Incorporating Morpholine and Oxetane into Benzimidazolequinone Anti-Tumour Agents: The Discovery of 1,4,6,9-Tetramethoxyphenazine from Hydrogen Peroxide and Hydroiodic Acid-Mediated Oxidative Cyclizations

Darren Conboy,[†] Styliana I. Mirallai,[‡] Austin Craig,[‡] Patrick McArdle,[‡] Ali A. Al-Kinani,[†] Stephen Barton,[†] and Fawaz Aldabbagh*[†,‡,§]

[†]Department of Pharmacy, School of Life Sciences, Pharmacy and Chemistry, Kingston University, Penrhyn Road, Kingston upon Thames, KT1 2EE, UK.

[‡]School of Chemistry, National University of Ireland Galway, University Road, Galway, H91 TK33, Ireland.

ABSTRACT: The reactivity of hydrogen peroxide and catalytic hydroiodic acid towards 3,6-dimethoxy-2-(cycloamino)anilines is tunable to give ring-fused benzimidazoles or 1,4,6,9-tetramethoxyphenazine in high yield. Mechanisms via a detected nitroso-intermediate are proposed for oxidative cyclization and the unexpected intermolecular displacement of the oxazine. An aqueous solution of molecular iodine is capable of the same transformations. Oxidative demethylation gave targeted benzimidazolequinones, including without cleavage of the incorporated oxetane.

Morpholine is prevalent in marketed drugs.[1] The replacement of functional groups with morpholine can increase metabolic stability and hydrophilicity.[2,3] Oxetane is a cyclic ether with similar hydrogen bonding avidity to morpholine, which has emerged as a polar alternative to the *gem*-dimethyl group in medicinal chemistry.[4,5] NAD(P)H:quinone oxidoreductase 1 (NQO1) is a reductase over-expressed in many solid tumours.[6,7] Benzimidazolequinones are reported excellent substrates for NQO1, which was demonstrated using recombinant human NQO1.[8] Computational docking has shown that a polar group (e.g. cyclic ether) four or five bonds away from the quinone functional group can lead to more efficient NQO1 binding.[9] This led us to target morpholine and spirocyclic oxetane ring-fused benzimidazolequinones **1** and **2** (Figure 1).

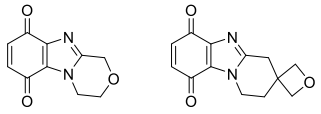
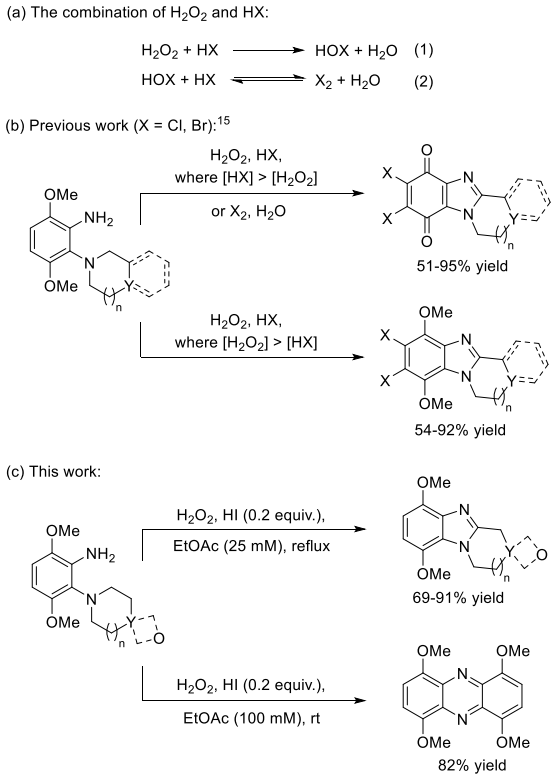


Figure 1. Synthetic targets.

Hydrogen peroxide is a cheap, low molar mass, odorless, and eco-friendly oxidant with high atom economy. H_2O_2 is an established mediator for the oxidative cyclization of *o*-cyclic amine substituted anilines to give ring-fused benzimidazoles.[10-15] We have shown that when H_2O_2 is combined with HX (where X = Cl or Br), the oxidative cyclization can be accompanied by a selective aromatic halogenation in one-pot.[13] When the same H_2O_2 and HX system was applied to 3,6-dimethoxy-2-(cycloamino)anilines, a tunable one-pot transformation was established (Scheme 1(b)).[15]

Scheme 1. H_2O_2 and HX-Mediated Transformations.

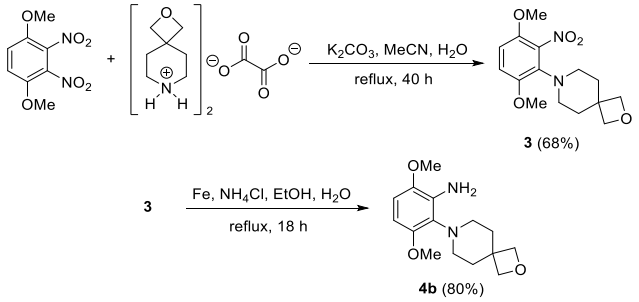


A higher molar ratio of H_2O_2 relative to HX resulted in halogenation and oxidative cyclization, while lower relative amounts of H_2O_2 to HX mediated one-pot halogenation, cyclization and quinone formation, generating halogenated ring-fused benzimidazolequinones. A larger proportion of the hydrohalic acid relative to hydrogen peroxide favors halogen (X_2) formation (Scheme 1(a)), and molecular chlorine and bromine in water were shown to independently mediate the six-electron oxidative transformation to give the halogenated ring-fused benzimidazolequinones. The

use of hydroiodic acid (HI) is preferred over the other hydrohalic acids for the synthesis of targets **1** and **2**, since the oxidative cyclization is more likely to occur without halogenation, as the electrophilicity of the halogens decreases from Cl_2>Br_2>I_2.[16] Herein, the reactivity of 3,6-dimethoxy-2-(cycloamino)anilines using H_2O_2 and a catalytic amount of HI in ethyl acetate is shown to be tunable to favor either the intramolecular reaction to give ring-fused benzimidazoles or the unexpected intermolecular reaction to give 1,4,6,9-tetramethoxyphenazine (Scheme 1 (c)).

