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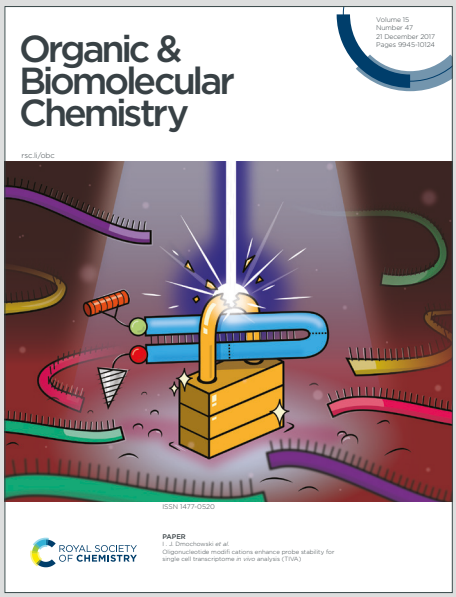

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One-pot Access to 2-Amino-3-arylbenzofurans: Direct Entry to Polyheterocyclic Chemical Spaces

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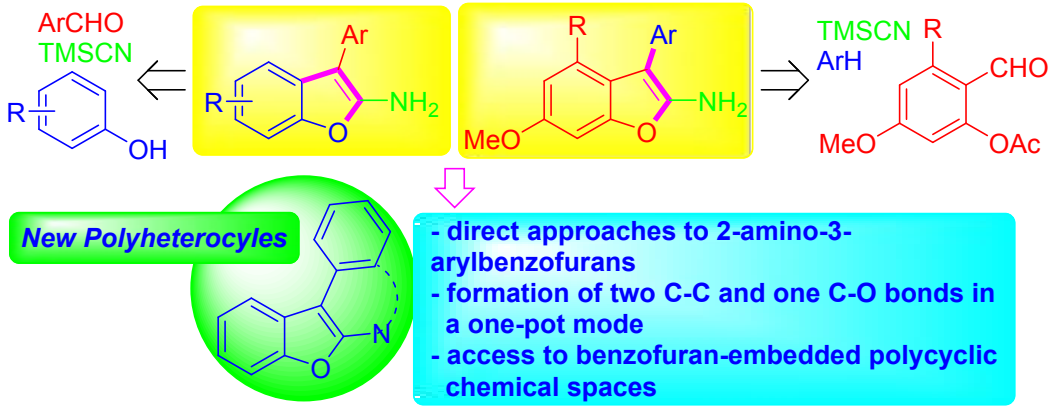
Exploitation of one-pot sequential assembly reactions provides two efficient synthetic routes to 2-amino-3-arylbenzofurans, versatile intermediates of novel polyheterocycles.



Abstract: As a means to make new benzofuran-embedded polycyclic structures, we established two efficient one-pot sequential coupling routes to 2-amino-3-arylbenzofurans and 2-amino-3-arylnaphtho[2,1-*b*]furans. Further ring formation (six- and seven-membered rings)

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with the resulting amine moiety at the C2 position of benzofurans was realized, leading to more expansion of benzofuran-based chemical space.

Keywords: Benzofuran; One-pot Reaction; Polycyclic Heteroaromatics; Hybrid structure; Chemical space; Diversity-oriented synthesis; Atom-economy

Introduction

In connection with a growing interest on polycyclic heteroaromatic systems[1] in various research fields such as medicinal and material chemistry, extension of polyaromatic chemical space through design and synthesis of new chemical scaffolds is highly required. In particular, it is desirable to assemble polyaromatic heterocycles by strategic use of one-pot coupling reactions,[2] thereby increasing the overall efficiency of the synthetic protocols. For example, great advances have been made in the syntheses of polycyclic benzofurans along this line due to their versatile properties including biological, electrochemical, and photochemical ones.[3] Recently, we have recently communicated on one-pot three-component approaches to diarylacetonitriles[4] and diarylmethylphosphonates[5] as versatile intermediates to get direct access to polyaromatic systems (Scheme 1a).

Scheme 1. Synthetic Plans

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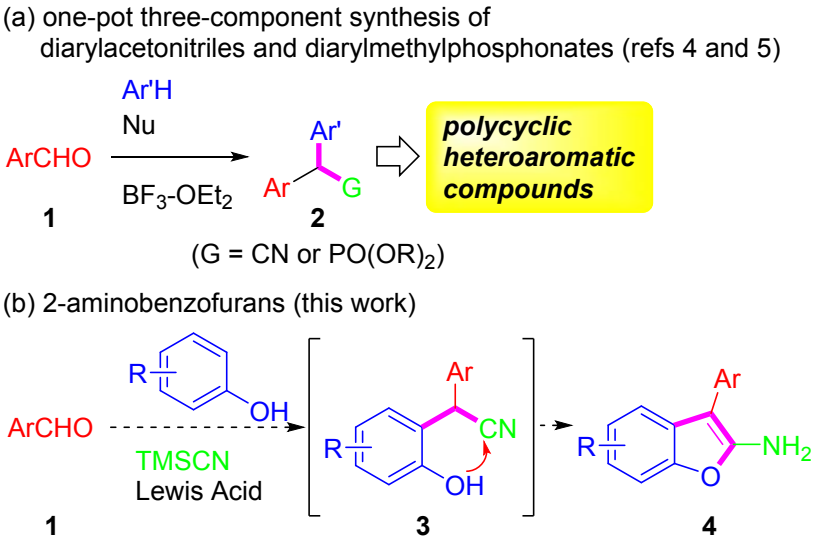

To extend these protocols, we envisioned that use of phenol as an electron-rich arene in coupling with aldehyde **1** and TMSCN in the presence of Lewis acid would lead to 2-aminobenzofuran **4** via further cyclization of intermediate **3** (Scheme 1b). Despite the importance of these compounds and their derivatives in the fields of medicinal and material science,[6] synthetic methods to get access to highly functionalized 2-aminobenzofurans are very limited.[7] As part of our synthetic efforts to broaden benzofuran chemical spaces,[8] here we wish to describe one-pot syntheses of 2-amino-3-arylbenzofurans and 2-amino-3-arylnaphtho[2,1-*b*]furans from commercially available starting materials.

Results and discussion

Reaction optimization was carried out with 3,4-dimethoxybenzaldehyde **(1a)**, 3,4-dimethoxyphenol, and TMSCN (Table 1).[9] Two conditions (**A** and **B**) were examined. In conditions **A**, 3,4-dimethoxyphenol was added to the premixed solution of aldehyde **1a**, TMSCN, and catalyst in appropriate solvent after 30 min. Unfortunately, the desired **4a** was not formed under various Lewis acid catalytic systems (entries 1-8). **3a** was isolated in variable

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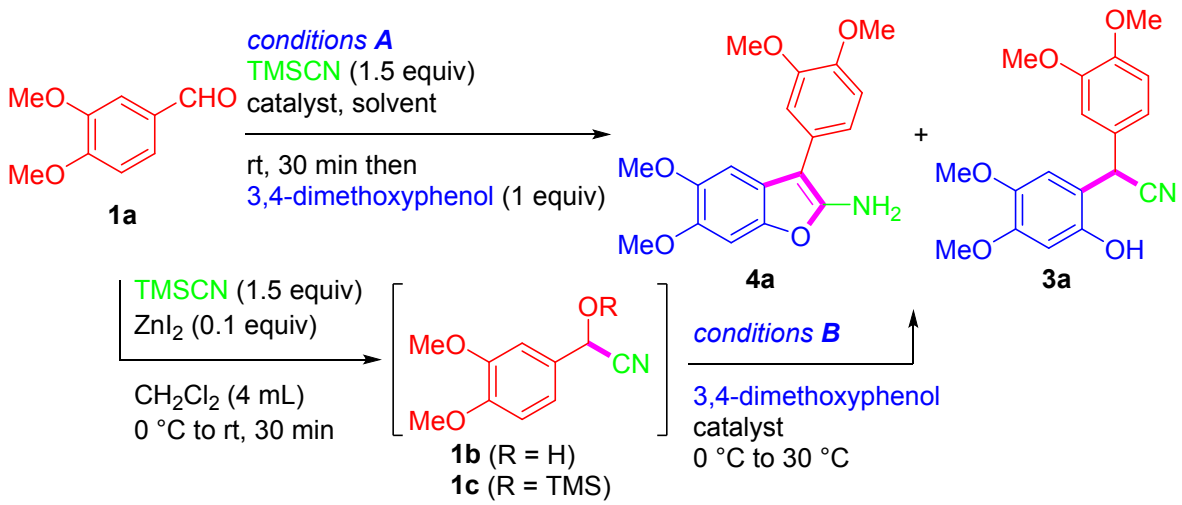
yields along with the recovered starting materials. When excess BF_3-OEt_2 (1.2 equiv to 2 equiv) was used, 2-aminobenzofuran **4a** was obtained in 20-47% yields (entries 9-11). In conditions **B**, cyanohydrin **1b** or **1c** was first formed by the action of ZnI_2 (0.1 equiv) before 3,4-dimethoxyphenol and additional catalyst were added.[10] While catalytic amount of $Bi(OTf)_3$, Ag(OTf), or $Cu(OTf)_2$ still gave **3a** as a major product, BF_3-OEt_2 (1.2 equiv) furnished **4a** (40%) and **3a** (31%) (entries 12-15). When BF_3-OEt_2 (2 equiv) was used, the best result was observed (entries 16 and 17).

Table 1. Reaction Optimization[a]



entry	catalyst (equiv)	solvent	time (h)	yield (%)[b]		
	conditions A			**1b**	**4a**	**3a**
1	$Bi(OTf)_3$ (0.2)	DCM	48	10	-	51
2	Ag(OTf) (0.2)	DCM	48	30	-	42
3	$Cu(OTf)_2$ (0.2)	DCM	48	20	-	38
4	$Yb(OTf)_3$ (0.2)	DCM	48	32	-	10
5	$Sc(OTf)_3$ (0.2)	DCM	48	10	-	20
6	$Zn(OTf)_2$ (0.2)	DCM	48	41	-	trace
7	$FeCl_3$ (0.2)	DCM	24	-	trace	34
8	ZnI_2 (0.2)	DCM	48	80	-	-
9	BF_3-OEt_2 (1.2)	DCM	24	-	20	31
10	BF_3-OEt_2 (1.5)	DCM	24	-	31	32
11	BF_3-OEt_2 (2.0)	DCM	48	-	47	15
	conditions B					

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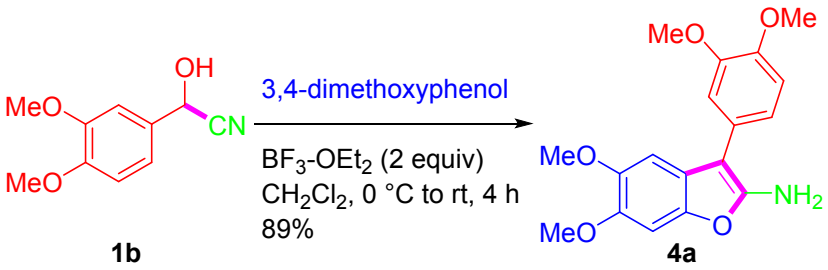
12	$Bi(OTf)_3$ (0.2)	DCM	24	-	trace	57
13	Ag(OTf) (0.2)	DCM	24	-	trace	68
14	$Cu(OTf)_2$ (0.2)	DCM	24	-	-	54
15	BF_3-OEt_2 (1.2)	DCM	24	-	40	31
16	BF_3-OEt_2 (1.5)	DCM	24	-	52	34
17	BF_3-OEt_2 (2.0)	DCM	14	-	78	10

[a] A mixture of **1a** (100 mg, 0.6 mmol, 1 equiv), TMSCN (1.5 equiv), 3,4-dimethoxyphenol (1 equiv), and catalyst in solvent (4 mL) was used. [b] Isolated yield (%).

To see if the reaction proceeded via cyanohydrin, the isolated intermediate **1b** was treated with 3,4-dimethoxyphenol and BF_3-OEt_2 (2 equiv) to afford **4a** in 89% yield (Scheme 2).

Scheme 2. Conversion of 1b to 4a



With these optimized conditions in hand, the reaction scope was first examined with various aldehydes and 3,4-dimethoxyphenol (Table 2). Overall, the corresponding 2-amino-3-arylbenzofurans **4b-l** were obtained in good to excellent yields. Uncyclized diarylacetontriles **3** were isolated as minor products in some cases (**3c**, **3e**, and **3g**). In case of *N*,*N*-dimethylaniline as a nucleophile, **3i** was obtained as a major product. Transformation of **3a** to **4a** was readily achieved upon exposure of **3a** to BF_3-OEt_2 in CH_2Cl_2 (Scheme 3). Thiophene-2-carboxaldehyde was employed to give 2-aminobenzofuran **4l** bearing a heterocycle at C3 site. As noted in our previous work, aldehydes bearing electron-donating group(s) at *ortho*-, and/or *para*-position(s) seemed to be crucial for successful three-component coupling process, implying the importance of resonance stabilization of the reaction intermediates, cyanohydrins, by alkoxyl and/or hydroxyl at *ortho*-, and/or *para*-position(s) under these conditions.[11]

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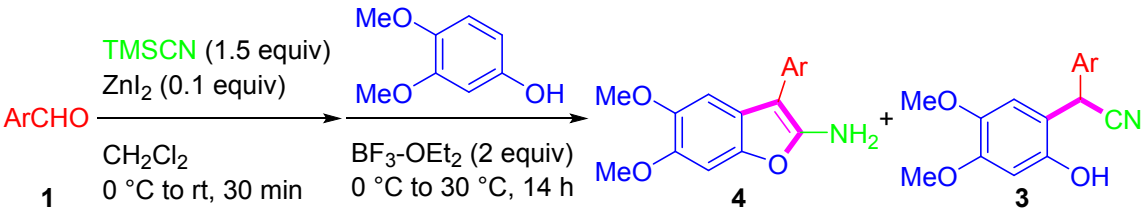
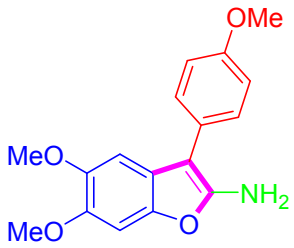
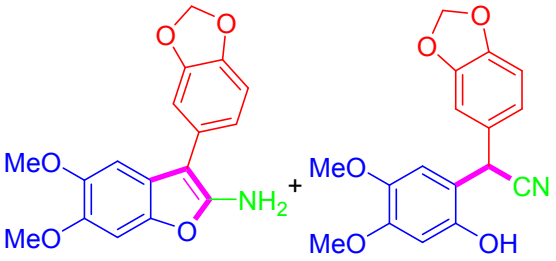
Table 2. Synthesis of 4 with 3,4-Dimethoxyphenol[a]

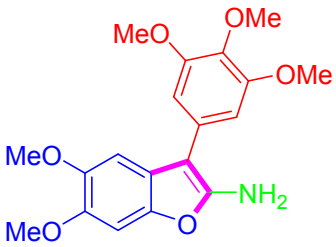




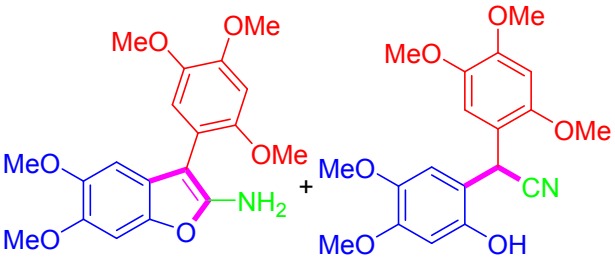
4b (83%)[b]



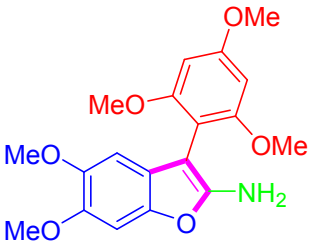
4c (64%) + **3c** (16%)



