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Synthesis of seven- and eight-membered [1,2-*a*] alicyclic ring-fused benzimidazoles and 3-aziridinylazepino[1,2-*a*]benzimidazolequinone as a potential antitumour agent

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ABSTRACT

Azepino and azocino[1,2-*a*]benzimidazoles were obtained either by treatment of 1-nitrophenyl-2-azacycloalkanes via a one-pot catalytic hydrogenation/acetylation or by treatment of the acetamides generated in the latter reaction with performic acid. This represents the first facile synthesis of eight-membered [1,2-*a*] alicyclic ring-fused benzimidazoles. 3-Methoxy-azepino[1,2-*a*]benzimidazole was elaborated to the novel potential cytotoxin, 3-(*N*-aziridinyl)-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole-1,4-dione. The synthesis included clarification of the reactivity of methoxy-substituted benzimidazoles towards nitration.

In 1990, Skibo and co-workers introduced pyrrolo[1,2-*a*]benzimidazolequinones (PBI) as a new class of bioreductive antitumour agents.[1–4] The 6-aziridinyl analogues were shown to be most cytotoxic against a variety of cancer cell lines (Fig. 1). Evidence for reductive activation of PBI to the hydroquinone was reported to lead to an intermediate that hydrogen bonds to the DNA major groove at the AT base pair with nucleophilic alkylation at the aziridine by the phosphate backbone of DNA resulting in hydrolytic strand cleavage.[1,3] More recently, our group has introduced [1,2-*a*] alicyclic ring-fused benzimidazolequinones with (e.g., **1** and **2**) and without an additional fused cyclopropane ring.[5–7] The cytotoxicity of these compounds towards human skin fibroblast cells was found to be in the nanomolar range (10^{-9} M) with cytotoxicity increasing under the hypoxic conditions associated with solid tumours.[6] Moreover, cyclopropapyrrolo[1,2-*a*]benzimidazolequinone **1** was shown to be more cytotoxic than six-membered analogue **2**. We now present the synthesis of novel 3-(*N*-aziridinyl)-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole-1,4-dione **3**, as part of our investigations into the variance of cytotoxicity with the size of the [1,2-*a*] alicyclic ring. The aziridine substituent in **3** is being investigated as an alkylating functionality towards cancerous cell DNA.

There are many reported synthetic approaches towards tricyclic five-, six- and seven-membered [1,2-*a*] alicyclic ring-fused benzimidazoles dating back to the 1950s.[1–4,6,8–22] The procedures can be categorized into the following cyclization protocols: (i) metal-catalyzed reduction of aromatic nitro groups to amines (or nitroso), which undergo acid-catalyzed cyclization onto adjacent azacycloalkanes;[1–4,9,11,13,14] (ii) nucleophilic displacement by the *N*-1 benzimidazole anion of halo substituents in 2-(ω-haloalkyl)benzimidazoles or generation of the benzimidazol-2-yl anion to undergo the inverse displacement reaction;[10,12,17,19] (iii) Rh-catalyzed reaction of *N*-alkenyl-1,2-diaminobenzene with H_2 and CO followed by annulation;[16] (iv) *N*-alkyl nucleophilic radical substitution onto the activated 2-position of benzimidazole;[6,18,21,22] and

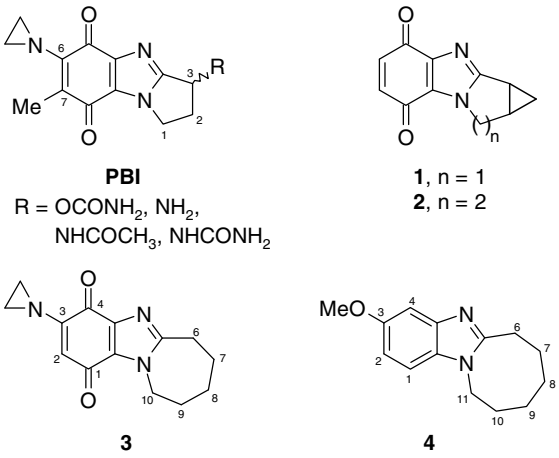

Figure 1.