The four-step synthesis of ring-fused benzimidazolequinones **1** and **2** began with nucleophilic aromatic substitution (S_NAr) of morpholine and 2-oxa-7-azaspiro[3.5]nonane[17] onto 1,4-dimethoxy-2,3-dinitrobenzene. The substitution using bis(2-oxa-7-azaspiro[3.5]nonan-7-ium) ethanedioate gave 7-(3,6-dimethoxy-2-nitrophenyl)-2-oxa-7-azaspiro[3.5]nonane (**3**) in 68% yield, when using K_2CO_3 (4 equiv) in a 5:1 acetonitrile:water mixture (Scheme 2). Reduction of nitrobenzenes with iron powder gave the aniline oxidative cyclization precursors in high yields with 3,6-dimethoxy-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)aniline (**4b**) formed in 80% yield.

Scheme 2. Preparation of 3,6-Dimethoxy-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)aniline (4b).

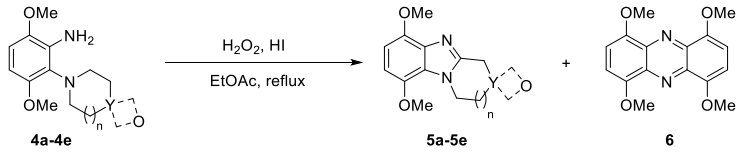


With 3,6-dimethoxy-2-(morpholin-4-yl)aniline (**4a**)[15] and spirocyclic oxetane analogue **4b** in hand, the oxidative cyclization using H_2O_2 and HI was investigated (Table 1). In keeping with the principles of green chemistry, ethyl acetate was chosen as the reaction solvent.[14,18] Morpholine **4a** did not undergo any transformation in EtOAc at reflux in the presence of H_2O_2 (20 equiv) alone. Addition of one stoichiometric equivalent of HI gave after 1 hour, 6,9-dimethoxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**5a**) in 56% yield along with an unexpected orange precipitate. Spectroscopic data identified the precipitate as 1,4,6,9-tetramethoxyphenazine (**6**), formed in 25% yield. Using less than stoichiometric amounts of HI (0.2 equiv), increased the yield of the desired benzimidazole **5a** to 69%, and less phenazine **6** formed in 19% yield. Using these conditions on substrate **4b** gave spirocyclic oxetane ring-fused benzimidazole **5b** in 74% yield with 11% phenazine **6** formed. The amount of phenazine **6** (12% yield) was consistent for other six-membered cyclizations, as demonstrated by conversion of 3,6-dimethoxy-2-(piperidin-1-yl)aniline (**4c**) to give 6,9-dimethoxy-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (**5c**) in 72% yield. Variation of ring-sizes was investigated, with the five- and seven-membered cyclizations of 3,6-dimethoxy-(2-pyrrolidin-1-yl)aniline (**4d**) and 2-(azepan-1-yl)-3,6-dimethoxyaniline (**4e**) proceeding in high yield to respectively give 5,8-dimethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (**5d**) and 1,4-dimethoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole (**5e**) in 89% and 91% yield. The absence of phenazine **6** from the latter reactions is consistent with previous observations of six-membered oxidative cyclizations being more difficult than those forming five and expanded ring-fused benzimidazole analogues.[14] For all reactions, chromatography was not required, with residues triturated in diethyl ether to afford benzimidazoles **5a**-**5e**.

Phenazine is the scaffold of secondary metabolites from *Pseudomonas* and *Streptomyces* with many natural and unnatural examples having potent biological activity, notably anti-cancer.[19,20] The oldest synthesis is the Wohl-Aue reaction,[21] which is known to be low-yielding, and reported to give 1,4,6,9-tetramethoxyphenazine (**6**) in 10% yield using potassium hydroxide in benzene (Scheme 3).[22] We attempted to improve this condensation of the aniline with nitrobenzene by using potassium *tert*-butoxide as base in toluene,[23] but the yield of **6** remained low, at 34%. We set about establishing a more facile route to **6** through manipulation of the optimized H_2O_2 and HI-mediated oxidative cyclization conditions for morpholine **4a** (Table 1). Given that phenazine **6** formation is an intermolecular reaction, it seemed plausible that the use of more concentrated conditions (less ethyl acetate) would lead to increased yields of **6**. This was indeed the case when reducing the amount of solvent by 4-fold, phenazine **6** became the major product in 47% yield with benzimidazole **5a** formed in 28% yield. The H_2O_2 and HI-mediated cyclization seemed to give the thermodynamic product, since the yield of cyclized benzimidazole **5a** became increasingly insignificant (4% then 2%), when reducing the reaction temperature from reflux to 40 °C to room temperature with phenazine **6** isolated in excellent yield of 82%. The requirement for higher temperatures for the cyclization may also be due to the nature of the oxidizing system, although hypoiodous acid (HOI) is formed, the mediating oxidant is unknown.[24,25]

Phenazine **6** was not formed when replacing HI (0.2 equiv) with HCl (0.2 equiv) (Scheme 4(a)). Under these conditions mainly recovered **4a** was observed with 4-chloro-3,6-dimethoxy-2-(morpholin-4-yl)aniline (**4f**) formed in 17% yield. The regioselectivity of the chlorination was confirmed by X-ray crystallography (Scheme 4(b) and Figure S1). The yield of chlorinated aniline **4f** increased to 76% through use of a stoichiometric equivalent of HCl with H_2O_2. The greater reactivity of catalytic amounts of HI relative to HCl, reflects the lower pK_a of HI,[26] and relative ease of oxidation of iodine,[27] which allows facile breakdown of H_2O_2.[24,25]

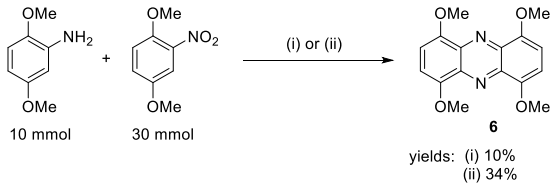
Table 1. Yields Obtained from H_2O_2 and HI-Mediated Reactions.[a]



