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BCl_3-promoted synthesis of benzofurans

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ABSTRACT

Lewis acidic nature of boron trichloride (BCl_3) to coordinate to the carbonyl functionality was exploited for the synthesis of benzofurans via dehydrative cyclization. This mild and efficient procedure allowed for facile access to a number of highly substituted benzofurans in a regioselective manner. The structural requirement for the successful cyclodehydration was examined in the cases, where competitive demethylation could occur.

Benzofurans are ubiquitous structural motifs in both natural products and synthetic pharmaceuticals.[1] As depicted in Figure 1, for instance, malibatol A exhibiting cytotoxicity to the host cells (CEM SS) in the antiviral assay was isolated from the organic extract of the leaves of *Hopea malibato* by Boyd and coworkers in 1998,[2] whereas shoreaphenol or hopeafuran was isolated from the bark of *Shorea robusta* or the stem wood of *Hopea utilis*.[3] Recently, iantheran A, a dimeric polybrominated benzofuran, was evaluated as a Na, K-ATPase inhibitor.[4]

Due to the remarkably diverse array of biological activities associated with this previledged structure,[5] a number of synthetic strategies have been developed.[6] Among these, cyclodehydration of aryloxyketones has been amply implemented for the synthesis of benzofurans, partly due to the easy preparation of cyclization precursor, aryloxyketones (Scheme 1).

A variety of Lewis acids or Brønsted acids have been utilized to effect the cyclodehydration approach. However, elevated temperatures are also required for the successful cyclodehydration of aryloxyketones to occur in many cases. Besides, unwanted rearrangement sometimes takes place under the certain harsh reaction conditions to afford a mixture of products.[7] Furthermore, a mixture of regioisomers results from the conditions where the aryloxyketones are submitted as a consequence of non-regioselective ring closure. In view of these drawbacks, search for the milder cyclodehydrating conditions is, therefore, still in demand. Recently, we discovered that boron trichloride (BCl_3) induces smooth cyclodehydration of aryloxyketones to afford benzofurans. Although it is well known for its ability to cleave ether linkages via coordination to the neighboring carbonyl functionality as a dealkylating agent, use of BCl_3 as a cyclodehydrating agent has not been disclosed yet in the literature.[8] Here, we wish to describe our findings.

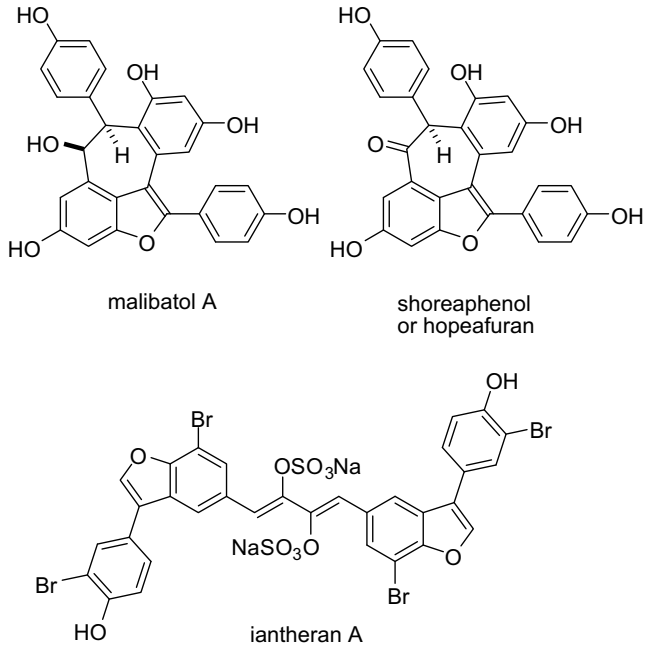

Figure 1. Some representative benzofuran-containing natural products.

