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Cu(I)-mediated lactone formation in subcritical water: a benign synthesis of benzopyranones and urolithins A–C

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ABSTRACT

Benzopyranones were successfully synthesized using Cu(I)-mediated C–O bond formation in subcritical water. A number of benzopyranone derivatives including polymethoxy benzopyranones, benzopyranopyridones, chromenoindolones, and furochromenones were synthesized in satisfactory yield. This methodology was further applied to synthesize the intestinal microbial metabolites, urolithins A, B, and C, which were found to exhibit potent antioxidant activity.

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1. Introduction

Recently, aqueous and microwave conditions have attracted both academic and industrial interests as an economical and environmentally friendly processes.[1–3] Water showed an important role as a reaction medium in organometallic reactions including Suzuki–Miyaura,[4,5] Negishi,[6] Stille,[7] and Sonogashira[8,9] cross-couplings. Because of its beneficial properties, such as inexpensiveness, environmentally friendliness, non-flammability, and safety, the role of water in research works has gained growing interest during the past decade.[10,11] Moreover, water has the dielectric constant (ε') higher than other organic solvents at room temperature, which can effectively absorb microwave energy and acts as pseudo-organic solvent at high temperature.[12] Apart from the superheated condition of water (>100 °C), supercritical water (SCW, >374 °C) has been widely studied in several fields[13–15] but some limitations retard its utilization due to its degenerative properties.[16] On the other hands, subcritical water (near-critical water, NCW), generated between 150 and 300 °C, is reliable to use under a milder condition and is still able to maintain its pseudo-organic solvent properties.[17,18]

Benzopyranone **1** is the structural motif of various natural oxygen heterocycles, which typically consist of dibenzo[*d*,*b*]pyran-6-one or 6*H*-benzo[*c*]chromen-6-one and these lactone containing natural products as shown in Fig. 1 have been isolated from various sources. Urolithins A–C (**2a**–**c**), the intestinal microbial metabolites produced by in vitro fermentation of punicalagins, show antioxidant activity.[19,20] They also showed colon cancer chemopreventive activities by inhibiting TCDD-induced CYP1-mediated EROD activity.[21] Alternariol (**3**), a metabolite of toxin-producing *Alternaria*

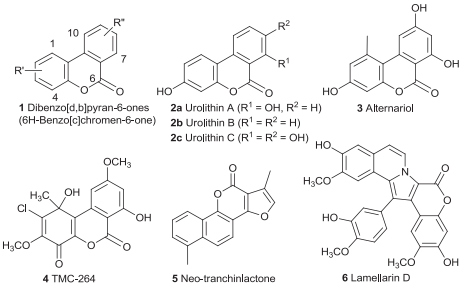

Fig. 1. Various natural lactone containing heterocycles.

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fungi, has been found to be the natural food contaminant in various grains, crops, and decayed fruits.[22,23] TMC-264 (**4**), isolated from the fermentation broth of a fungus *Phoma* sp. TC 1674, displays potent inhibitory activity against tyrosine phosphorylation of STAT6.[24] Neo-tranchinlactone (**5**), isolated from *Salvia miltiorrhiza* and first synthesized by Lee,[25] shows potent and selective anti-breast cancer activity.[26] The complex benzopyranone lamellarin D (**6**), isolated from a marine organism,[27] displays potent cytotoxic activity against multidrug-resistant tumor cell lines and is highly cytotoxic to prostate-cancer cell lines.[28–30] Due to the potential uses as pharmacologically active compounds, benzopyranones have attracted much interest from various groups including ours.[31] Adhering to the economical aspect and 'Green Chemistry' concept, in this study we report a short synthesis of benzopyranones using Cu(I)-mediated C–$O_{carboxylate}$ bond formation in subcritical water. Our protocol was also extended to synthesize the antioxidant benzopyranones, urolithins A (**2a**), B (**2b**), and C (**2c**).[19]

2. Results and discussion

To delve deeper and intensify our research in this direction, Cu(I)-catalyzed/microwave-assisted C–$O_{carboxylate}$ bond formation of 2-halobiarylcarboxylates **7a** and **7b** was studied by varying the types of bidentate ligands **8** in subcritical water under the basic conditions. A set of bidentate ligands[32] (Fig. 2), including *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (**8a**, TMEDA, L1), phenanthroline (**8b**, Phen, L2), bipyridine (**8c**, Bip, L3), methyl 2-oxocyclohexane carboxylate (**8d**, MOCHC, L4), ethyl 2-oxocyclohexanecarboxylate (**8e**, EOCHC, L5), 2-acetyl-cyclohexanone (**8f**, ACH, L6), and 2-benzoylcyclohexanone (**8g**, BCH, L7), was examined together with sub-stoichiometric amount, 50 mol % of CuI or copper(I) thiophene-2-carboxylate (CuTC) as catalysts and Cs_2CO_3 or K_2CO_3 as bases in subcritical water using microwave irradiation.

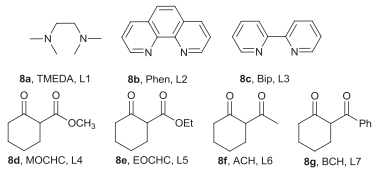
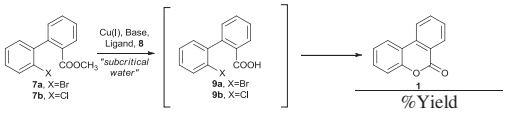


Fig. 2. Ligands under screening.