Entry	Aniline	Y	n	HI (mmol)	Time (h)	Yield of **5a-5e** (%)[b]	Yield of **6** (%)[b, c]
1	**4a**	O	1	0.0	16	**5a**, 0	0
2	**4a**	O	1	1.0	1	**5a**, 56	25
3	**4a**	O	1	0.2	1	**5a**, 69	19
4	**4b**		1	0.2	1	**5b**, 74	11
5	**4c**	CH_2	1	0.2	1	**5c**, 72	12
6	**4d**	CH_2	0	0.2	1	**5d**, 89	0
7	**4e**	CH_2	2	0.2	1	**5e**, 91	0
8	**4a**	O	1	0.2[d]	1	**5a**, 28	47
9	**4a**	O	1	0.2[d, e]	16	**5a**, 4	79
10	**4a**	O	1	0.2[d, f]	24	**5a**, 2	82

[a]Conditions: Aniline (1.0 mmol), H_2O_2 (20.0 mmol), EtOAc (40 mL). [b]Isolated. [c]Precipitate. [d]EtOAc (10 mL). [e]40 °C. [f]rt.

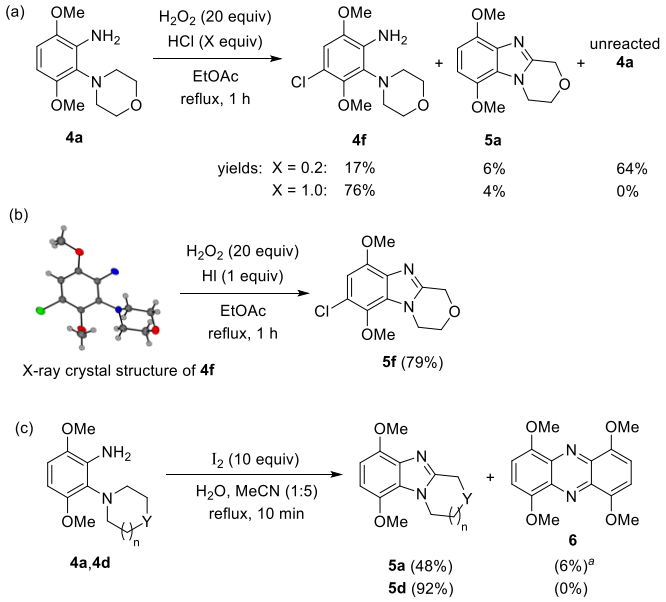
Scheme 3. Wohl-Aue Reaction.[a]



[a]Conditions: (i) KOH (90 mmol), benzene (50 mL), reflux, 5 h.[22]
(ii) *t*-BuOK (40 mmol), toluene (50 mL), reflux, 16 h.

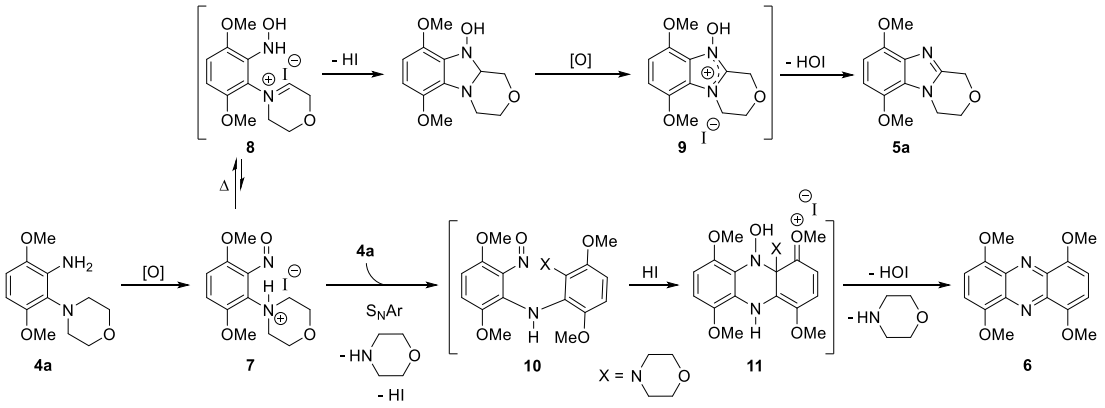
Recently, chlorine (50 equiv) and bromine (50 equiv) with water (100 equiv) have been established as mediators for six-electron oxidation, converting 3,6-dimethoxy-2-(cycloamino)anilines into cyclized benzimidazolequinones (Scheme 1(b)).[15] Molecular iodine is however, a less powerful oxidizing agent,[27] and using the latter conditions did not give benzimidazolequinones, but mixtures of difficult to separate iodinated aromatics. In the iodine-mediated reactions, ethyl acetate was replaced by acetonitrile, since the former solvent is immiscible with water. Using iodine (10 equiv) in 20% aqueous acetonitrile, a 4-electron oxidation occurred in 10 minutes to give cyclized non-iodinated benzimidazoles (Scheme 4(c)). Morpholine **4a** and pyrrole **4d** were converted to 6,9-dimethoxy[1,4]oxazino[4,3-*a*]benzimidazole (**5a**) and 5,8-dimethoxypyrrolo[1,2-*a*]benzimidazole (**5d**) in 48% and 92% yield respectively. Similar to the H_2O_2 and HI-mediated reaction, the five-membered cyclization was regioselective, and did not give phenazine, however the less favored morpholine cyclization gave side-products, including **6** in 6% yield. Presumably for iodine in water, the concentration of HOI is greater than in the H_2O_2 and HI-mediated reactions (in Table 1) resulting in intractable iodinated side-products.

Scheme 4. Alternative Oxidative Conditions and X-ray Crystal Structure with Cyclization of 4-Chloro-3,6-dimethoxy-2-(morpholin-4-yl)aniline (4f) (Thermal Ellipsoids Set at 40% Probability).



