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Pirfenidone structural isosteres: design, synthesis and spectral study

Abstract: Series of 5-substituted arylpyridin-2(1*H*)-ones and arylpyrimidin-4(3*H*)-ones were designed and synthesized based on pirfenidone, a compound which shows promising therapeutic effects for treatment of fibrosis. The compounds **1a–c**, **2a–c** and **3a–c** were obtained under mild conditions by arylation of the appropriate heterocyclic amines with arylboronic acids under Chan-Lam-Evans conditions. The synthesis of the useful synthon *N*-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-(1*H*)-pyridin-2-one (**4**) is also reported. All compounds were characterized by spectral and elemental analysis and structural elucidation by ^{1}H and ^{13}C NMR is discussed herein.

Keywords: arylboronic acid; Chan-Lam-Evans reaction; pirfenidone; pyridone; pyrimidone.

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Introduction

Liver fibrosis represents the results of a sustained wound healing response to chronic hepatic cell injury that originates due to various causes, including viral infections, e.g., hepatitis B and C viruses; and metabolic disorders such as that of alcohol ingestion (Friedman, 2003; Guzman, 2008). The end-stage progression of hepatic fibrosis is known as cirrhosis and it is characterized by regenerative nodules surrounded by dense functionless fibrotic tissue (Guzman, 2008).

Several studies on experimental animal models of liver fibrosis showed possible spontaneous resolution of fibrous tissues after the removal of the fibrogenic stimulus (Issa et al., 2001). Similar results were also observed in human patients with liver fibrosis due to autoimmune hepatitis (Dufour et al., 1997) and biliary etiology (Hammel et al., 2001). However, the need for other means of treatment is vital, especially when the removal of the causative factor is unlikely. Recently, the different antifibrotic agents that inhibit the accumulation or resolve the already accumulated excess fibrous tissues in extracellular matrix (ECM) have been summarized (El Bialy et al., 2011a). These agents are thought to target one or more of the three stages involved in the process of fibrosis formation, i.e., the triggering stage, fibrogenesis and ECM accumulation (El Bialy et al., 2011a). One of these agents is pirfenidone (**1a** in Scheme 1) that was recently approved for the treatment of idiopathic pulmonary fibrosis (IPF) (Liu et al., 2009). Pirfenidone showed promising results in a liver fibrosis model by the inhibition of collagen synthesis, reduction of the production of number of cytokines and fibroblast proliferation (Di Sario et al., 2004). In the present investigation, the design and synthesis of new compounds with possible antifibrotic activity based on the structure of pirfenidone are reported. Structural modifications were designed to test the effect of altering the electronic character of phenyl group (**1a–c**), replacing the methyl group with the approximately same size bromine substituent but with the bromine being slightly more lipophilic (**2a–c**), and by replacing the pyridone with the more hydrophilic pyrimidone ring (**3a–c**). Although some of these compounds appeared previously in the literature (Stajer et al., 1987; Li and Dixon, 2004; Blatt et al., 2006; Kossen et al., 2009), we did not find associated physical or spectral data.

Results and discussion

Synthesis of compounds **1a–c, 2a–c** and **3a–c** was achieved employing a one-step coupling reaction performed under mild reaction conditions known as the Chan-Lam-Evans reaction (Chan and Lam, 2005; Rauws and Maes, 2012). The reaction involved the use of different arylboronic acids and CuII-containing catalyst in CH_2Cl_2 at room temperature (Chan and Lam, 2005; Sanjeeva Rao and Wu, 2012) (Scheme 1).

Boronic acids are synthesized from other boron-containing compounds (Hall, 2005) and used in many reactions forming C–C bonds in the presence of a palladium catalyst as in Suzuki-Miyaura coupling reaction (Suzuki, 2005), or C-heteroatom (N or O) bonds using copper catalyst as in Chan-Lam coupling reaction (Chan and Lam, 2005; Rauws and Maes, 2012; Sanjeeva Rao and Wu, 2012).

Herein, the appropriate arylboronic acid was allowed to react with the N-containing system (pyridone/pyrimidone), in the presence of $Cu(OAc)_2$ as a catalyst. The reaction is thought to start with a transmetalation step where the aryl moiety is transferred from the boronic acid to the $Cu(OAc)_2$ forming $ArCu^{II}OAc$. Another portion of $Cu(OAc)_2$ oxidizes the produced $ArCu^{II}(OAc)$ into $ArCu^{III}(OAc)_2$. The latter Cu^{III} species easily forms the C–N bond in the final product with reductive elimination of $Cu^{I}OAc$. The final step represents the oxidation of the produced $Cu^{I}OAc$ into $Cu^{II}(OAc)_2$ completing the catalytic cycle (King et al., 2009).