Interestingly, increasing the temperature to 300 °C for 10 min with Cs_2CO_3 and ligand L1, the lactone product (**1**) was obtained in excellent yield (Table 1, entry 9). Various bidentate ligands, L2–L7 (**8b**–**g**) were then studied using these optimized conditions to give product **1** in poor to good yields (15–78%) (Table 1, entries 10–15). From these experiments, the effectiveness of various ligands for the lactone formation was found to be as followed: TMEDA, L1>Bip, L3>BCH, L7>Phen, L2>ACH, L6>EOCHC, L5>EOCHC, L4. The relative effectiveness of the ligands agrees well with the previous report by Buchwald.[33] This mechanistic study also suggested that the bidentate ligand L1 was more suitable to furnish C–O bond than β-diketone or β-keto ester ligands.[33] This similar trend was also observed the comparison between bidentate and β-diketone or β-keto ester ligands (Table 1, entries 9–15). The C–$O_{carboxylate}$ bond formation was decreased when K_2CO_3 was used as a base instead of Cs_2CO_3 (Table 1, entries 16–18). The decreasing of CuTC to 25 mol % the lower yield of the lactone formation was obtained in 67% yield (Table 1, entry 19). This may support that the sub-stoichiometric amount was the suitable condition for our investigation. The lactone product was also furnished in low yield under refluxing conditions (Table 1, entry 20).

Table 1
Synthesis of 5-amido-8,9-dimethoxy-6-aryl-2,3-dihydrobenzo[*d*]azocin-4-ones **1**[a]

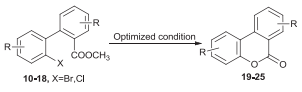


Entry	X	Cu(I)	Condition[b]	Base/Ligand, **8**[c]	%Yield		
					1	**7**	**9**
1	Br	CuTC	A	—	19	62	—
2	Br	CuI	A	—	8	56	—
3	Br	CuTC[d]	B	—	14	56	—
4	Br	CuI[d]	B	—	10	18	—
5	Br	CuTC	B	Cs_2CO_3/**8a**	60	—	—
6	Br	CuI	B	Cs_2CO_3/**8a**	57	—	—
7	Cl	CuTC	B	Cs_2CO_3/**8a**	16	—	53
8	Cl	CuI	B	Cs_2CO_3/**8a**	17	—	39
9	**Br**	**CuTC**	**C**	**Cs_2CO_3/8a**	**99**	—	—
10	Br	CuTC	C	Cs_2CO_3/**8b**	47	—	—
11	Br	CuTC	C	Cs_2CO_3/**8c**	78	—	—
12	Br	CuTC	C	Cs_2CO_3/**8d**	15	—	23
13	Br	CuTC	C	Cs_2CO_3/**8e**	30	19	24
14	Br	CuTC	C	Cs_2CO_3/**8f**	43	24	33
15	Br	CuTC	C	Cs_2CO_3/**8g**	60	—	40
16	Br	CuTC	C	K_2CO_3/**8a**	62	—	—
17	Br	CuTC	C	K_2CO_3/**8b**	36	—	—
18	Br	CuTC	C	K_2CO_3/**8c**	73	—	—
19	Br	CuTC[e]	C	Cs_2CO_3/**8a**	67	2	8
20	Br	CuTC	D	Cs_2CO_3/**8a**	29	—	11

The entries in bold signifies the best optimized condition.
[a] Unless otherwise noted, the reactions were performed in 10 mL microwave vessel, compound **7** (0.2 mmol), Cu(I) salts (0.1 mmol) in water (1 mL).
[b] Condition A: 200 W, 200 °C, 100 psi, 20 min; condition B: 300 W, 250 °C, 280 psi, 20 min; condition C: 300 W, 300 °C, 250 psi, 10 min; condition D: refluxing condition up to 24 h.
[c] Ligands under screening are shown in Fig. 2.
[d] Cu(I) salts (2 equiv) CuTC=copper(I) thiophene carboxylate.
[e] CuTC (0.25 equiv) was used.

In the above screening, we found that the best conditions to form the C–$O_{carboxylate}$ bond of benzopyranone was the use of TMEDA as ligand in the presence of Cs_2CO_3 in subcritical water at 300 °C. Various biaryl carboxylates **10**–**18** were prepared using the Suzuki–Miyaura coupling reaction.[31a] With these starting materials in hand, we then studied the Cu(I)-mediated C–$O_{carboxylate}$ lactone formation of benzopyranones **19**–**25** as shown in Table 2.

Table 2
Synthesis of the benzopyranone derivatives using the optimized conditions[a]



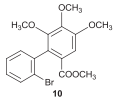
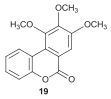
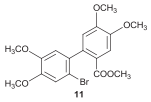
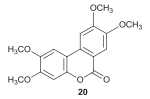
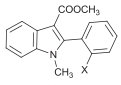
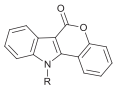
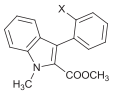
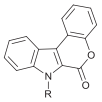
Entry	Substrate	Product	Yield[b] (%)
1			39[c]
2			31[c]
3			46
4			66

Table 2 (*continued*)

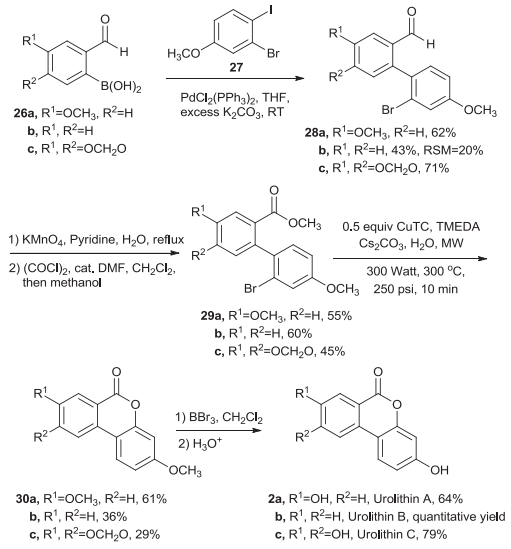
Entry	Substrate	Product	Yield[b] (%)
5	 **14**, X=Br **15**, X=Cl	 **23a**, R=Me **23b**, R=H	66, 10[d]
6			73[e]
7	 **16**, X=Br **17**, X=Cl	 **24a**, R=Me **24b**, R=H	45, 11[f]
8			47, 4[g]
9	 **18**	 **25**	30