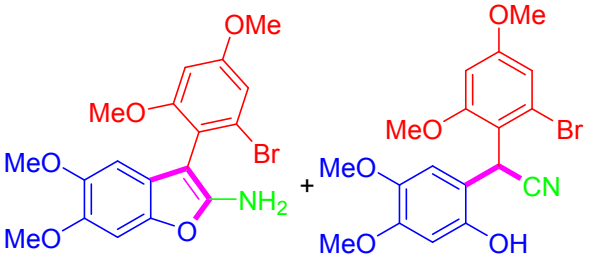
4d (72%)



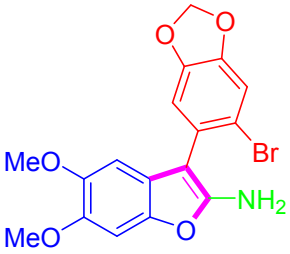
4e (80%) + **3e** (9%)



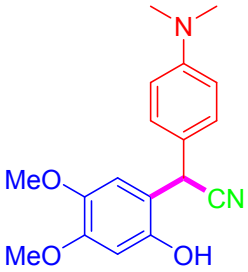
4f (62%)



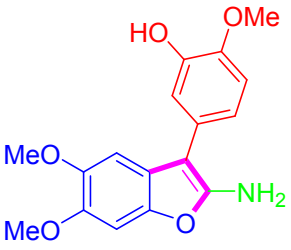
4g (74%) + **3g** (7%)



4h (44%)



3i (82%)



4j (61%)

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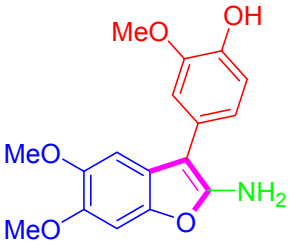
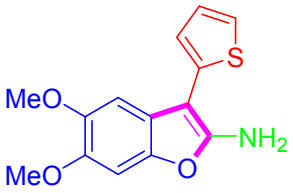


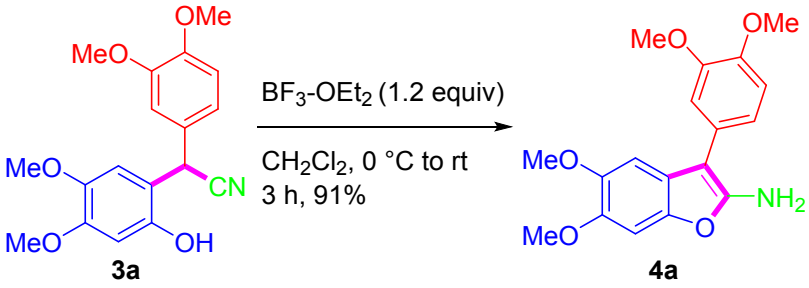
4k (54%)



4l (47%)

[a] After a mixture of **1** (100 mg, 1 equiv), TMSCN (1.5 equiv), and ZnI_2 (0.1 equiv) in DCM (4 mL) was stirred at rt for 30 min, 3,4-dimethoxyphenol (1 equiv) and BF_3-Et_2O (2 equiv) were added at 0 °C. The reaction mixture was stirred at 30 °C for 14 h. [b] Isolated yield (%).

Scheme 3. Conversion of 3a to 4a



Next, this coupling was carried out with different phenols. As shown in Table 3, variously substituted phenols were successfully employed as nucleophiles in this process to furnish the corresponding 2-amino-3-arylbenzofurans. Alkoxyl, alkyl, aryl, or halogen substituent of the phenol was well tolerated under these conditions. Use of 2-naphthol produced 2-amino-3-arylnaphtho[2,1-*b*]furans **4u-x**. When 3-methoxyphenol and 3-phenylphenol were used, respectively, the desired 2-aminobenzofurans (**4y** and **4aa**) were isolated as minor products. The uncyclized adducts (**4y'** and **4aa'**) were obtained as major products as a consequence of alternative nucleophilic attack of phenols to the intermediates, cyanohydrins. Surprisingly, 4-bromophenol gave unwanted adduct **4z'** whereas 4-chlorophenol provided the desired 2-aminobenzofuran **4r**. Interestingly, the isomerized products (**4ab'** and **4ac'**) were mainly observed from the reactions with 3,4,5-trimethoxyphenol. We believe that this isomerization

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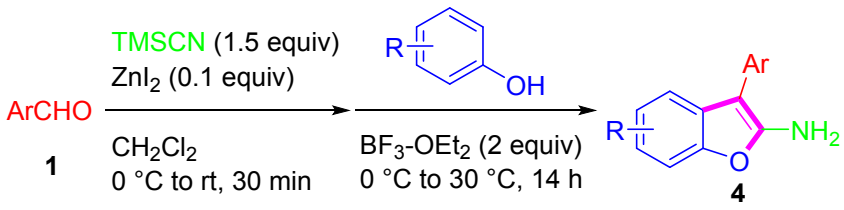
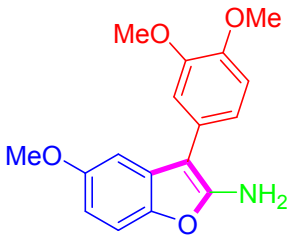
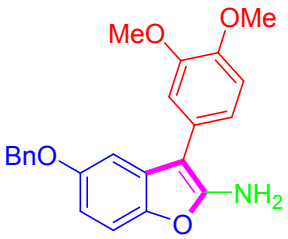
may be caused to avoid the steric clash between methoxyl and aryl at the C3 site of benzofuran (Scheme 4). An sp^3 carbon at the C3 position via isomerization would be expected to release the steric strain.

Table 3. Synthesis of 4 with Different Phenols or 2-Naphthol[a]

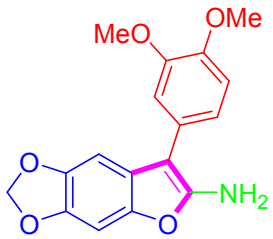




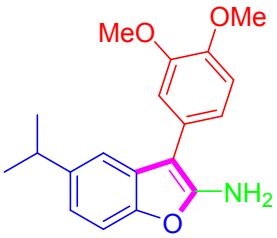
4m (78%)[b]



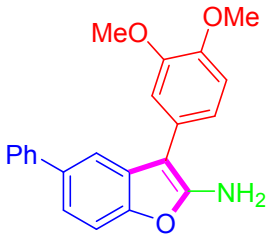
4n (70%)



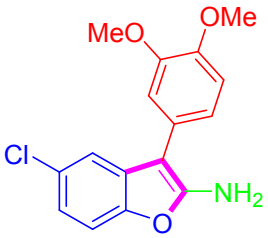
4o (75%)



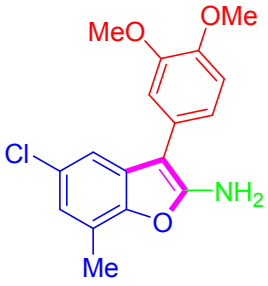
4p (70%)



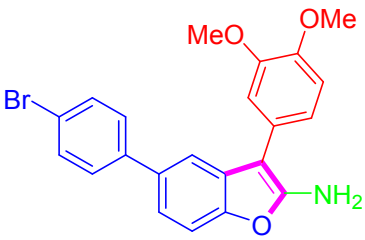
4q (71%)



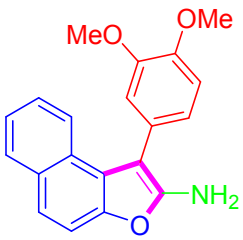
4r (63%)



4s (61%)



4t (60%)



4u (70%)

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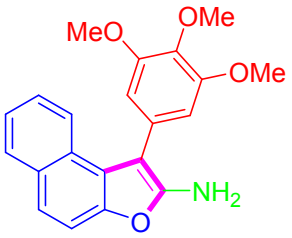
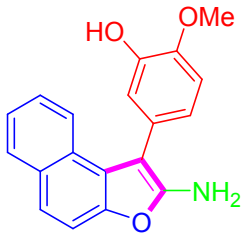
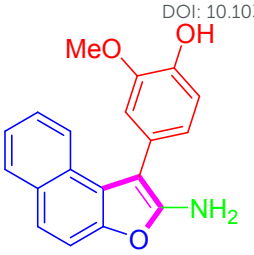


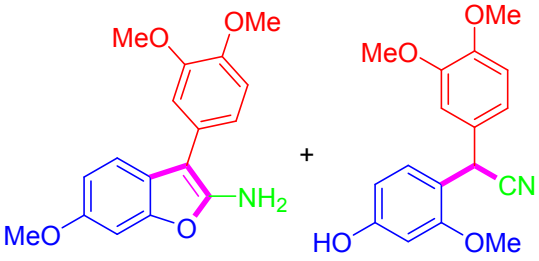
4v (63%)



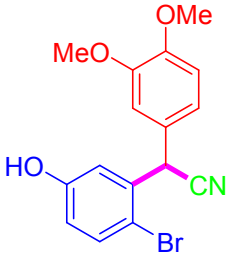
4w (50%)



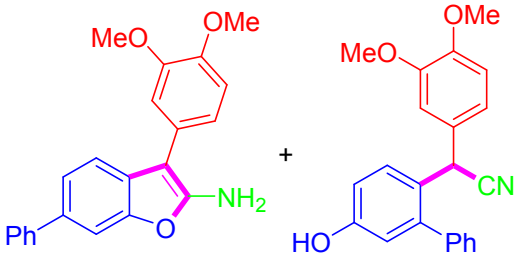
4x (47%)



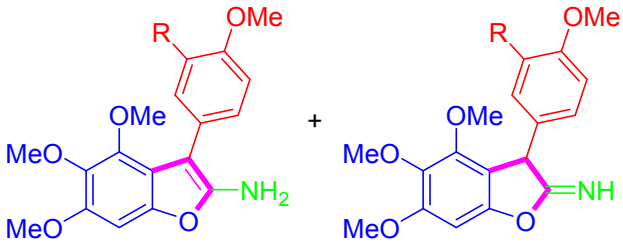
4y (21%) + **4y'** (60%)



4z' (58%)



4aa (20%) + **4aa'** (63%)



R = OMe: **4ab** (4%) + **4ab'** (56%)

R = H: **4ac'** (51%)

[a] After a mixture of **1** (100 mg, 1 equiv), TMSCN (1.5 equiv), and ZnI_2 (0.1 equiv) in DCM (4 mL) was stirred at rt for 30 min, phenol or 2-naphthol (1 equiv) and BF_3-Et_2O (2 equiv) were added at 0 °C. The reaction mixture was stirred at 30 °C for 14 h. [b] Isolated yield (%).

Scheme 4. Rationale for the Formation of 4ab' and 4ac'

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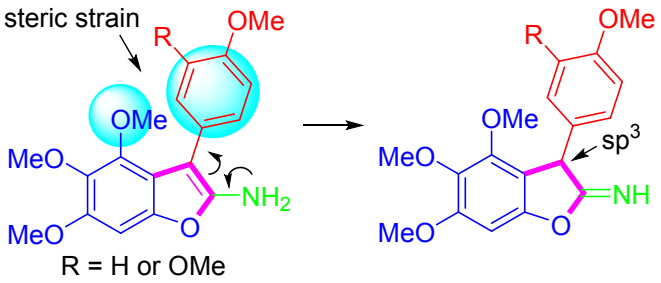
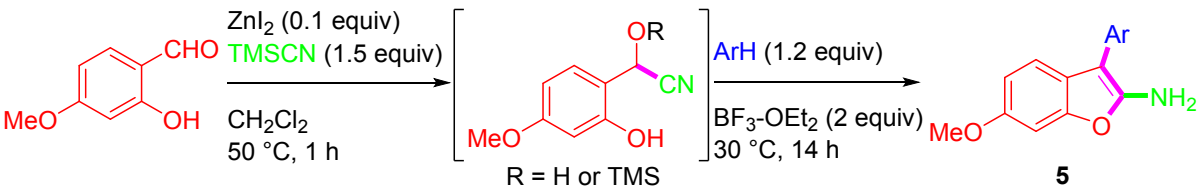


In the meantime, we also investigated the possibility that the corresponding 2-amino-3-arylbenzofurans **5** would be formed by participation of the neighboring hydroxyl group when salicylaldehydes such as 4-methoxy-2-hydroxybenzaldehyde were allowed to react with TMSCN and arene(s) in the presence of Lewis acid (Table 4). Indeed, this combination provided access to 2-amino-3-arylbenzofurans **5a-d** albeit in modest yields. After some optimization, however, we discovered that protection of the hydroxyl as an acetate improves the efficiency of this process (Table 5). Although this protection did not allow direct cyclization after three-component coupling event, the overall yields of this two-step procedure were much better than the one-pot process shown in Table 4. Thus, 2-acetoxybenzaldehydes **6** were employed to make diarylacetonitriles **7**, which underwent base-mediated cyclization[12] to furnish **5**.

Table 4. Synthesis of 5a-d[a]



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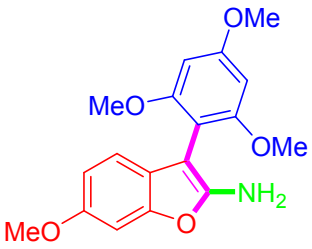
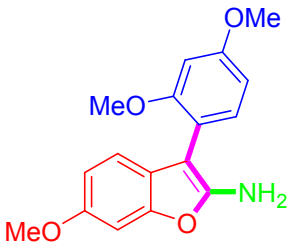
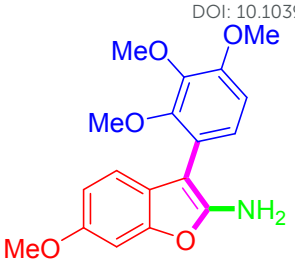


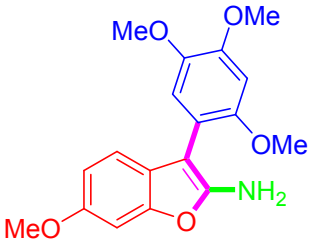
5a (38%)[b]



5b (40%)



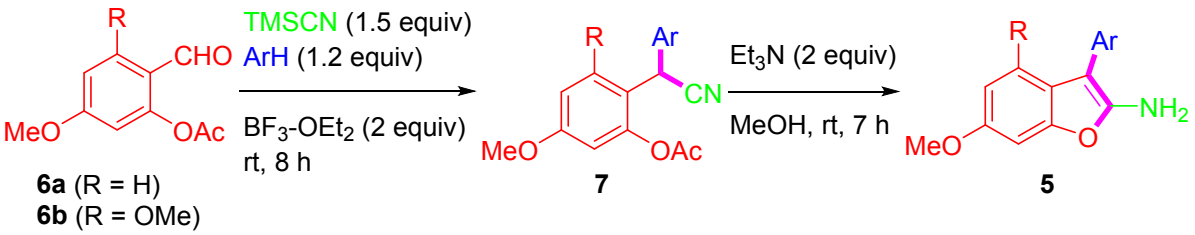
5c (39%)



5d (48%)

[a] After a mixture of 2-hydroxy-4-methoxybenzaldehyde (100 mg, 0.66 mmol, 1 equiv), TMSCN (1.5 equiv), and ZnI_2 (0.1 equiv) in DCM (4 mL) was stirred at 50 °C for 1 h, ArH (1.2 equiv) and BF_3-Et_2O (2 equiv) were added at 0 °C. The reaction mixture was stirred at 30 °C for 14 h. [b] Isolated yield (%).

