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## Ring-fused dimethoxybenzimidazole-benzimidazolequinone (DMBBQ): tunable halogenation and quinone formation using NaX/Oxone†

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Ring-fused benzimidazolequinones are well-known anti-tumour agents, but dimeric ring-fused adducts are new. The alicyclic [1,2-*a*] ring-fused dimethoxybenzimidazole-benzimidazolequinone (DMBBQ) intermediate allows late-stage functionalization of bis-*p*-benzimidazolequinones. DMBBQs are chlorinated and brominated at the *p*-dimethoxybenzene site using nontoxic sodium halide and Oxone in HFIP/water. X-ray crystallography is used to rationalize site preference in terms of the discontinuity in conjugation in the DMBBQ system. Quinone formation occurs by increasing *in situ* halogen generation and water. Conversely, radical trifluoromethylation occurs at the quinone of the DMBBQ.

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## Introduction

Alicyclic ring-fused benzimidazolequinones are potent anti-tumour agents (Scheme 1a), studied as synthetic alternatives to mitomycin C.<sup>1–4</sup> Cerium(IV) ammonium nitrate oxidizes *p*-dimethoxybenzenes to *p*-benzoquinones,<sup>5</sup> and to dimeric adducts.<sup>6</sup> Bis-chloromethylbenzimidazolequinone **1** was reported in 38% yield (Scheme 1b) from the oxidation of 2-(chloromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole using CAN (2.9 equiv.).<sup>7</sup> Bis-*p*-quinone **1** exhibited greater cytotoxicity against solid tumour cell lines than monomeric benzimidazolequinones. Recently, the CAN oxidation of 4,7-dimethoxybenzimidazole alkoxyamine **2** was used to give the bis-benzimidazolequinone **3** (Scheme 1c).<sup>8</sup>

Dimethoxybenzimidazole-benzimidazolequinone (DMBBQ) **4a** was obtained in high yield (86%) when using less CAN, and in contrast to bis-*p*-quinone **3**, DMBBQ **4a** was insensitive to light. Radical trifluoromethylation of **4a** using Langlois' reagent (NaSO<sub>2</sub>CF<sub>3</sub>) occurred at the quinone to give **4b** in 54% yield.<sup>8</sup>

Elemental chlorine and bromine are corrosive, toxic, and ordinarily inconvenient for synthesis. The useful halogen is however generated *in situ* from the oxidation of a benign and inexpensive alkali metal halide.<sup>9</sup> Oxone (2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>) is a stable, safe and cheap external oxidant.<sup>10</sup> The active ingredient of Oxone is potassium peroxydisulfate (KHSO<sub>5</sub>) and when accompanied by stoichiometric equivalents of halide (NaX) can generate molecular halogen (X<sub>2</sub>) for electrophilic chlorination and bromination (Scheme 1d). The halide with Oxone gives oxidative transformations with an accompanying halogenation of naphthols and phenols,<sup>11</sup> and with and without halogenation for indoles.<sup>12,13</sup> Other metal-free oxidations, such as *N*-bromosuccinimide (NBS) with a small amount of H<sub>2</sub>SO<sub>4</sub>,<sup>14,15</sup> and PhI(OCOCH<sub>3</sub>)<sub>2</sub> (PIFA),<sup>8,16,17</sup> are reported to induce conversion of *p*-dimethoxybenzenes to *p*-quinones without halogenation. The disadvantage of using NBS and PIFA is the generation of organic waste products. Moreover, the combination of H<sub>2</sub>O<sub>2</sub> with HX gives chlorinated and brominated alicyclic [1,2-*a*] ring-fused benzimidazolequinones from *p*-dimethoxybenzene precursors.<sup>18</sup> The accompanying aromatic halogenation is considered advantageous, since it offers further functionalization opportunities. However, unlike monomeric benzimidazoles, milder room-temperature conditions are required for Cl<sub>2</sub> and Br<sub>2</sub> generation when using DMBBQs as the substrates (see below), which

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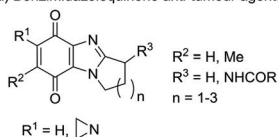
† Electronic supplementary information (ESI) available: Fig. S1–S4 and X-ray crystallography Tables S1–S3 and <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra (PDF). CIF files available for compounds **8**, **11a** and **13**. CCDC 1948449 2022191 2022190. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00032b

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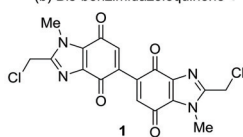


## Previous work

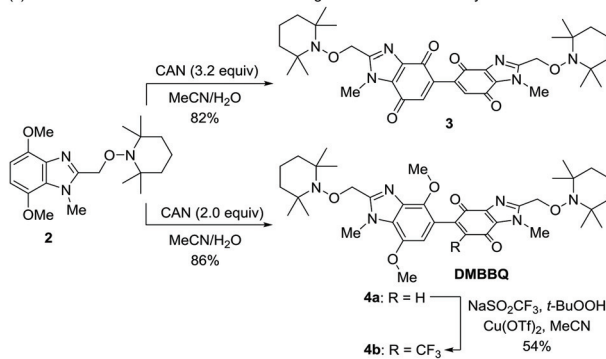
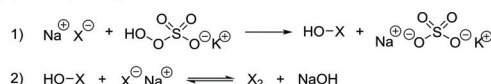
(a) Benzimidazolequinone anti-tumour agents



(b) Bis-benzimidazolequinone 1

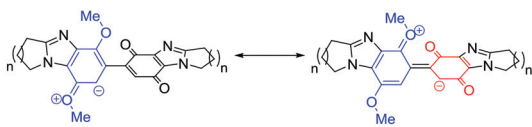


(c) CAN-mediated oxidative dimerization with regioselective trifluoromethylation

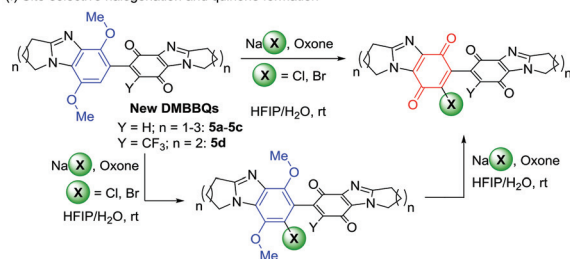
(d) Oxone (KHSO<sub>5</sub>)-mediated halide oxidation

## This work

(e) Classical resonance structures predict activation at both CH-sites



(f) Site-selective halogenation and quinone formation

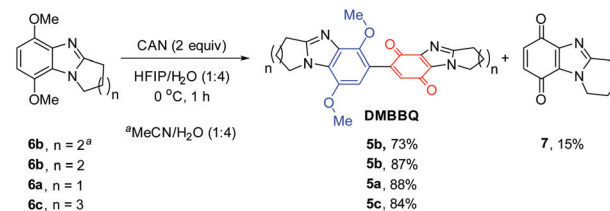


Scheme 1 Development of DMBBQs as precursors to difunctionalized bis-benzimidazolequinones.

led us to use NaX/Oxone. The use of Oxone is unprecedented in oxidative demethylations to give *p*-quinones. Herein, we disclose selective chlorination and bromination of novel CAN-derived alicyclic ring-fused DMBBQs at the aromatic site, despite possible activation at the quinone (Scheme 1e). Electrophilic aromatic halogenation of DMBBQs 5a-5d (Scheme 1f) is accompanied by one-pot quinone formation.