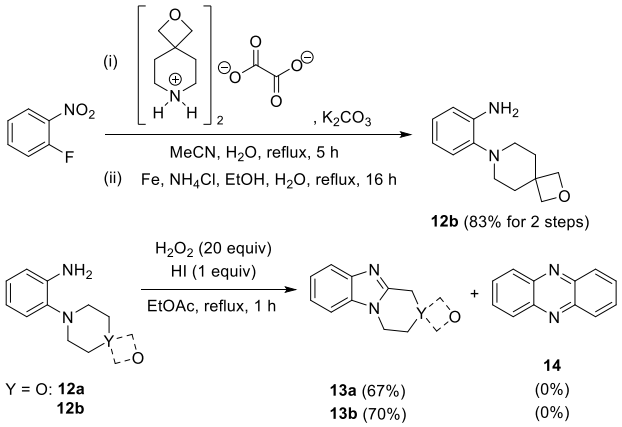
[a]& an intractable mixture of iodinated benzimidazoles.

Scheme 5. Proposed Mechanisms for the H_2O_2 and HI (Catalyst) Mediated Transformations Using 3,6-Dimethoxy-2-(morpholin-4-yl)aniline (4a).



Common to the oxidative cyclization of *o*-cyclic amine substituted anilines to give benzimidazoles,[10,28] and the Wohl-Aue and other phenazine syntheses,[19,20,29] is the likelihood of a nitroso-intermediate. Transformations via the *N*-oxide of the *tert*-amine of **4a** are unlikely, with amine *N*-oxides isolated intermediates only when the primary NH_2 is deactivated to an acetamide.[30,31] We were however unable to isolate a nitroso-intermediate, although encouragingly GC-MS of the reaction mixture (entry 10, Table 1) after 1 hour revealed an EI-MS fragmentation pattern supporting the formation of intermediate **7** (Figure S2, Scheme 5). The existence of highly reactive nitroso-intermediate **7** is supported by Meth-Cohn, who also refuted claims of isolations of *o*-nitroso-*tert*-anilines, including the nitrosation of *p*-benzyldimethylaniline, which gave only the nitro-compound.[32] Nitroso **7** should undergo a formal 1,5-hydride shift to the likely hydroxylamine **8**,[28,32-34] which subsequently cyclizes and is oxidized to give benzimidazole **5a**. The unexpected 1,4,6,9-tetramethoxyphenazine (**6**) formation via nitroso intermediate **7** would involve intermolecular reaction of **7** with starting aniline **4a** resulting in nucleophilic aromatic substitution adduct **10**. The proposed formation of iodide **11** is reminiscent of the Bamberger-Ham reaction for making phenazine-*N*-oxides,[35] where two nitrosobenzenes substituted with *para*-electron-donating (through resonance) groups condense under acidic conditions.[19,20] It is known that HOI reacts with H_2O_2 via a reduction to generate additional HI,[24,25] which would favor conversion of **10** to **11**. Further the yield of phenazine **6** is increased when using a full equivalent of HI (entry 2, Table 1). Similar to the conversion of hydroxylamine salts **9** and **11** into products **5a** and **6** respectively, Nguyen et al. also proposed iodide as a direct reductant for removal of oxygen in iodine-catalyzed reductive cyclizations of *o*-nitro-*tert*-anilines to give benzimidazoles.[33] The necessity for the electron-donating (OMe) group in our H_2O_2 and HI-mediated synthesis of phenazine was investigated using 2-(morpholin-4-yl)aniline (**12a**)[13] and 2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)aniline (**12b**), prepared from 1-fluoro-2-nitrobenzene (Scheme 6). In both cases, oxidative cyclization adducts (**13a**[33] and **13b**) were exclusively isolated in moderate yields (67 and 70%) after column chromatography with phenazine **14**[36] not observed. The presence of appropriately positioned OMe groups does not however guarantee phenazine formation. Surprisingly chloride **4f** exclusively cyclized to give 7-chloro-6,9-dimethoxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**5f**) in 79% isolated yield (Scheme 4(b)), using the H_2O_2 and HI reaction conditions (in Table 1), which favored formation of **6**. Presumably electronic effects of the Cl substituent circumvent the S_NAr step (in Scheme 5).

Scheme 6. Preparation of 2-(2-Oxa-7-azaspiro[3.5]nonan-7-yl)aniline (12b) and Oxidative Cyclizations.

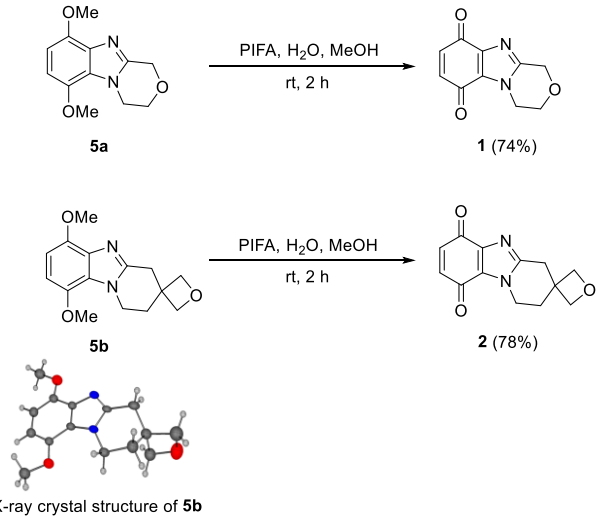


The structure of 6',9'-dimethoxy-1',2'-dihydro-4'*H*-spiro[oxetane-3,3'-pyrido[1,2-*a*]benzimidazole] (**5b**) was confirmed by X-ray crystallography prior to being subjected to oxidative demethylation (Scheme 7 and Figure S3). The hypervalent iodine reagent [bis(trifluoroacetoxy)iodo]benzene (PIFA) in water at room temperature is reported to convert *p*-dimethoxybenzenes to quinones.[37] This mild procedure was used to give target ether-containing ring-fused benzimidazolequinones **1** and **2** in 74% and 78% yield from 6,9-dimethoxy-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**5a**) and spirocyclic oxetane ring-fused benzimidazole (**5b**) respectively. Importantly, PIFA unlike other oxidants,[38,39] had no apparent adverse effect on the integrity of the oxetane motif.