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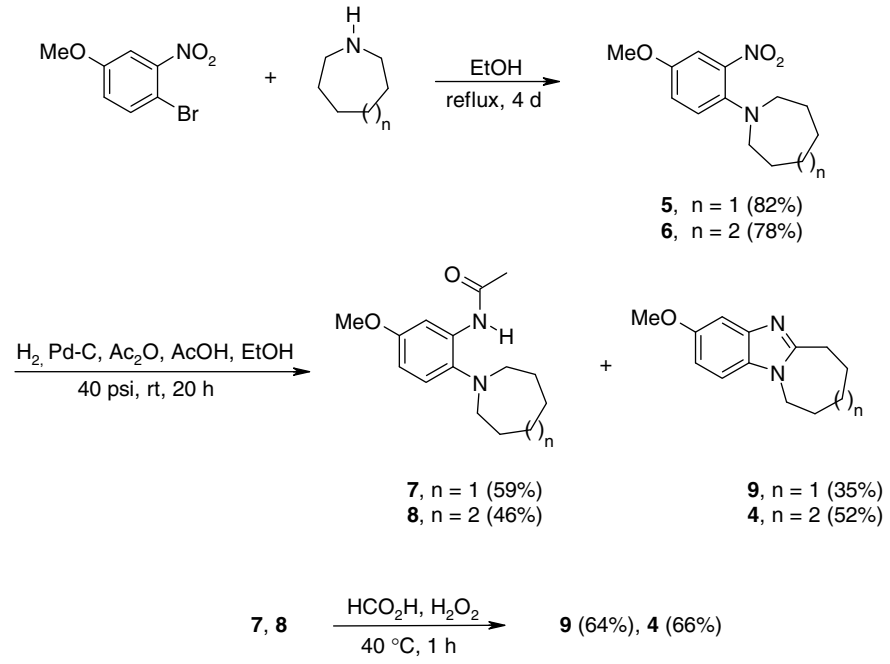
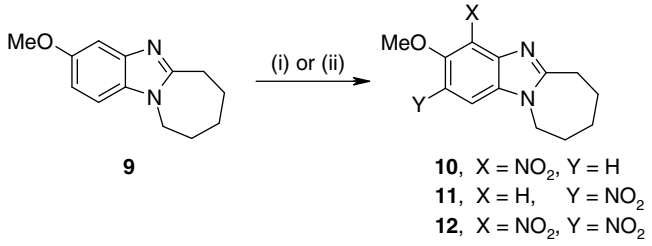


Scheme 1. Synthesis of azepino and azocino[1,2-*a*] alicyclic ring-fused benzimidazoles.

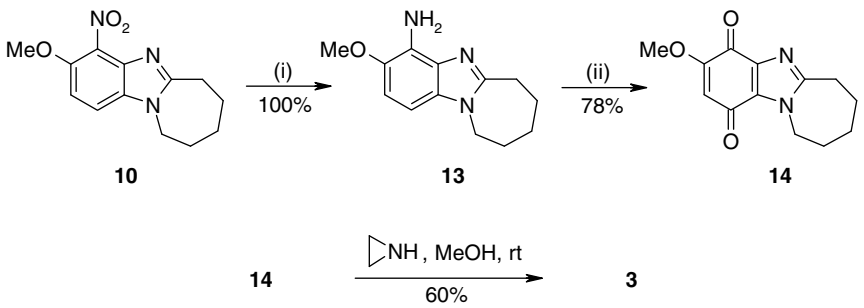
(v) *N*-nucleophilic anionic aromatic substitution using activated aromatic amidine analogues.[8,15,20] However, none of these synthetic approaches have thus far been reported to give eight-membered [1,2-*a*] alicyclic ring-fused benzimidazoles (e.g., **4**). Thus, we now report the efficient use of the annulation protocol in category (i) to give azepino and azocino[1,2-*a*]benzimidazoles. This outlines the versatility and simplicity of this approach to give alicyclic ring-fused benzimidazoles, and consequent elaboration to the benzimidazolequinone cytotoxins.

Alicyclic ring-fused benzimidazoles were prepared in three synthetic steps, according to Scheme 1. The first step involved nucleophilic substitution of the bromine atom in 4-bromo-3-nitroanisole by the cyclic amines, azepane and azocane ($n = 1$ and 2, respectively), by heating an ethanol solution under reflux for four days. 1-(4-Methoxy-2-nitrophenyl)azepane **5** was obtained in 82% yield directly after an aqueous/organic extraction, however, due to the less hydrophilic nature of azocane, purification by column chromatography was required to separate 1-(4-methoxy-2-nitrophenyl)azocane **6** in 78% yield. Preparation of acetamides **7** and **8** by one-pot catalytic hydrogenation and acetylation using H_2/Pd-C at 40 psi was carried out in respective yields of 59% and 46%. These relatively low yields for **7** and **8** were due to the unexpected simultaneous formation of the required ring closed adducts **9** and **4** in yields of 35% and 52%, respectively. It seems that the cyclization is more favourable when longer hydrogenation times and larger azacycloalkanes are used compared to the literature pyrrolidine and piperidine series.[2,9] The separated acetamides **7** and **8** were then treated with performic acid (generated in situ from HCO_2H, H_2O_2) to give azepino and azocino[1,2-*a*]benzimidazoles **9** and **4**[23] in ~65% yield. The mechanism for this cyclization probably involves oxidation to the iminium ion followed by nucleophilic attack by the adjacent acetamido nitrogen.[1,2]

Zhou and Skibo reported nitration at the 5-position (in 38% yield) when 6-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole was treated with fuming nitric acid using a salt-ice water bath for 5 min.[2] In our hands this procedure gave an almost equal mixture of two nitro isomers **10**[24] and **11** when using 3-methoxy-



Scheme 2. Reagents and conditions: (i) Fuming HNO_3, 0 °C, 7 min gave **10** (37%) and **11** (35%); (ii) 50:50 Fuming HNO_3: concd H_2SO_4, rt, 24 h gave **12** (74%).