[a] Reaction conditions: biaryl ester (0.2 mmol), CuTC (0.5 equiv), Cs_2CO_3 (0.5 equiv), TMEDA (1.0 equiv) in water (1 mL), MW (300 W), 300 °C, 250 psi, 10 min.
[b] Isolated yields.
[c] Reaction time 20 min.
[d] % Yield of **23a** and **23b** from **14**.
[e] % Yield of **23a** from **15**.
[f] % Yield of **24a** and **24b** from **16**.
[g] % Yield of **24a** and **24b** from **17**.

The polyoxygenated benzopyranones **19** and **20** were synthesized from tri- and tetra-methoxybiaryl carboxylates **10** and **11**, respectively, in moderate yields (Table 2, entries 1 and 2).[31a] In these reactions, the reaction time was increased to 20 min.

In order to demonstrate the versatility of our strategy in the synthesis of benzopyranone derivatives, we then directed our attention to synthesize the chromenopyridinones **21** and **22**.[34] 3-Arylisonicotinate **12** and 2-arylnicotinate **13** were prepared from the corresponding pyridine derivatives using Suzuki–Miyaura cross-coupling reaction with 2-haloarylboronic acids as previously reported.[31a] The chromenopyridinones **21** and **22** were obtained in moderate yields (46–66%) (Table 2, entries 3 and 4). Fused heteroaromatic rings, tetracyclic chromenoindolones **23a** and **23b** were prepared from the corresponding 2-arylindole-3-carboxylates **14** (X=Br) or **15** (X=Cl).[31a,35] Compounds **24a** and **24b** could also be obtained under the same conditions from 3-arylindole-2-carboxylates **16** (X=Br) or **17** (X=Cl).[31a,35] The reaction of 2-(2-bromophenyl)indole-3-carboxylate **14** gave a mixture of the lactone products, *N*-methyl chromenoindolone **23a** (66%) together with the demethylated chromenoindolone **23b** (10%) (Table 2, entry 5). In contrast, the reaction of 2-(2-chlorophenyl)indole-3-carboxylate **15** gave only *N*-methyl chromenoindolone **23a** in good yield (73%) (Table 2, entry 6). When 3-arylindole-2-carboxylates **16** and **17** were employed, both compounds gave a mixture of *N*-methyl chromenoindolone **24a** and demethylated chromenoindolone **24b** (Table 2, entries 7 and 8). The by-products **23b** and **24b** may be the result of the halide generated from the Cu(I)-mediated reaction and act as a nucleophile to attack the indole *N*-methyl group, giving halomethanes and the N-demethylated products. The benzopyranone derivative, furochromenone **25**[36–39] was also successfully prepared from 2-arylfuran-3-carboxylate **18** in 30% yield (Table 2, entry 9).

The utility of this method was further demonstrated with the synthesis of natural benzopyranones urolithins A–C (**2a**–**c**).[19] Our synthetic route was performed using the same sequence of reactions requiring five steps from commercially available boronic acids **26a**–**c** as shown in Scheme 1. The reaction of boronic acids **26a**–**c** and 2-bromo-1-iodo-4-methoxybenzene **27** was performed using $PdCl_2(PPh_3)_2$ under basic conditions in THF at room temperature to afford the desired 2′-bromo-4′-methoxy-(1,1′-biphenyl)-2-carbaldehydes **28a**–**c** in moderate to good yields (43–71%). 2-Bromo-1-iodo-4-methoxybenzene **27** was prepared from the selective *para*-iodination of 3-bromoanisole.[40] The transformation of carbaldehydes **28a**–**c** to biaryl esters **29a**–**c** was conducted by oxidation followed by esterification. Treatment of biaryl esters **29a**–**c** with 0.5 equiv of CuTC in the presence of TMEDA and Cs_2CO_3 in subcritical water for 10 min furnished the methyl ether of urolithins A–C (**30a**–**c**), which were further demethylated with BBr_3 in dichloromethane at 0 °C. These conditions gave urolithins A–C (**2a**–**c**) in 15%, 9%, and 7% overall yield, respectively, over four steps.



Scheme 1. Synthesis of urolithins A–C.

The antioxidant radical-scavenging of urolithins A–C and cytotoxic activities are summarized in Table 3. Urolithin C (**2c**) scavenged 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical with IC_{50} value of 12.6±0.9 μM, which is better than the reference compound, ascorbic acid at 21.2 μM. Superoxide anion radical formation in the xanthine/xanthine oxidase (XXO) and xanthine oxidase (IXO) assays was not inhibited by urolithins A–C. Compounds **2a**–**c** inhibited aromatase activity (AIA) with IC_{50} values of 13.2±1.4, 11.9±1.0, and 21.6±0.6 μM, respectively.