In summary, H_2O_2 and HI-mediated oxidative cyclization of 3,6-dimethoxy-2-(cycloamino)anilines to give the ring-fused benzimidazoles can be tuned to alternatively give 1,4,6,9-tetramethoxyphenazine (**6**) in high yield. Phenazine formation is however not ubiquitous and competes with the

six-membered cyclization only when the 3,6-dimethoxy-2-(cycloamino)anilines are suitably activated. The detection of nitroso-intermediate **7**, has led to a proposed mechanism for this new HI-catalyzed reaction. Future work will establish the anti-tumor activity and NQO1 specificity of the synthesized benzimidazolequinones.

Scheme 7. Oxidative Demethylation and X-ray Crystal Structure of 6',9'-Dimethoxy-1',2'-dihydro-4'*H*-spiro[oxetane-3,3'-pyrido[1,2-*a*]benzimidazole] (5b) (Thermal Ellipsoids Set at 40% Probability).



Experimental Section

Materials

All chemicals were obtained from commercial sources and used without further purification. 1,4-Dimethoxy-2,3-dinitrobenzene was prepared from 1,4-dimethoxybenzene (Sigma Aldrich, 99% (GC)) and nitric acid (Honeywell Fluka, 64-66%).[40] Bis(2-oxa-7-azaspiro[3.5]nonan-7-ium) ethanedioate was prepared using the procedure described by our group.[17] The preparations of 3,6-dimethoxy-2-(morpholin-4-yl)aniline (**4a**), 3,6-dimethoxy-2-(piperidin-1-yl)aniline (**4c**), 3,6-dimethoxy-2-(pyrrolidin-1-yl)aniline (**4d**) and 2-(azepan-1-yl)-3,6-dimethoxyaniline (**4e**) were previously reported using the S_NAr of morpholine (Alfa Aesar, 99%), piperidine (Sigma Aldrich, 99%), pyrrolidine (Acros, +99%), and azepane (Fluorochem, >98%) respectively onto 1,4-dimethoxy-2,3-dinitrobenzene, followed by reduction with iron powder (Alfa Aesar, reduced, 99%).[14,15] 2,5-Dimethoxyaniline was prepared by the reduction of 1,4-dimethoxy-2-nitrobenzene (TCI, >99.0% (GC)) using iron powder.[41] 2-(Morpholin-4-yl)aniline (**12a**)[13] was prepared by the S_NAr of morpholine onto 1-fluoro-2-nitrobenzene (Fluorochem, 99%), followed by reduction with iron powder. H_2O_2 (Honeywell Fluka, 50% w/v in water, stabilized), HI (Sigma Aldrich, 57% w/v in water), HCl (Sigma Aldrich, 37% w/v in water), I_2 (VWR, ≥99%, resublimed), and PIFA (Sigma Aldrich, 97%) were used as received. Thin layer chromatography (TLC) was performed on TLC silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel (Apollo Scientific 60/40–63 μm).

Measurements

Melting points: Melting points were measured on a Stuart Scientific melting point apparatus SMP1, except for 1,4,6,9-tetramethoxyphenazine (**6**) recorded using differential scanning calorimetry (DSC) performed on a Mettler Toledo DSC822 differential scanning calorimeter, using standard aluminum pans.

Gas chromatography: GC-MS used to detect the formation of nitrosoarene **7** was performed on an Agilent 6890N Series GC system equipped with an Agilent 5973 Inert Mass Selective Detector (EI) and an SGE, 25 m, ID 0.25 mm, FD 0.25 μm column. The carrier gas used was He at a flow rate of 1.3 mL/min. The injector heated to 80 °C and the oven temperature increased from 80 to 280 °C at the rate of 10 °C/min and increased to 320 °C at 40 °C/min.

Infrared (IR) spectroscopy: IR spectra were recorded using a Perkin-Elmer Spec 1 with ATR attached.

Nuclear Magnetic Resonance (NMR) spectroscopy: NMR spectra for compounds **2**, **3**, **4b** and **5b** were recorded using a Jeol ECX 400 MHz instrument equipped with a DEC AXP 300 computer workstation. NMR Spectra for all other compounds were recorded using a Bruker Avance II 400 MHz spectrometer. The chemical shifts are in ppm relative to tetramethylsilane. ^{13}C-NMR spectra at 100 MHz are with complete proton decoupling. NMR assignments are supported by Distortionless Enhancement by Polarization Transfer (DEPT) and ^{1}H-^{1}H and ^{1}H-^{13}C correlation.

High resolution mass spectrometry (HRMS): HRMS spectra were obtained using ESI time-of-flight mass spectrometer (TOFMS) on a Waters LCT Mass Spectrometry instrument. The precision of all accurate mass measurements was better than 5 ppm.

X-ray crystallography: A single crystal of **4f** was grown from CH_2Cl_2 at 2 °C, and a single crystal of **5b** was grown by slow evaporation from CH_2Cl_2. Single crystal data was collected using an Oxford Diffraction Xcalibur system operated using the CrysAlisPro software and the data collection temperature was controlled at 298 K using a Cryojet system from Rigaku Oxford Diffraction. The crystal structures were solved using ShelxT version 2014/55,[42] and refined using ShelxL version 2017/1,[43] both of which were operated within the Oscail software package.[44] Crystallographic data for compounds **4f** and **5b** was deposited with the Cambridge Crystallographic Data Centre with deposit number of CCDC 1917886 and CCDC 1917885 respectively. This data is available free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax +44 1223 336033; or e-mail deposit@ccdc.cam.ac.uk).