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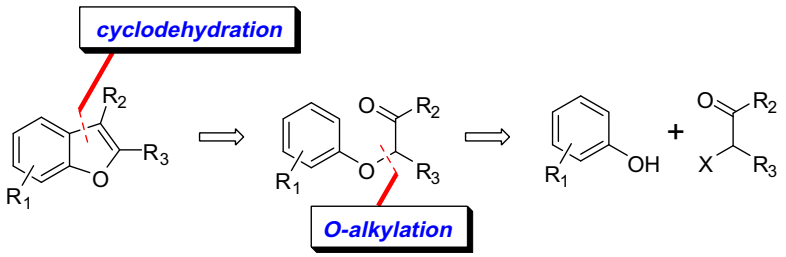
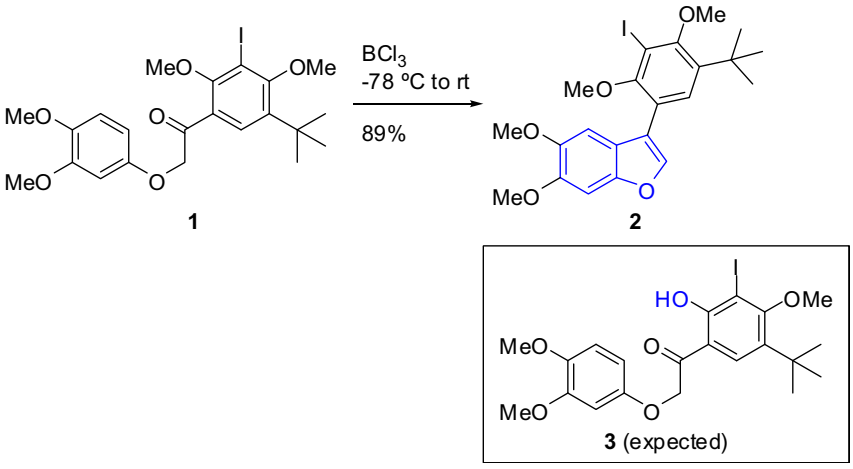
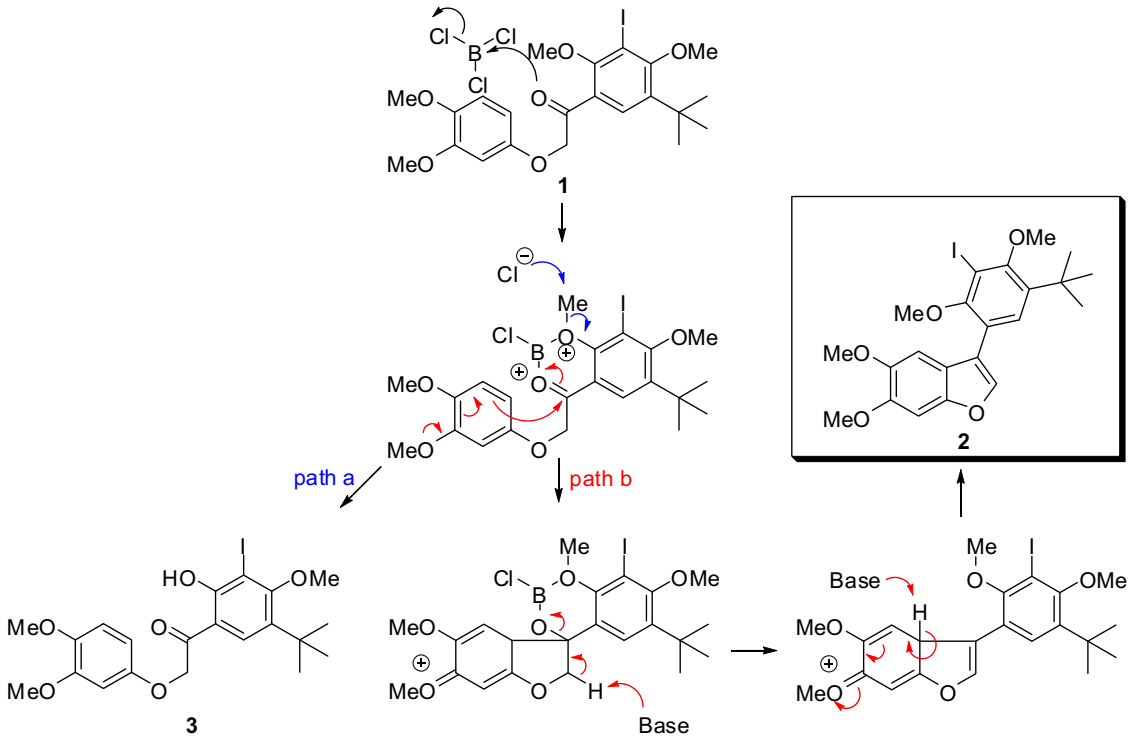