Scheme 3. Reagents and conditions: (i) H_2, Pd-C, EtOH, 40 psi; (ii) Fremy oxidation, rt.

7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **9** as the substrate (Scheme 2). Furthermore, if the nitration time is increased or the traditional concentrated nitric/sulfuric acid mixture is used over a substantially longer reaction time period,[6] only the 2,4-dinitrated product **12** is obtained. This indicates that the reason for the low yields of the required nitro isomer both in our case and most probably in the literature example[2] was due to the activating nature of the methoxy substituent facilitating electrophilic nitration at both adjacent vacant positions.

Catalytic hydrogenation of **10** to the 4-amino adduct **13** followed by oxidation using Fremy oxidation gave benzimidazolequinone **14** in 78% yield (Scheme 3). It is noteworthy that this is the first time the intermediate aromatic amine in benzimidazolequinone forming reaction sequences has been successfully isolated and partially characterized.[25] Substitution of the 3-methoxy substituent of **14** by aziridine[2,26] gave target **3** in 60% yield.[27]

In conclusion, facile preparations of novel methoxy-substituted seven- and eight-membered [1,2-*a*] alicyclic ring-fused benzimidazoles have been accomplished, and the former converted to the 3-aziridinyl-substituted benzimidazolequinone. A full paper is in preparation describing the synthesis of other [1,2-*a*] alicyclic ring-fused benzimidazolequinones with associated biological activity results assessing the influence of ring size on cytotoxicity.