Experimental Procedures

*Synthesis of 3,6-Dimethoxy-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)aniline (**4b**).* 1,4-Dimethoxy-2,3-dinitrobenzene (0.680 g, 2.98 mmol), bis(2-oxa-7-azaspiro[3.5]nonan-7-ium) ethanedioate (2.053 g, 5.96 mmol) and K_2CO_3 (1.647 g, 11.92 mmol) in MeCN (30 mL) and H_2O (6 mL) were heated at reflux for 40 h. The mixture was evaporated, dissolved in EtOAc (30 mL) and washed with brine (3 x 20 mL). The organic extract was dried ($MgSO_4$), evaporated, and purified

by column chromatography using gradient elution of petroleum ether/EtOAc to give *7-(3,6-dimethoxy-2-nitrophenyl)-2-oxa-7-azaspiro[3.5]nonane (**3**)* (0.624 g, 68%) as a yellow solid; R_f 0.44 (1:1 pet. ether/EtOAc); m.p. 125-127 °C; ν_{max} (neat, cm^{-1}) 2931, 2861, 2841, 1539 (NO_2), 1495, 1381 (NO_2), 1256, 1094, 1057; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.83 (d, *J* = 9.2 Hz, 1H), 6.74 (d, *J* = 9.2 Hz, 1H), 4.42 (s, 4H, OCH_2), 3.80 (s, 3H, Me), 3.78 (s, 3H, Me), 2.97-2.90 (br.s, 4H), 1.88-1.80 (br.s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 152.7, 144.5, 141.9, 133.9 (all C), 112.9, 109.4 (both CH), 82.1 (OCH_2), 56.8, 56.2 (both Me), 47.8 (CH_2), 38.4 (C), 35.6 (CH_2); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{15}H_{21}N_2O_5$ 309.1449; Found 309.1450.

Nitrobenzene **3** (0.616 g, 2.00 mmol), iron powder (0.357 g, 6.40 mmol) and NH_4Cl (55 mg, 1.00 mmol) in EtOH (40 mL) and H_2O (12 mL) were heated at reflux for 18 h. The mixture was filtered through Celite®, evaporated, dissolved in EtOAc (80 mL) and washed with brine (2 x 60 mL). The organic extract was dried ($MgSO_4$), evaporated, and purified by column chromatography using gradient elution of petroleum ether/EtOAc to give **4b** (0.445 g, 80%) as an off-white solid; R_f 0.33 (3:1 pet. ether/ EtOAc); m.p. 138-140 °C; ν_{max} (neat, cm^{-1}) 3444, 3338, 2989, 2917, 2856, 2830, 1605, 1556, 1490, 1258, 1107; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.54 (d, *J* = 8.8 Hz, 1H), 6.13 (d, *J* = 8.8 Hz, 1H), 4.56 (s, 2H, OCH_2), 4.40 (s, 2H, OCH_2), 4.37-4.27 (br.s, disappears with D_2O, 2H, NH_2), 3.78 (s, 3H, Me), 3.71 (s, 3H, Me), 3.14 (t, *J* = 12.1 Hz, 2H), 2.75 (d, *J* = 11.4 Hz, 2H), 2.13 (d, *J* = 12.4 Hz, 2H), 1.79-1.66 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 153.6, 142.1, 135.4, 126.3 (all C), 107.5, 99.0 (both CH), 82.8, 81.7 (both OCH_2), 56.1, 55.5 (both Me), 47.3 (CH_2), 38.6 (C), 36.7 (CH_2); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{15}H_{23}N_2O_3$ 279.1709; Found 279.1701.

*Synthesis of 2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)aniline (**12b**).* 1-Fluoro-2-nitrobenzene (0.296 g, 2.10 mmol), bis(2-oxa-7-azaspiro[3.5]nonan-7-ium) ethanedioate (0.722 g, 2.10 mmol) and K_2CO_3 (1.161 g, 8.40 mmol) in MeCN (20 mL) and H_2O (4 mL) were heated at reflux for 5 h. The mixture was evaporated, dissolved in EtOAc (20 mL) and washed with brine (3 x 20 mL). The organic extract was dried ($MgSO_4$), evaporated, and purified by column chromatography using gradient elution of petroleum ether/EtOAc to give *7-(2-nitrophenyl)-2-oxa-7-azaspiro[3.5]nonane* (0.489 g, 94%) as an orange solid; R_f 0.38 (3:2 pet. ether/EtOAc); m.p. 95-96 °C; ν_{max} (neat, cm^{-1}) 2931, 2859, 2814, 1603, 1567, 1519 (NO_2), 1488, 1463, 1444, 1384, 1343 (NO_2), 1298, 1234, 1167, 1129; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.76 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.48-7.43 (m, 1H), 7.11 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.05-7.00 (m, 1H), 4.48 (s, 4H, OCH_2), 2.95 (t, *J* = 5.5 Hz, 4H), 2.02 (t, *J* = 5.5 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 146.3, 143.3 (both C), 133.4, 125.9, 121.7, 121.2 (all CH), 81.6 (OCH_2), 49.2 (CH_2), 38.3 (C), 34.9 (CH_2); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{13}H_{17}N_2O_3$ 249.1239; Found 249.1245.

The above nitrobenzene (0.480 g, 1.94 mmol), iron powder (0.347 g, 6.21 mmol) and NH_4Cl (52 mg, 0.97 mmol) in EtOH (30 mL) and H_2O (10 mL) were heated at reflux for 16 h. The mixture was filtered through Celite®, evaporated, dissolved in EtOAc (60 mL) and washed with brine (2 x 40 mL). The organic extract was dried ($MgSO_4$), evaporated, and purified by column chromatography using gradient elution of petroleum ether/EtOAc to give **12b** (0.372 g, 88%) as a pale brown solid; R_f 0.35 (3:2 pet. ether/ EtOAc); m.p. 137-139 °C; ν_{max} (neat, cm^{-1}) 3408, 3325, 3032, 2914, 2856, 2806, 2740, 2677, 1617, 1501, 1461, 1438, 1425, 1383, 1289, 1211, 1135, 1125; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.94-6.86 (m, 2H), 6.74-6.65 (m, 2H), 4.46 (s, 4H, OCH_2), 4.02-3.87 (br.s, disappears with D_2O, 2H, NH_2), 2.89-2.60 (br.s, 4H), 2.06-1.86 (br.s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 141.6, 139.6 (both C), 124.6, 119.8, 118.5, 115.1 (all CH), 81.9 (OCH_2), 48.7 (CH_2), 38.6 (C), 35.9 (CH_2); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{13}H_{19}N_2O$ 219.1497; Found 219.1487.