## Results and discussion

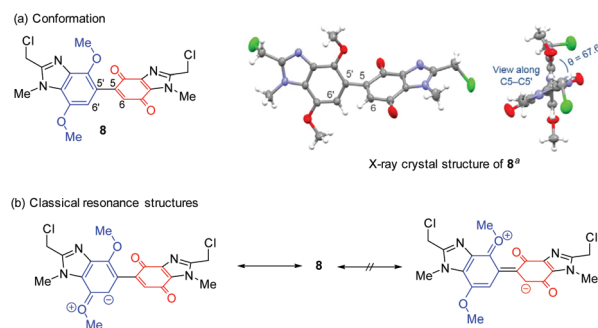
Five to seven-membered alicyclic ring-fused dimethoxybenzimidazoles 6a-6c are readily available,<sup>17</sup> and used to prepare new DMBBQs 5a-5c. DMBBQ 5b was prepared in 73% yield by



Scheme 2 Synthesis of alicyclic ring-fused DMBBQs.

optimizing the conditions for CAN-oxidation of 6b in MeCN/H<sub>2</sub>O (Scheme 2).<sup>5-8</sup> The latter solvent system also gave pyrido [1,2-*a*]benzimidazolequinone 7 in 15% yield. Replacing the MeCN with hexafluoroisopropanol (HFIP) improved the yield of the required DMBBQ 5b to 87% with no monomeric benzimidazolequinone 7 detected. Similar high yields (88 and 84%) using HFIP/H<sub>2</sub>O were obtained for the formation of pyrrolo- and azepino ring-fused DMBBQs 5a and 5c from 6a and 6c, respectively. The formation of 7 requires the intervention of a water molecule at the CAN generated radical cation to prevent dimerization.<sup>6,18</sup> The persistence of radical cation intermediates in HFIP,<sup>19</sup> and their shielding from water due to the formation of heterogeneous environments,<sup>20</sup> may account for the exclusive CAN-mediated dimerization.

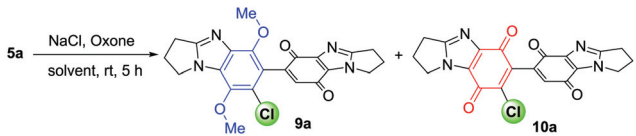
DMBBQs 5a-5c were insufficiently crystalline for X-ray crystallography. However, the premise for the regioselective halogenation was supported by the preparation of bis(chloromethyl)-substituted DMBBQ 8 (76% yield), in an analogous fashion to 1 (see above),<sup>7,8</sup> but using less CAN (2.0 equiv.). The crystal structure of dimethylchloride 8 showed that the aromatic and quinone rings adopt an out-of-plane conformation with respect to each other (Scheme 3 and Fig. S1†). The torsion angle ( $\theta$ ) of 67.6° describes the angle between the planes of the benzimidazole and benzimidazolequinone, which prevents effective orbital overlap over both rings, ruling out resonance activation of the 6-quinone position. Cyclic voltammetry and TD-DFT on DMBBQ 4a, provides further support for the site-selectivity for the electrophilic substitution with localized HOMO and LUMO at the respective dimethoxybenzimidazole and benzimidazolequinone motifs.<sup>8</sup>



<sup>a</sup>X-ray crystal structure of 8 (Figure S1) with thermal ellipsoids set at 50% probability, except for the hydrogen atoms at a fixed radius of 0.2 Å.

Scheme 3 Evidence for MeO-activation at only the aromatic-CH.



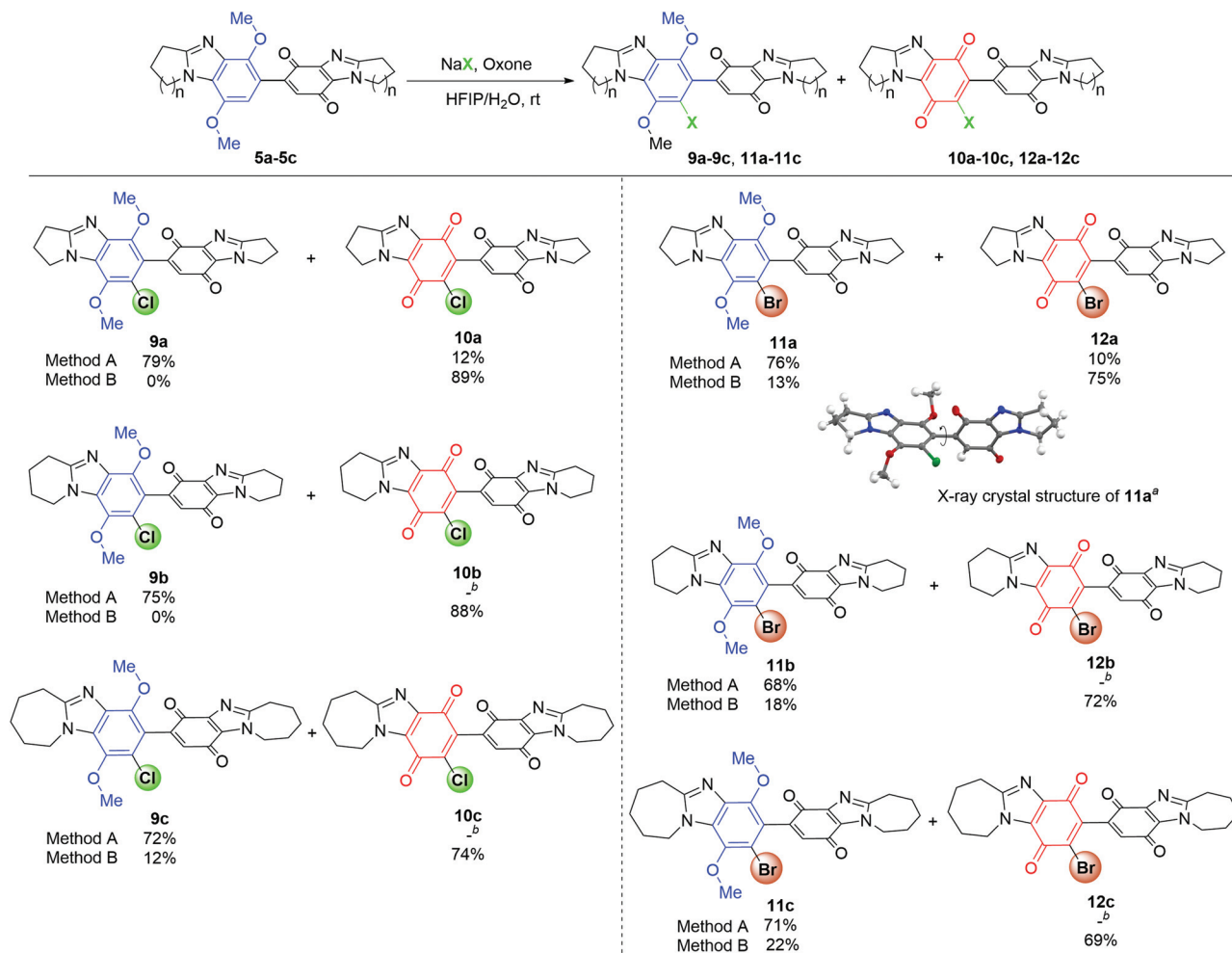
Table 1 Optimization<sup>a</sup>


Entry	NaCl (mmol)	KHSO <sub>5</sub> <sup>b</sup> (mmol)	Solvent	Yield <sup>c</sup> (%) of 9a	Yield <sup>c</sup> (%) of 10a
1 <sup>d</sup>	—	—	MeCN	21	0 <sup>e</sup>
2	0.20	0.24	MeCN/H <sub>2</sub> O	39 (52)	0
3	0.20	0.24	HFIP/H <sub>2</sub> O	51 (43)	0
4	0.40	0.24	HFIP/H <sub>2</sub> O	79	12
5 <sup>f</sup>	0.80	0.80	HFIP/H <sub>2</sub> O	15	71
6 <sup>g</sup>	0.80	0.80	HFIP/H <sub>2</sub> O	0	89