The structures of all compounds **1a–c**, **2a–c** and **3a–c** were verified using microanalytical and spectral analysis. The ^{1}H NMR spectra show peaks at δ 7.55–7.37 integrated as five protons to confirm the presence of an unsubstituted phenyl group incorporated into the pyridone and pyrimidone ring systems in compounds **1a**, **2a** and **3a**. Compounds with *para*-methoxyphenyl group (**1b**, **2b** and **3b**) exhibit in their ^{1}H NMR spectra the characteristic singlet of methoxy group at δ 3.8. The shielding effect of this group is noticeable especially on the adjacent protons in its *ortho* positions, where, for example, a doublet peak equivalent to two protons (H-3′-5′) appears at δ 7.03 in compound **2b** compared to an apparent triplet at δ 7.51 in the unsubstituted compound **2a**.

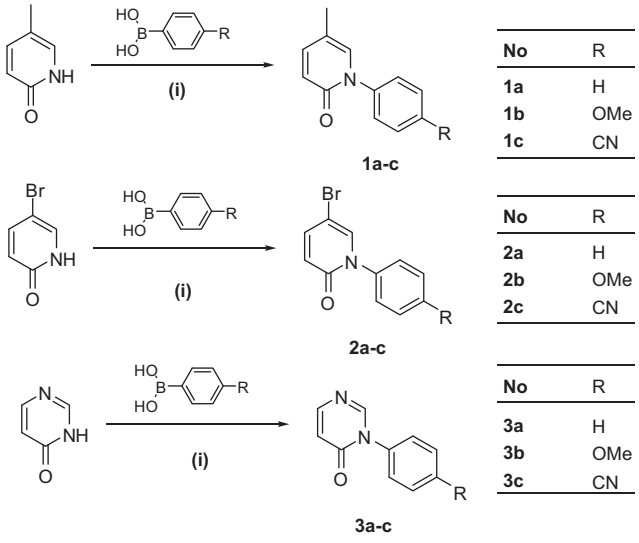
Similarly, the strong deshielding effect of the -CN group in compounds **1c**, **2c** and **3c** on the neighboring protons is obvious. For example, a doublet peak equivalent to two protons appears at δ 8.02 (H-3′-5′) in the ^{1}H NMR spectrum of compound **3c** compared to an apparent triplet at δ 7.55 for the unsubstituted compound **3a**.

Structures of all compounds were also confirmed by studying their ^{13}C NMR spectra. Peaks that represent classical aromatic carbons appear at δ 126.7–129.2 in compounds **1a**, **2a** and **3a** corresponding to five unsubstituted phenyl carbons (C2′/6′), (C3′/5′) and C4′. The sixth carbon C1′ signal appears deshielded at δ 137.1–141.0 due to its direct attachment to the heterocyclic N atom. Compounds **1b**, **2b** and **3b** were characterized by having a peak at δ 55.4 corresponding to the -OCH_3 group, whereas compounds **1c**, **2c** and **3c** have a peak at δ 116.4–118.3 corresponding to the -CN group.

The effect of the presence of the methoxy group in compounds **1b**, **2b** and **3b** on the directly attached carbon (C-4′) and on carbons in its *ortho* positions (C3′/C5′) is evident; where C-4′ appears as more deshielded and C3′/C5′ as a more shielded peak than their corresponding carbons in the unsubstituted phenyl-containing compounds **1a**, **2a** and **3a**. Conversely, the carbon directly attached to -CN in compounds **1c**, **2c** and **3c** is more shielded, whereas carbons at *ortho* positions (C3′/C5′) appear to be more deshielded than their corresponding carbons in compounds **1a**, **2a** and **3a** (Tables 1–3).