H_2O_2 and HX-Mediated Transformations

Reaction conditions are given in Table 1 and Schemes 4(b), and 6 for H_2O_2 and HI, and in Scheme 4(a) for H_2O_2 and HCl. H_2O_2 and HX were sequentially added dropwise to a stirred solution of the anilines (1 mmol) in EtOAc (10 or 40 mL) at the indicated reaction temperatures. For the room temperature reaction of aniline **4a**, the addition of H_2O_2 and HI were done over ice, and the mixture was then allowed to warm to room temperature. At the end of the reaction, the solution was filtered, and the orange precipitate washed with EtOAc (30 mL) to give 1,4,6,9-tetramethoxyphenazine (**6**). The filtrate was washed with Na_2CO_3 (satd., 60 mL), and dried ($MgSO_4$). The organic extract was evaporated, and the residue triturated from Et_2O to give benzimidazoles **5a**-**5d**. Azepane **5e** did not require purification. The residues of **4f**, **5f**, **13a** and **13b** were purified by column chromatography using gradient elution of petroleum ether/EtOAc.

*6,9-Dimethoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole (**5a**)* (0.161 g, 69%, Table 1, entry 3); pale brown solid; m.p. 109-111 °C; ν_{max} (neat, cm^{-1}) 2929, 2827, 1523, 1475, 1440, 1426, 1402, 1316, 1259, 1227, 1193, 1165, 1119, 1103, 1084; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.45 (AB_q, *J* = 8.6 Hz, 2H), 4.92 (s, 2H, 1-CH_2), 4.41 (t, *J* = 5.2 Hz, 2H), 4.03 (t, *J* = 5.2 Hz, 2H), 3.87 (s, 3H, Me), 3.79 (s, 3H, Me); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 146.3, 145.8, 141.8, 134.4, 125.0 (all C), 102.8, 102.0 (both CH), 65.5 (1-CH_2), 64.3 (CH_2), 55.9, 55.8 (both Me), 44.9 (CH_2); HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{12}H_{15}N_2O_3$ 235.1083; Found 235.1081, and *1,4,6,9-tetramethoxyphenazine (**6**)* (29 mg, 19%); orange solid; m.p. (DSC) onset 351.2 °C, peak max 355.9 °C (lit m.p.[26] >360 °C); ν_{max} (neat, cm^{-1}) 3075, 3010, 2900, 2833, 1177, 1622, 1492, 1456, 1445, 1437, 1322, 1266, 1248, 1197, 1157, 1127, 1109; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.97 (s, 4H), 4.09 (s, 12H, Me); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 148.8, 135.6 (both C), 106.0 (CH), 56.1 (Me); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O_4$ 301.1188; Found 301.1179.

*6',9'-Dimethoxy-1',2'-dihydro-4'H-spiro[oxetane-3,3'-pyrido-[1,2-a]benzimidazole] (**5b**)* (0.203 g, 74%); off-white solid; m.p. 166-167 °C; ν_{max} (neat, cm^{-1}) 3004, 2931, 2865, 2837, 1810, 1606, 1523, 1441, 1260, 1223, 1100, 1082; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.47 (s, 2H), 4.53 (AB_q, *J* = 6.1 Hz, 4H, OCH_2), 4.45 (t, *J* = 6.3 Hz, 2H, 1'-CH_2), 3.92 (s, 3H, Me), 3.83 (s, 3H, Me), 3.32 (s, 2H, 4'-CH_2), 2.34 (t, *J* = 6.3 Hz, 2H, 2'-CH_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 148.2, 145.6, 141.8, 135.0, 125.3 (all C), 102.6, 101.8 (both CH), 80.8 (OCH_2), 55.93, 55.89 (both Me), 41.7 (1'-CH_2), 37.7 (C), 35.0 (4'-CH_2), 31.3 (2'-CH_2); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3$ 275.1396; Found 275.1380, and *1,4,6,9-tetramethoxyphenazine (**6**)* (17 mg, 11%).

*6,9-Dimethoxy-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**5c**)* (0.167 g, 72%); brown solid; spectral data and melting point consistent with the literature,[14] and *1,4,6,9-tetramethoxyphenazine (**6**)* (18 mg, 12%).

*5,8-Dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (**5d**)* (0.194 g, 89%); off-white solid; spectral data and melting point consistent with the literature.[14]

*1,4-Dimethoxy-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole (**5e**)* (0.224 g, 91%); brown oil; spectral data consistent with the literature.[14]

*4-Chloro-3,6-dimethoxy-2-(morpholin-4-yl)aniline (**4f**)* (0.207 g, 76%); R_f 0.51 (1:1 pet. ether/EtOAc); pale brown solid; m.p. 149-151 °C; ν_{max} (neat, cm^{-1}) 3434, 3335, 2960, 2909, 2881, 2843, 1596, 1549, 1480, 1456, 1445, 1419, 1261, 1177, 1153, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.65 (s, 1H), 3.98-3.88 (br.s, 2H), 3.87 (s, 3H, Me), 3.81 (s, 3H, Me), 3.78-3.63 (br.s, 2H), 3.52-3.35 (br.s, 2H), 2.87-2.68 (br.s, 2H), NH_2 is absent; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 148.9, 143.6, 133.7, 130.5, 114.8 (all C), 109.3 (CH), 68.4 (2 x CH_2), 61.8, 56.0, (both Me), 51.0 (2 x CH_2); HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{12}H_{18}N_2O_3Cl$ 273.1006; Found 273.1012; and *6,9-dimethoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole (**5a**)* (9 mg, 4%); R_f 0.35 (EtOAc).

*7-Chloro-6,9-dimethoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole (**5f**)* (0.212 g, 79%); R_f 0.43 (EtOAc); brown solid; m.p. 144-146 °C; ν_{max} (neat, cm^{-1}) 2931, 2836, 2359, 1605, 1508, 1473, 1428, 1399, 1309, 1212, 1153, 1111, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 1H), 5.00 (s, 2H, 1-CH_2), 4.44 (t, *J* = 5.2 Hz, 2H), 4.17 (t, *J* = 5.2 Hz, 2H), 3.96 (s, 3H, Me), 3.94 (s, 3H, Me); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 147.7, 147.0, 136.7, 133.4, 128.5, 120.5 (all C), 104.8 (CH), 65.5, 64.1 (CH_2), 62.5, 56.1 (both Me), 44.2 (CH_2); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{14}N_2O_3Cl$ 269.0693; Found 269.0685.