Table 3
Radical scavenging, antioxidant, and aromatase inhibitory activities of synthetic urolithins A–C[a]

Urolithin	IC_{50} [μM]				Unit
	DPPH	IXO	AIA	HL-60[b]	ORAC[c]
A	>250	157.6±14.5	13.2±1.4	>100	3.0±0.5
B	>250	334.3±1.8	11.9±1.0	86.8±13.6	3.0±0.7
C	12.6±0.9	165.0±3.6	21.6±0.6	>100	5.5±0.5

[a] Positive controls for each assay are as follows: DPPH: ascorbic acid (IC_{50}=21.2 μM); IXO: allopurinol (IC_{50}=3.0 μM); aromatase inhibition (AIA): ketoconazole (IC_{50}=2.4 μM).
[b] HL-60: Human Promyelocytic Leukemia cells.
[c] The results are expressed as ORAC units: 1 ORAC unit equals the net protection of β-phytoerythrin produced by 1 μM of Trolox.

They also exhibited the potent antioxidant activity in oxygen radical absorbance capacity (ORAC) assay with 3.0±0.5, 3.0±0.7, and 5.5±0.5 ORAC units, respectively (Table 3).[41] The urolithin B can also inhibit the proliferation of leukemia cell with the IC_{50} value of 86.8±13.6 μM.

3. Conclusion

In summary, we have reported the synthesis of various benzopyranones and urolithins A–C (**2a**–**c**) based on the green chemistry principle using the one-pot lactone formation from biaryl esters under microwave irradiation with the catalytic amount of CuTC. With the environmental consideration, the successful use of water, the ideal green solvent, in the key lactone formation further adds the merit of the protocol. The biological activity evaluation of urolithins A–C (**2a**–**c**) showed the potent antioxidant activity in ORAC assay while urolithin C (**2c**) exhibited the radical-scavenging activity.

4. Experimental section

4.1. General methods

Microwave reaction was performed in CEM Discover. Melting points were measured using a Thermo Fisher Scientific IA920 digital melting point instrument, which was reported without correction. ^{1}H NMR spectra were recorded on Bruker AV-300 (300 MHz) and Bruker AV-400 (400 MHz) using deuterochloroform as solvent with tetramethylsilane as an internal standard and dimethylsulfoxide-d_6 for some compounds. ^{13}C NMR spectra were recorded on Bruker AV-300 (75 MHz) and Bruker AV-400 (100 MHz) using deuterochloroform as solvent with tetramethylsilane as an internal standard and dimethylsulfoxide-d_6 for some compounds. Infrared spectra (IR) were obtained on Perkin–Elmer System 2000FT-IR and JASCO A-302 spectrometers. Mass Spectrometry was performed with an AEI-MS-902. High Resolution Mass Spectrometry was performed with a MicroTOFLC, Bruker Daltonics. Column chromatography was carried out using Fluka aluminum oxide (type 507 C neutral; 100–125 mesh) and Merck silica gel (70–230 mesh ASTM). Thin layer chromatography (TLC) and preparative thin layer chromatography (PTLC) were carried out on silica gel (E. Merck PF 254). All reagents were purified and dried according to the standard procedures. Solvents were removed using Eyela Aspirator A-2S and Büchi Rotavapor R110. All products were evacuated by a Christ Freeze Dryer Unit Alpha l/6, to remove the last traces of solvents.

4.2. General procedure for the preparation of biarylcarboxylate esters (7a, 7b, and 10–18)

A solution of 2-halophenylboronic acid (2.0 equiv), 2-halophenylcarboxylate (1.0 equiv), and 10 mol % $Pd(PPh_3)_4$ in the solvent mixture, toluene/EtOH/10%Na_2CO_3 (5:1:2), was refluxed overnight. After the complete reaction was observed by TLC, water was added to quench (25 mL) and partitioned with EtOAc (3×25 mL) to obtain the crude product. The crude product was then purified by flash column chromatography or preparative thin layer chromatography (EtOAc/Hexane) to obtain the product. Compounds **7a**, **7b**, **10**, **11**, and **14**–**17** were previously reported in the literature.[31a]

*4.2.1. Methyl 3-(2-bromophenyl)isonicotinate (**12**).* Yellow oil (143 mg, 68%). R_f 0.43 (30% EtOAc/Hexane). IR (UATR): ν_{max} 2951, 1734, 1434, 1273, 1105, 756 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, J=4.5 Hz, 1H), 8.59 (s, 1H), 7.84 (d, J=4.8 Hz, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.41 (t, J=7.5 Hz, 1H), 7.31–7.25 (m, 2H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 151.5, 149.5, 138.4, 137.1, 135.8, 132.2, 130.2, 129.4, 127.1, 123.1, 122.7, 52.4. EI-MS: m/z (%) 291 (M+H$^+$, 0.01), 212 (100), 197 (38), 126 (20). TOF-HRMS calcd for $C_{13}H_{11}BrNO_2$: 291.9967; found 291.9956, 293.9939.

*4.2.2. Methyl 2-(2-chlorophenyl)nicotinate (**13**).* Yellow oil (792 mg, quantitative yield). R_f 0.14 (10% EtOAc/Hexane). IR (UATR): ν_{max} 2951, 1725, 1565, 1424, 1273, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (d, J=3.9 Hz, 1H), 8.31 (d, J=8.1 Hz, 1H), 7.43–7.34 (m, 5H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 157.4, 151.8, 139.5, 138.0, 132.1, 130.0, 129.3, 128.8, 126.8, 126.6, 122.4, 52.3. EI-MS: m/z (%) 247 (M$^+$, 0.04), 212 (100), 197 (32). TOF-HRMS calcd for $C_{13}H_{11}ClNO_2$: 248.0472; found 248.0474, 250.0456.