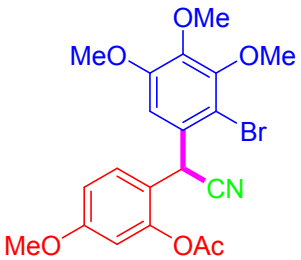
Table 5. Synthesis of 5e-5j[a]



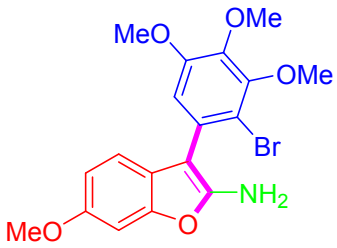
6a (R = H)
6b (R = OMe)

7

5



7e (95%)[b]



5e (92%)

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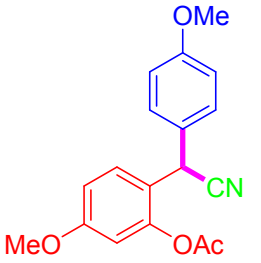
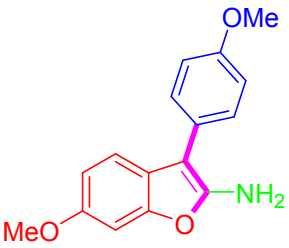
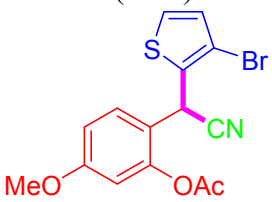


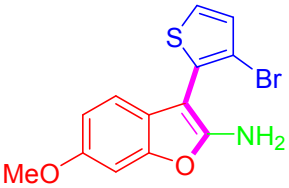
7f (81%)



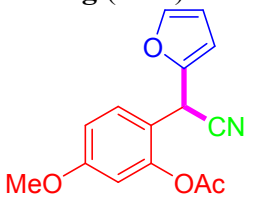
5f (87%)



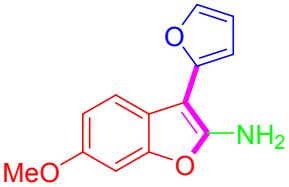
7g (68%)



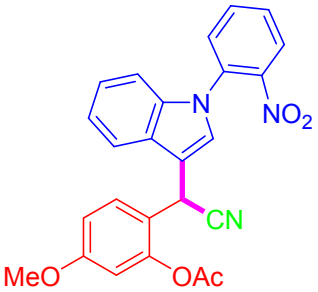
5g (89%)



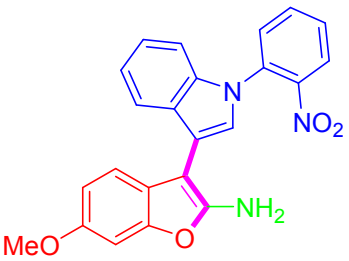
7h (61%)[c]



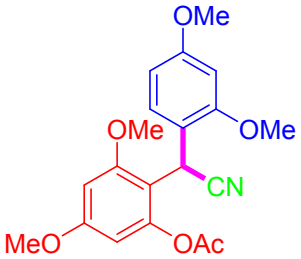
5h (74%)



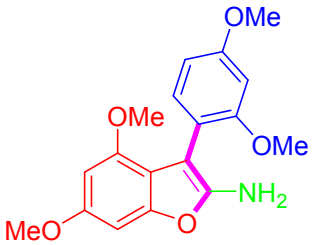
7i (60%)



5i (77%)



7j (84%)



5j (73%)

[a] A mixture of **6** (100 mg, 1 equiv), ArH (1.2 equiv), TMSCN (1.5 equiv), and BF_3-Et_2O (2 equiv) in DCM (4 mL) was stirred at rt for 8 h. A mixture of **7** (50 mg, 1 equiv) and Et_3N (2 equiv) in MeOH (4-5 mL) was stirred at rt for 7 h. [b] Isolated yield (%). [c] Furan (2.5 equiv) was used.

Next, further synthetic elaboration of the resulting 2-amino-3-arylbenzofurans was attempted.

As shown in Table 6, reaction conditions for oxidative Pictet-Spengler ring closure[13] of **4a**

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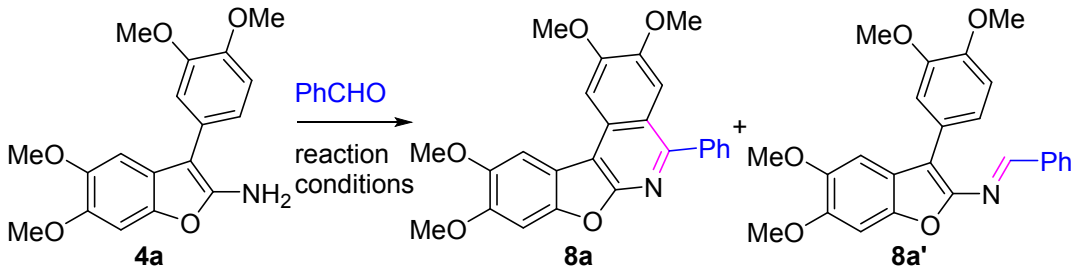
were optimized. While formation of imine **8a'** was so facile in the presence of TFA, DBSA, BF_3-OEt_2, or $FeCl_3$, the desired ring cyclized product **8a** was not observed in most cases (entries 1-8). Although reaction with $Yb(OTf)_3$ (0.2 equiv) at rt gave an excellent yield of **8a'**, reaction at 90 °C provided a mixture of **8a** (35) and **8a'** (51) (entries 9 and 10). Toluene as a solvent rather resulted in inferior outcome (entry 11). Finally, $Yb(OTf)_3$-catalyzed reaction in DCE at 130 °C delivered benzofuran-isoquinoline hybrid[14,15] skeleton **8a** in 89% yield (entry 12).

Table 6. Synthetic Application: Oxidative Pictet-Spengler Reaction[a]



entry	catalyst (equiv)	solvent	temperature (°C)	time (h)	yield (%)[b] **8a**	**8a'**
1	TFA (0.2)	DCM	rt	1.5		86
2	TFA (0.2)	DCM	60	24		79
3	DBSA (0.1)	THF	60	1		87
4	DBSA (0.1)	THF	60	24		81
5	PTSA (0.2)	THF	60	4		72
6	DBSA (0.2)	toluene	120	22	trace	70
7	BF_3-OEt_2 (1.2)	DCE	80	32	16	61
8	$FeCl_3$ (0.1)	DCE	80	24		45
9	$Yb(OTf)_3$ (0.2)	DCE	rt	3		97
10	$Yb(OTf)_3$ (0.2)	DCE	90	12	35	51
11	$Yb(OTf)_3$ (0.2)	toluene	130	12	15	41
12	$Yb(OTf)_3$ (0.2)	DCE	130	14	89	

[a] To a mixture of **4a** (50 mg, 0.15 mmol, 1 equiv) and benzaldehyde (0.3 mmol, 2 equiv) in solvent (2 mL) was added catalyst at rt. The reaction mixture was stirred at the indicated temperature for the indicated time. [b] Isolated yield (%).

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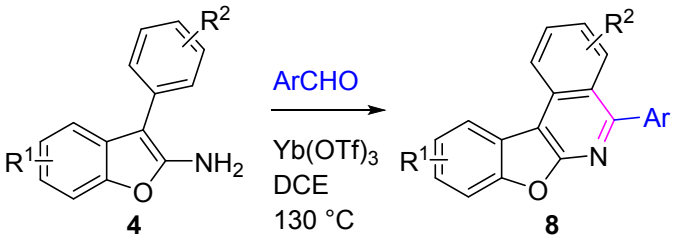
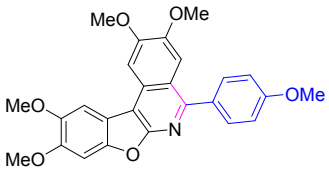
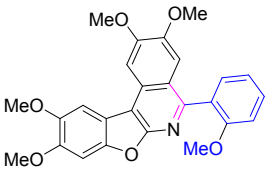
Under these conditions, several 2-amino-3-arylbenzofurans were converted to the corresponding fluorescent polycyclic products **8** (Table 7). Electron-rich as well as electron-poor arylaldehydes were incorporated in the range of 30-94% yields. Use of *trans*-cinnamaldehyde in this reaction provided **8h** albeit in modest yield.

Table 7. Synthesis of 8[a]

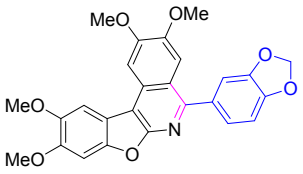




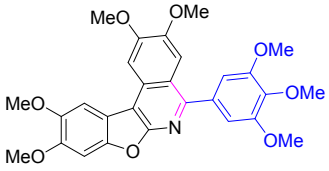
8b (88%, 38 h)[b]



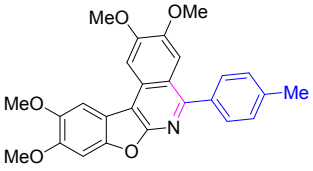
8c (91%, 27 h)



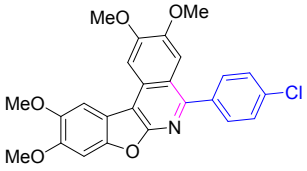
8d (30%, 50 h)



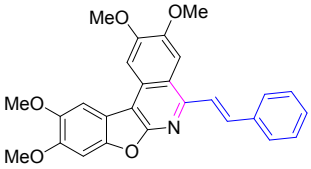
8e (30%, 40 h)



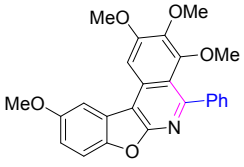
8f (52%, 27 h)



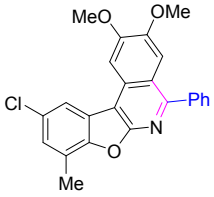
8g (56%, 14 h)



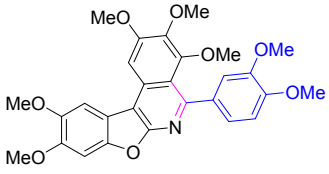
8h (35%, 21 h)



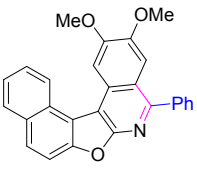
8i (86%, 23 h)



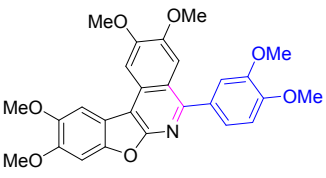
8j (56%, 12 h)



8k (37%, 25 h)



8l (94%, 3 h)



8m (63%, 20 h)

[a] To a mixture of **4** (50 mg, 1 equiv) and aldehyde (2 equiv) in DCE (2 mL) was added $Yb(OTf)_3$ (0.2 equiv) at rt. The reaction mixture was stirred at 130 °C for the indicated time. [b] Isolated yield (%), reaction time (h).

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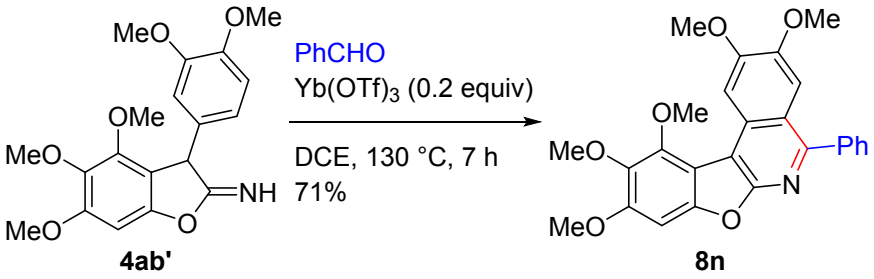
Oxidative Pictet-Spengler cyclization of **4ab'** with benzaldehyde also worked well to give **8n** (Scheme 5).

Scheme 5. Oxidative Pictet-Spengler Reaction of 4ab'



In addition, subsequent construction of 7-membered rings was successfully realized (Scheme 6). Use of 3,4-dimethoxyphenylacetonitrile and methyl 3,4-dimethoxyphenylacetate as nucleophiles in these three-component couplings with **6a** and TMSCN afforded amidine **10** and lactam **13** through the intermediates **9** and **11**, respectively. While base-mediated cyclization of **11** at rt gave a mixture of **12** and **13**, heating the reaction mixture at 80 °C cleanly produced **13** in 91% yield. The resulting two novel tetracyclic ring systems may be useful heterocyclic scaffolds for further biological study.

Scheme 6. Syntheses of 9-13

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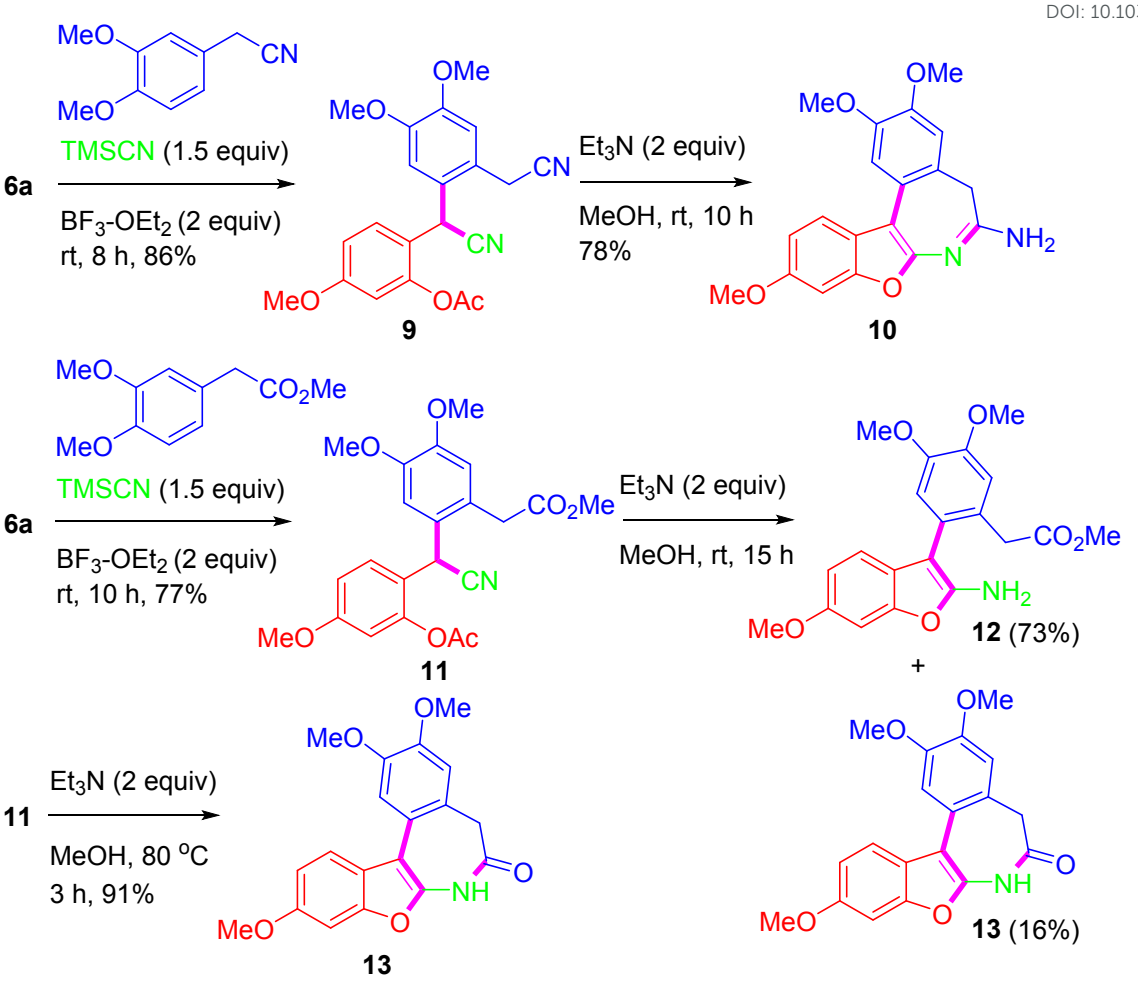

Conclusions

In summary, two highly efficient direct one-pot approaches to 2-amino-3-arylbenzofurans and 2-amino-3-arylnaphtho[2,1-*b*]furans were accomplished via Lewis acid-mediated sequential coupling reactions where multi-bond formation (two C-C and one C-O) took place. Versatility of the resulting compounds was demonstrated through additional cyclizations leading to three novel polyheterocyclic systems, benzofuro[2,3-*c*]isoquinoline, 5*H*-benzo[*d*]benzofuro[2,3-*b*]azepin-6-amine, and 5,7-dihydro-6*H*-benzo[*d*]benzofuro[2,3-*b*]azepin-6-one, respectively. We hope that our one-pot assembly protocols enabling rapid access to new benzofuran-based chemical space would be useful for drug discovery research with unique molecular entities.