Scheme 1.

In the course of our medicinal program, we needed to convert **1** to **3**. For this purpose, BCl_3 was chosen since it had been widely used for selective demethylation of methoxy benzene compounds bearing a carbonyl functional group at the ortho position. Thus, BCl_3 (1.0 M solution in CH_2Cl_2, 1.2 equiv) was added to a solution of **1** in CH_2Cl_2 at −78 °C. After the addition was complete, the reac-

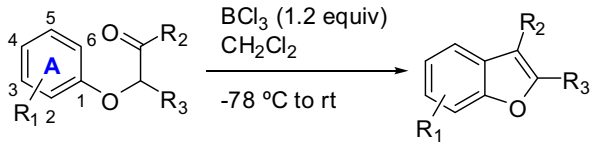


Scheme 2.



Scheme 3.

Table 1



4 **5**

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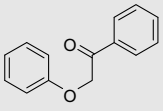
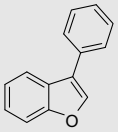
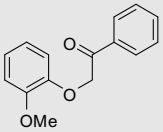
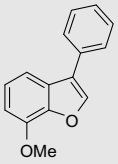
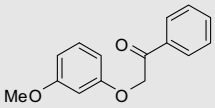
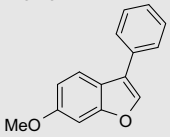
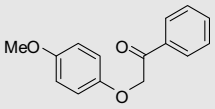
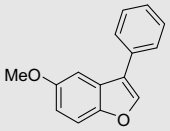
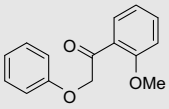
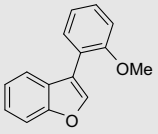
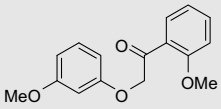
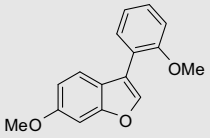
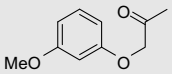
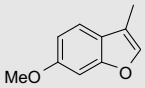
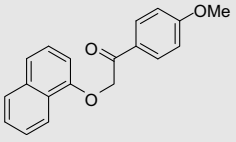
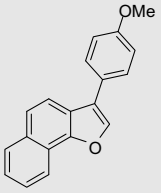
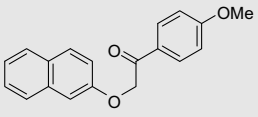
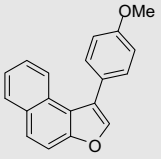
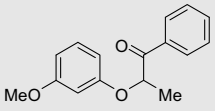
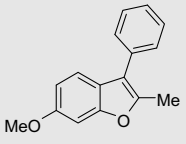
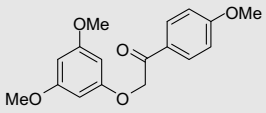
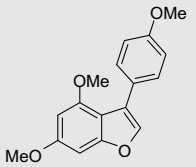
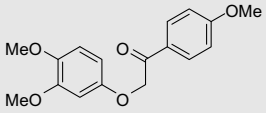
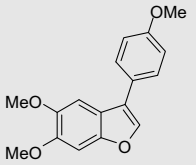
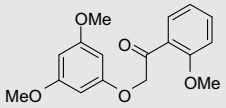
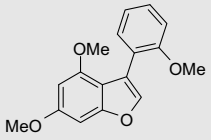
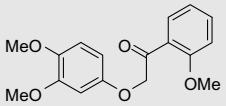
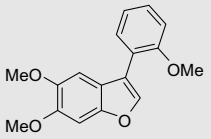
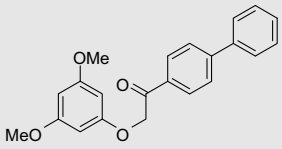
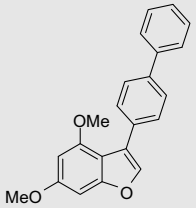
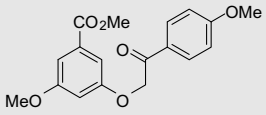
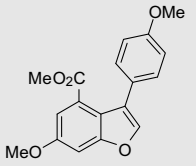
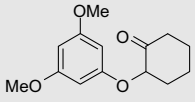
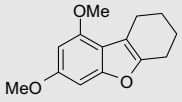
1		**4a**		**5a**	42
2		**4b**		**5b**	63
3		**4c**		**5c**	90
4		**4d**		**5d**	89
5		**4e**		**5e**	30[a]
6		**4f**		**5f**	66
7		**4g**		**5g**	59
8		**4h**		**5h**	85
9		**4i**		**5i**	83
10		**4j**		**5j**	99