In anticipation of performing further modifications of the pirfenidone structure, the synthesis of a useful synthon **4** was achieved using the method adopted previously (El Bialy et al., 2011b) as outlined in Scheme 2. The previously prepared compound **2b** was boronated by palladium catalyzed cross-coupling reaction via its interaction with bis(pinacolato)diboron in the presence of bis(dibenzylideneacetone)palladium, $[Pd(dba)_2]$ as catalyst, tricyclohexylphosphine (PCy_3) as ligand, KOAc as base and anhydrous dioxane as solvent, at 80–90°C (El Bialy et al., 2011b).

The structure of compound **4** was verified by microanalytical and spectral analysis. Its ^{1}H NMR spectrum exhibits the presence of the three peaks at δ 7.67, 7.56 and 6.45, of one proton each, characteristic for the three pyridone protons. It also shows the two doublet peaks, of two protons each, showing an AB-system pattern at δ 7.33 and 7.03, characteristic for the four protons of the substituted phenyl group, which is also consistent with the results of compound **2b**. In addition, it shows one singlet at δ 1.25, equivalent for 12 protons assigned for the four methyl groups of the boronate ester.



No	R
1a	H
1b	OMe
1c	CN

No	R
2a	H
2b	OMe
2c	CN

No	R
3a	H
3b	OMe
3c	CN

Scheme 1 Synthesis of compounds **1a–c**, **2a–c** and **3a–c**. Reagents and conditions: (**i**) $Cu(OAc)_2{\cdot}H_2O$, pyridine, molecular sieves 4 Å, CH_2Cl_2.

	C2	C3	C4	C5	C6	C1′	C2′,6′	C3′,5′	C4′	CH3	Extra C
1a	160.4	120.2	136.1	114.0	143.0	141.0	126.7	129.0	127.9	16.3	–
1b	160.6	120.1	133.9	113.8	142.9	136.4	127.8	114.1	158.6	16.3	55.4 OCH_3
1c	160.1	120.3	135.2	110.7	144.6	143.5	128.0	133.1	114.6	16.3	118.3 CN

Table 1 ^{13}C NMR data of compounds **1a–c.**

^{13}C NMR spectrum of compound **4** shows eight peaks in the aromatic region equivalent to ten carbons. In the aliphatic region, it shows three different peaks which match the proposed structure, bearing in mind that the carbon atom directly attached to boron atom does not appear in the spectrum, which is consistent with the previously reported results for similar compounds (El Bialy et al., 2011b).

Conclusion

The synthesis of **1a–c**, **2a–c** and **3a–c** obtained under mild conditions by arylation of the appropriate heterocyclic amines with aryl boronic acids under Chan-Lam-Evans conditions is reported and analysis of their ^1H and ^{13}C NMR spectral data is presented. The biological evaluation of the possible antifibrotic activity of these compounds will be completed and published elsewhere.

Experimental

Melting points were recorded using a Thomas-Hoover (Uni-Melt) capillary melting point apparatus and are uncorrected. Thin layer chromatography (TLC) analysis was carried out on silica gel 60 F 254 precoated aluminum sheets and detected under UV light. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 employing a Bruker Avance 400 MHz spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA, USA). All chemicals and solvents were purchased from Aldrich Chemical Co. or VWR.

Preparation of 5-methyl-*N*-aryl-(1*H*)-pyridin-2-ones 1a–c

A mixture of 5-methylpyridin-2(1*H*)-one (1.09 g, 0.01 mol), the appropriate aryl boronic acid (0.012 mol), Cu(II) acetate monohydrate (2.74 g, 0.014 mol), pyridine (1.6 mL, 0.02 mol), molecular sieves 4 Å (7 g) and CH_2Cl_2 (25 mL) was stirred for 24 h at room temperature. The solvent was evaporated and the residue was stirred with EtOAc (2×200 mL) and filtered. The combined organic layers were transferred into a separating funnel, washed with water and brine solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using EtOAc/hexanes (9:1) as eluent. The three targeted compounds **1a–c** appeared previously in the literature (Li and Dixon, 2004; Blatt et al., 2006; Kossen et al., 2009) respectively; however, no physical or spectral data were reported.

5-Methyl-*N*-phenyl-(1*H*)-pyridin-2-one (1a, pirfenidone) Yield 12%; mp 99–101°C; ^1H NMR: δ 7.52 (s, 1H, H-6), 7.49 (d, 1H, J = 8 Hz, H-4), 7.44–7.37 (m, 5H, Ar-H), 6.43 (d, 1H, J = 8 Hz, H-3), 2.05 (s, 3H, CH_3); ^{13}C NMR: δ 160.4 (C-2), 143.0 (C-6), 141.0 (C-1′), 136.1 (C-4), 129.0 (C-3′-5′), 127.9 (C-4′), 126.7 (C-2′-6′), 120.2 (C-3), 114.0 (C-5), 16.3 (CH_3). Anal. Calcd for $C_{12}H_{11}NO$ (185.22): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.52; H, 6.17; N, 7.36.