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Synthetic efforts to generate new heterocyclic chemical space via one-pot assembly of readily available building blocks as well as biological application of the resulting products are being continuously made.

Experimental Section

General Methods

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized with UV light. Melting points were measured using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS was measured with an electrospray ionization (ESI) and Q-TOF mass analyzer.

General Procedure for the Synthesis of 4:

To a stirred solution of 3,4-dimethoxybenzaldehyde **1a** (100 mg, 0.6 mmol, 1 equiv) and trimethylsilyl cyanide (112 μL, 0.9 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL) at 0 °C under N_2 atmosphere was added ZnI_2 (19 mg, 0.06 mmol, 0.1 equiv). After being stirred at rt for 30 min, the reaction mixture was cooled down to 0 °C and 3,4-dimethoxyphenol (92 mg, 0.6 mmol, 1

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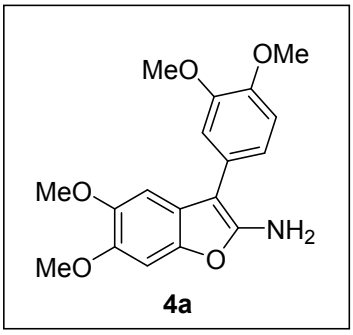
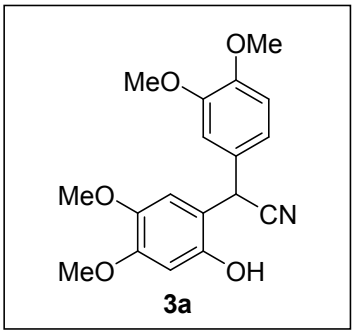
equiv) was added at once, which was followed by dropwise addition of BF_3-OEt_2 (112 µL, 1.2 mmol, 2.0 equiv) for a period of 2-3 min. The reaction mixture was allowed to stir at 30 °C for 14 h. After completion of reaction, indicated by TLC, the reaction mixture was diluted with CH_2Cl_2 (15-20 mL), washed with aq. $NaHCO_3$ (5 mL x 2) and brine solution (5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography on silica gel (15-20% EtOAc/hexanes) afforded 2-aminobenzofuran **4a**.

3-(3,4-Dimethoxyphenyl)-5,6-dimethoxybenzofuran-2-amine (4a). Off-white solid (154 mg, 78%); mp: 110-112 °C; R_f = 0.3 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.0 Hz, 2H), 7.00 – 6.91 (m, 3H), 4.16 (s, 2H), 3.91 (s, 6H), 3.89 (s, 3H), 3.87 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.5, 149.6, 147.5, 146.5, 145.3, 143.9, 126.0, 122.2, 119.9, 112.1, 110.9, 100.4, 95.8, 94.9, 56.6, 56.6, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336, found 330.1334.



4a

2-(3,4-Dimethoxyphenyl)-2-(2-hydroxy-4,5-dimethoxyphenyl)acetonitrile (3a). Colorless viscous liquid (20 mg, 10%); R_f = 0.2 in 40% EtOAc; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 8.2 Hz, 1H), 6.88 (s, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 6.41 (s, 1H), 6.11 (s, 1H), 5.46 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.8, 149.3, 148.7, 147.2, 143.4, 128.1, 120.3, 119.8, 113.7, 112.2, 111.4, 110.8, 101.2, 56.8, 56.0, 56.0, 56.0, 35.6; **HRMS**



3a

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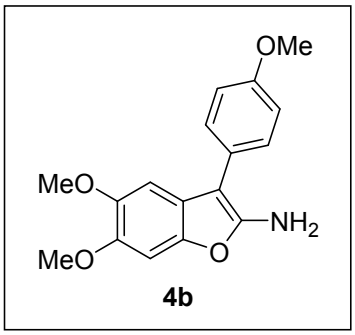
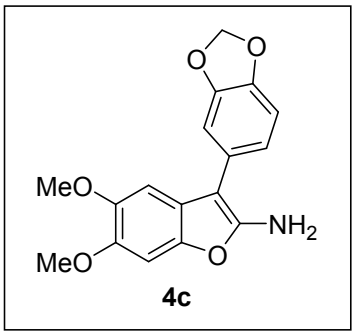
(ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336, found 330.1336.

5,6-Dimethoxy-3-(4-methoxyphenyl)benzofuran-2-amine (4b). Light brown viscous liquid (181 mg, 83%); R_f = 0.3 in 30% EtOAc; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 3.2 Hz, 2H), 4.12 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 152.4, 146.5, 145.2, 143.9, 128.7, 128.7, 125.7, 122.3, 114.8, 114.8, 100.4, 95.7, 94.8, 56.7, 56.7, 55.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_4$ 300.1230, found 300.1237.



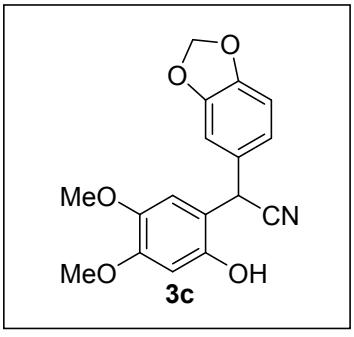
4b



4c

3-(Benzo[*d*][1,3]dioxol-5-yl)-5,6-dimethoxybenzofuran-2-amine (4c). Light green solid (133 mg, 64%); mp: 145-147 °C; R_f = 0.3 in 30% EtOAc; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.97 – 6.86 (m, 4H), 5.98 (s, 2H), 4.16 (s, 2H), 3.88 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.5, 148.3, 146.5, 145.8, 145.2, 143.8, 127.1, 122.0, 120.7, 109.1, 108.1, 101.1, 100.3, 95.7, 94.8, 56.6, 56.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}NO_5$ 314.1023, found 314.1024.

2-(Benzo[*d*][1,3]dioxol-5-yl)-2-(2-hydroxy-4,5-dimethoxyphenyl)acetonitrile (3c). Light blue solid (33 mg, 16%); mp: 84-86 °C; R_f = 0.25 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 6.3 Hz,



3c

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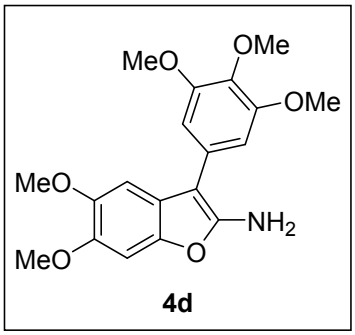
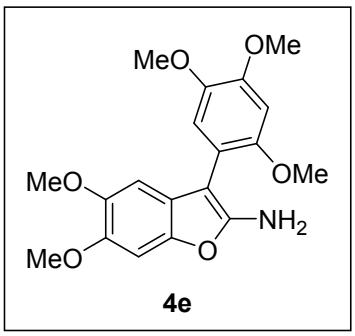
2H), 6.77 (d, J = 8.0 Hz, 1H), 6.40 (s, 1H), 5.95 (s, 2H), 5.41 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ152.5, 148.3, 146.5, 145.8, 145.2, 143.8, 127.1, 122.0, 120.7, 109.1, 108.1, 101.1, 100.3, 95.7, 94.8, 56.6, 56.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}NO_5$ 314.1023, found 314.1022.

5,6-Dimethoxy-3-(3,4,5-trimethoxyphenyl)benzofuran-2-amine (4d). Off-white solid (132 mg, 72%); mp: 91-93 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.95 (s, 1H), 6.73 (s, 2H), 4.20 (s, 2H), 3.90 (s, 12H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.0, 154.0, 152.7, 146.6, 145.4, 144.0, 136.5, 129.1, 122.0, 104.8, 104.8, 100.5, 95.9, 95.1, 61.1, 56.7, 56.7, 56.4, 56.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1442, found 360.1445.



4d



4e

5,6-Dimethoxy-3-(2,4,5-trimethoxyphenyl)benzofuran-2-amine (4e). Light brown liquid (146 mg, 80%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.92 (d, J = 6.1 Hz, 2H), 6.67 (s, 1H), 4.39 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.2, 150.2, 148.3, 146.2, 144.9, 144.3, 143.9, 122.9, 113.7, 112.9, 100.5, 99.6, 95.8, 90.8, 57.4, 56.6, 56.5, 56.5, 56.2; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1442, found 360.1446.

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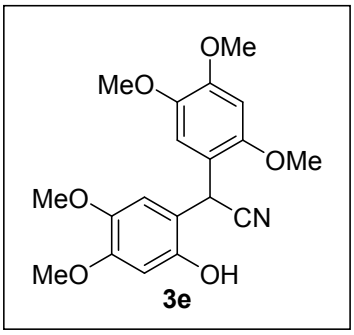
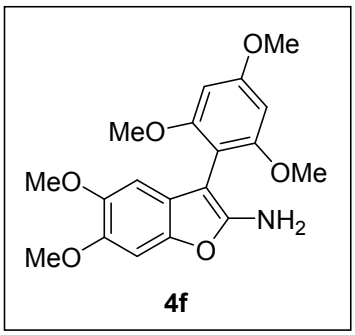
2-(2-Hydroxy-4,5-dimethoxyphenyl)-2-(2,4,5-trimethoxyphenyl)acetonitrile (3e).



3e

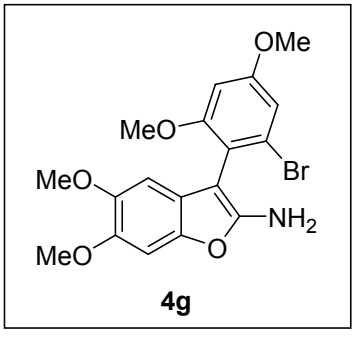
Colorless viscous liquid (16 mg, 9%); R_f = 0.2 in 30% EtOAc; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 6.53 (s, 1H), 6.43 (s, 1H), 6.14 (s, 1H), 5.58 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.0, 149.9, 149.7, 147.2, 143.9, 143.5, 120.1, 115.1, 113.1, 112.3, 111.8, 101.8, 97.7, 56.9, 56.8, 56.8, 56.3, 56.0, 30.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1442, found 360.1447.

5,6-Dimethoxy-3-(2,4,6-trimethoxyphenyl)benzofuran-2-amine (4f). Light brown liquid (113 mg, 62%); R_f = 0.3 in 30% EtOAc; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.58 (s, 1H), 6.28 (s, 2H), 4.01 (s, 2H), 3.88 (s, 6H), 3.82 (s, 3H), 3.81 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.8, 158.8, 158.8, 153.5, 145.9, 144.8, 144.2, 123.5, 102.5, 102.2, 95.5, 91.4, 91.4, 88.3, 56.7, 56.6, 56.0, 56.0, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1442, found 360.1440.



4f

3-(2-Bromo-4,6-dimethoxyphenyl)-5,6-dimethoxybenzofuran-2-amine (4g). Light purple solid (123 mg, 74%); mp: 116-118 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.88 (s, 1H), 6.55 (s, 1H), 6.53 (s, 1H), 3.91 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.6, 159.7, 153.3, 146.2, 145.0, 143.9, 126.6, 122.9, 114.5,



4g

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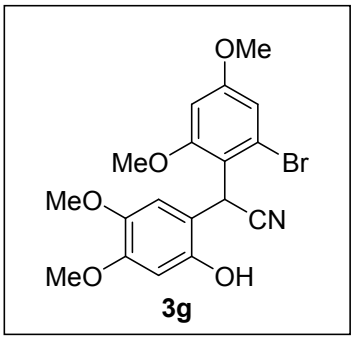
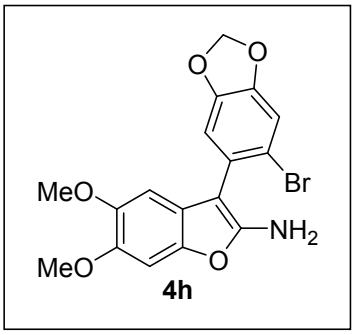
109.5, 101.7, 98.6, 95.7, 91.8, 56.7, 56.6, 56.2, 55.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_5$ 408.0441, found 408.0447.

2-(2-Bromo-4,6-dimethoxyphenyl)-2-(2-hydroxy-4,5-dimethoxyphenyl)acetonitrile (3g).



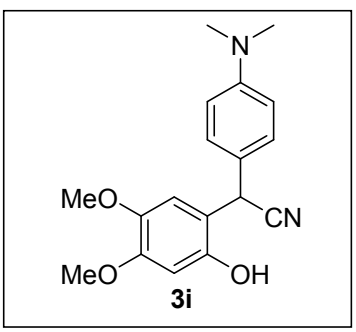
3g

Colorless viscous liquid (12 mg, 7%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.48 (d, J = 2.2 Hz, 1H), 6.39 (s, 1H), 5.89 (s, 1H), 5.59 (s, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 158.6, 149.8, 147.6, 142.9, 125.4, 118.7, 115.6, 113.6, 111.2, 110.6, 101.5, 99.4, 56.8, 56.5, 56.1, 55.8, 32.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_5$ 408.0441, found 408.0441.



4h

3-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-5,6-dimethoxybenzofuran-2-amine (4h). Light brown viscous liquid (76 mg, 44%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.93 (s, 1H), 6.89 (s, 1H), 6.65 (s, 1H), 6.02 (d, *J* = 7.3 Hz, 2H), 4.01 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.62, 148.0, 147.8, 146.5, 145.3, 143.7, 126.4, 122.7, 115.0, 113.4, 111.4, 102.1, 100.7, 95.7, 95.4, 56.7, 56.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}BrNO_5$ 392.0128, found 392.0129.



3i

2-(4-(Dimethylamino)phenyl)-2-(2-hydroxy-4,5-

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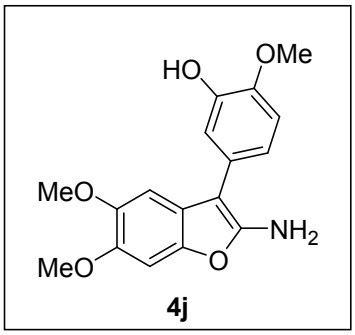
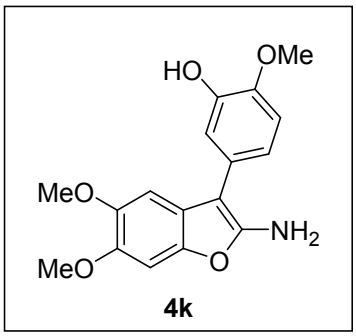
dimethoxyphenyl)acetonitrile (3i). Off-white solid (171 mg, 82%); mp:157-159 °C R_f = 0.3 in 50% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 1H), 5.37 (s, 1H), 4.96 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.94 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.3, 149.7, 146.7, 143.7, 128.4, 128.4, 122.7, 120.5, 114.4, 112.9, 112.9, 112.3, 101.5, 56.8, 56.2, 40.6, 40.6, 35.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_3$ 313.1547, found 313.1548.

5-(2-Amino-5,6-dimethoxybenzofuran-3-yl)-2-methoxyphenol (4j). Off-white solid (127 mg, 61%); mp: 158-160 °C; R_f = 0.2 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 7.04 – 6.90 (m, 4H), 5.77 (s, 1H), 4.16 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.5, 146.5, 146.3, 145.2, 144.9, 143.9, 126.8, 122.1, 119.3, 113.8, 111.6, 100.5, 95.7, 94.7, 56.7, 56.7, 56.2; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_5$ 316.1179, found 316.1179.



