2 H), 3.32 (s, 3 H), 2.36 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 154.8, 142.2, 142.0, 141.0, 137.6, 131.8, 130.4, 128.8, 128.3, 128.2, 127.3, 126.4, 121.8, 110.0, 107.7, 64.1, 45.1, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$: 416.1969; found: 416.1959.

Anal. Calcd for $C_{25}H_{25}N_3O_3 \cdot 0.50\ H_2O$: C, 70.74; H, 6.17; N, 9.90. Found: C, 70.74; H, 6.04; N, 10.11.

2-[5-{4-[(Dimethylamino)methyl]phenyl}-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (8f)

Prepared from **7b** (150 mg, 367 μmol) and 4-$BrC_6H_4NMe_2$ (78.7 mg, 367 μmol) as a brown solid; yield: 107 mg (70%); mp 64–66 °C.

IR (ATR): 1774, 1668, 1595, 1489, 1385 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.41 (m, 5 H), 7.40–7.32 (m, 4 H), 7.32–7.26 (m, 1 H), 7.23 (d, *J* = 8.3 Hz, 1 H), 7.04 (s, 1 H), 4.35 (s, 2 H), 3.48 (s, 2 H), 3.32 (s, 3 H), 2.28 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 154.8, 142.1, 142.0, 139.6, 138.1, 137.7, 131.7, 130.5, 129.6, 128.9, 127.2, 127.2, 121.7, 110.1, 107.4, 64.0, 45.4, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$: 416.1969; found: 416.1961.

Anal. Calcd for $C_{25}H_{25}N_3O_3 \cdot 0.75\ H_2O$: C, 69.99; H, 6.23; N, 9.79. Found: C, 70.27; H, 6.16; N, 9.48.

***N*-Methyl-2-[2-oxo-5-(pyridin-2-yl)-1,3-benzoxazol-3(2*H*)-yl]-*N*-phenylacetamide (8g)**

Compound **8g** was prepared from **7b** (150 mg, 367 μmol) and 2-bromopyridine (35.0 μL, 367 μmol) as a beige solid; yield: 92.5 mg (70%); mp 166–168 °C (*i*-PrOH).

IR (ATR): 1786, 1660, 1587, 1471, 1464 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.9 Hz, 1 H), 7.79–7.73 (m, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.53 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.37 (d, *J* = 7.3 Hz, 2 H), 7.29–7.23 (m, 2 H), 4.39 (s, 2 H), 3.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 156.7, 154.7, 149.5, 143.4, 142.0, 136.9, 135.9, 132.0, 130.4, 128.9, 127.3, 122.2, 121.4, 120.6, 110.0, 107.4, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_3$: 360.1343; found: 360.1341.

Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.05; H, 4.83; N, 11.67.

2-[5-(6-Aminopyridin-2-yl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (8h)
Prepared from **7b** (100 mg, 245 μmol) and 6-bromopyridin-2-amine (42.4 mg, 245 μmol) as a white solid; yield: 59.1 mg (64%); mp 214–216 °C (*i*-PrOH).

IR (ATR): 1782, 1662, 1593, 1462, 1441 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.55–7.48 (m, 4 H), 7.44 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.36 (d, *J* = 7.3 Hz, 2 H), 7.22 (d, *J* = 8.3 Hz, 1 H), 7.05 (d, *J* = 7.3 Hz, 1 H), 6.48 (d, *J* = 7.3 Hz, 1 H), 4.55 (s, 2 H), 4.38 (s, 2 H), 3.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 158.2, 155.3, 154.8, 143.1, 142.0, 138.5, 136.2, 131.6, 130.4, 128.8, 127.3, 121.4, 110.9, 109.8, 107.3, 107.2, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}N_4O_3$: 375.1452; found: 375.1450.

Anal. Calcd for $C_{21}H_{18}N_4O_3 \cdot 0.25\ H_2O$: C, 66.57; H, 4.92; N, 14.79. Found: C, 66.69; H, 4.74; N, 14.55.

2-[5-(6-Methoxypyridin-2-yl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (8i)
Prepared from **7b** (55.0 mg, 135 μmol) and 2-bromo-6-methoxypyridine (25.3 mg, 135 μmol) as a white solid; yield: 35.6 mg (68%); mp 179–181 °C (*i*-PrOH).

IR (ATR): 1778, 1668, 1597, 1576, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.64 (m, 1 H), 7.58 (d, *J* = 1.7 Hz, 1 H), 7.52 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.36–7.29 (m, 3 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 4.39 (s, 2 H), 4.05 (s, 3 H), 3.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 163.7, 154.8, 153.9, 143.3, 142.1, 139.3, 135.6, 131.6, 130.4, 128.9, 127.2, 121.4, 112.9, 110.0, 109.2, 107.0, 53.3, 43.9, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_4$: 390.1448; found: 390.1445.

Anal. Calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.49; H, 4.83; N, 10.60.

2-[5-(5-Cyanopyridin-3-yl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-methyl-*N*-phenylacetamide (8j)
Prepared from **7b** (245 mg, 600 μmol) and 5-bromopyridine-3-carbonitrile (110 mg, 600 μmol) as a white solid; yield: 172 mg (75%); mp 270–272 °C (MeOH).