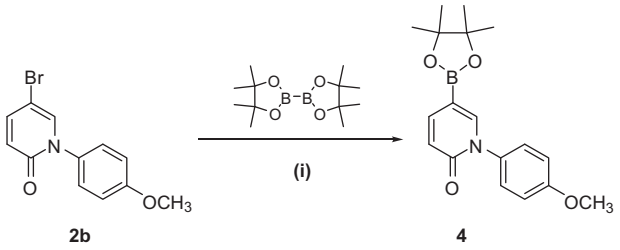
5-Methyl-*N*-(4-methoxyphenyl)-(1*H*)pyridin-2-one (1b) Yield 18%; mp 95–96°C; ^1H NMR: δ 7.39 (s, 1H, C-6), 7.36 (d, 1H, J = 9 Hz

	C2	C3	C4	C5	C6	C1′	C2′,6′	C3′,5′	C4′	Extra C
2a	159.8	122.0	138.7	97.0	143.2	140.0	129.1	128.4	129.1	–
2b	160.1	121.8	132.9	96.8	143.0	139.0	127.9	114.1	159.0	55.5 OCH_3
2c	159.6	118.2	122.1	97.6	143.6	138.1	128.2	133.2	111.2	116.4 CN

Table 2 ^{13}C NMR data of compounds **2a–c**.

	C2	C4	C5	C6	C1′	C2′,6′	C3′,5′	C4′	Extra C
3a	153.6	159.8	115.7	152.0	137.1	127.1	129.2	129.0	–
3b	159.4	160.0	114.3	152.3	128.3	129.8	115.5	153.5	55.5 OCH_3
3c	153.3	159.2	115.5	151.1	140.7	128.1	133.0	111.7	117.1 CN

Table 3 ^{13}C NMR data of compounds **3a–c**.



2b 4

Scheme 2 Synthesis of compound **4**. Reagents and conditions: (**i**) bis(dibenzylideneacetone) palladium, tricyclohexylphosphine, KOAc, dioxane, 80–90°C.

H-4), 7.29 (d, 2H, *J* = 8 Hz, H-2′-6′), 7.02 (d, 2H, *J* = 8 Hz, H-3′-5′), 6.40 (d, 1H, *J* = 9 Hz, H-3), 3.80 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3); ^{13}C NMR: δ 160.6 (C-2), 158.6 (C-4′), 142.9 (C-6), 136.4 (C-1′), 133.9 (C-4), 127.8 (C-2′-6′), 120.1 (C-3), 114.1 (C-3′-5′), 113.8 (C-5), 55.4 (OCH_3), 16.3 (CH_3). Anal. Calcd for $C_{13}H_{13}NO_2$ (215.25): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.43; H, 6.21; N, 6.33.

5-Methyl-*N*-(4-cyanophenyl)-(1*H*)-pyridin-2-one (**1c**) Yield 26%; mp 188–189°C; ^{1}H NMR: δ 7.99 (d, 2H, *J* = 8 Hz, H-3′-5′), 7.66 (d, 2H, *J* = 8 Hz, H-2′-6′), 7.48 (s, 1H, H-6), 7.41 (d, 1H, *J* = 9 Hz, H-4), 6.46 (d, 1H, *J* = 9 Hz, H-3), 2.05 (s, 3H, CH_3); ^{13}C NMR: δ 160.1 (C-2), 144.6 (C-6), 143.5 (C-1′), 135.2 (C-4), 133.1 (C-3′-5′), 128.0 (C-2′-6′), 120.3 (C-3), 118.3 (CN), 114.6 (C-4′), 110.7 (C-5), 16.3 (CH_3). Anal. Calcd for $C_{13}H_{10}N_2O$ (210.23): C, 74.27; H, 4.79; N, 13.33. Found: C, 73.98; H, 4.94; N, 13.18.