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23. *3-Methoxy-6,7,8,9,10,11-hexahydroazocino[1,2-a]benzimidazole* (**4**): A mixture of *N*-(2-azocan-1-yl-5-methoxyphenyl)acetamide **8** (0.640 g, 2.32 mmol), HCO_2H (95%, 3.2 ml) and H_2O_2 (30%, 1.6 ml) was stirred at 40 °C for 1 h. H_2O (10 ml) was added, and the mixture was neutralized using NH_4OH and extracted into $CHCl_3$ (3 × 25 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The resultant brown residue was purified by column chromatography using silica gel as absorbent with a gradient elution of EtOAc and MeOH to yield **4** (0.354 g, 66%) as a white solid. R_f 0.36 ($CHCl_3$–MeOH 95:5); mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.22–1.28 (m, 2H, 9-CH_2), 1.48–1.53 (m, 2H, 8-CH_2), 1.81–1.87 (m, 2H, 10-CH_2), 1.88–1.94 (m, 2H, 7-CH_2), 2.98 (t, *J* = 6.2 Hz, 2H, 6-CH_2), 3.84 (s, 3H, CH_3), 4.21 (t, *J* = 6.0 Hz, 2H, 11-CH_2), 6.85–6.88 (dd, *J* = 2.6 Hz, 8.7 Hz, 1H, 2-H), 7.15 (d, *J* = 8.7 Hz, 1H, 1-H), 7.20 (d, *J* = 2.6 Hz, 1H, 4-H) ppm; ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 23.80 (9-CH_2), 25.38 (8-CH_2), 26.86 (6-CH_2), 29.64 (10-CH_2), 31.11 (7-CH_2), 41.24 (11-CH_2), 55.69 (CH_3), 101.62 (4-CH), 109.36 (1-CH), 111.30 (2-CH), 128.93 (C), 143.47 (C), 155.83 (C), 156.67 (C) ppm;[28] IR (neat) 1031, 1111, 1151, 1202, 1340, 1414, 1442, 1489, 1620, 2858, 2925 cm^{-1}; *m/z* (CI) 231 ([M+H]$^+$, 100%); HRMS (ESI): found MH$^+$, 231.1495. $C_{14}H_{19}N_2O$ requires, 231.1497. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.73; H, 7.67; N, 12.42.
24. *3-Methoxy-4-nitro-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole* **10**: 3-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole **9** (0.100 g, 0.462 mmol) and fuming HNO_3 (1 ml) were stirred at 0 °C for 7 min. H_2O (10 ml) was added, the mixture neutralized using $NaHCO_3$ and extracted into $CHCl_3$ (2 × 25 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The resultant yellow residue was purified by column chromatography using silica gel as absorbent with EtOAc as eluent to yield **10** (45 mg, 37%) as a yellow solid. R_f 0.58 (EtOAc–MeOH 95:5); mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.77–1.86 (m, 4H, CH_2), 1.92–1.97 (m, 2H, CH_2), 3.12 (t, *J* = 5.5 Hz, 2H, 6-CH_2), 3.94 (s, 3H, CH_3), 4.13 (t, *J* = 4.8 Hz, 2H, 10-CH_2), 6.96 (d, *J* = 8.9 Hz, 1H, 2-H), 7.32 (d, *J* = 8.9 Hz, 1H, 1-H) ppm; ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 24.86 (CH_2), 28.17 (CH_2), 29.84 (6-CH_2), 30.37 (CH_2), 44.73 (10-CH_2), 57.56 (CH_3), 107.74 (2-CH), 112.06 (1-CH), 130.42 (C), 131.58 (C), 135.89 (C), 147.77 (C), 160.73 (Ar-5a-C) ppm;[28] IR (neat) 1095, 1157, 1198, 1221, 1238, 1276, 1325 (NO_2), 1358, 1414, 1438, 1468, 1486, 1507, 1523 (NO_2), 1591, 1634 cm^{-1}; Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.68; H, 6.17; N, 15.76. The second fraction eluted was *3-methoxy-2-nitro-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole* **11** (43 mg, 35%) as a yellow solid.
25. *4-Amino-3-methoxy-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole* **13**: A mixture of 3-methoxy-4-nitro-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]- benzimidazole **10** (90 mg, 0.344 mmol) and Pd-C (10%, 10 mg) in EtOH (50 ml) was agitated under 40 psi H_2 at 20 °C for 8 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness to yield **13** (80 mg, 100%) as a brown residue (not purified further). ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.69–1.76 (m, 4H, CH_2), 1.83–1.88 (m, 2H, CH_2), 3.00 (t, *J* = 5.5 Hz, 2H, 6-CH_2), 3.82 (s, 3H, CH_3), 3.99 (t, *J* = 4.8 Hz, 2H, 10-CH_2), 4.38 (bs, 2H, NH_2), 6.51 (d, *J* = 8.7 Hz, 1H, Ar-H), 6.82 (d, *J* = 8.7 Hz, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 25.73 (CH_2), 28.70 (CH_2), 30.05 (CH_2), 30.96 (CH_2) 44.56 (10-CH_2) 57.74 (CH_3), 96.53 (CH), 109.20 (CH), 127.67 (C), 131.49 (C), 131.86 (C), 141.09 (C), 156.29 (Ar-5a-C) ppm.
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27. *3-(N-Aziridinyl)-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole-1,4-dione* **3**: A mixture of 3-methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole-1,4-dione **14** (69 mg, 0.280 mmol) and ethyleneimine (0.78 ml, 14.56 mmol) in MeOH (11.0 ml) was stirred at rt for 2 h. The mixture was evaporated and the red residue was purified by column chromatography using silica gel as absorbent with $CHCl_3$ as eluent. The isolated red quinone was recrystallized from $CHCl_3$/hexane (9:1) to yield **3** (43 mg, 60%) as a red powder. R_f 0.52 ($CHCl_3$–MeOH 95:5); mp 175–177 °C (dec); ^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 1.67–1.73 (m, 2H, CH_2), 1.75–1.80 (m, 2H, CH_2), 1.85–1.91 (m, 2H, CH_2), 2.20 (s, 4H, aziridine-CH_2), 2.98 (t, *J* = 5.6 Hz, 2H, 6-CH_2), 4.54–4.61 (m, 2H, 10-CH_2), 5.75 (s, 1H, 2-H) ppm; ^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 24.88 (CH_2), 27.75 (aziridine CH_2), 28.12 (CH_2), 29.17 (6-CH_2), 30.70 (CH_2), 45.61 (10-CH_2), 116.04 (2-CH), 130.87 (C), 139.32 (C), 156.70 (C), 157.75 (C), 176.76 (C=O), 179.08 (C=O) ppm;[28] IR (neat) 1072, 1099, 1128, 1263, 1301, 1354, 1440, 1471, 1519, 1574, 1635 (C=O), 1678 (C=O) cm^{-1}; *m/z* (CI) 258 ([M+H]$^+$, 100%); HRMS (ESI): found MH$^+$, 258.1245. $C_{14}H_{16}N_3O_2$ requires, 258.1243; Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.34; H, 5.88; N, 16.34. Found: C, 65.64; H, 5.51; N, 16.85.
28. Assignments for compounds **3**, **4** and **10** are supported by HMQC ^{1}H-^{13}C NMR 2D spectra. A 2D COSY ^{1}H-^{1}H NMR correlation was also carried out on compound **4**.