*4.2.3. Methyl 2-(2-chlorophenyl)furan-3-carboxylate (**18**).* Yellow solid (92 mg, 80%). R_f 0.34 (20% EtOAc/Hexane). Mp: 61 °C. IR (UATR): ν_{max} 2952, 1720, 1619, 1470, 1439, 1299, 755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48–7.46 (m, 3H), 7.40–7.38 (m, 2H), 6.85 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 155.0, 142.2, 134.1, 131.9, 130.6, 129.6, 129.3, 126.1, 116.2, 111.3, 51.4. EI-MS: m/z (%) 236 (M$^+$, 3), 201 (100), 186 (35), 170 (8). TOF-HRMS calcd for $C_{12}H_{10}ClO_3$: 237.0313; found 237.0315, 239.0284.

4.3. General procedure for the preparation of benzopyranones (19–25, and 30a–c)

In a 10 mL microwave vessel, to a mixture of methyl 2-halobiarylcarboxylate ester (0.2 mmol, 1.0 equiv), CuTC (0.1 mmol, 0.5 equiv), Cs_2CO_3 (0.1 mmol, 0.5 equiv) in deionized water (2 mL) was added TMEDA (0.2 mmol, 1.0 equiv) via microsyringe. The mixture was allowed to stir at room temperature for 15 min and then placed into the microwave instrument. The reaction was then irradiated based on conditions appropriate for each reaction (see Table 1.) and reactions followed by TLC. After completion, the suspension was filtered through silica gel and washed with EtOAc (4×25 mL). The solvent was removed under reduced pressure to give a pale yellow solid, which was then purified by PTLC (EtOAc/Hexane) to give the product. Compounds **1**, **19**, **20**, **23**, and **24** were previously reported in the literature.[31a,34]

*4.3.1. 5H-Chromeno[4,3-c]pyridin-5-one (**21**).* White solid (15.3 mg, 46%). R_f 0.34 (20% EtOAc/Hexane). Mp: 159 °C. IR (UATR): ν_{max} 1735, 1609, 1411, 1277, 1240, 1086, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.87 (d, J=5.1 Hz, 1H), 8.19 (d, J=9.6 Hz, 1H), 8.17 (d, J=7.2 Hz, 1H), 7.56 (t, J=7.3 Hz, 1H), 7.44–7.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 151.6, 149.4, 145.4, 131.4, 128.5, 126.9, 125.2, 122.4, 122.0, 118.0, 115.7. EI-MS: m/z (%) 197 (M$^+$, 100), 169 (42), 142 (13), 114 (20). TOF-HRMS calcd for $C_{12}H_8NO_2$: 198.0549; found 198.0543.

*4.3.2. 5H-Chromeno[4,3-b]pyridin-5-one (**22**).* Yellow solid (49.3 mg, 62%). R_f 0.40 (20% EtOAc/Hexane). Mp: 146 °C. IR (UATR): ν_{max} 1736, 1727, 1602, 1449, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (dd, J=4.6, 2.0 Hz, 1H), 8.62 (dd, J=8.1, 1.8 Hz, 1H), 8.58 (dd, J=7.9, 1.5 Hz, 1H), 7.59 (td, J=8.2, 1.5 Hz, 1H), 7.52 (dd, J=7.9, 4.5 Hz, 1H), 7.40 (td, J=9.0, 1.2 Hz, 1H), 7.38 (d, J=8.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 155.6, 152.5, 151.8, 138.1, 132.2, 124.9, 124.6, 123.7, 119.2, 117.3, 117.1. EI-MS: m/z (%) 197 (M$^+$, 100), 169 (39), 140 (17), 114 (15), 70 (11). TOF-HRMS calcd for $C_{12}H_8NO_2$: 198.0549; found 198.0545.

*4.3.3. 11-Methylchromeno[4,3-b]indol-6(11H)-one (**23a**).* Brown solid (18 mg, 66%): R_f 0.51 (50% EtOAc/Hexane). Mp: 241 °C. IR (UATR): ν_{max} 3053, 2940, 2686, 1655, 1541, 1441, 1389, 1107, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31–8.28 (m, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.47–7.30 (m, 6H), 3.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 144.3, 136.8, 134.3, 132.2, 130.8, 130.6, 129.4, 126.8, 126.6, 123.1, 122.3, 122.2, 109.7, 104.9, 30.5. EI-MS: m/z (%) 250 (M+H$^+$, 76), 249 (M$^+$, 15), 165 (31), 149 (56), 86 (59), 83 (100). HRMS (microTOF): m/z calcd for $C_{16}H_{12}NO_2$ (M+H$^+$) 250.0858; found 250.0862. *Chromeno[4,3-b]indol-6(11H)-one* (**23b**). Brown solid (2 mg, 10%): R_f 0.46 (40% EtOAc/Hexane). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.96 (d, *J*=7.8 Hz, 1H), 7.60–7.52 (m, 2H), 7.46 (t, *J*=7.5 Hz, 1H), 7.56–7.10 (m, 4H).

*4.3.4. 7-Methylchromeno[3,4-b]indol-6(7H)-one (**24a**).* White solid (2 mg, 45%): R_f 0.40 (20% EtOAc/Hexane). Mp: 170 °C. IR (UATR): ν_{max} 2960, 2913, 2850, 1705, 1467, 1259, 1016, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.32–8.25 (m, 2H), 7.58–7.41 (m, 6H), 4.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 152.2, 150.8, 141.2, 127.3, 127.2, 124.5, 123.2, 122.8, 121.8, 121.3, 121.0, 118.9, 117.1, 111.0, 31.5. EI-MS: *m*/*z* (%) 250 ($M+H^+$, 17), 249 (M^+, 100), 248 (55), 165 (12), 149 (12), 86 (24). HRMS (microTOF): *m*/*z* calcd for $C_{16}H_{12}NO_2$ ($M+H^+$) 250.0866; found 250.0862. *Chromeno[3,4-b]indol-6(7H)-one* (**24b**). Brown solid (0.4 mg, 11%): R_f 0.46 (40% EtOAc/Hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, *J*=7.8 Hz, 1H), 7.67 (dd, *J*=7.5, 1.2 Hz, 1H), 7.47–7.38 (m, 2H), 7.31–7.21 (m, 4H).