<sup>a</sup> Conditions: DMBQ 5a (0.20 mmol), MeCN or HFIP (2 mL), H<sub>2</sub>O (0.1 mL). <sup>b</sup> Used as Oxone. <sup>c</sup> Isolated yields. Values in parentheses recovered 5a. <sup>d</sup> H<sub>2</sub>O<sub>2</sub> (4 mmol), HCl (0.20 mmol), MeCN (2 mL), reflux, 1 h. <sup>e</sup> Intractable mixture. <sup>f</sup> 16 h. <sup>g</sup> HFIP (2 mL), H<sub>2</sub>O (0.2 mL), 9 h.

Chlorination of pyrrolo-fused dimer 5a was initially attempted using H<sub>2</sub>O<sub>2</sub> with HCl under conditions which mediated the regioselective chlorination of anilines (Table 1).<sup>17</sup> Reaction monitoring by TLC indicated the complete consumption of 5a after 1 h of reflux, but a low yield of 7'-chloride 9a (21%) was attributed to the formation of intractable baseline decomposition products. The requirement for milder conditions, led us to investigate the room temperature Oxone/NaCl reaction.

Addition of an aqueous solution of NaCl (1 equiv.) and Oxone (KHSO<sub>5</sub>, 1.2 equiv.) to 5a in MeCN gave chloride 9a in 39% yield, with column chromatography providing 52% recovery of 5a (Table 1). Polyfluorinated alcohols improve yields for NaCl/Oxone-mediated aliphatic and aromatic chlorinations,<sup>21</sup> and are known to accelerate aromatic chlorination in systems that generate *in situ* Cl<sub>2</sub>.<sup>22</sup> The reaction solvent was thus changed from MeCN to HFIP, with a greater consumption of



**Scheme 4** Halogenation and quinone formation. Conditions: Method A is the same as Table 1, entry 4. Method B is the same as Table 1, entry 6. Isolated yields. <sup>a</sup> X-ray crystal structure (Fig. S2†) with thermal ellipsoids set at 50% probability, except for the hydrogen atoms at a fixed radius of 0.2 Å. The torsional angle highlighted is 79.2°. <sup>b</sup> Inseparable with 5b or 5c.





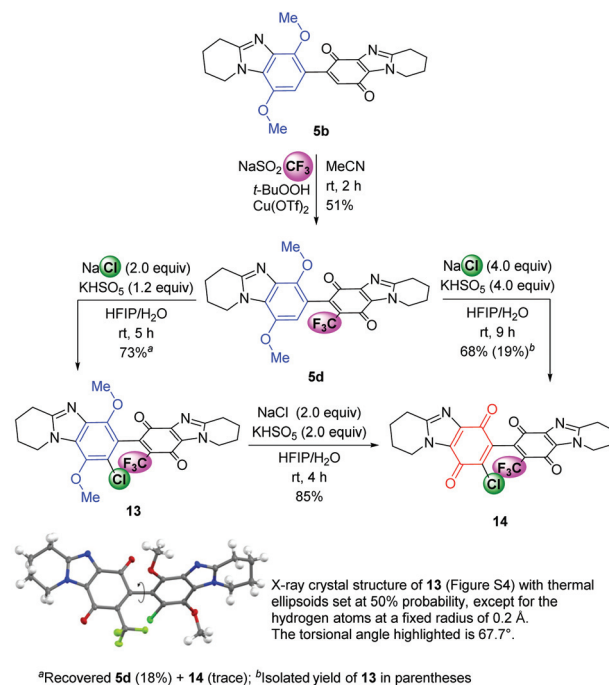
substrate **5a** observed, and **9a** isolated in an improved yield of 51%. The highest yield of **9a** (79%) after 5 h was obtained using a greater amount of NaCl (2 equiv.) with chlorination also accompanied by oxidation to give the bis-*p*-quinone **10a** in 12% yield. Cl<sub>2</sub> and water are responsible for conversion of the *p*-dimethoxybenzimidazole to benzimidazolequinone.<sup>18</sup> Thus, optimized conditions for one-pot chlorination and quinone formation were achieved by increasing the amount of KHSO<sub>5</sub> (4 equiv.) and NaCl (4 equiv.), so increasing the likelihood of NaCl reaction with HOCl, over HOCl reaction with the substrate **5a** (Scheme 1d). These conditions favoured Cl<sub>2</sub> formation and gave bis-benzimidazolequinone **10a** in 71% yield, with an increase in water from 5 to 10% relative to HFIP giving exclusively **10a** in 89% yield after 9 h.

The conditions which favored selective chlorination over quinone formation (entry 4, Table 1) were applied to pyrido and azepino-ring fused DMBBQs **5b** and **5c** to respectively give **9b** (75%) and **9c** (72%) (Method A, Scheme 4). In these cases, column chromatography removed co-eluting mixtures of substrates **5b** and **5c** with respective bis-*p*-quinones **10b** and **10c**. The optimized conditions for quinone formation (entry 6, Table 1) were applied to **5b** and **5c** to respectively give **10b** and **10c** in isolated yields of 88 and 74%, with only the latter giving some dimethoxybenzene intermediate, **9c** in 12% yield (Method B, Scheme 4).

NaBr replaced NaCl to facilitate regioselective bromination of **5a–5c** (using entry 4, Table 1 conditions). There was a marginal decrease in the tendency for bromination compared to chlorination. Complete consumption of **5a** occurred with the difference in *R<sub>f</sub>* values allowing separation of 7'-bromo-DMBBQ **11a** from bis-*p*-quinone **12a** by column chromatography in respective yields of 76% and 10% (Method A, Scheme 4). X-ray crystallographic structure determination for **11a** supported the site for bromination (Scheme 4 and Fig. S2†).

Under the same conditions, the pyrido- and azepino[1,2-*a*]-fused dimers **5b** and **5c** gave selectively brominated DMBBQs **11b** and **11c** in respective yields of 68% and 71%. In a similar manner to the chlorinations, ring-expanded DMBBQs **5b** and **5c** were less reactive towards bromination than the pyrrolo-fused DMBBQ **5a** with unreacted material separated by column chromatography as inseparable mixtures with respective bis-*p*-quinones **12b** and **12c**. One-pot bromination and quinone formation (entry 6, Table 1 conditions) gave mostly the brominated dimeric quinones **12a–12c** (69–75% yield), however column chromatography separated some dimethoxybenzimidazole intermediates **11a–11c** (13–22% yield). The lower yields (with Method B) of brominated quinones **12a–12c** are presumably due to the inferior oxidizing ability of Br<sub>2</sub> relative to Cl<sub>2</sub>.<sup>23</sup> The presence of a red-brown vapour in the NaBr/Oxone-mediated oxidative brominations is evidence for the *in situ* formation of Br<sub>2</sub> (Fig. S3†).