4j

4-(2-Amino-5,6-dimethoxybenzofuran-3-yl)-2-methoxyphenol (4k). Off-white viscous liquid (112 mg, 54%); R_f = 0.2 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 – 6.98 (m, 3H), 6.95 (d, *J* = 3.1 Hz, 2H), 5.65 (s, 1H), 4.11 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.4, 147.2, 146.5, 145.4, 144.2, 144.0, 125.3, 122.3, 120.8, 115.3, 110.4, 100.5, 95.8, 95.3, 56.7, 56.7, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_5$ 316.1179, found 316.1174.



4k

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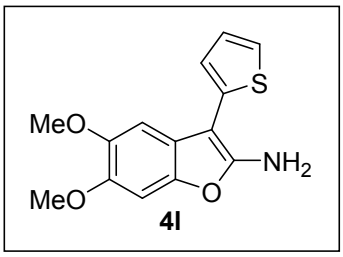
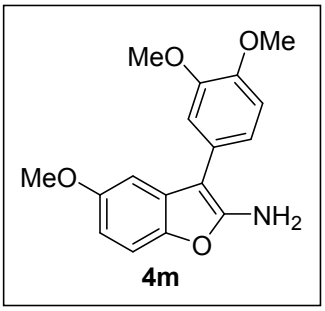
5,6-Dimethoxy-3-(thiophen-2-yl)benzofuran-2-amine (4l). Colorless viscous liquid (115 mg, 47%); R_f = 0.2 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 5.0, 4.0 Hz, 1H), 7.18 – 7.09 (m, 3H), 6.93 (s, 1H), 4.38 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.2, 146.7, 145.5, 143.8, 135.4, 127.8, 122.6, 122.5, 121.5, 100.9, 95.7, 89.8, 56.7, 56.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_3S$ 276.0689, found 276.0691.



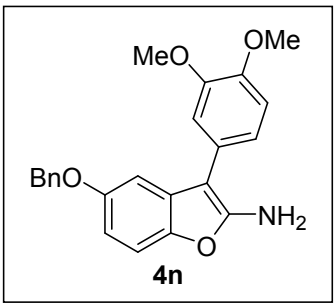
4l



4m

3-(3,4-Dimethoxyphenyl)-5-methoxybenzofuran-2-amine (4m). Off-white solid (140 mg, 78%); mp: 180-182 °C; R_f = 0.3 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 1H), 7.09 – 7.01 (m, 2H), 7.01 – 6.94 (m, 2H), 6.66 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.28 (s, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4, 154.2, 149.6, 147.5, 144.7, 131.0, 125.9, 119.9, 112.1, 111.0, 110.2, 107.8, 101.5, 94.5, 56.1, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_4$ 300.1230, found 300.1237.

5-(Benzyloxy)-3-(3,4-dimethoxyphenyl)benzofuran-2-amine (4n). Brown solid (157 mg, 70%); mp: 114-116 °C; R_f = 0.2 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (dd, *J* = 8.3, 6.0 Hz, 1H), 7.19 (d, *J* = 8.7 Hz,



4n

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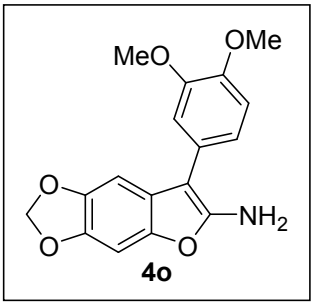
1H), 7.07 – 7.00 (m, 3H), 6.97 (d, J = 8.7 Hz, 1H), 6.74 (dd, J = 8.7, 2.5 Hz, 1H), 5.07 (s, 2H), 4.28 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.6, 154.2, 149.6, 147.5, 144.9, 137.6, 131.0, 128.6, 128.6, 127.9, 127.6, 127.5, 125.9, 119.9, 112.1, 110.9, 110.2, 108.8, 102.8, 94.5, 70.9, 56.1, 56.12; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}NO_4$ 376.1543, found 376.1538.

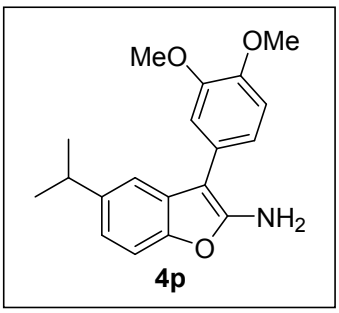
7-(3,4-Dimethoxyphenyl)-[1,3]dioxolo[4,5-*f*]benzofuran-6-amine (4o). Pale yellow solid,



4o

(141 mg, 75%); mp: 186-188 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 7.9 Hz, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 5.92 (s, 2H), 4.13 (s, 2H), 3.91 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.7, 149.6, 147.5, 144.3, 144.3, 143.2, 125.8, 123.4, 119.9, 112.0, 110.9, 100.9, 97.3, 95.5, 93.4, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}NO_5$ 314.1023, found 314.1025.

3-(3,4-Dimethoxyphenyl)-5-isopropylbenzofuran-2-amine (4p). Light yellow solid (131 mg,



4p

70%); mp: 135-137 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, J = 1.1 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.13 – 7.06 (m, 2H), 7.00 – 6.96 (m, 2H), 4.28 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.05 – 2.92 (m, 1H), 1.29 (d, J = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6, 149.5, 148.4, 147.4, 143.9, 130.2, 126.1, 120.0, 119.4, 114.6, 112.1, 111.1, 109.6, 94.2, 56.1, 56.1, 34.4, 24.7, 24.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_3$ 312.1594, found 312.1591.

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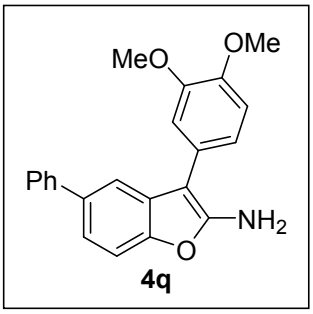
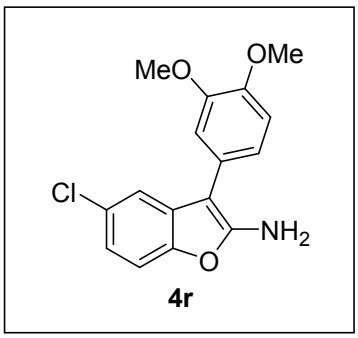
3-(3,4-Dimethoxyphenyl)-5-phenylbenzofuran-2-amine (4q). Brown solid (147 mg, 71%);



4q

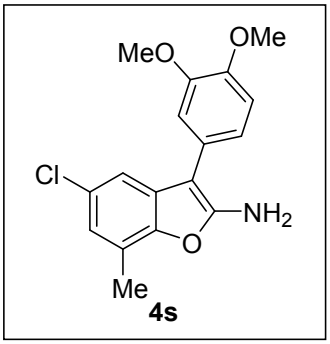
mp: 111-113 °C; R_f = 0.25 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.29 (m, 3H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 4.34 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.9, 149.6, 149.6, 147.6, 142.2, 136.8, 130.8, 128.8, 128.8, 127.5, 127.5, 126.8, 125.8, 120.5, 120.2, 115.8, 112.1, 111.1, 110.0, 94.3, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_3$ 346.1438, found 346.1435.



4r

5-Chloro-3-(3,4-dimethoxyphenyl)benzofuran-2-amine (4r). Light yellow solid (114 mg, 63%); mp: 138-141 °C; R_f = 0.25 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.06 – 6.95 (m, 4H), 4.35 (s, 2H), 3.93 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5, 149.7, 148.3, 147.8, 131.8, 128.8, 125.1, 120.7, 120.1, 116.8, 112.1, 110.9, 110.8, 93.9, 56.2, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ClNO_3$ 304.0735, found 304.0735.

5-Chloro-3-(3,4-dimethoxyphenyl)-7-methylbenzofuran-2-amine (4s). Yellow solid (116 mg, 61%); mp: 148-150 °C; R_f = 0.3 in 25% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, J = 1.7 Hz, 1H), 7.02 (d, *J* = 6.3 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.87 (s, 1H), 4.34 (s, 2H),



4s

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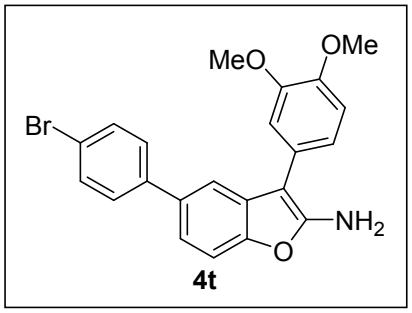
3.92 (s, 6H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 149.7, 147.7, 147.1, 131.1, 128.5, 125.4, 122.0, 121.3, 120.1, 114.4, 112.1, 110.9, 94.2, 56.2, 56.1, 14.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}ClNO_3$ 318.0891, found 318.0895.

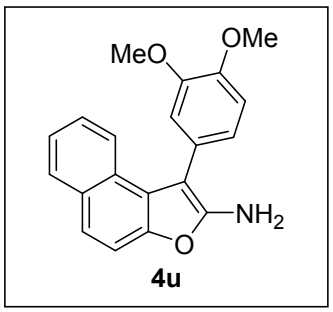
5-(4-Bromophenyl)-3-(3,4-dimethoxyphenyl)benzofuran-2-amine (4t). Brown solid (152 mg, 60%); mp: 144-146 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ



4t

7.58 (d, *J* = 1.2 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.07 (d, *J* = 6.2 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 1H), 4.33 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.1, 149.7, 149.6, 147.6, 141.1, 135.5, 131.8, 131.8, 130.9, 129.0, 129.0, 125.6, 120.9, 120.2, 120.2, 115.5, 112.1, 111.1, 110.1, 94.2, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}BrNO_3$ 424.0543, found 424.0540.

1-(3,4-Dimethoxyphenyl)naphtho[2,1-*b*]furan-2-amine (4u). Off-white solid (134 mg, 70%); mp: 84-86 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87



4u

(d, *J* = 8.5 Hz, 2H), 7.53 (s, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.12 – 7.04 (m, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 4.11 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 153.7, 149.3, 148.4, 146.3, 131.1, 128.8, 127.1, 126.1, 124.9, 124.0, 123.6, 122.7, 121.5, 113.8, 111.7, 111.4, 97.2, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}NO_3$ 320.1281, found 320.1283.

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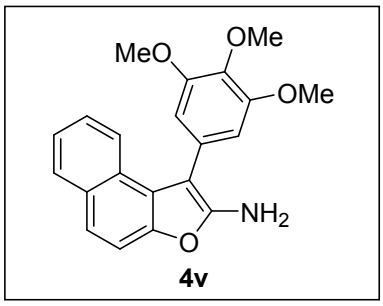
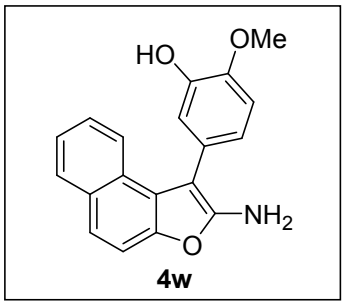
1-(3,4,5-Trimethoxyphenyl)naphtho[2,1-*b*]furan-2-amine (4v). Light green solid (112 mg, 63%); mp: 116-118 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95



4v

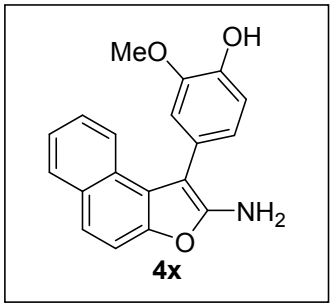
(d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.55 (s, 2H), 7.48 – 7.27 (m, 2H), 6.78 (s, 2H), 4.18 (s, 2H), 3.98 (s, 3H), 3.87 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.8, 153.8, 153.8, 153.7, 146.4, 137.2, 131.2, 129.3, 128.9, 126.9, 125.1, 124.1, 123.7, 121.6, 111.4, 107.5, 107.5, 97.3, 61.1, 56.3, 56.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}NO_4$ 350.1387, found 350.1387.



4w

5-(2-Aminonaphtho[2,1-*b*]furan-1-yl)-2-methoxyphenol(4w). Light purple viscous liquid (99 mg, 50%); R_f = 0.3 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.13 (s, 1H), 7.07 – 6.98 (m, 2H), 5.74 (s, 1H), 4.09 (s, 2H), 3.99 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 146.3, 146.1, 146.0, 131.1, 128.8, 127.2, 126.8, 125.0, 123.9, 123.7, 122.5, 121.4, 116.7, 116.7, 111.4, 111.3, 97.2, 56.2; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_3$ 306.1125, found 306.1124.

4-(2-Aminonaphtho[2,1-*b*]furan-1-yl)-2-methoxyphenol (4x). Light purple viscous liquid (94 mg, 47%); R_f = 0.3 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.54 (s, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.9



4x

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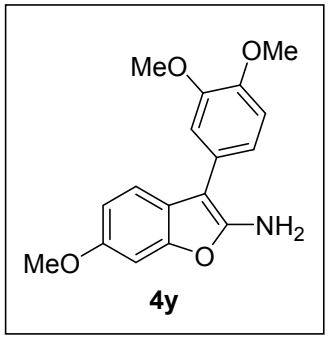
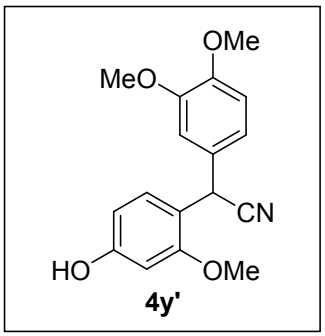
Hz, 1H), 7.10 – 7.00 (m, 3H), 5.75 (s, 1H), 4.10 (s, 2H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 147.0, 146.3, 145.1, 131.1, 131.1, 128.9, 127.1, 125.4, 125.0, 124.0, 123.6, 123.6, 121.5, 115.1, 113.2, 111.4, 97.4, 56.2; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_3$ 306.1125, found 306.1124.

3-(3,4-Dimethoxyphenyl)-6-methoxybenzofuran-2-amine (4y). Brown solid (38 mg, 21%); mp: 103-105 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 1.5 Hz, 1H), 6.82 (dd, J = 8.4, 1.4 Hz, 1H), 4.18 (s, 2H), 3.92 (s, 6H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 152.4, 150.7, 149.6, 147.4, 126.1, 123.5, 119.8, 117.3, 112.0, 110.9, 110.4, 96.5, 94.3, 56.1, 56.1, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_4$ 300.1230, found 300.1229.



4y

2-(3,4-Dimethoxyphenyl)-2-(4-hydroxy-2-methoxyphenyl)acetonitrile (4y'). Colorless viscous liquid (107 mg, 60%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 9.3 Hz, 2H), 6.45 – 6.36 (m, 2H), 6.26 (s, 1H), 5.39 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.6, 157.3, 149.1, 148.6, 129.5, 128.2, 120.5, 120.1, 116.4, 111.4, 110.9, 107.6, 99.4, 56.0, 56.0, 55.7, 35.5; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{17}NO_4Na$ 322.1050, found 322.1053.



4y'

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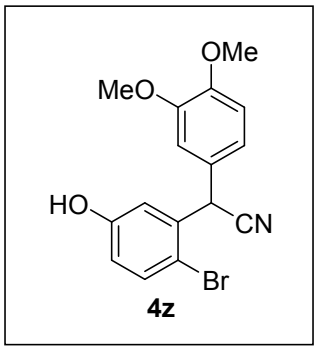
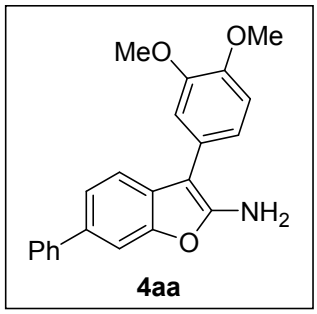
2-(2-Bromo-5-hydroxyphenyl)-2-(3,4-dimethoxyphenyl)acetonitrile (4z). Colorless viscous liquid (121 mg, 58%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 2H), 6.87 – 6.77 (m, 4H), 6.05 (s, 1H), 5.04 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 155.9, 149.4, 148.9, 129.0, 129.0, 128.5, 120.2, 120.2, 116.1, 116.1, 111.5, 110.7, 56.0, 56.0, 41.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}BrNO_3$ 348.0230, found 348.0233.