*4.3.5. 4H-Furo[3,2-c]chromen-4-one (**25**).* Brown solid (20 mg, 30%): R_f 0.14 (10% EtOAc/Hexane). Mp: 171 °C. IR (UATR): ν_{max} 1686, 1483, 1313, 1146, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J*=1.5 Hz, 1H), 7.48–7.29 (m, 4H), 6.87 (d, *J*=1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 156.3, 142.5, 134.3, 132.1, 130.9, 129.7, 129.2, 128.1, 126.2, 111.6. EI-MS: *m*/*z* (%): 187 ($M+H^+$, 100), 170 (2), 149 (6), 131 (5), 115 (14). TOF-HRMS calcd for $C_{11}H_7O_3$: 187.0389; found 187.0385.

*4.3.6. 3,8-Dimethoxy-6H-benzo[c]chromen-6-one (**30a**).* Yellow solid (37 mg, 61%). R_f 0.43 (50% CH_2Cl_2/Hexane). Mp: 124 °C. IR (UATR): ν_{max} 2924, 2846, 1732, 1623, 1491, 1319, 1295 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, *J*=9.0 Hz, 1H), 7.85 (d, *J*=8.7 Hz, 1H), 7.75 (d, *J*=2.7 Hz, 1H), 7.36 (dd, *J*=8.8, 3.0 Hz, 1H), 6.90 (dd, *J*=9.0, 2.5 Hz, 1H), 6.85 (d, *J*=2.4 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 160.6, 159.0, 151.5, 128.5, 124.3, 123.1, 122.7, 120.9, 112.3, 111.2, 110.9, 101.4, 55.6 (2C). EI-MS: *m*/*z* (%) 256 (M^+, 23), 241 (15), 178 (20), 149 (16). TOF-HRMS calcd for $C_{15}H_{13}O_4$: 257.0808; found 257.0811.

*4.3.7. 3-Methoxy-6H-benzo[c]chromen-6-one (**30b**).* Yellow solid (3 mg, 36%): R_f 0.46 (10% EtOAc/Hexane). Mp: 107 °C. IR (UATR): ν_{max} 2924, 2846, 1732, 1623, 1491, 1319, 1295 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, *J*=8.1 Hz, 1H), 8.01 (d, *J*=8.4 Hz, 1H), 7.95 (d, *J*=8.1 Hz, 1H), 7.79 (t, *J*=7.8 Hz, 1H), 7.51 (t, *J*=8.1 Hz, 1H), 6.92 (d, *J*=8.7 Hz, 1H), 6.88 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 135.1, 134.8, 130.5, 127.7, 124.4, 123.9, 123.7, 121.0, 119.1, 112.4, 111.1, 101.6, 55.6. EI-MS: *m*/*z* (%) 256 (M^+, 23), 241 (14), 178 (20), 149 (16). TOF-HRMS calcd for $C_{14}H_9O_3$: 213.0546; found 213.0554.

*4.3.8. 3-Methoxy-6H-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-c]chromen-6-one (**30c**).* Brown solid (2 mg, 29%): R_f 0.43 (50% CH_2Cl_2/Hexane). Mp: 118 °C. IR (UATR): ν_{max} 2921, 2849, 2155, 1716, 1612, 1480, 1270, 1034, 935 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.19 (d, *J*=8.4 Hz, 1H), 7.91 (s, 1H), 7.53 (s, 1H), 6.99–6.95 (m, 2H), 6.24 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2, 154.6, 151.9, 148.3, 132.9, 130.0, 125.0, 113.4, 112.7, 111.9, 107.4, 103.0, 101.6, 101.5, 56.2 EI-MS: *m*/*z* (%) 271 ($M+H^+$, 100), 256 (53), 241 (29), 128 (12). TOF-HRMS calcd for $C_{15}H_{11}O_5$: 271.0610; found 271.0603.

4.4. General procedure for the preparation of 2-bromo-1-iodo-4-methoxybenzene (27)

A mixture of 3-bromophenol (0.53 mmol, 1.0 equiv), I_2 (0.53 mmol, 1.0 equiv), and CF_3COOAg (0.80 mmol, 1.5 equiv) in $CHCl_3$ (5 mL) was stirred under Ar atmosphere for 3 h. The reaction was quenched with saturated $Na_2S_2O_3$ (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The solvent was then removed by rotary evaporation to give the brown crude oil. The crude product was purified by flash column chromatography (Hexane 100%) to obtain product as pink oil (57 mg, 35%): R_f 0.51 (20% EtOAc/Hexane). IR (UATR): ν_{max} 2975, 1578, 1460, 1283, 1223, 1032, 840 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J*=8.7 Hz, 1H), 7.20 (d, *J*=2.4 Hz, 1H), 6.60 (dd, *J*=8.7, 2.1 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 140.1, 129.8, 118.3, 115.3, 89.4, 55.5. EI-MS: *m*/*z* (%) 312 ($M+H^+$, 87), 297 (17), 172 (30), 63 (100). TOF-HRMS calcd for C_7H_6BrIO: 311.8641; found 311.8645, 313.8622.