Preparation of 5-bromo-*N*-aryl-(1*H*)-pyridin-2-ones 2a–c

Following the same procedure adopted for the preparation of compounds **1a–c**, compounds **2a–c** were prepared using 5-bromopyridin-2(1*H*)-one (1.74 g, 0.01 mol), as a starting material instead of 5-methylpyridin-2(1H)-one. The targeted compounds **2a,b** appeared previously in the literature (Li and Dixon, 2004); however, no physical or spectral data were reported.

5-Bromo-*N*-phenyl-(1*H*)-pyridin-2-one (2a) Yield 56%; mp 76–78°C; ^{1}H NMR: δ 7.94 (d, 1H, *J* = 2 Hz, H-6), 7.62 (dd, 1H, *J* = 2, 10 Hz, H-4), 7.51 (t, 2H, *J* = 7 Hz, H-3′,5′), 7.46 (t, 1H, *J* = 7 Hz, H-4′), 7.42 (d, 2H, *J* = 7 Hz, H-2′-6′), 6.48 (d, 1H, *J* = 10 Hz, H-3); ^{13}C NMR: δ 159.8 (C-2), 143.2 (C-6), 140.0 (C-1′), 138.7 (C-4), 129.1 (C-3′-5′), 128.4 (C-4′), 126.8 (C-2′-6′), 122.0 (C-3), 97.0 (C-5). Anal. Calcd for $C_{11}H_8BrNO$ (250.09): C, 52.83; H, 3.22; N, 5.60. Found: C, 53.12; H, 3.07; N, 5.52.

5-Bromo-*N*-(4-methoxyphenyl)-(1*H*)-pyridin-2-one (2b) Yield 37%; mp 97–99°C; ^{1}H NMR: δ 7.90 (d, 1H, 2 Hz, H-6), 7.59 (dd, 1H, *J* = 2, 9.8 Hz, H-4), 7.33 (d, 2H, *J* = 9 Hz, H-2′-6′), 7.03 (d, 2H, *J* = 9 Hz, H-3′-5′), 6.45 (d, 1H, *J* = 9.8 Hz, H-3), 3.80 (s, 3H, OCH_3); ^{13}C NMR: δ 160.1 (C-2), 159.0 (C-4′), 143.0 (C-6), 139.0 (C-1′), 132.9 (C-4), 127.9 (C-2′-6′), 121.8 (C-3), 114.1 (C-3′-5′), 96.8 (C-5), 55.5 (OCH_3). Anal. Calcd for $C_{12}H_{10}BrNO_2$ (280.12): C, 51.45; H, 3.60; N, 5.00. Found: C, 51.72; H, 3.59; N, 5.02.

5-Bromo-*N*-(4-cyanophenyl)-(1*H*)-pyridin-2-one (2c) Yield 15%; mp 196–200°C; ^{1}H NMR: δ 8.03 (d, 1H, *J* = 3 Hz, H-6), 8.00 (d, 2H, *J* = 8 Hz, H-3′-5′), 7.69 (d, 2H, *J* = 8 Hz, H-2′-6′), 7.65 (dd, 1H, *J* = 3, 10 Hz, H-4), 6.50 (d, 1H, *J* = 10 Hz, H-3); ^{13}C NMR: δ 159.6 (C-2), 143.6 (C-6), 138.1 (C-1′), 133.2 (C-3′-5′), 128.2 (C-2′-6′), 122.1 (C-4), 118.2 (C-3), 116.4 (CN), 111.2 (C-4′), 97.6 (C-5). Anal. Calcd for $C_{12}H_7BrN_2O$ (275.10): C, 52.39; H, 2.56; N, 10.18. Found: C, 52.64; H, 2.43; N, 10.00.

Preparation of *N*^{3}-aryl-pyrimidin-4-ones 3a–c

Following the same procedure adopted for the preparation of compounds **1a–c**, compounds **3a–c** were prepared using pyrimidin-4(3*H*)-one (0.96 g, 0.01 mol), as a starting material instead of 5-methylpyridin-2(1*H*)-one. Products were purified by column chromatography on silica gel, using EtOAc/hexane (7:3) as eluent. The targeted compound **3a** appeared in the literature (Stajer et al., 1987); however, no spectral data were reported.