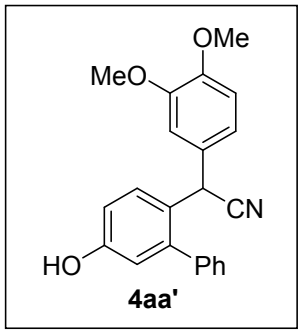
4z

3-(3,4-Dimethoxyphenyl)-6-phenylbenzofuran-2-amine (4aa). Yellow solid , (41 mg, 20%); mp: 121-123 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 1.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.13 – 7.07 (m, 2H), 7.00 (d, *J* = 8.1 Hz, 1H), 4.35 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.9, 150.6, 149.6, 147.6, 141.7, 134.6, 129.5, 128.9, 128.9, 127.2, 127.2, 126.8, 125.9, 122.5, 119.9, 117.2, 112.1, 111.0, 108.6, 94.1, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_3$ 346.1438, found 346.1442.



4aa

2-(3,4-Dimethoxyphenyl)-2-(5-hydroxy-[1,1'-biphenyl]-2-yl)acetonitrile (4aa'). Light yellow solid (130 mg, 63%); mp: 81.2-83.4 °C; R_f = 0.2 in 30% EtOAc in hexane; (**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 14.0, 7.0 Hz, 4H), 7.22 (d, *J* = 5.2



4aa'

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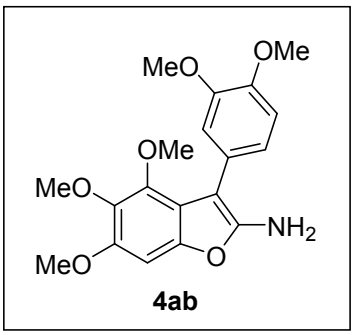
Hz, 2H), 6.86 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.50 (s, 1H), 5.76 (s, 1H), 5.16 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.6, 149.1, 148.6, 143.2, 139.8, 130.2, 129.1, 129.1, 129.0, 128.7, 128.7, 127.9, 126.0, 120.7, 119.8, 117.3, 115.6, 111.3, 110.7, 56.0, 55.9, 38.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_3$ 346.1438, found 346.1438.

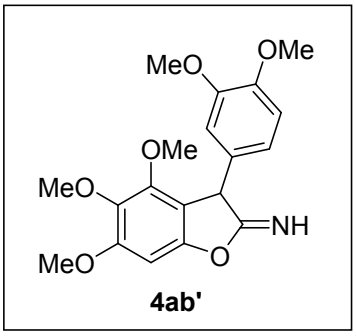
3-(3,4-Dimethoxyphenyl)-4,5,6-trimethoxybenzofuran-2-amine (4ab). Light yellow liquid



4ab

(9 mg, 4%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 1.8 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.93 (dd, *J* = 6.3, 4.9 Hz, 1H), 6.74 (s, 1H), 4.09 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.4, 149.4, 148.9, 147.5, 146.5, 145.5, 144.8, 139.1, 125.7, 121.1, 116.0, 113.1, 111.1, 94.3, 91.8, 61.8, 61.7, 56.7, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{21}NO_6Na$ 382.1261, found 382.1267.

3-(3,4-Dimethoxyphenyl)-4,5,6-trimethoxybenzofuran-2(3*H*)-imine (4ab'). White solid (120 mg, 56%); mp: 163-165 °C; R_f = 0.2 in 50% EtOAc in hexane; **^{1}H NMR** (400 MHz,



4ab'

$CDCl_3$) δ 6.68 (d, *J* = 8.8 Hz, 1H), 6.60 (d, *J* = 6.8 Hz, 2H), 5.47 (s, 1H), 5.41 (s, 1H), 4.59 (s, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 3.77 (s, 3H), 3.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.6, 166.0, 165.0, 149.6, 148.7, 121.6, 121.2, 118.1, 111.4, 110.9, 106.3, 105.5, 79.6, 56.3, 56.2, 55.9, 55.8, 53.4, 43.8; **HRMS**

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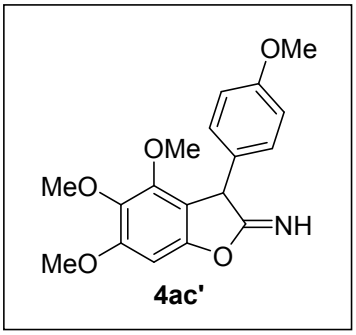
(ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1442, found 360.1440.

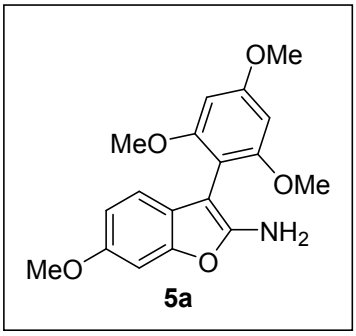
4,5,6-Trimethoxy-3-(4-methoxyphenyl)benzofuran-2(3*H*)-imine (4ac'). White solid (123 mg, 51%); mp: 187-189 °C; R_f = 0.2 in 50% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 1H), 5.43 (s, 1H), 4.61 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.20 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.7, 166.1, 165.1, 160.1, 129.6, 129.6, 121.4, 118.3, 114.2, 106.4, 105.6, 79.7, 56.4, 56.3, 55.3, 53.5, 43.6, 43.6; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{19}NO_5Na$ 352.1155, found 352.1156.



4ac'

General Procedure for the Synthesis of 5a-5d:

To a stirred solution of 4-methoxy-2-hydroxybenzaldehyde (100 mg, 0.66 mmol, 1 equiv), and trimethylsilyl cyanide (124 µL, 0.99 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL) at 0 °C under N_2 atmosphere was added ZnI_2 (21 mg, 0.066 mmol, 0.1 equiv). After being stirred at 50 °C for 1 h, the reaction mixture was cooled down to 0 °C and 1,3,5-trimethoxyphenol (133 mg, 0.792 mmol, 1.2 equiv) was added at once, which was followed by dropwise addition of BF_3-OEt_2 (166 µL, 1.32 mmol, 2.0 equiv). After being stirred at 30 °C for 14 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aq. $NaHCO_3$ (5 mL x 2) and brine solution (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography on silica gel (10-15% EtOAc in hexanes) afforded **5a**.



5a

6-Methoxy-3-(2,4,6-trimethoxyphenyl)benzofuran-2-amine

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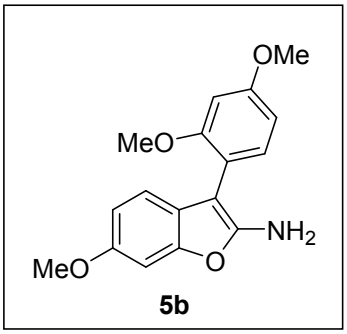
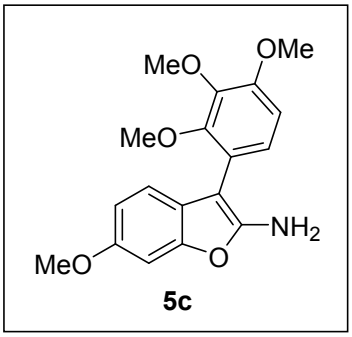
(5a). Light brown viscous liquid (82 mg, 38%); R_f = 0.2 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.97 – 6.87 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 2H), 4.01 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.79 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.8, 158.9, 158.9, 155.3, 153.4, 150.8, 124.7, 119.3, 110.0, 102.2, 96.1, 91.4, 87.8, 87.8, 56.1, 56.1, 56.1, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336, found 330.1339.



5b

3-(2,4-Dimethoxyphenyl)-6-methoxybenzofuran-2-amine (5b). Light yellow viscous liquid (79 mg, 40%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.66 – 6.60 (m, 2H), 4.26 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 157.1, 155.5, 152.9, 151.0, 130.6, 124.5, 117.6, 114.3, 110.2, 105.5, 99.7, 96.3, 90.6, 56.0, 56.1, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_4$ 300.1230, found 300.1231.

6-Methoxy-3-(2,3,4-trimethoxyphenyl)benzofuran-2-amine (5c). Light brown viscous liquid (85 mg, 39%); R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 6.92 (s, 1H), 6.83 – 6.78 (m, 2H), 4.60 (s, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 153.1, 152.1, 151.1, 150.5, 143.0, 124.2, 123.9, 119.8, 117.4, 110.2, 108.6, 96.4, 89.9, 61.4, 61.2, 56.3, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336, found 330.1337.



5c

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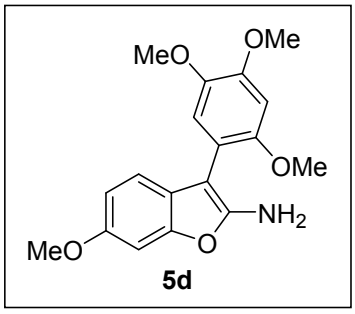
6-Methoxy-3-(2,4,5-trimethoxyphenyl)benzofuran-2-amine (5d). Light yellow solid, mp: 100-102 °C; R_f = 0.2 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 1H), 7.09 (s, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.68 (s, 1H), 4.42 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 153.1, 151.1, 150.1, 148.3, 144.1, 124.3, 117.3, 113.9, 113.1, 110.2, 99.8, 96.5, 90.3, 57.7, 56.6, 56.3, 56.1; HRMS (ESI-QTOF) m/z $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336, found 330.1330.



5d

General Procedure for the Synthesis of 7e-7j, 9, and 11:

To a stirred solution of 2-formyl-5-methoxyphenyl acetate **6a** (100 mg, 0.515 mmol, 1 equiv), various arenes (0.62 mmol, 1.2 equiv), and trimethylsilyl cyanide (97 µL, 0.77 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added BF_3-OEt_2 (130 µL, 1.03 mmol, 2.0 equiv). After being stirred at room temperature for 8 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aq. $NaHCO_3$ (5 mL x 2) and brine solution (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography on silica gel (15-20% EtOAc in hexanes) afforded **7**.

General Procedure for the Synthesis of 5e-5j, 10, 12, and 13:

To a stirred solution of **7e** (50 mg, 0.11 mmol, 1 equiv) in anhydrous methanol (4 mL) was added Et_3N (31 µL, 0.22 mmol, 2 equiv). After being stirred at rt for 7 h (the reaction mixture

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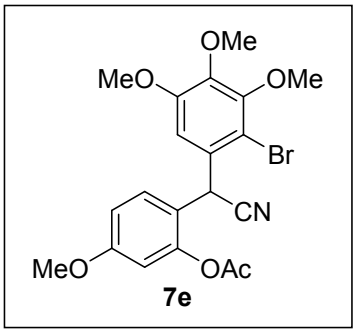
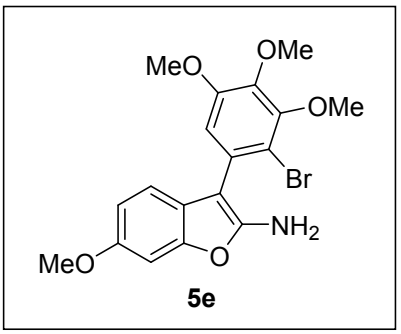
was stirred at 80 °C for 3 h in the case of **13**), the reaction mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography on silica gel with 10-15% EtOAc/hexanes as the eluents to give **5e**.

2-((2-Bromo-3,4,5-trimethoxyphenyl)(cyano)methyl)-5-methoxyphenyl acetate (7e). Colorless viscous liquid (219 mg, 95%); R_f = 0.2 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 1H), 6.89 (s, 1H), 6.79 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 5.73 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8, 160.0, 154.6, 153.30, 148.9, 142.3, 130.2, 120.9, 118.4, 118.2, 117.9, 111.9, 111.7, 108.9, 60.9, 60.9, 56.4, 55.7, 34.5, 21.2; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{20}BrNO_6Na$ 472.0366, found 472.0363.



7e

3-(2-Bromo-3,4,5-trimethoxyphenyl)-6-methoxybenzofuran-2-amine (5e). Off-white solid (41 mg, 92%); mp: 108-110 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.06 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.58 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.6, 153.5, 153.4, 150.6, 142.1, 123.9, 120.2, 119.3, 118.7, 118.7, 112.6, 110.1, 96.3, 91.1, 61.5, 61.3, 56.4, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_5$ 408.0441, found 408.0448.



5e

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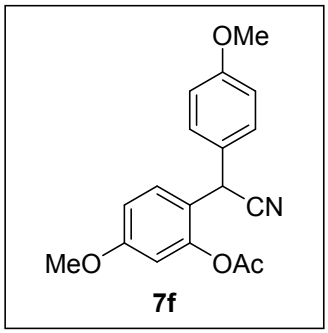
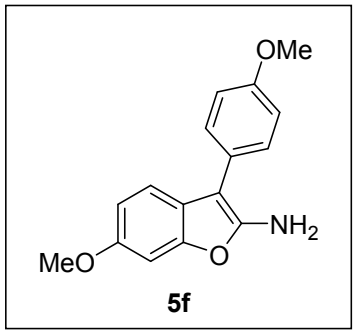
2-(Cyano(4-methoxyphenyl)methyl)-5-methoxyphenyl acetat (7f). Light yellow viscous liquid (130 mg, 81%); R_f = 0.3 in 20% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.78 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 5.15 (s, 1H), 3.75 (s, 6H), 2.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.4, 160.3, 159.3, 148.7, 129.8, 128.6, 128.6, 126.8, 119.8, 119.3, 114.4, 112.2, 112.2, 109.2, 55.5, 55.3, 36.3, 20.8; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{17}NO_4Na$ 334.1050, found 334.1045.



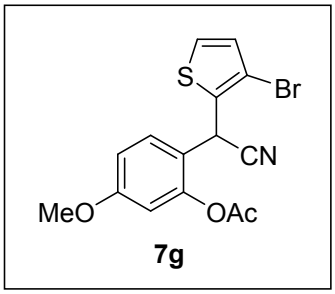
7f



5f

6-Methoxy-3-(4-methoxyphenyl)benzofuran-2-amine (5f). Orange viscous liquid (38 mg, 87%); R_f = 0.35 in 20% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 1.5 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.13 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 155.80, 152.3, 150.7, 128.7, 128.7, 125.7, 123.6, 117.4, 114.7, 114.7, 110.4, 96.4, 94.3, 56.0, 55.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}NO_3$ 270.1125, found 270.1124.

2-((3-Bromothiophen-2-yl)(cyano)methyl)-5-methoxyphenyl acetate (7g). Colorless viscous liquid (127 mg, 68%); R_f = 0.3 in 20% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.6 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.96 (d, *J* = 5.3 Hz, 1H), 6.85 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.75 (d, *J* = 1.9 Hz, 1H), 5.58 (s, 1H), 3.81 (s, 3H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz,



7g

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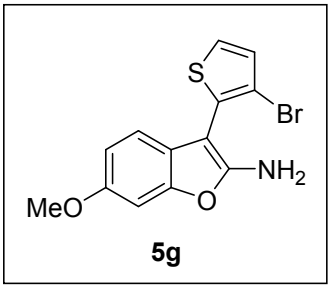
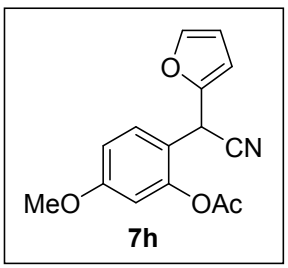
$CDCl_3$) δ 168.3, 160.9, 148.8, 133.2, 130.1, 129.4, 126.8, 118.0, 117.3, 112.2, 110.9, 109.5, 55.7, 32.3, 21.1; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{12}BrNO_3SNa$ 387.9613, found 387.9619.