4.5. General procedure for the preparation of biarylcarboxaldehydes (28a–c)

The mixture of 2-formylphenyl boronic acid **26a–c** (1.0 equiv), 2-bromo-1-iodo-4-methoxybenzene **27** (2.0 equiv), and 5 mol % $PdCl_2(PPh_3)_2$ in THF (5 mL) was stirred under Ar atmosphere at room temperature. A solution of 2 N K_2CO_3 (25 mL) was then transferred into the reaction via syringe until the reaction turned a brown-red solution. The reaction was allowed to stir at room temperature overnight. After checking by TLC, the reaction was quenched with water and partitioned with EtOAc to obtain the dark-brown crude oil. The crude product was purified by flash chromatography or preparative thin layer chromatography (EtOAc/Hexane) to obtain the product.

*4.5.1. 2′-Bromo-4,4′-dimethoxy-[1,1′-biphenyl]-2-carbaldehyde (**28a**).* Yellow solid (32 mg, 62%): R_f 0.40 (5% EtOAc/Hexane). Mp: 104 °C. IR (UATR): ν_{max} 2916, 2848, 2344, 1688, 1601, 1481 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.50 (d, *J*=2.5 Hz, 1H), 7.25–7.19 (m, 4H), 6.94 (dd, *J*=8.4, 2.5 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 159.9, 159.4, 137.3, 134.9, 132.4, 132.3, 130.5, 124.6, 121.0, 117.8, 113.4, 109.7, 55.6, 55.5. EI-MS: *m*/*z* (%) 230 (M^+, 1), 241 (100), 198 (28), 121 (14). TOF-HRMS calcd for $C_{15}H_{14}BrO_3$: 321.0120; found 321.0132, 323.0117.

*4.5.2. 2′-Bromo-4′-methoxy-[1,1′-biphenyl]-2-carbaldehyde (**28b**).* Pink oil (20 mg, 43%): R_f 0.26 (5% EtOAc/Hexane). IR (UATR): ν_{max} 2838, 2933, 1693, 1597, 1221, 1033, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.02 (dd, *J*=7.7, 1.1 Hz, 1H), 7.64 (td, *J*=7.5, 1.4 Hz, 1H), 7.52 (t, *J*=7.6 Hz, 1H), 7.32 (dd, *J*=7.5, 0.6 Hz, 1H), 7.24 (d, *J*=1.0 Hz, 1H), 7.22 (m, 1H), 6.96 (dd, *J*=8.4, 2.5 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 160.0, 144.2, 133.9, 133.4, 132.0, 131.2, 130.8, 128.2, 126.9, 124.0, 117.8, 113.5, 55.6. EI-MS: *m*/*z* (%) 290 (M^+, 0.35), 211 (100), 196 (11), 168 (25), 139 (30), 105 (6). TOF-HRMS calcd for $C_{14}H_{12}BrO_2$: 291.0015; found 291.0022, 293.0000.

*4.5.3. 6-(2-Bromo-4-methoxyphenyl)benzo[d][1,3]dioxole-5-carbaldehyde (**28c**).* Brown oil (38 mg, 71%): R_f 0.37 (5% EtOAc/Hexane). IR (UATR): ν_{max} 2909, 2849, 1680, 1602, 1476, 1235, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.44 (s, 1H), 7.21 (d, *J*=2.4 Hz, 1H), 7.19 (d, *J*=8.8 Hz, 1H), 6.92 (dd, *J*=8.6, 2.4 Hz, 1H), 6.20 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 160.0, 151.9, 141.6, 132.2, 130.4, 124.3, 117.9, 114.4, 113.4, 110.7, 110.6, 105.9, 102.0, 55.6. EI-MS: *m*/*z* (%) 334 ($M+H^+$, 1), 255 (100), 212 (23), 197 (10), 154 (10). TOF-HRMS calcd for $C_{15}H_{12}BrO_4$: 334.9913; found 334.9911, 336.9891.

4.6. General procedure for the preparation of biaryl esters (29a–c)

To a solution of 2′-bromo-4′-methoxy-(1,1′-biphenyl)-2-carbaldehydes **28a–c** (1.0 equiv), pyridine (5 mL) in water (15 mL) was added $KMnO_4$ (2.0 equiv) at ambient atmosphere. The reaction was then refluxed and monitored by TLC until the starting material was completely oxidized. The reaction was cooled to room temperature and acidified with 2 N HCl to afford a white

precipitate. The white solid was recrystallized with EtOAc/Hexane (1:4) to obtain the biaryl carboxylic acid. The obtained product was then placed into a round bottom flask and dissolved in CH_2Cl_2 (25 mL). To a precooled (0 °C) solution of carboxylic acid and DMF (3 drops) was added dropwise oxalyl chloride slowly. The reaction was stirred at the same temperature for 2 h, and then concentrated under reduced pressure to afford a yellow residue. The residue was then esterified with methanol (25 mL) at room temperature. The reaction was quenched with water and extracted with EtOAc (3×25 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the residue, which was purified by flash column chromatography (5–95% EtOAc/Hexane) to give the biaryl esters.

*4.6.1. Methyl 2′-bromo-4,4′-dimethoxy-[1,1′-biphenyl]-2-carboxylate (**29a**).* Colorless oil (113 mg, 55%): R_f 0.29 (20% EtOAc/Hexane). IR (UATR): ν_{max} 2949, 2837, 1727, 1601, 1479 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J=2.4 Hz, 1H), 7.23–7.08 (m, 4H), 6.90 (dd, J=8.4, 2.4 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 158.9, 158.7, 134.5, 134.3, 132.5, 131.5, 130.7, 123.6, 117.8, 117.3, 114.6, 113.0, 55.4 (2C), 52.1. EI-MS: m/z (%) 350 (M^+, 2), 271 (100), 256 (60), 241 (39), 225 (10), 187 (8). TOF-HRMS calcd for $C_{16}H_{16}BrO_4$: 351.0226; found 351.0230, 353.0212.