3-Phenyl-(3*H*)-pyrimidin-4-one (3a) Yield 14%; mp 146–148°C (lit. mp 147–149°C); ^{1}H NMR: δ 8.41 (s, 1H, H-2), 7.99 (d, 1H, *J* = 6 Hz, H-6), 7.55 (t, 2H, *J* = 7 Hz, H-3′-5′), 7.513 (d, 1H, *J* = 7 Hz, H-4′), 7.47 (d, 2H, *J* = 7 Hz, H-2′-6′), 6.52 (d, 1H, *J* = 6 Hz, H-5); ^{13}C NMR: δ 159.8 (C-4), 153.6 (C-2), 152.0 (C-6), 137.1 (C-1′), 129.2 (C-3′-5′), 129.0 (C-4′), 127.1 (C-2′-6′), 115.7 (C-5).

3-(4-Methoxyphenyl)-(3*H*)-pyrimidin-4-one (3b) Yield 25%; mp 212°C; ^{1}H NMR: δ 8.40 (s, 1H, H-2), 7.97 (d, 1H, *J* = 6 Hz, H-6), 7.38 (d, 2H, *J* = 9 Hz, H-2′-6′), 7.07 (d, 2H, *J* = 9 Hz, H-3′-5′), 6.49 (d, 1H, *J* = 6 Hz, H-5), 3.81 (s, 3H, OCH_3); ^{13}C NMR: δ 160.0 (C-4), 159.4 (C-2), 153.5 (C-4′), 152.3 (C-6), 129.8 (C-2′-6′), 128.3 (C-1′), 115.5 (C-3′-5′), 114.3 (C-5), 55.5 (OCH_3). Anal. Calcd for $C_{11}H_{10}N_2O_2$ (202.21): C, 67.00; H, 3.58; N, 21.31. Found: C, 67.21; H, 3.69; N, 21.04.

3-(4-Cyanophenyl)-(3*H*)-pyrimidin-4-one (3c) Yield 10%; mp 214°C; ^{1}H NMR: δ 8.44 (s, 1H, H-2), 8.02 (d, 2H, *J* = 8 Hz, H-3′-5′), 7.99 (d, 1H, *J* = 6 Hz, H-6), 7.73 (d, 2H, *J* = 8 Hz, H-2′-6′), 6.53 (d, 1H, *J* = 6 Hz H-5); ^{13}C NMR: δ 159.2 (C-4), 153.3 (C-2), 151.1 (C-6), 140.7 (C-1′), 133.0 (C-3′-5′), 128.1 (C-2′-6′), 117.1 (CN), 115.5 (C-5), 111.7 (C-4′). Anal. Calcd for $C_{11}H_7N_3O$ (197.19): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.61; H, 4.89; N, 13.71.

Preparation of *N*-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-(1*H*)-pyridin-2-one (4)

Bis(dibenzylideneacetone) palladium (0.143 g, 0.25 mmol) and tricyclohexyl phosphine (0.168 g, 0.6 mmol) were added to a two-necked flask containing degassed dioxane (30 mL). The solution was stirred for 30 min at 25°C. Compound **2b** (1.4 g, 5 mmol), KOAc (0.736 g, 7.5 mmol) and bis(pinacolato)diboron (1.4 g, 5.5 mmol) were added sequentially, and the mixture was vigorously stirred. The mixture was warmed to 90–100°C for 24 h, while stirring under nitrogen atmosphere. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (150 mL). The solution was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, using EtOAc/hexanes (2:8)

as eluent: yield 37%; mp 140°C; ^{1}H NMR: δ 7.67 (s, 1H, H-6), 7.56 (d, 1H, *J* = 9 Hz, H-4), 7.33(d, 2H, *J* = 9 Hz, H-2′-6′), 7.03 (d, 2H, *J* = 9 Hz, H-3′-5′), 6.45 (d, 1H, *J* = 9 Hz, H-3), 3.81 (s, 3H, OCH_3), 1.25 (s, 12H, 4 CH_3); ^{13}C NMR: δ 161.6 (C-2), 158.9 (C-4′), 146.7 (C-6), 143.4 (C-1′), 133.3 (C-4), 127.8 (C-2′-6′), 120.0 (C-3), 114.2 (C-3′-5′), 83.8 (2 C-O), 55.4 (OCH_3), 24.6 (4 CH_3). Anal. Calcd for $C_{18}H_{22}BNO_4$ (327.18): C, 66.08; H, 6.78; N, 4.28. Found: C, 66.23; H, 6.90; N, 4.31.

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