(*continued on next page*)

Table 1 (*continued*)

Entry	4		5		Yield (%)
11		**4k**		**5k**	95
12		**4l**		**5l**	91
13		**4m**		**5m**	93
14		**4n**		**5n**	86
15		**4o**		**5o**	96
16		**4p**		**5p**	84[b]
17		**4q**		**5q**	88

[a] The demethylated product **5e′** was also isolated in about 30% yield.
[b] 2.5 equiv of BCl_3 was used.

tion mixture was stirred at rt for 30 min. Surprisingly, however, benzofuran **2** was isolated as a major product instead of the expected phenol **3** (see Scheme 2).

Certainly, the formation of this benzofuran **2** can be rationalized as depicted in Scheme 3. The initial coordination of BCl_3 to the carbonyl oxygen can induce subsequent steps in two ways. One option is demethylation as can be seen in path a. Alternatively, the nucleophilic attack of the neighboring aromatic moiety to the carbonyl group followed by dehydration would lead to benzofuran **2** (path b). Obviously, the rate of cyclization seemed to be faster than that of demethylation in this case. Intrigued by this result, we decided to further explore the generality of this reaction with other aryloxyketones.

The requisite aryloxyketones were easily prepared from the reaction of phenols or naphthols with αα-bromoketones in the presence of potassium carbonate. When these aryloxyketones were exposed to BCl_3, the corresponding benzofurans were obtained as outlined in Table 1.[9,10] When there was no substitution of electron-donating group at the phenolic part (ring A) of aryloxyketones, modest yields of benzofurans were obtained (entries 1 and 5).[11] Aryloxyketones bearing a methoxy group at the *ortho*, *meta*, or *para* position of ring **A** were then treated with BCl_3, respectively. While **4c** and **4d** were converted to the corresponding benzofurans **5c** and **5d** in excellent yields, **5b** was produced from **4b** in 63% yield (entries 2–4). When R_2 was a 2-methoxyphenyl and ring **A** had a 3-methoxyl, competitive demethylation was reduced and the desired cyclization occurred to afford 3-arylbenzofuran in a reasonable yield (entry 6). Additional methoxy group at 4 or 5 position of ring **A** increased the product yields dramatically (entries 13 and 14). In addition, aryloxyketones **4k** and **4l**