3-(3-Bromothiophen-2-yl)-6-methoxybenzofuran-2-amine (5g). Yellow viscous liquid (39 mg, 89%); R_f = 0.35 in 20% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 5.4 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 5.4 Hz, 1H), 6.91 (d, *J* = 2.2 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.35 (s, 2H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 153.6, 150.6, 130.9, 130.3, 125.8, 123.7, 117.9, 110.5, 108.8, 96.5, 86.2, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}BrNO_2S$ 323.9688, found 323.9692.



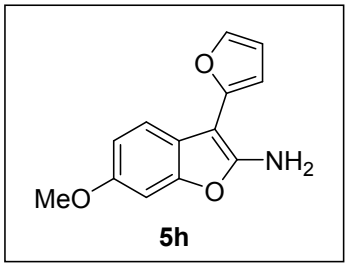
5g

2-(Cyano(furan-2-yl)methyl)-5-methoxyphenyl acetate (7h). Colorless viscous liquid (85 mg, 61%); R_f = 0.3 in 20% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 0.8 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 5.27 (s, 1H), 3.80 (s, 3H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 160.8, 148.9, 147.1, 143.4, 129.9, 117.1, 116.9, 112.5, 110.9, 109.4, 108.5, 55.7, 31.7, 21.0; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{13}NO_4Na$ 294.0737, found 294.0735.



7h

3-(Furan-2-yl)-6-methoxybenzofuran-2-amine (5h). Deep brown liquid (31 mg, 74%); R_f =



5h

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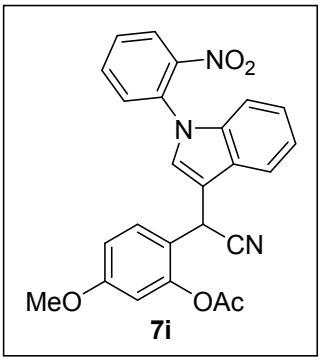
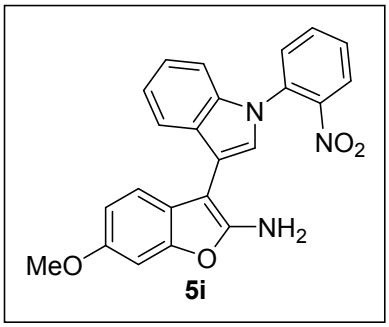
0.35 in 20% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 1.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.51 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.38 (d, *J* = 3.3 Hz, 1H), 4.79 (s, 2H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 153.7, 150.8, 149.2, 139.4, 120.9, 117.7, 111.3, 110.5, 102.1, 96.6, 86.1, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{12}NO_3$ 230.0812, found 230.0816.



7i

2-(Cyano(1-(2-nitrophenyl)-1*H*-indol-3-yl)methyl)-5-methoxyphenyl acetate (7i). Yellow viscous liquid (136 mg, 60%); R_f = 0.2 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.63 – 7.44 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.15 (m, 2H), 7.13 – 7.05 (m, 2H), 6.80 – 6.75 (m, 2H), 5.49 (s, 1H), 3.80 (s, 3H), 2.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.9, 160.5, 149.1, 146.3, 137.6, 134.1, 132.3, 130.2, 129.9, 129.1, 127.4, 126.2, 125.8, 124.0, 121.5, 119.4, 118.9, 118.6, 112.4, 112.1, 109.9, 109.3, 55.7, 28.8, 21.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}N_3O_5$ 442.1397, found 442.1393.

6-Methoxy-3-(1-(2-nitrophenyl)-1*H*-indol-3-yl)benzofuran-2-amine (5i). Yellow solid (35 mg, 77%); mp: 105-107 °C; R_f = 0.4 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.70 (d, *J* = 7.3 Hz, 2H), 7.62 – 7.57 (m, 1H), 7.27 – 7.19 (m, 5H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.14 (s, 2H), 3.85 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.7, 153.3, 150.9, 146.2, 137.1, 133.9, 132.9, 129.7, 128.4, 128.1,



5i

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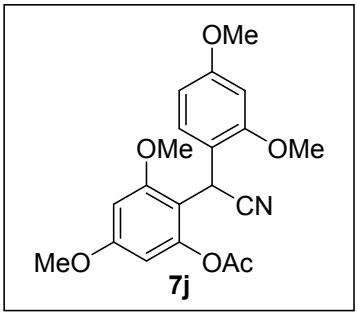
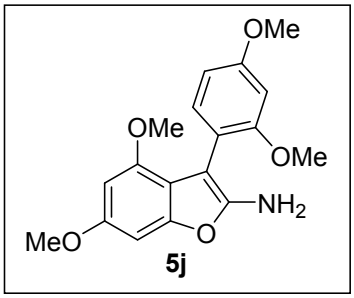
125.9, 125.9, 124.4, 123.6, 121.2, 121.1, 117.9, 110.4, 109.9, 96.5, 86.9, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{17}N_3O_4Na$ 422.1111, found 422.1106.



7j

2-(Cyano(2,4-dimethoxyphenyl)methyl)-3,5-dimethoxyphenyl acetate (7j). Light brown solid (139 mg, 87%); mp: 138-140 °C; R_f = 0.2 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.1 Hz, 1H), 6.42 (d, *J* = 6.6 Hz, 2H), 6.35 (d, *J* = 5.8 Hz, 2H), 5.69 (s, 1H), 3.78 (s, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8, 160.7, 160.5, 158.5, 157.6, 150.1, 129.4, 119.6, 115.3, 108.2, 104.1, 100.4, 98.6, 96.9, 56.1, 55.7, 55.6, 55.4, 25.8, 21.2; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{21}NO_6Na$ 394.1261, found 394.1265.

3-(2,4-Dimethoxyphenyl)-4,6-dimethoxybenzofuran-2-amine (5j). Light brown solid (33 mg, 73%); mp: 104-106 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.2 Hz, 1H), 6.62 – 6.53 (m, 3H), 6.31 (s, 1H), 4.04 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 157.3, 156.3, 152.9, 151.7, 151.7, 133.3, 114.3, 113.2, 104.7, 98.9, 94.6, 90.8, 88.6, 56.0, 55.9, 55.6, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336, found 330.1334.



5j

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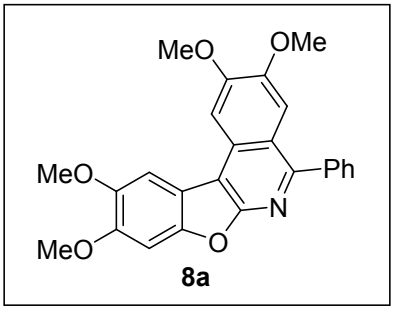
General Procedure for the Synthesis of 8:

To a solution of 2-amino-3-arylbenzofuran **4a** (50 mg, 0.152 mmol) and benzadehyde (31 µL, 0.3 mmol, 2.0 equiv) in DCE (2 mL) was added $Yb(OTf)_3$ (19 mg, 0.03 mmol, 0.2 equiv) at rt. After being stirred at 130 °C for 14 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with aq. $NaHCO_3$ (5 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography on silica gel (hexanes/EtOAc) afforded **8a**.

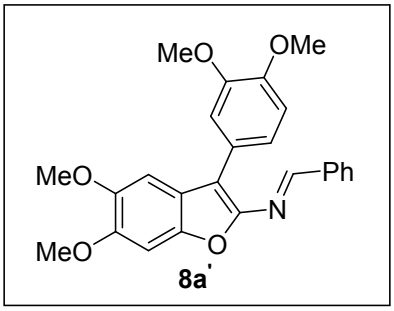
2,3,9,10-Tetramethoxy-5-phenylbenzofuro[2,3-*c*]isoquinoline (8a). Pink white solid (56 mg, 89%); mp: 201-203 °C; R_f = 0.35 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$)



8a

δ 7.80 (d, *J* = 7.4 Hz, 2H), 7.68 (s, 1H), 7.64 (s, 1H), 7.61 – 7.48 (m, 4H), 7.28 (s, 1H), 4.21 (s, 3H), 4.09 (s, 3H), 4.04 (s, 3H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 154.6, 153.3, 149.7, 149.5, 148.3, 146.5, 139.8, 130.2, 130.2, 129.8, 128.7, 128.5, 128.5, 120.0, 115.2, 107.6, 107.5, 104.3, 101.6, 96.3, 57.2, 56.4, 56.1, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{21}NO_5Na$ 438.1312, found 438.1312.

(*E*)-*N*-(3-(3,4-Dimethoxyphenyl)-5,6-dimethoxybenzofuran-2-yl)-1-phenylmethanimine (8a'). Yellow viscous liquid (61 mg, 97%); R_f = 0.4 in 30% EtOAc in hexane; **^{1}H NMR** (400



8a'

MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.85 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.44 – 7.35 (m, 4H), 7.17 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.96 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)

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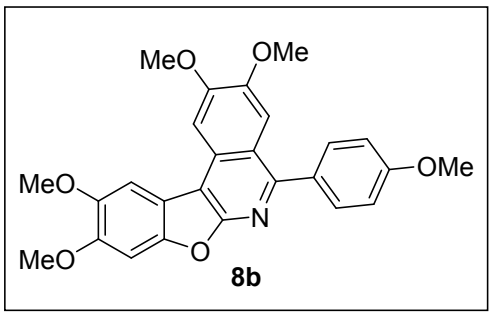
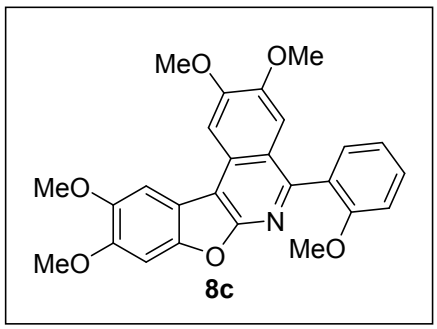
δ 153.7, 151.1, 149.1, 148.8, 148.4, 146.7, 146.5, 136.8, 130.9, 128.7, 128.7, 128.5, 128.5, 125.1, 121.4, 120.4, 115.2, 113.0, 111.2, 102.1, 95.1, 56.4, 56.2, 55.9, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{24}NO_5$ 418.1649, found 418.1651.



8b

2,3,9,10-Tetramethoxy-5-(4-methoxyphenyl)benzofuro[2,3-*c*]isoquinoline (8b). Brown white solid (59 mg, 88%); mp: 208-210 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.59 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.20 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.14 (s, 3H), 4.02 (s, 3H), 4.01 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.04, 158.9, 154.4, 153.1, 149.6, 149.3, 148.1, 146.4, 132.3, 131.6, 131.6, 129.8, 119.9, 115.2, 113.9, 113.9, 107.6, 107.2, 104.2, 101.5, 96.2, 57.1, 56.4, 56.1, 55.9, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_6$ 446.1598, found 446.1600.

2,3,9,10-Tetramethoxy-5-(2-methoxyphenyl)benzofuro[2,3-*c*]isoquinoline (8c). Brown solid (62 mg, 91%); mp: 229-231 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.53 – 7.30 (m, 5H), 7.19 (s, 1H), 7.04 (d, *J* = 6.9 Hz, 1H), 4.12 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.88 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 158.7, 154.3, 153.2, 149.7, 149.4, 148.2, 146.4, 141.0, 129.8, 129.4, 122.6, 119.9, 115.3, 115.1, 114.9, 107.7, 107.5, 104.2, 101.5, 96.2, 57.1, 56.3, 56.1, 55.9, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for



8c

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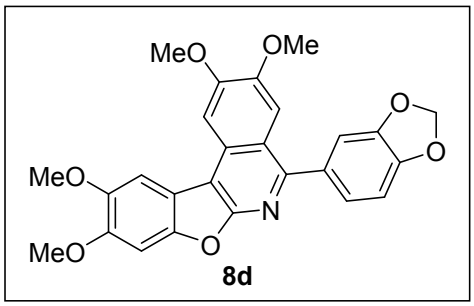
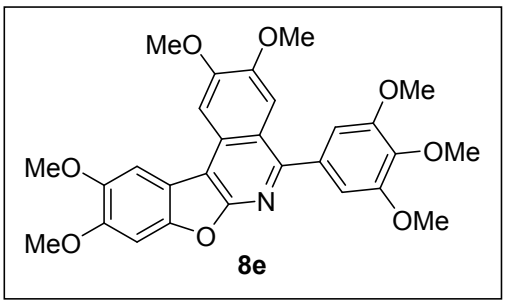
$C_{26}H_{24}NO_6$ 446.1598, found 446.1594.



8d

5-(Benzo[*d*][1,3]dioxol-5-yl)-2,3,9,10-tetramethoxybenzofuro[2,3-*c*]isoquinoline (8d). Brown solid (21 mg, 30%); mp: 229-231 °C; R_f = 0.2 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.58 (s, 1H), 7.55 (s, 1H), 7.29 (d, *J* = 3.8 Hz, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.07 (s, 2H), 4.17 (s, 3H), 4.05 (s, 3H), 4.02 (s, 3H), 3.92 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 154.1, 153.3, 149.8, 149.5, 148.3, 148.1, 148.0, 146.5, 133.8, 129.9, 124.2, 120.0, 115.2, 110.7, 108.3, 107.6, 107.5, 104.4, 101.7, 101.5, 96.3, 57.2, 56.4, 56.2, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_7$ 460.1391, found 460.1391.

2, 3, 9, 10-Tetramethoxy-5-(3,4,5-trimethoxyphenyl)benzofuro[2,3-*c*]isoquinoline (8e). Brown solid (23 mg, 30%); mp: 253-255 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.51 (s, 1H), 7.26 (s, 1H), 7.19 – 7.10 (m, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.18 (s, 3H), 4.07 (s, 3H), 4.02 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 157.3, 154.6, 151.7, 149.9, 149.6, 148.7, 147.8, 146.6, 141.3, 136.1, 132.0, 121.9, 115.8, 115.3, 112.8, 110.1, 107.2, 104.6, 98.1, 96.4, 61.4, 61.4, 57.3, 56.5, 56.1, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_8$ 506.1809, found 506.1808.



8e

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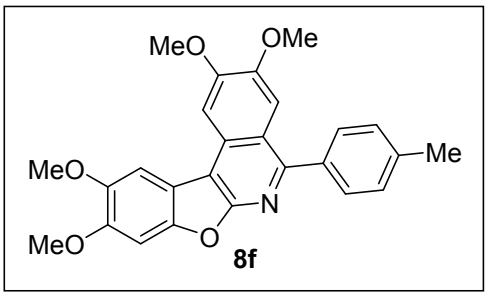
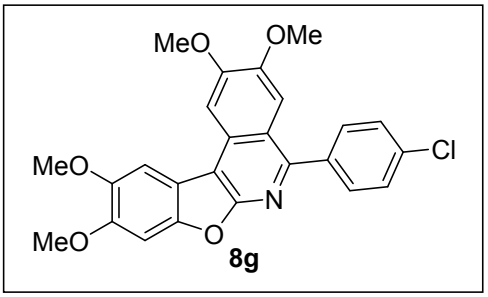


2,3,9,10-Tetramethoxy-5-(*p*-tolyl)benzofuro[2,3-*c*]isoquinoline (8f). Brown solid (34 mg, 52%); mp: 221-223 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.59 (s, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.21 (s, 1H), 4.14 (s, 3H), 4.02 (s, 3H), 4.00 (s, 3H), 3.89 (s, 3H), 2.47 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 154.8, 153.2, 149.6, 149.4, 148.2, 146.4, 138.5, 136.9, 130.1, 130.1, 129.8, 129.2, 129.2, 120.0, 115.2, 107.7, 107.4, 104.2, 101.5, 96.2, 57.1, 56.4, 56.1, 55.9, 21.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_5$ 430.1649, found 430.1641.