Functionalization at both available alicyclic ring-fused DMBBQ CH-positions was established. Trifluoromethylation at the quinone of **5b** gave substrate **5d** in a similar moderate yield (51%, Scheme 5) to that reported for DMBBQ **4b**.<sup>8</sup> Using



Scheme 5 Radical and electrophilic functionalization.

the Langlois' reagent, intractable baseline products were observed and Baran *et al.* have attributed peroxide reaction with sulfonate as a significant wastage reaction.<sup>24</sup> The 'CF<sub>3</sub> radical is considered weakly nucleophilic,<sup>25</sup> and reported CH-alkylations occur at the 'electron-poor' quinone.<sup>26,27</sup> Chlorination with quinone formation to give the fully functionalized bis-*p*-quinone **14** can be carried out in one or two steps with **5d** depending on the desire to isolate more of the intermediate chloride **13**. Using the optimized conditions for chlorination only (Table 1, entry 4 conditions) gave **13** in 73% yield, with the regioselectivity confirmed by the X-ray crystal structure (Scheme 5 and Fig. S4†). The torsional angle is almost identical to that of **8**, indicating the substituents of **13** have no influence on the adopted solid-state geometry. Oxidation of isolated DMBBQ **13** using NaCl and Oxone gave bis-*p*-quinone **14** in 85% yield. Increasing the amount of NaCl and Oxone to favour one pot oxidative chlorination (Table 1, entry 6 conditions), gave bis-*p*-quinone **14** from **5d** in 68% yield, with some intermediate DMBBQ **13** (19%) separated by column chromatography. The smaller yields for chlorides **13** and **14** reflect the deactivation of the trifluoromethylated DMBBQs **5d** and **13** towards the electrophilic oxidizing mixture.

NaX/Oxone system is clearly an efficient system for ring-fused DMBBQs, allowing one-pot halogenation and quinone formation. The reality is transformations developed for our specific heterocyclic system (ring-fused DMBBQs) are not readily transferable to other similar systems. According to the literature,<sup>28</sup> halogenation using NaX/Oxone would not be site-selective where there are other available heterocyclic CH-positions, *e.g.* the non-functionalised imidazole-2-position.



Nevertheless, future work will aim to take advantage of the difference in reactivity between the two DMBBQ-CHs to increase scope to other site-selective functionalizations.

## Conclusions

New alicyclic [1,2-*a*] ring-fused DMBBQs undergo one-pot electrophilic aromatic substitution and oxidative demethylation to give halogenated bis-*p*-quinones using the harmless and inexpensive NaX/Oxone system. The tuneable system gives mainly the site-selective chlorination and bromination intermediate at lower halogen concentrations. The torsion angle in DMBBQs supports the chemoselectivity by lack of MeO-activation at the quinone-CH. HFIP enhances the oxidative aromatic halogenation and for the first time is used in CAN-mediated oxidative aromatic couplings, which formed DMBBQs. Overall, this article details the synthesis in good to excellent yields of new ring-fused bis-benzimidazolequinone heterocyclic systems, and provides reliable late-stage methods for incorporating two different substituents into bis-*p*-quinones.

## Experimental

### Materials

All chemicals obtained from commercial sources used as received. 5,8-Dimethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**6a**), 6,9-dimethoxy-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (**6b**), and 1,4-dimethoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole (**6c**) were prepared in 89%, 72% and 91% yield respectively, according to our reported oxidative ring-closure of the appropriate 3,6-dimethoxy-2-(cycloamino) aniline.<sup>17</sup> 1,2,3,4-Tetrahydropyrido[1,2-*a*]benzimidazole-6,9-dione (**7**) has melting point, chromatographic and spectroscopic data consistent with that previously reported.<sup>29</sup> 2-(Chloromethyl)-4,7-dimethoxy-1-methyl-1*H*-benzimidazole was prepared in 85% yield by *N*-methylation and chlorination of (4,7-dimethoxy-1*H*-benzimidazol-2-yl)methanol.<sup>8</sup> Thin layer chromatography (TLC) was performed on TLC silica gel 60 F<sub>254</sub> plates. Flash column chromatography was carried out on silica gel (Apollo Scientific 60/40–63 μm) and dry column vacuum chromatography used Apollo Scientific silica gel (ZEOPrep 60 and 15–35 μm particle size).<sup>30</sup>

### Measurements

All melting points were measured on a Stuart Scientific melting point apparatus SMP1. IR spectra were recorded using a PerkinElmer Spec 1 with ATR attached.

All NMR spectra were recorded using a Bruker Avance III 400 MHz spectrometer equipped with a 5 mm BBFO+, broadband autotune probe and controlled with TopSpin 3.5.7 acquisition software and IconNMR 5.0.7 automation software Copyright © 2017 Bruker BioSpin GmbH. The exception was 2,2'-bis(chloromethyl)-4',7'-dimethoxy-1,1'-dimethyl-1*H*,1'*H*-[5,5'-bibenzimidazole]-4,7-dione (**8**) recorded on a JEOL ECX

400 MHz NMR spectrometer equipped with a DEC AXP 300 computer workstation. The chemical shifts are in ppm relative to TMS. <sup>13</sup>C NMR spectra at 100 MHz are with complete proton decoupling. NMR assignments are supported by DEPT-135. <sup>19</sup>F NMR spectra were obtained at 376 MHz using automatic digital lock correction in the absence of an internal standard.

HRMS spectra were obtained at the National Mass Spectrometry Facility at Swansea University using a Waters Xevo G2-S or Thermo Scientific LTQ Orbitrap XL 1 mass spectrometer with an Atmospheric Solids Analysis Probe (ASAP), except for DMBBQ **8** obtained at NUI Galway using ESI time-of-flight mass spectrometer (TOFMS) in positive mode using a Waters LCT Mass Spectrometer. The precision of all accurate mass measurements was better than 5 ppm.

A single crystal of **8** was grown by slow evaporation from 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Fig. S1†). Single crystal data for **8** was collected at 299 K using an Oxford Diffraction Xcalibur (equipped with a Mo Kα X-ray source and a Sapphire detector) using the CrysAlis<sup>Pro</sup> software at NUI Galway.

Single crystals of 7'-bromo-5',8'-dimethoxy-2,2',3,3'-tetrahydro-1*H*,1'*H*-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,8-dione (**11a**) and 8'-chloro-6',9'-dimethoxy-8-(trifluoromethyl)-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,9-dione (**13**) were grown at room temperature by slow evaporation from 1,2-dichloroethane and vapour diffusion of hexane into 1,2-dichloroethane, respectively (Fig. S2 and S4†). X-ray diffraction data on single crystals of compounds **11a** and **13** were collected using an Agilent Oxford Diffraction SuperNova (equipped with a microfocus Cu Kα X-ray source, a Cryojet5®, and an Atlas CCD detector) using the CrysAlis<sup>Pro</sup> software at University College London.

The crystal structures of **8**, **11a**, and **13** were solved using SHELXT<sup>31</sup> and refined using SHELXL,<sup>32</sup> both of which were operated from within either the Oscale<sup>33</sup> or the OLEX2<sup>34</sup> software packages. For compound **11a**, a split atom model for the disorder of the methoxy group containing atom O(3) was used to model the disorder, which refined to 72.5% for the methyl group of C(13A) compared to 27.5% for the methyl group of C(13B).