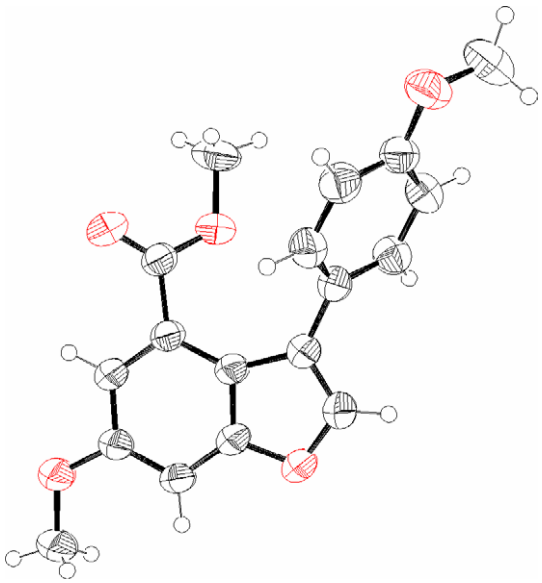


Figure 2. Crystal structure of **5p**.

bearing a 4-methoxyphenyl at R_2 site underwent smooth dehydrative cyclization to furnish excellent yields of **5k** and **5l**, respectively (entries 11 and 12).

Methylketone **4g** was transformed to the cyclized product **5g** in 59% yield (entry 7). Naphthofurans were accessed in good yields (entries 8 and 9). Interestingly, only one regioisomer **5i** was isolated in case of **4i**.[12,13] Substrates having substituents at both R_2 and R_3 positions also worked well under these conditions to give the highly substituted benzofurans (entries 10 and 17). Biphenyl containing benzofuran **5o** was also prepared in 96% yield (entry 15). Intriguingly, one regioisomer **5p** was isolated from the reaction of **4p** with BCl_3 (entry 16).[14] The structure of **5p** was unambiguously determined on the basis of an X-ray crystallographic analysis (Fig. 2).[15]

In summary, we discovered that boron trichloride (BCl_3) is a very mild and convenient reagent for the synthesis of benzofurans and naphthofurans via dehydrative cyclization. By varying the electron density and substitution pattern of the phenolic part of aryloxyketones, we were able to find the structural requirement for the successful cyclization even when competitive demethylation via coordination of BCl_3 to the carbonyl functionality can be possible. Currently, efforts are being made to apply this protocol to the synthesis of benzofuran-containing natural products as well as other heterocycles and will be reported in due course.