5-(4-Chlorophenyl)-2,3,9,10-tetramethoxybenzofuro[2,3-*c*]isoquinoline (8g). Yellow solid (38 mg, 56%); mp: 235-237 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 3.9 Hz, 2H), 7.51 (s, 1H), 7.47 (s, 1H), 7.24 (s, 1H), 7.22 (s, 1H), 4.16 (s, 3H), 4.04 (s, 3H), 4.01 (s, 3H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 153.3, 152.9, 149.8, 149.4, 148.4, 146.4, 138.1, 134.6, 131.4, 130.9, 128.6, 119.7, 114.9, 107.8, 106.9, 105.4, 104.2, 102.3, 101.5, 96.1, 57.0, 56.3, 56.0, 55.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}ClNO_5$ 450.1103; found 450.1107.



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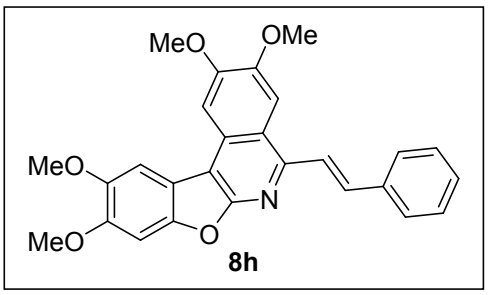
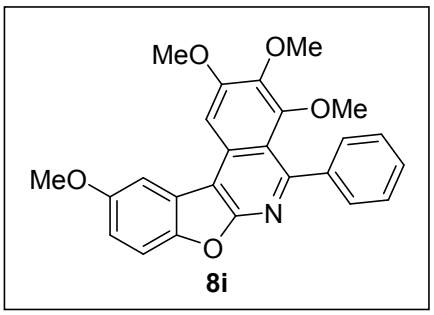
(*E*)-2,3,9,10-Tetramethoxy-5-styrylbenzofuro[2,3-*c*]isoquinoline (8h). Brown solid (23 mg, 35%); mp: 250-252 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 15.2 Hz, 1H), 7.88 (d, *J* = 15.5 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.64 (s, 1H), 7.50 (d, *J* = 4.2 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.22 (s, 1H), 4.16 (s, 3H), 4.11 (s, 3H), 4.05 (s, 3H), 4.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 153.2, 149.8, 149.5, 148.5, 148.5, 146.5, 137.2, 135.5, 129.7, 128.9, 128.9, 128.7, 127.5, 127.5, 122.7, 120.2, 115.4, 107.9, 104.5, 104.3, 101.8, 96.2, 57.2, 56.5, 56.1, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}NO_5$ 442.1649, found 442.1652.



8h

2,3,4,10-Tetramethoxy-5-phenylbenzofuro[2,3-*c*]isoquinoline (8i). White solid (17.2 mg, 86%); mp: 180-181 °C; R_f = 0.3 in 25% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.4 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.60-7.56 (m, 1H), 7.55 (s, 2H), 7.47-7.40 (m, 2H), 7.29 (s, 1H), 7.11 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.18 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 157.8, 157.2, 156.2, 154.4, 151.8, 149.0, 143.4, 140.6, 132.7, 129.1, 128.8, 127.2, 126.2, 124.4, 122.0, 115.8, 112.7, 106.8, 102.9, 98.1, 61.4, 61.1, 56.3, 56.2; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}NO_5$ 416.1492, found 416.1501.



8i

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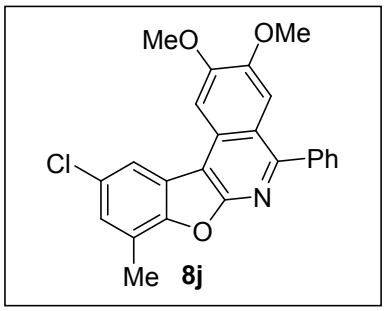
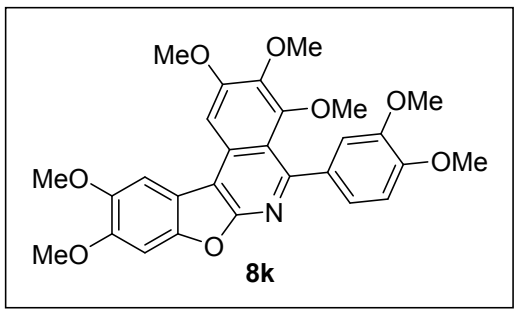
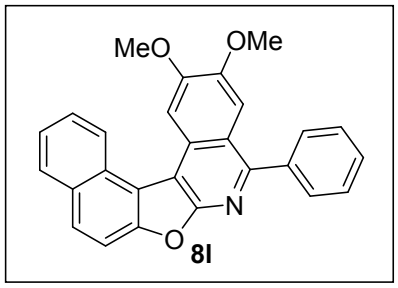
10-Chloro-2,3-dimethoxy-8-methyl-5-phenylbenzofuro[2,3-*c*]isoquinoline (8j). Light yellow solid (36 mg, 56%); mp: 208-210 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81 – 7.76 (m, 2H), 7.58 – 7.48 (m, 5H), 7.27 (s, 1H), 4.17 (s, 3H), 3.87 (s, 3H), 2.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 157.3, 153.9, 151.3, 148.6, 139.5, 130.6, 130.2, 130.2, 128.9, 128.6, 128.6, 128.5, 127.5, 124.3, 124.1, 120.1, 118.6, 107.8, 106.6, 101.6, 56.4, 55.9, 15.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}ClNO_3$ 404.1048, found 404.1047.



5-(3,4-Dimethoxyphenyl)-2,3,4,9,10-pentamethoxybenzofuro[2,3-*c*]isoquinoline (8k). Off-white solid (26 mg, 37%); mp: 222-224 °C; R_f = 0.3 in 35% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 7.26 (s, 1H), 7.03 (s, 2H), 4.19 (s, 3H), 4.07 (s, 3H), 4.02 (s, 3H), 3.95 (s, 3H), 3.93 (s, 6H), 3.92 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.8, 154.4, 153.4, 153.3, 153.3, 149.9, 149.6, 148.4, 146.6, 138.5, 135.3, 129.9, 119.9, 115.2, 107.7, 107.6, 107.5, 107.5, 104.5, 101.7, 96.4, 61.1, 57.2, 56.4, 56.4, 56.4, 56.2, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_8$ 506.1809, found 506.1809.



2,3-Dimethoxy-5-phenylnaphtho[1',2':4,5]furo[2,3-*c*]isoquinoline (8l). Yellow solid (60 mg, 94%); mp: 182-184 °C; R_f = 0.3 in 40% EtOAc in



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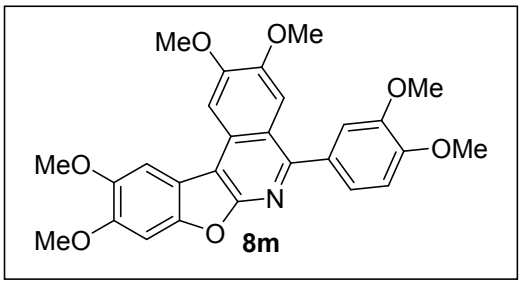
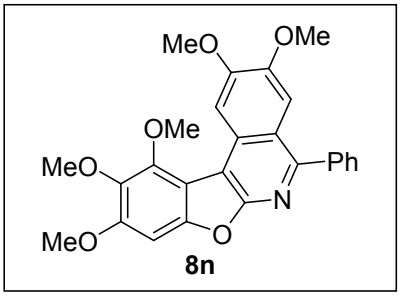
hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.5 Hz, 1H), 8.39 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.85 (dd, *J* = 7.9, 2.4 Hz, 3H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 7.59 (t, *J* = 7.5 Hz, 3H), 7.53 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.19 (s, 3H), 3.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 156.1, 152.7, 152.7, 148.2, 139.7, 131.3, 130.2, 130.2, 130.2, 130.1, 128.9, 128.8, 128.6, 128.6, 128.5, 126.2, 125.0, 124.6, 120.6, 118.3, 113.1, 109.0, 107.9, 104.8, 56.3, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}NO_3$ 406.1438, found 406.1435.

5-(3,4-Dimethoxyphenyl)-2,3,9,10-tetramethoxybenzofuro[2,3-*c*]isoquinoline (8m). White solid (45 mg, 63%); mp: 241-243 °C; R_f = 0.3 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 7.64 (s, 1H), 7.39 (s, 1H), 7.36 (s, 1H), 7.28 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 4.21 (s, 3H), 4.08 (s, 3H), 4.04 (s, 3H), 4.00 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0, 154.6, 153.4, 149.8, 149.6, 149.5, 149.1, 148.3, 146.6, 132.6, 130.0, 122.9, 120.1, 115.3, 113.4, 110.9, 107.8, 107.4, 104.6, 101.8, 96.4, 57.3, 56.5, 56.2, 56.2, 56.2, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_7$ 476.1704; found, 476.1700.



8m

2,3,9,10,11-Pentamethoxy-5-phenylbenzofuro[2,3-*c*]isoquinoline (8n). White solid (44 mg, 71%); mp: 163-165 °C; R_f = 0.2 in 25% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.79 (d, *J* = 7.0 Hz, 2H), 7.60-7.44 (m, 4H), 7.04 (s, 1H), 4.20 (s, 3H), 4.19 (s, 3H), 3.98 (s, 6H), 3.87 (s, 3H); **^{13}C**



8n

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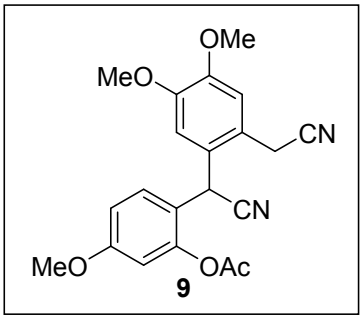
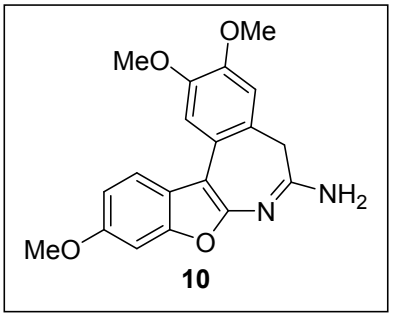
NMR (100 MHz, $CDCl_3$) δ 158.5, 155.0, 153.9, 152.9, 151.0, 148.3, 147.7, 139.9, 138.9, 130.2, 130.1, 130.1, 128.6, 128.5, 128.5, 120.3, 110.8, 108.3, 107.0, 105.6, 92.2, 62.5, 61.5, 56.5, 56.2, 55.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_6$ 446.1598, found 446.1598.



9

2-(Cyano(2-(cyanomethyl)-4,5-dimethoxyphenyl)methyl)-5-methoxyphenyl acetate (9). Yellow viscous liquid (168 mg, 86%); R_f = 0.3 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.95 (s, 1H), 6.91 (s, 1H), 6.76 (s, 1H), 6.74 (s, 1H), 5.28 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.48 (s, 2H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8, 160.9, 149.4, 149.3, 149.2, 129.4, 124.1, 120.2, 118.2, 117.7, 117.2, 113.1, 112.7, 112.4, 109.5, 56.3, 56.2, 55.7, 33.8, 20.9, 20.9; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{20}N_2O_5Na$ 403.1264, found 403.1263.

2,3,10-Trimethoxy-5*H*-benzo[*d*]benzofuro[2,3-*b*]azepin-6-amine (10). Light brown solid (35 mg, 78%); mp: 94-96 °C; R_f = 0.35 in 40% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$)



10

δ 7.06 (s, 1H), 6.94 (s, 1H), 6.93 (d, *J* = 4.6 Hz, 1H), 6.88 (s, 1H), 6.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.98 – 3.93 (m, 3H), 3.89 – 3.84 (m, 3H), 3.84 – 3.80 (m, 3H), 3.67 (d, *J* = 18.5 Hz, 1H), 3.58 (d, *J* = 18.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 156.0, 152.9, 150.7, 149.0, 124.1, 123.3, 122.4, 118.8, 116.9, 113.9, 111.9, 110.6, 96.7, 91.9, 56.2, 56.1, 56.0, 21.4; **HRMS** (ESI-

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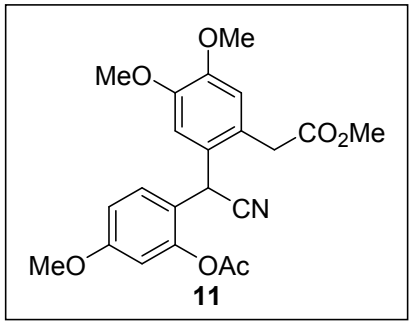
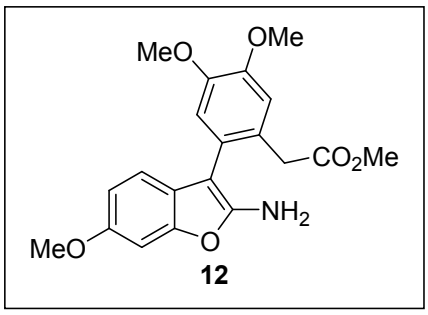
QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}N_2O_4$ 339.1339, found 339.1330.



11

Methyl 2-(2-((2-acetoxy-4-methoxyphenyl)(cyano)methyl)-4,5-dimethoxyphenyl)acetate (11). Colorless viscous liquid (164 mg, 77%); R_f = 0.25 in 30% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 6.76 – 6.68 (m, 3H), 5.56 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.61 (s, 3H), 3.44 (s, 1H), 3.43 (s, 1H), 2.24 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 168.6, 160.4, 149.1, 148.9, 148.6, 129.6, 125.0, 124.5, 119.1, 118.9, 114.4, 112.3, 112.0, 109.2, 56.1, 56.0, 55.6, 52.2, 37.9, 33.6, 20.8; **HRMS** (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{23}NO_7Na$ 436.1367, found 436.1363.

Methyl 2-(2-(2-amino-6-methoxybenzofuran-3-yl)-4,5-dimethoxyphenyl)acetate (12). Light brownish yellow viscous liquid (33 mg, 73%); R_f = 0.4 in 50% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 3.6 Hz, 2H), 6.75 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.19 (s, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 3.58 (d, *J* = 16.3 Hz, 1H), 3.54 (d, *J* = 16.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 155.7, 153.3, 150.5, 148.5, 148.4, 126.6, 125.1, 124.2, 116.9, 113.8, 113.1, 110.2, 96.4, 92.4, 56.0, 55.9, 52.0, 52.0, 38.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_6$ 372.1442, found 372.1443.



12

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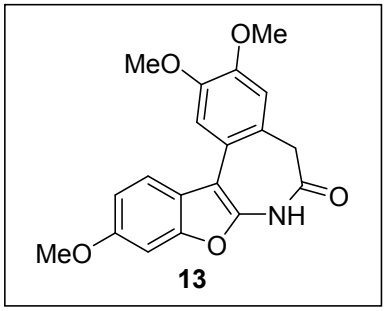
2,3,10-Trimethoxy-5,7-dihydro-6*H*-benzo[*d*]benzofuro[2,3-*b*]azepin-6-one (13). White solid (37 mg, 91%); mp: 280-282 °C; R_f = 0.3 in 50% EtOAc in hexane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.26 (s, 1H), 7.04 (d, *J* = 1.3 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.90 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.56 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 157.7, 152.3, 149.4, 148.9, 144.1, 122.7, 122.7, 120.2, 119.6, 112.7, 111.9, 108.6, 105.1, 96.8, 56.3, 56.1, 55.9, 42.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_5$ 340.1179, found 340.1171.



13

Conflicts of interest

There are no conflicts to declare.

Electronic Supplementary Information (ESI) available:

^{1}H and ^{13}C NMR spectra of synthesized compounds and Table S1

Acknowledgements

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[9] The full optimization table S1 is in the ESI.

[10] See the Experimental Section for details.

[11] When *p*-tolualdehyde was treated with 3,4-dimethoxyphenol under these conditions, only 30% of the cyanohydrin compound was isolated out of the complex mixture. Even resubjection of the cyanohydrin to 3,4-dimethoxyphenol (1 equiv) and BF_3-OEt_2 (2 equiv) in CH_2Cl_2 at 30 °C for prolonged time did not give the desired product.

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