*3,4-Dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole (**13a**)* (0.117 g, 67%); pale brown solid; R_f 0.21 (EtOAc); spectral data and melting point consistent with the literature.[33]

*1',2'-dihydro-4'H-spiro[oxetane-3,3'-pyrido[1,2-a]benzimidazole] (**13b**)* (0.149 g, 70%); off-white solid; R_f 0.23 (1:10 MeOH/EtOAc) m.p. 141-143 °C; ν_{max} (neat, cm^{-1}) 3052, 2936, 2864, 1668, 1616, 1516, 1485, 1457, 1417, 1371, 1344, 1319, 1283, 1228, 1161; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73-7.67 (m, 1H), 7.33-7.28 (m, 1H), 7.28-7.22 (m, 2H), 4.59 (AB_q, *J* = 6.2 Hz, 4H, OCH_2), 4.14 (t, *J* = 6.3 Hz, 2H, 1'-CH_2), 3.40 (s, 2H, 4'-CH_2), 2.47 (t, *J* = 6.3 Hz, 2H, 2'-CH_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 149.5, 143.2, 134.3 (all C), 122.4, 122.2, 119.2, 108.9 (all CH), 80.6 (OCH_2), 38.8 (1'-CH_2), 38.0 (C), 34.9 (4'-CH_2), 30.7 (2'-CH_2); HRMS (ESI) *m/z* $[M + H]^+$ $C_{13}H_{15}N_2O$ Calcd for 215.1184; Found 215.1180.

Modified Wohl-Aue Reaction

Reaction conditions are given in Scheme 3. At the end of the reaction, the mixture was filtered, and the precipitate washed with water (30 mL) to give **6** (1.02 g, 34%) as an orange solid. Spectral data and melting point of phenazine **6** is consistent with the above.

Aqueous I_2-mediated transformations

Anilines (1.00 mmol) in MeCN (10 mL) and H_2O (2 mL) were heated to reflux. I_2 (10.00 mmol) was added, and the mixture was stirred at reflux for 10 min. The mixture was filtered, and the precipitate washed with water (20 mL) to give phenazine **6**. The filtrate was washed with Na_2CO_3 (satd., 20 mL) and $Na_2S_2O_3$ (1 M, 20 mL), and the organic extract was dried ($MgSO_4$) and evaporated to dryness. Benzimidazole **5d** did not require purification. The residue of benzimidazole **5a** was purified by column chromatography using gradient elution of petroleum ether/EtOAc.

*6,9-Dimethoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole (**5a**)* (0.112 g, 48%), R_f 0.35 (EtOAc); and *1,4,6,9-tetramethoxyphenazine (**6**)* (9 mg, 6%). Spectral data and melting points for **5a** and **6** were consistent with the above.

*5,8-Dimethoxy-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (**5d**)* (0.201 g, 92%); off-white solid; spectral data and melting point consistent with the literature.[14]

General Procedure for the Synthesis of Quinones 1 and 2.

Benzimidazole (0.26 mmol) and PIFA (0.447 g, 1.04 mmol) in H_2O (29 mL) and MeOH (0.75 mL) were stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography using gradient elution of petroleum ether/EtOAc and EtOAc/MeOH.

*3,4-Dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione (**1**)* (39 mg, 74%); yellow solid; R_f 0.41 (EtOAc); m.p. (decomp. >165 °C); ν_{max} (neat, cm^{-1}) 2924, 1664 (C=O), 1584, 1531, 1475, 1436, 1379, 1345, 1317, 1289, 1225, 1202, 1112, 1095, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.68 (AB_q, *J* = 10.4 Hz, 2H), 4.99 (s, 2H, 1-CH_2), 4.44 (t, *J* = 5.2 Hz, 2H), 4.14 (t, *J* = 5.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 180.9, 178.1 (both C=O), 148.0, 141.2 (both C), 136.6, 135.8 (both CH), 130.1 (C), 65.0 (1-CH_2), 63.3, 44.7 (both CH_2); HRMS (ESI) *m/z* $[M + H]^+$ $C_{10}H_9N_2O_3$ Calcd for 205.0613; Found 205.0623.

*1',2'-Dihydro-4'H-spiro[oxetane-3,3'-pyrido[1,2-a]benzimidazole]-6',9'-dione (**2**)* (49 mg, 78%); yellow oil; R_f 0.44 (1:10 MeOH/EtOAc); ν_{max} (neat, cm^{-1}) 2929, 1661 (C=O), 1510, 1487, 1446, 1350, 1270, 1202, 1132; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.62 (AB_q, *J* = 10.4 Hz, 2H), 4.56 (AB_q, *J* = 6.2 Hz, 4H, OCH_2), 4.38 (t, *J* = 6.2 Hz, 2H, 1'-CH_2), 3.32 (s, 2H, 4'-CH_2), 2.38 (t, *J* = 6.2 Hz, 2H, 2'-CH_2); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 181.1, 178.2 (both C=O), 151.9, 149.9 (both C), 136.5, 136.0 (both CH), 130.2 (C), 80.5 (OCH_2), 41.7 (1'-CH_2), 37.2 (C), 34.4 (4'-CH_2), 30.4 (2'-CH_2); HRMS (ESI) *m/z* $[M + H]^+$ $C_{13}H_{13}N_2O_3$ Calcd for 245.0926; Found 245.0923.

ASSOCIATED CONTENT

Supporting Information. The supporting information is available free of charge via http://pubs.acs.org at DOI: XXXXXXX. GC-MS, ^{1}H and ^{13}C NMR spectra, and crystallographic data (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: f.aldabbagh@kingston.ac.uk

Present Addresses

§ Department of Pharmacy, School of Life Sciences, Pharmacy and Chemistry, Kingston University, Penrhyn Road, Kingston upon Thames, KT1 2EE, UK.

Notes

The authors declare no competing financial interest.

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