IR (ATR): 1778, 1657, 1595, 1385, 1246 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (d, *J* = 2.2 Hz, 1 H), 8.87 (d, *J* = 2.2 Hz, 1 H), 8.11 (dd, *J* = 2.2, 2.2 Hz, 1 H), 7.55 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.47 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.40–7.26 (m, 4 H), 7.04 (d, *J* = 1.5 Hz, 1 H), 4.38 (s, 2 H), 3.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 154.3, 151.6, 150.8, 143.4, 141.8, 137.4, 136.6, 132.6, 131.8, 130.6, 129.1, 127.3, 122.0, 116.5, 110.9, 110.1, 107.6, 44.0, 37.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_4O_3$: 385.1295; found: 385.1294.

Anal. Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58. Found: C, 68.39; H, 4.10; N, 14.46.

***N*-Methyl-2-[5-(2-methylpyridin-3-yl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-phenylacetamide (8k)**
Prepared from **7b** (70.0 mg, 171 μmol) and 3-bromo-5-methylpyridine (35.4 mg, 206 μmol) as a beige solid; yield: 37.4 mg (59%); mp 152–154 °C (*i*-PrOH).

IR (ATR): 1786, 1670, 1597, 1497, 1427 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.9 Hz, 1 H), 7.54–7.47 (m, 3 H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 2 H), 7.28–7.23 (m, 1 H), 7.23–7.17 (m, 1 H), 7.04 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.80 (s, 1 H), 4.33 (s, 2 H), 3.31 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 156.0, 154.7, 148.2, 142.1, 141.9, 137.4, 136.3, 136.0, 131.5, 130.5, 128.9, 127.2, 123.4, 121.0, 109.9, 109.3, 43.9, 37.8, 23.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_3$: 374.1499; found: 374.1493.

Anal. Calcd for $C_{22}H_{19}N_3O_3 \cdot 0.25\ H_2O$: C, 69.92; H, 5.20; N, 11.12. Found: C, 70.23; H, 5.21; N, 10.78.

***N*-Methyl-2-[5-(2-methylpyridin-3-yl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-*N*-[4-(trifluoromethyl)phenyl]acetamide (8l)**
Prepared from **7c** (81.7 mg, 171 μmol) and 3-bromo-5-methylpyridine (35.4 mg, 206 μmol) as a pale-yellow solid; yield: 46.8 mg (62%); mp 167–169 °C (*i*-PrOH).

IR (ATR): 1794, 1667, 1612, 1381, 1323 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 4.9, 1.7 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 2 H), 7.54–7.46 (m, 3 H), 7.29–7.24 (m, 2 H), 7.20 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.05 (dd, *J* = 8.3, 1.7 Hz, 1 H), 6.83 (s, 1 H), 4.34 (s, 2 H), 3.34 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 156.0, 154.6, 148.3, 145.1, 142.1, 137.4, 136.3, 136.2, 136.1, 131.3, 127.8 (m), 127.7 (m), 127.6 (m), 123.6, 121.0, 110.1, 109.3, 43.9, 37.8, 23.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}F_3N_3O_3$: 442.1373; found: 442.1359.

Anal. Calcd for $C_{23}H_{18}F_3N_3O_3 \cdot 0.25\ H_2O$: C, 61.95; H, 4.18; N, 9.42; F, 12.78. Found: C, 62.13; H, 4.19; N, 9.26; F, 12.63.

***tert*-Butyl (2-Oxo-5-phenyl-1,3-benzoxazol-3(2*H*)-yl)acetate (9)**
Bis(pinacolato)diboron (277 mg, 1.10 mmol), $Pd_2(dba)_3$ (45.8 mg, 50.0 μmol), PCy_3 (33.7 mg, 120 μmol), and KOAc (147 mg, 1.50 mmol) were added to a suspension of ester **4** (328 mg, 1.00 mmol) in 1,4-dioxane (6.0 mL) at r.t. The mixture was stirred at reflux for 15 h then cooled to r.t. PhBr (116 μL, 1.10 mmol) and 1 M aq K_2CO_3 (3.0 mL) were added, and the mixture was refluxed with stirring for a further 5.5 h then cooled to r.t. H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2 × 15 mL). The organic layer was separated, washed with brine (10 mL), dried ($NaSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane–EtOAc (1:7)] to give a yellow solid; yield: 84.6 mg (26%); mp 99–100 °C (MeOH).

IR (ATR): 1759, 1743, 1485, 1230, 1026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.50 (m, 2 H), 7.45 (dd, *J* = 7.4, 7.4 Hz, 2 H), 7.40–7.32 (m, 2 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 7.05 (d, *J* = 1.7 Hz, 1 H), 4.50 (s, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 154.7, 142.1, 140.6, 138.0, 131.3, 128.9, 127.5, 127.2, 122.0, 110.3, 107.2, 83.5, 43.9, 28.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{20}NO_4$: 326.1387; found: 326.1395.

Anal. Calcd for $C_{19}H_{19}NO_4 \cdot 0.25\ H_2O$: C, 69.18; H, 5.96; N, 4.25. Found: C, 69.32; H, 5.85; N, 4.64.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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