Crystallographic data for compounds **8**, **11a** and **13** were deposited with the Cambridge Data Centre with deposition numbers CCDC 1948449, 2022191, and 2022190,† respectively.

### Synthesis of alicyclic ring-fused DMBBQs (5a–5c)

CAN (8.793 g, 16.04 mmol) in H<sub>2</sub>O (80 mL) was added over 30 min to ring-fused benzimidazoles **6a–6c** (8.00 mmol) in HFIP (20 mL) at 0 °C. The solution was stirred for 30 min and evaporated to dryness. H<sub>2</sub>O (200 mL) was added, and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 150 mL). The organic extracts were dried (MgSO<sub>4</sub>), evaporated, and purified by flash column chromatography using gradient elution of CH<sub>2</sub>Cl<sub>2</sub>/MeOH.

5',8'-Dimethoxy-2,2',3,3'-tetrahydro-1*H*,1'*H*-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,8-dione (**5a**). (1.423 g, 88%); red solid; *R*<sub>f</sub> 0.33 (19:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp 189–191 °C; ν<sub>max</sub>



(neat,  $\text{cm}^{-1}$ ) 1674 (C=O), 1650 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.64 (s, 1H, 7-H), 6.42 (s, 1H, 7'-H), 4.33–4.25 (m, 4H), 4.16 (s, 3H, Me), 3.88 (s, 3H, Me), 3.07–2.97 (m, 4H), 2.80–2.65 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 180.0, 177.9 (both C=O), 160.7, 160.3, 147.6, 146.4, 143.5, 141.7, 141.6 (all C), 133.0 (7-CH), 129.5, 125.7, 117.2 (all C), 104.3 (7'-CH), 61.2, 55.9 (both Me), 45.1, 45.0, 26.54, 26.51, 23.4, 22.9 (all  $\text{CH}_2$ ); HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_4$  405.1563; found 405.1557;  $m/z$  407 (4%), 406 (27), 405 ( $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_4$ , 100).

**6',9'-Dimethoxy-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,9-dione (5b).** (1.502 g, 87%); red solid;  $R_f$  0.34 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp 176–177 °C;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1675 (C=O), 1645 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.64 (s, 1H, 8-H), 6.41 (s, 1H, 8'-H), 4.44 (t,  $J$  = 5.3 Hz, 2H), 4.39–4.32 (m, 2H), 4.13 (s, 3H, Me), 3.86 (s, 3H, Me), 3.10–2.99 (m, 4H), 2.11–1.92 (m, 8H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 180.3, 178.4 (both C=O), 151.7, 150.9, 146.7, 143.3, 142.7, 141.7, 136.5 (all C), 133.9 (8-CH), 130.0, 127.3, 117.3 (all C), 104.5 (8'-CH), 61.3, 55.9 (both Me), 45.6, 45.4, 25.7, 24.9, 23.1, 22.3, 20.5, 19.8 (all  $\text{CH}_2$ ); HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{25}\text{N}_4\text{O}_4$  433.1876; found 433.1871;  $m/z$  435 (5%), 434 (27), 433 ( $\text{C}_{24}\text{H}_{25}\text{N}_4\text{O}_4$ , 100).

**1',4'-Dimethoxy-7,7',8,8',9,9',10,10'-octahydro-6H,6'H-[3,3'-biazepino[1,2-*a*]benzimidazole]-1,4-dione (5c).** (1.545 g, 84%); red solid;  $R_f$  0.40 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp 169–171 °C;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1674 (C=O), 1650 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.63 (s, 1H, 2-H), 6.45 (s, 1H, 2'-H), 4.70–4.55 (m, 4H), 4.16 (s, 3H, Me), 3.88 (s, 3H, Me), 3.12–3.01 (m, 4H), 1.98–1.72 (m, 12H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 180.4, 179.0 (both C=O), 158.1, 157.4, 146.3, 143.7, 142.0, 141.1, 136.2 (all C), 134.2 (2-CH), 130.4, 127.8, 116.6 (all C), 105.1 (2'-CH), 61.4, 55.9 (both Me), 46.1, 45.8, 30.9, 30.8, 29.8, 29.3, 28.9, 28.3, 25.6, 25.0 (all  $\text{CH}_2$ ); HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}_4$  461.2189; found 461.2187;  $m/z$  463 (5%), 462 (29), 461 ( $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}_4$ ), 431 (5).

**Synthesis of 2,2'-bis(chloromethyl)-4',7'-dimethoxy-1,1'-dimethyl-1H,1'H-[5,5'-bibenzimidazole]-4,7-dione (8).** CAN (0.438 g, 0.80 mmol) in  $\text{H}_2\text{O}$  (5 mL) was added dropwise to 2-(chloromethyl)-4,7-dimethoxy-1-methyl-1H-benzimidazole (96 mg, 0.40 mmol) in MeCN (5 mL) at 0 °C. The solution was stirred for 20 min and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  15 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), evaporated, and the residue purified by dry column vacuum chromatography with EtOAc and hexanes as eluent to give the *title compound* 8 (68 mg, 76%); red crystals; mp >350 °C;  $R_f$  0.35 (4 : 1 EtOAc : hexanes);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1655 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.70 (s, 1H), 6.47 (s, 1H), 4.79 (s, 2H), 4.76 (s, 2H), 4.15 (s, 3H, OMe), 4.09 (s, 3H, NMe), 4.07 (s, 3H, NMe), 3.89 (s, 3H, OMe);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 179.7, 178.7 (both C=O), 149.6, 148.7, 147.0, 144.2, 142.7, 141.1, 136.1 (all C), 134.5 (CH), 131.8, 128.8, 117.1 (all C), 105.9 (CH), 61.6, 56.1 (both OMe), 36.8, 35.6 (both  $\text{CH}_2$ ), 33.0, 32.6 (both NMe); HRMS (ESI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_4^{35}\text{Cl}_2$  449.0783; found 449.0778.

## $\text{H}_2\text{O}_2/\text{HCl}$ -mediated chlorination

$\text{H}_2\text{O}_2$  (50% w/v in water, 0.227 mL, 4.0 mmol) and HCl (37% w/v in water, 17  $\mu\text{L}$ , 0.20 mmol) were sequentially added dropwise to a stirred solution of DMBBQ 5a (81 mg, 0.20 mmol) in MeCN (2 mL), and heated at reflux for 1 h. The solution was cooled and EtOAc (2 mL) added, and washed with  $\text{Na}_2\text{CO}_3$  (satd., 2 mL). The organic extract was dried ( $\text{MgSO}_4$ ), evaporated, and the residue purified by flash column chromatography using gradient elution of  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  to give 7'-chloro-5',8'-dimethoxy-2,2',3,3'-tetrahydro-1H,1'H-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,8-dione (9a) (18 mg, 21%); orange crystals;  $R_f$  0.41 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp (decomp >206 °C);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1674 (C=O), 1653 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.58 (s, 1H, 7-H), 4.30 (t,  $J$  = 7.2 Hz, 4H), 4.17 (s, 3H, Me), 3.94 (s, 3H, Me), 3.09–2.97 (m, 4H), 2.80–2.70 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 179.4, 177.7 (both C=O), 160.9, 160.8, 146.3, 145.7, 144.5, 140.1, 137.2 (all C), 135.5 (7-CH), 129.7, 128.8, 119.2, 117.3 (all C), 62.6, 61.3 (both Me), 45.1, 44.5, 26.6, 26.5, 23.3, 22.9 (all  $\text{CH}_2$ ); HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4^{35}\text{Cl}$  439.1173; found 439.1171;  $m/z$  442 (9%), 441 ( $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4^{37}\text{Cl}$ , 36), 440 (25), 439 ( $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4^{35}\text{Cl}$ , 100).