References and notes

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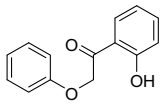
8. Although BBr_3 was used to make benzofurans via demethylation and cyclodehydration, only four examples are shown and the yields are low. Dupont, R.; Cotelle, P. *Synthesis* **1999**, 1651.
9. *General procedure*: To a stirred solution of **4** (0.4 mmol) in CH_2Cl_2 (3 mL) was added BCl_3 (1.2 equiv, 1.0 M solution in CH_2Cl_2) at −78 °C. After being stirred at rt for 1 h, the reaction mixture was quenched with cold H_2O. The mixture was extracted with CH_2Cl_2 two times. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the benzofuran or naphthofuran **5**.
10. *Spectral data*: **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.6, 1.7 Hz, 1H), 7.78 (s, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.54 (dd, J = 7.6, 1.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.40–7.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 141.3, 132.1, 129.0, 127.5, 127.4, 126.5, 124.6, 123.0, 122.3, 120.4, 111.8; HRMS (EI) calcd for $[C_{14}H_{10}O]^+$: m/z 194.0732, found: 194.0736. Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.50–7.32 (m, 4H), 7.23 (t, J = 7.9 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 145.2, 141.4, 132.0, 128.9, 128.2, 127.5, 127.4, 123.7, 122.7, 122.7, 106.6, 56.1; HRMS (EI) calcd for $[C_{15}H_{12}O_2]^+$: m/z 224.0837, found: 224.0835. Compound **5c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.67 (d, J = 8.6 Hz, 1H), 7.61 (dd, J = 8.3, 1.4 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.37–7.29 (m, 1H), 7.05 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 8.7, 2.3 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 156.9, 140.4, 132.3, 129.0, 127.4, 127.3, 122.1, 120.6, 119.8, 112.1, 96.2, 55.7; HRMS (EI) calcd for $[C_{15}H_{12}O_2]^+$: m/z 224.0837, found: 224.0833. Compound **5d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64–7.58 (m, 2H), 7.52–7.41 (m, 3H), 7.40–7.33 (m, 1H), 7.26 (d, J = 2.6 Hz, 1H), 6.96 (dd, J = 8.9, 2.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 150.8, 142.2, 132.2, 129.0, 127.5, 127.4, 127.0, 122.4, 113.3, 112.2, 102.9, 56.0; HRMS (EI) calcd for $[C_{15}H_{12}O_2]^+$: m/z 224.0837, found: 224.0839. Compound **5e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.73 (dd, J = 7.4, 1.8 Hz, 1H), 7.63 (dd, J = 7.5, 1.7 Hz, 1H), 7.54 (dd, J = 8.0, 1.1 Hz, 1H), 7.38–7.21 (m, 3H), 7.10–7.00 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 155.2, 143.8, 130.0, 128.5, 127.2, 124.1, 122.6, 121.2, 120.9, 120.8, 117.5, 111.6, 111.2, 55.5; HRMS (EI) calcd for $[C_{15}H_{12}O_2]^+$: m/z 224.0837, found: 224.0835. Compound **5f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.65-7.56 (m, 2H), 7.33 (td, J = 7.9, 1.7 Hz, 1H), 7.10–6.97 (m, 3H), 6.90 (dd, J = 8.7, 2.3 Hz, 1H), 3.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 156.8, 156.1, 142.8, 129.8, 128.4, 121.4, 121.1, 120.8, 120.5, 117.4, 111.7, 111.2, 96.0, 55.7, 55.5; HRMS (EI) calcd for $[C_{16}H_{14}O_3]^+$: m/z 254.0943, found: 254.0946. Compound **5g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 1.2 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 6.90 (dd, J = 8.5, 2.2 Hz, 1H), 3.86 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.2, 140.5, 122.5, 119.5, 115.5, 111.2, 96.0, 55.7, 7.9; HRMS (EI) calcd for $[C_{10}H_{10}O_2]^+$: m/z 162.0681, found: 162.0683. Compound **5h**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.63–7.53 (m, 3H), 7.48 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 151.3, 139.9, 131.5, 128.8, 128.3, 126.4, 125.3, 124.6, 123.5, 123.1, 122.1, 121.6, 120.1, 118.8, 114.5, 55.4; HRMS (EI) calcd for $[C_{19}H_{14}O_2]^+$: m/z 274.0994, found: 274.0993. Compound **5i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.62 (s, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.43–7.31 (m, 2H), 7.01 (d, J = 7.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 153.1, 141.6, 131.0, 130.8, 128.9, 128.4, 125.9, 125.8, 125.2, 124.3, 124.0, 123.3, 121.0, 114.1, 112.7, 55.4; HRMS (EI) calcd for $[C_{19}H_{14}O_2]^+$: m/z 274.0994, found: 274.0991. Compound **5j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.40 (m, 5H), 7.37–7.29 (m, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.84 (dd, J = 8.6, 2.3 Hz, 1H), 3.84 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 154.9, 150.2, 133.0, 128.8, 128.7, 127.0, 122.2, 119.5, 116.6, 111.2, 95.9, 55.8, 12.8; HRMS (EI) calcd for $[C_{16}H_{14}O_2]^+$: m/z 238.0994, found: 238.0991. Compound **5k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, J = 8.8, 2.1 Hz, 2H), 7.42 (s, 1H), 6.77 (dt, J = 8.8, 2.1 Hz, 2H), 6.95 (d, J = 2.0 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 3.83 (s, 6H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 158.9, 157.8, 154.7, 139.3, 130.4, 124.8, 122.3, 113.4, 110.0, 94.5, 88.3, 55.7, 55.4, 55.3; HRMS (EI) calcd for $[C_{17}H_{16}O_4]^+$: m/z 284.1049, found: 284.1053. Compound **5l**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.53 (dd, J = 8.2, 0.7 Hz, 2H), 7.18 (s, 1H), 7.09 (s, 1H), 7.02 (dd, J = 8.3, 0.7 Hz, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 150.4, 148.2, 146.7, 139.7, 128.5, 124.7, 122.0, 118.5, 114.5, 101.6, 95.6, 56.5, 56.2, 55.3; HRMS (EI) calcd for $[C_{17}H_{16}O_4]^+$: m/z 284.1049, found: 284.1055. Compound **5m**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.48 (dd, J = 7.4, 1.7 Hz, 1H), 7.35 (td, J = 7.6, 1.8 Hz, 1H), 7.04 (dd, J = 7.5, 0.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.35 (d, J = 1.9 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.8, 157.5, 155.0, 141.2, 132.1, 128.8,