*4.6.2. Methyl 2′-bromo-4′-methoxy-[1,1′-biphenyl]-2-carboxylate (**29b**).* Yellow oil (19 mg, 60%): R_f 0.34 (5% EtOAc/Hexane). IR (UATR): ν_{max} 2946, 2927, 1725, 1602, 1475, 1435, 1256, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (dd. J=9.0, 0.9 Hz, 1H), 7.53 (td, J=7.5, 1.5 Hz, 1H), 7.43 (td, J=7.6, 1.2 Hz, 1H), 7.23 (dd, J=7.5, 1.2 Hz, 1H), 7.17 (d, J=2.7 Hz, 1H), 7.15 (d, J=6.9 Hz, 1H), 7.11 (s, 1H), 6.89 (dd, J=8.4, 2.7 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 159.0, 141.8, 134.7, 131.6, 131.4, 130.4, 129.9, 127.6, 123.0, 117.3, 113.4, 112.9, 55.3, 51.9. EI-MS: m/z (%) 320 (M^+, 2), 241 (100), 226 (53), 139 (27). TOF-HRMS calcd for $C_{15}H_{14}BrO_3$: 321.0121; found 321.0119, 323.0111.

*4.6.3. Methyl 6-(2-bromo-4-methoxyphenyl)benzo[d][1,3]dioxole-5-carboxylate (**29c**).* Brown solid (18 mg, 45%): R_f 0.31 (20% EtOAc/Hexane). Mp: 85 °C. IR (UATR): ν_{max} 2949, 2901, 1724, 1601, 1478, 1240, 1032, 852 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.17 (d, J=2.7 Hz, 1H), 7.11 (d, J=8.7 Hz, 1H), 6.89 (dd, J=8.4, 2.7 Hz, 1H), 6.67 (s, 1H), 6.09 (s, 2H), 3.84 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 150.2, 147.0, 138.1, 134.7, 130.7, 130.4, 123.7, 123.3, 117.3, 113.0, 111.4, 109.9, 102.0, 55.4, 51.9. EI-MS: m/z (%) 364 (M^+, 1), 285 (100), 270 (70), 255 (29), 143 (21). TOF-HRMS calcd for $C_{16}H_{13}BrO_5$: 365.0019; found 365.0021, 367.0007.

4.7. General procedure for the preparation of urolithins A–C (2a–c)

A solution of methyl ether of urolithins A–C **30a–c** (1.0 equiv) was cooled at 0 °C under Ar atmosphere and was added BBr_3 slowly. Once the stating material was completely consumed by TLC, a solution of 2 N HCl was added to acidify and partitioned with EtOAc to give the crude product. The crude product was purified by size exclusion chromatography to obtain the product.

*4.7.1. 3,8-Dihydroxy-6H-benzo[c]chromen-6-one (**2a**).* Brown solid (7 mg, 64%): R_f 0.06 (20% EtOAc/Hexane). Mp: 331 °C. IR (UATR): ν_{max} 3332, 3140, 1703, 1614, 1458, 1273 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.20 (br s, 1H), 8.10 (d, J=9.0 Hz, 1H), 8.01 (d, J=8.7 Hz, 1H), 7.50 (d, J=2.7 Hz, 1H), 7.31 (dd, J=8.7, 2.7 Hz, 1H), 6.79 (dd, J=8.5, 2.4 Hz, 1H), 6.71 (d, J=2.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 159.8, 152.1, 135.3, 135.1, 129.7, 127.7, 124.8, 121.6, 118.9, 113.2, 109.4, 102.9. EI-MS: m/z (%) 228 (M^+, 100), 200 (13), 115 (20). TOF-HRMS calcd for $C_{13}H_9O_4$: 229.0495; found 229.0493.

*4.7.2. 3-Hydroxy-6H-benzo[c]chromen-6-one (**2b**).* Brown solid (10 mg, quantitative yield): R_f 0.14 (20% EtOAc/Hexane). Mp 207 °C. IR (UATR): ν_{max} 3254, 2919, 1691, 1625, 1608, 1315, 1276 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.36 (s, 1H), 8.25 (d, J=8.1 Hz, 1H), 8.18 (dd, J=7.3, 1.2 Hz, 1H), 8.15 (d, J=8.7 Hz, 1H), 7.88 (td, J=7.0, 1.5 Hz, 1H), 7.57 (td, J=7.6, 0.9 Hz, 1H), 6.85 (dd, J=8.7, 2.4 Hz, 1H), 6.75 (d, J=2.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 159.8, 152.1, 135.3, 135.1, 129.7, 127.7, 124.8, 121.6, 118.9, 113.2, 109.4, 102.9. EI-MS: m/z (%) 212 (M^+, 100), 184 (21), 128 (17), 127 (15). TOF-HRMS calcd for $C_{13}H_9O_3$: 213.0546; found 213.0548.

*4.7.3. 3,8,9-Trihydroxy-6H-benzo[c]chromen-6-one (**2c**).* Olive-green solid (4 mg, 79%): R_f 0.028 (10% EtOAc/Hexane). Mp: >333 °C. IR (UATR): ν_{max} 3230, 1690, 1614, 1461, 1278 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.12 (br s, 3H), 7.85 (d, J=8.7 Hz, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 6.77 (dd, J=8.2, 2.4 Hz, 1H), 6.67 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.7, 159.0, 153.8, 151.8, 146.5, 129.6, 124.1, 114.6, 113.2, 111.3, 110.2, 107.2, 103.4. EI-MS: m/z (%) 224 (M^+, 100), 216 (11), 129 (17), 97 (34), 83 (40), 69 (55). TOF-HRMS calcd for $C_{13}H_9O_5$: 245.0444; found 245.0445.

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Supplementary data

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