## NaX/Oxone-mediated halogenation (method A)

Oxone (74 mg, 0.12 mmol, containing  $\text{KHSO}_5$ , 0.24 mmol) and NaCl (23 mg, 0.40 mmol) or NaBr (41 mg, 0.40 mmol) in  $\text{H}_2\text{O}$  (0.1 mL) were added over the course of 5 min to a stirred solution of DMBBQ 5a–5d (0.20 mmol) in HFIP (2 mL) at room temperature, and stirred for 5 h.

## NaX/Oxone-mediated halogenation and quinone formation (method B)

Oxone (0.246 g, 0.40 mmol, containing  $\text{KHSO}_5$ , 0.80 mmol) and NaCl (47 mg, 0.80 mmol) or NaBr (82 mg, 0.80 mmol) in  $\text{H}_2\text{O}$  (0.2 mL) were added over the course of 5 min to a stirred solution of DMBBQ 5a–5d (0.20 mmol) in HFIP (2 mL) at room temperature, and stirred for 9 h.

## Reaction work-up for methods A and B

$\text{H}_2\text{O}$  (5 mL) was added, and the mixture extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The organic extracts were dried ( $\text{MgSO}_4$ ), evaporated to dryness, and purified by flash column chromatography using gradient elution of  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ .

**7'-Chloro-5',8'-dimethoxy-2,2',3,3'-tetrahydro-1H,1'H-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,8-dione (9a).** (Method A: 69 mg, 79%); (Method B: 0%); orange crystals; spectroscopic data and melting point were consistent with the above.

**7-Chloro-2,2',3,3'-tetrahydro-1H,1'H-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,5',8,8'-tetrone (10a).** (Method A: 10 mg, 12%); (Method B: 73 mg, 89%); yellow crystals;  $R_f$  0.35 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp (decomp >207 °C);  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1659 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.55 (s, 1H, 7'-H), 4.31 (q,  $J$  = 7.6 Hz, 4H), 3.06–2.98 (m, 4H), 2.83–2.73 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.2, 176.3, 176.2, 168.9 (all C=O), 162.2, 161.3, 146.4, 145.8, 141.6, 140.6, 138.1 (all C), 135.3 (7'-





CH), 129.6, 128.7 (both C), 45.5, 45.2, 26.5, 26.4, 23.1, 22.9 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl 409.0703; found 409.0703; *m/z* 412 (8%), 411 (C<sub>20</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub><sup>37</sup>Cl, 35), 410 (23), 409 (C<sub>20</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl, 100).

**8'-Chloro-6',9'-dimethoxy-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,9-dione (9b).** (Method A: 70 mg, 75%); (Method B: 0%); orange crystals; *R*<sub>f</sub> 0.39 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >197 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1676 (C=O), 1653 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.56 (s, 1H, 8-H), 4.46–4.32 (m, 4H), 4.13 (s, 3H, Me), 3.94 (s, 3H, Me), 3.11–3.01 (m, 4H), 2.16–1.95 (m, 8H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 179.6, 178.2 (both C=O), 151.7, 151.5, 145.5, 143.8, 141.6, 138.1 (all C), 136.3 (8-CH), 135.1, 130.24, 130.19, 119.6, 117.7 (all C), 62.5, 61.4 (both Me), 45.4, 44.8, 25.7, 25.0, 23.0, 22.3, 20.4, 19.8 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl 467.1486; found 467.1482; *m/z* 471 (2%), 470 (9), 469 (C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub><sup>37</sup>Cl, 35), 468 (27), 467 (C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl, 100).

**8-Chloro-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,6',9,9'-tetrone (10b).** (Method A: inseparable with **5b**, 0%); (Method B: 77 mg, 88%); yellow crystals; *R*<sub>f</sub> 0.34 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >212 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1655 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.54 (s, 1H, 8'-H), 4.37 (q, *J* = 5.9 Hz, 4H), 3.04 (t, *J* = 6.3 Hz, 4H), 2.13–1.96 (m, 8H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 177.4, 176.8, 176.4, 169.1 (all C=O), 153.3, 152.3, 142.4, 141.7, 141.2, 139.9, 137.4 (all C), 136.2 (8'-CH), 130.2, 129.3 (both C), 45.8, 45.5, 25.0, 24.9, 22.2, 22.1, 19.7, 19.5 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl 437.1017; found 437.1016; *m/z* 440 (8%), 439 (C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub><sup>37</sup>Cl, 35), 438 (25), 437 (C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl, 100).

**2'-Chloro-1',4'-dimethoxy-7,7',8,8',9,9',10,10'-octahydro-6H,6'-H-[3,3'-biazepino[1,2-*a*]benzimidazole]-1,4-dione (9c).** (Method A: 71 mg, 72%); (Method B: 12 mg, 12%); orange crystals; *R*<sub>f</sub> 0.43 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >234 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1675 (C=O), 1651 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.56 (s, 1H, 2-H), 4.73–4.46 (m, 4H), 4.15 (s, 3H, Me), 3.90 (s, 3H, Me), 3.15–3.01 (m, 4H), 1.99–1.74 (m, 12H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 179.7, 178.7 (both C=O), 158.2, 157.9, 145.7, 143.4, 140.9, 137.5 (all C), 136.7 (2-CH), 134.7, 130.5, 130.3, 120.1, 117.1 (all C), 61.59, 61.56 (both Me), 45.9, 45.3, 30.9, 30.8, 29.7, 29.3, 28.9, 28.1, 25.5, 24.9 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl 495.1799; found 495.1801; *m/z* 499 (2%), 498 (10), 497 (C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub><sup>37</sup>Cl, 36), 496 (29), 495 (C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl, 100).

**2-Chloro-7,7',8,8',9,9',10,10'-octahydro-6H,6'-H-[3,3'-biazepino[1,2-*a*]benzimidazole]-1,1',4,4'-tetrone (10c).** (Method A: inseparable with **5c**, 0%); (Method B: 69 mg, 74%); yellow crystals; *R*<sub>f</sub> 0.40 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >237 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1659 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.50 (s, 1H, 2'-H), 4.75–4.61 (m, 2H), 4.61–4.51 (m, 2H), 3.16–2.99 (m, 4H), 2.03–1.69 (m, 12H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 177.4, 177.3, 176.3, 169.7 (all C=O), 159.7, 158.8, 142.6, 141.1, 140.5, 139.5, 137.0 (all C), 136.5 (2'-CH), 130.5, 129.7 (both C), 46.3, 46.0, 30.73, 30.65 (all CH<sub>2</sub>), 29.3 (2 × CH<sub>2</sub>), 28.1, 28.0, 24.8, 24.7 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl 465.1330; found 465.1326; *m/z* 468 (9%), 467 (C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub><sup>37</sup>Cl, 36), 466 (27), 465 (C<sub>24</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub><sup>35</sup>Cl, 100).