121.7, 120.2, 117.8, 111.3, 110.8, 94.8, 88.5, 56.0, 55.7, 55.6; HRMS (EI) calcd for $[C_{17}H_{16}O_4]^+$: m/z 284.1049, found: 284.1055. Compound **5n**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.57 (dd, J = 7.5, 1.7 Hz, 1H), 7.34 (td, J = 7.5, 1.8 Hz, 1H), 7.13 (s, 1H), 7.09 (dd, J = 7.5, 1.1 Hz, 1H), 7.08 (s, 1H), 7.04 (d, J = 7.9 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 149.9, 148.0, 146.4, 142.7, 129.9, 128.5, 121.2, 120.8, 119.1, 117.9, 111.3, 102.8, 95.4, 56.5, 56.3, 55.4; HRMS (EI) calcd for $[C_{17}H_{16}O_4]^+$: m/z 284.1049, found: 284.1047. Compound **5o**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.60 (m, 5H), 7.55 (d, J = 2.4 Hz, 1H), 7.46 (td, J = 7.8, 1.6 Hz, 2H), 7.35 (td, J = 7.4, 1.9 Hz, 1H), 7.26 (d, J = 2.5 Hz, 1H), 6.71 (t, J = 2.1 Hz, 1H), 6.38 (t, J = 2.1 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 158.0, 154.7, 141.0, 140.0, 139.9, 131.4, 129.6, 128.8, 127.2, 127.1, 126.7, 126.8, 122.5, 109.8, 94.6, 88.4, 55.8, 55.4; HRMS (EI) calcd for $[C_{22}H_{18}O_3]^+$: m/z 330.1256, found: 330.1255. Compound **5p**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 1.3 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 158.9, 157.3, 157.0, 142.9, 129.6, 125.7, 125.4, 122.4, 119.0, 113.6, 113.0, 100.2, 56.0, 55.3, 51.6; HRMS (EI) calcd for $[C_{18}H_{16}O_5]^+$: m/z 312.0998, found: 312.0996. Compound **5q**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.26 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.80–2.70 (m, 2H), 2.70–2.60 (m, 2H), 1.95–1.83 (m, 2H), 1.83–1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.9, 154.1, 151.0, 112.2, 112.1, 93.6, 88.4, 55.7, 55.4, 23.3, 23.0, 22.9, 22.2; HRMS (EI) calcd for $[C_{14}H_{16}O_3]^+$: m/z 232.1099, found: 232.1097.

11. Exposure of **4e** to 3 equiv of BCl_3 led to the only demethylated product **5e′**.



5e'

12. Mashiraqui, S. H.; Patil, M. B.; Sangvikar, Y.; Ashraf, M.; Mistry, H. D.; Daub, E. T. H.; Meetsma, A. *J. Heterocycl. Chem.* **2005**, *42*, 947. 45% isolated yield of **5i** upon treatment of **4i** with CH_3SO_3H was reported in this Letter.
13. For other synthesis and biological evaluation of 5i as a novel anticancer agent, see: Srivastava, V.; Negi, A. S.; Kumar, J. K.; Faridi, U.; Sisodia, B. S.; Darokar, M. P.; Luqman, S.; Khanuja, S. P. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 911.
14. No reaction took place with 1 equiv of BCl_3, which is believed to be consumed as a consequence of the coordination to the ester moiety in **4p**.
15. CCDC 694499 contains the supplementary crystallographic data for compound **5p**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.