**7'-Bromo-5',8'-dimethoxy-2,2',3,3'-tetrahydro-1H,1'-H-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,8-dione (11a).** (Method A: 73 mg, 76%); (Method B: 12 mg, 13%); orange crystals; *R*<sub>f</sub> 0.38 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >209 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1674 (C=O), 1652 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.55 (s, 1H, 7-H), 4.31 (t, *J* = 7.2 Hz, 4H), 4.16 (s, 3H, Me), 3.93 (s, 3H, Me), 3.09–2.99 (m, 4H), 2.81–2.71 (m, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 179.3, 177.8 (both C=O), 160.81, 160.79, 146.3, 146.1, 145.9, 140.8, 138.2 (all C), 135.4 (7-CH), 129.7, 128.9, 118.9, 109.6 (all C), 62.8, 61.4 (both Me), 45.1, 44.5, 26.6, 26.5, 23.3, 22.9 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub><sup>79</sup>Br 483.0668; found 483.0670; *m/z* 487 (5%), 486 (24), 485 (C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub><sup>81</sup>Br, 100), 484 (24), 483 (C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub><sup>79</sup>Br, 97).

**7-Bromo-2,2',3,3'-tetrahydro-1H,1'-H-[6,6'-bipyrrolo[1,2-*a*]benzimidazole]-5,5',8,8'-tetrone (12a).** (Method A: 12 mg, 13%); (Method B: 68 mg, 75%); yellow crystals; *R*<sub>f</sub> 0.33 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >209 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1662 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.53 (s, 1H, 7'-H), 4.31 (q, *J* = 6.6 Hz, 4H), 3.07–2.97 (m, 4H), 2.83–2.71 (m, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 177.1, 176.4, 175.7, 169.0 (all C=O), 162.0, 161.3, 146.2, 145.8, 142.5, 141.9, 136.8 (all C), 134.8 (7'-CH), 129.7, 128.4 (both C), 45.4, 45.2, 26.5, 26.4, 23.1, 22.9 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>14</sub>O<sub>4</sub>N<sub>4</sub><sup>79</sup>Br 453.0193; found 453.0180; *m/z* 456 (22%), 455 (C<sub>20</sub>H<sub>14</sub>O<sub>4</sub>N<sub>4</sub><sup>81</sup>Br, 97), 454 (22), 453 (C<sub>20</sub>H<sub>14</sub>O<sub>4</sub>N<sub>4</sub><sup>79</sup>Br, 100).

**8'-Bromo-6',9'-dimethoxy-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,9-dione (11b).** (Method A: 69 mg, 68%); (Method B: 18 mg, 18%); orange crystals; *R*<sub>f</sub> 0.37 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >186 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1675 (C=O), 1652 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.54 (s, 1H, 8-H), 4.47–4.34 (m, 4H), 4.11 (s, 3H, Me), 3.93 (s, 3H, Me), 3.11–3.02 (m, 4H), 2.16–1.96 (m, 8H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 179.6, 178.2 (both C=O), 151.8, 151.5, 145.6, 145.4, 141.6, 139.1 (all C), 136.2 (8-CH), 135.8, 130.4, 130.2, 119.4, 110.1 (all C), 62.7, 61.5 (both Me), 45.4, 44.8, 25.7, 25.0, 23.1, 22.3, 20.4, 19.8 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub><sup>79</sup>Br 511.0981; found 511.0984; *m/z* 515 (6%), 514 (26), 513 (C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub><sup>81</sup>Br, 100), 512 (26), 511 (C<sub>24</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub><sup>79</sup>Br, 97).

**8-Bromo-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,6',9,9'-tetrone (12b).** (Method A: inseparable with **5b**, 0%); (Method B: 69 mg, 72%); yellow crystals; *R*<sub>f</sub> 0.34 (19 : 1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH); mp (decomp >220 °C);  $\nu_{\max}$  (neat, cm<sup>-1</sup>) 1655 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.51 (s, 1H, 8'-H), 4.37 (t, *J* = 5.6 Hz, 4H), 3.05 (t, *J* = 6.3 Hz, 4H), 2.14–1.96 (m, 8H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 177.3, 176.9, 175.9, 169.3 (all C=O), 153.2, 152.3, 141.7, 141.6, 141.19, 141.17, 137.9 (all C), 135.6 (8'-CH), 130.2, 129.0 (both C), 45.7, 45.5, 25.0, 24.9, 22.2, 22.1, 19.7, 19.5 (all CH<sub>2</sub>); HRMS (ASAP) *m/z*: calcd for [M + H]<sup>+</sup> C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub><sup>79</sup>Br 481.0511; found 481.0512; *m/z* 485 (3%), 484 (24), 483 (C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub><sup>81</sup>Br, 97), 482 (26), 481 (C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub><sup>79</sup>Br, 100).

**2'-Bromo-1',4'-dimethoxy-7,7',8,8',9,9',10,10'-octahydro-6H,6'-H-[3,3'-biazepino[1,2-*a*]benzimidazole]-1,4-dione (11c).** (Method A: 76 mg, 71%); (Method B: 24 mg, 22%); orange crys-



tals;  $R_f$  0.42 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp (decomp  $>243^\circ\text{C}$ );  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1675 ( $\text{C}=\text{O}$ ), 1651 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.53 (s, 1H, 2-H), 4.73–4.45 (m, 4H), 4.14 (s, 3H, Me), 3.89 (s, 3H, Me), 3.15–3.00 (m, 4H), 1.99–1.69 (m, 12H);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 179.7, 178.8 (both  $\text{C}=\text{O}$ ), 158.3, 157.9, 145.9, 145.0, 140.9, 138.4 (all C), 136.6 (2-CH), 135.5, 130.5, 130.4, 118.8, 110.8 (all C), 61.7, 61.6 (both Me), 45.9, 45.3, 30.89, 30.85, 29.7, 29.4, 28.9, 28.2, 25.5, 24.9 (all  $\text{CH}_2$ ); HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_4$   $^{79}\text{Br}$  539.1294; found 539.1297;  $m/z$  543 (5%), 542 (27), 541 ( $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_4$   $^{81}\text{Br}$ , 100), 540 (28), 539 ( $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_4$   $^{79}\text{Br}$ , 97).

**2-Bromo-7,7',8,8',9,9',10,10'-octahydro-6H,6'H-[3,3'-biazepino [1,2-*a*]benzimidazole]-1,1',4,4'-tetrone (12c).** (Method A: inseparable with **5c**, 0%); (Method B: 70 mg, 69%); yellow crystals;  $R_f$  0.40 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp (decomp  $>232^\circ\text{C}$ );  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1659 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.49 (s, 1H, 2'-H), 4.78–4.64 (m, 2H), 4.62–4.48 (m, 2H), 3.16–2.99 (m, 4H), 2.05–1.68 (m, 12H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.4, 177.3, 175.9, 169.8 (all  $\text{C}=\text{O}$ ), 159.6, 158.7, 141.3, 141.0, 140.8, 140.5, 138.2 (all C), 135.9 (2'-CH), 130.5, 129.3 (both C), 46.2, 46.0, 30.74, 30.66 (all  $\text{CH}_2$ ), 29.3 (2  $\times$   $\text{CH}_2$ ), 28.1, 28.0, 24.8, 24.7 (all  $\text{CH}_2$ ); HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4$   $^{79}\text{Br}$  509.0824; found 509.0826;  $m/z$  513 (4%), 512 (26), 511 ( $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4$   $^{81}\text{Br}$ , 100), 510 (26), 509 ( $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4$   $^{79}\text{Br}$ , 97).

**Synthesis of 6',9'-dimethoxy-8-(trifluoromethyl)-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,9-dione (5d).** *t*-BuOOH (0.864 mL, 9.09 mmol) was added over the course of 10 min to a stirred solution of DMBBQ **5b** (0.543 g, 1.26 mmol),  $\text{NaSO}_2\text{CF}_3$  (0.591 g, 3.78 mmol) and  $\text{Cu}(\text{OTf})_2$  (45 mg, 0.12 mmol) in MeCN (15 mL) at room temperature, and the mixture stirred for 2 h.  $\text{H}_2\text{O}$  (60 mL) was added, and the mixture extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  45 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ), evaporated to dryness and purified by flash column chromatography using gradient elution of  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  to give the *title compound* **5d** (0.321 g, 51%); amorphous red solid;  $R_f$  0.39 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp  $177\text{--}179^\circ\text{C}$ ;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1682 ( $\text{C}=\text{O}$ ), 1663 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.24 (s, 1H, 8'-H), 4.52–4.32 (m, 4H), 4.12 (s, 3H, Me), 3.84 (s, 3H, Me), 3.06 (q,  $J = 6.5$  Hz, 4H), 2.13–1.92 (m, 8H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.5, 174.1 (both  $\text{C}=\text{O}$ ), 153.1, 150.8, 147.73, 147.70, 142.3, 141.0, 135.6 (all C), 130.2 (q,  $^2J_{\text{C-F}} = 27.2$  Hz, 8-C), 129.9, 127.4 (C), 121.8 (q,  $^1J_{\text{C-F}} = 276.6$  Hz,  $\text{CF}_3$ ), 114.4 (C), 103.6 (d,  $J = 2.1$  Hz, 8'-CH), 61.0, 55.9 (both Me), 45.7, 45.6, 25.7, 25.0, 23.1, 22.2, 20.5, 19.6 (all  $\text{CH}_2$ );  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ :  $-56.48$ ; HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_4\text{F}_3$  501.1750; found 501.1752;  $m/z$  503 (5%), 502 (28), 501 ( $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_4\text{F}_3$ , 100).

**8'-Chloro-6',9'-dimethoxy-8-(trifluoromethyl)-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,9-dione (13).** (Method A: 78 mg, 73%); (Method B: 11 mg, 19%); brown crystals;  $R_f$  0.44 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp  $163\text{--}166^\circ\text{C}$ ;  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1683 ( $\text{C}=\text{O}$ ), 1668 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.48–4.36 (m, 4H), 4.15 (s, 3H, Me), 3.93 (s, 3H, Me), 3.07 (q,  $J = 6.6$  Hz, 4H), 2.15–2.06 (m, 4H), 2.06–1.96 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$

NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.7, 173.7 (both  $\text{C}=\text{O}$ ), 153.1, 151.4 (both C), 144.29–144.17 (m, C), 144.1, 141.0, 137.7, 134.3 (all C), 131.7 (q,  $^2J_{\text{C-F}} = 27.5$  Hz, 8-C), 130.4, 130.1 (both C), 121.5 (q,  $^1J_{\text{C-F}} = 276.4$  Hz,  $\text{CF}_3$ ), 118.5, 115.2 (both C), 62.6, 61.1 (both Me), 45.7, 44.8, 25.7, 25.0, 23.0, 22.2, 20.4, 19.6 (all  $\text{CH}_2$ );  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ :  $-58.95$ ; HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_4\text{F}_3$   $^{35}\text{Cl}$  535.1360; found 535.1357;  $m/z$  539 (2%), 538 (9), 537 ( $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_4\text{F}_3$   $^{37}\text{Cl}$ , 35), 536 (27), 535 ( $\text{C}_{25}\text{H}_{23}\text{N}_4\text{O}_4\text{F}_3$   $^{35}\text{Cl}$ , 100).

**8-Chloro-8'-(trifluoromethyl)-1,1',2,2',3,3',4,4'-octahydro[7,7'-bipyrido[1,2-*a*]benzimidazole]-6,6',9,9'-tetrone (14).** (Method A: trace); (Method B: 69 mg, 68%); orange crystals;  $R_f$  0.49 (19 : 1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ); mp (decomp.  $>239^\circ\text{C}$ );  $\nu_{\text{max}}$  (neat,  $\text{cm}^{-1}$ ) 1669 ( $\text{C}=\text{O}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.39 (t,  $J = 5.9$  Hz, 4H), 3.05 (t,  $J = 6.2$  Hz, 4H), 2.15–2.06 (m, 4H), 2.06–1.96 (m, 4H);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 175.7, 175.5, 172.1, 168.6 (all  $\text{C}=\text{O}$ ), 153.7, 153.4, 141.6, 140.7, 140.5, 139.8, 137.1 (all C), 132.0 (q,  $^2J_{\text{C-F}} = 28.3$  Hz, 8'-C), 130.2, 129.5 (both C), 121.0 (q,  $^1J_{\text{C-F}} = 277.0$  Hz,  $\text{CF}_3$ ), 45.9, 45.8, 25.00, 24.99 (all  $\text{CH}_2$ ), 22.1 (2  $\times$   $\text{CH}_2$ ), 19.51, 19.48 (both  $\text{CH}_2$ );  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ :  $-59.03$ ; HRMS (ASAP)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{17}\text{N}_4\text{O}_4\text{F}_3$   $^{35}\text{Cl}$  505.0891; found 505.0889;  $m/z$  508 (12%), 507 ( $\text{C}_{23}\text{H}_{17}\text{N}_4\text{O}_4\text{F}_3$   $^{37}\text{Cl}$ , 34), 506 (25), 505 ( $\text{C}_{23}\text{H}_{17}\text{N}_4\text{O}_4\text{F}_3$   $^{35}\text{Cl}$ , 100).

### Oxidation of DMBBQ 13

Oxone (74 mg, 0.12 mmol, containing  $\text{KHSO}_5$ , 0.24 mmol) and NaCl (14 mg, 0.24 mmol) in  $\text{H}_2\text{O}$  (0.12 mL) were added over the course of 5 min to a stirred solution of DMBBQ **13** (64 mg, 0.12 mmol) in HFIP (1.2 mL) at room temperature, and stirred for 4 h.  $\text{H}_2\text{O}$  (3 mL) was added, and the mixture extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  3 mL). The organic extracts were dried ( $\text{MgSO}_4$ ), evaporated to dryness, and purified by flash column chromatography using gradient elution of  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  to give bis-*p*-quinone **14** (51 mg, 85%); orange crystals; spectral data and melting point were consistent with the above.

## Author contributions

D. Conboy – investigation, methodology and writing; P. Kiely – investigation and visualization; J. C. Bear – investigation (X-ray); J. K. Cockcroft – investigation (X-ray); P. Farràs – supervision; P. McArdle – investigation (X-ray); R. J. Singer – resources; D. A. Smith – supervision; F. Aldabbagh – conceptualization, funding acquisition, main supervision and writing.

## Conflicts of interest

There are no conflicts to declare.

## Note after first publication

This article replaces the version published on 05 March 2021, in which part of Scheme 1 was missing.





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