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Synthesis of dimethyl substituted benzimidazoles containing cyclopropane fused onto five to eight membered [1,2-*a*]alicyclic rings and influence of methyl group substituents on cytotoxicity of benzimidazolequinones

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Abstract

Upon thermolysis 5,6-dimethyl-*N*-[(allyl, but-3-enyl, pent-4-enyl and hex-5-enyl-benzimidazol-2-yl)methylene]-(*trans*)-2,3-diphenyl-aziridin-1-amines (Eschenmoser hydrazones) form cyclopropane fused onto pyrrolo-, pyrido-, azepino- and azocino[1,2-*a*]benzimidazoles in 70, 50, 77 and 11% yield, respectively. The latter reaction also gave carbene insertion products. Dimethyl group substituents were found to significantly reduce the cytotoxicity of benzimidazolequinone towards human skin fibroblast cells.

Keywords: Antitumor agents; Aziridinylimines; Cycloaddition; Heterocycles

1. Introduction

Hypoxic cells form a significant part of solid tumours.[1] These O_2-deficient cells are slow to divide, and become resistant to conventional cancer treatments including, radiation, chemotherapy (medicines), surgery or combinations of these treatments. We are interested in preparing [1,2-*a*]alicyclic ring fused benzimidazolequinones that exhibit selective cytotoxicity towards hypoxic cells.[2] Among the compounds we recently reported were cyclopropa[3,4]pyrrolo[1,2-*a*]benzimidazole-3,6-dione **1** and cyclopropa[3,4]pyrido[1,2-*a*]benzimidazole-5,8-dione **2** (Fig. 1), which were found to possess cytotoxicity towards human skin fibroblast cells in the nanomolar (10^{-9} M) range, as determined using the MTT assay.[2–4] This work was inspired by Moody's work on cyclopropamitosene (CPM), the cyclopropane analogue of aziridinomitosene {formed after reductive activation of mitomycin C (MMC, Fig. 1)}.[5–9] CPM was reported to be 34 times more cytotoxic under hypoxic than oxygenated conditions, while the clinically used antitumour agent MMC showed only a two-fold increase in cytotoxicity under hypoxic conditions.[7,8] The main reason given for the greater selectivity towards hypoxia was CPM (E_{redox} vs Fc (DMF)=−1.395 V) being more easily reduced than MMC (E_{redox} vs Fc (DMF)=−1.421 V).[8] Moreover, the benzimidazolequinones **1** (E_{redox} vs Fc (DMF)=−1.052 V) and **2** (E_{redox} vs Fc

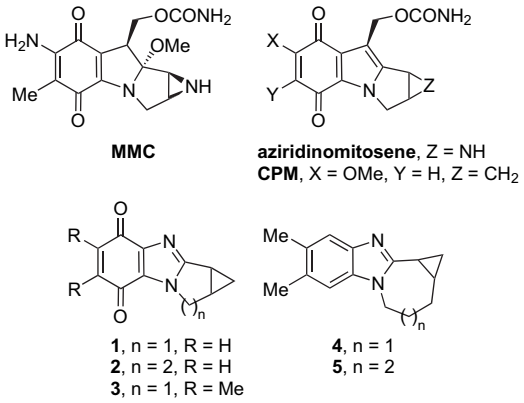

Figure 1. Bioreductive anti-tumour agents and target compounds.

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(DMF)=−1.074 V) are more easily reduced than both indolequinones MMC and CPM, which may be a reason for their significantly greater cytotoxicity.[2–4]

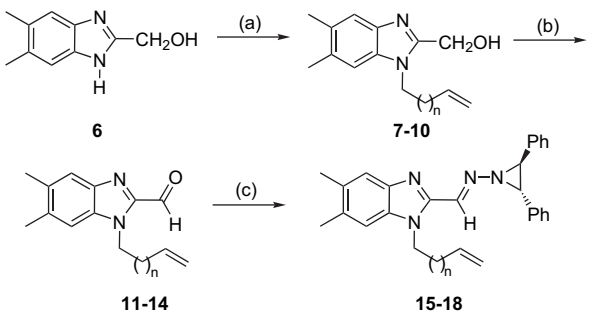
Under hypoxic conditions, reversible single electron reduction of CPM or the benzimidazolequinone analogues leads to the formation of reactive semi-quinone radical anions that are speculated to induce ring-opening of the cyclopropane ring.[7–9] The cytotoxic effect is then thought to be induced by hydrogen abstraction from DNA leading to strand cleavage. The reductive potential and thus the subsequent cytotoxicity can be modified by incorporating substituents on the oxidising quinone moiety. Since **1** is more selective towards hypoxic conditions than **2**,[2] we decided to investigate the effect of inductively electron donating 4,5-dimethyl substituents on the cytotoxicity of cyclopropapyrrolo[1,2-*a*]benzimidazolequinone. This paper includes the synthesis of 4,5-dimethylcyclopropa[3,4]pyrrolo[1,2-*a*]benzimidazole-3,6-dione **3** and its cytotoxicity assays under aerobic and hypoxic conditions.

The methodology used to form pyrrolo and pyrido[1,2-*a*]benzimidazoles containing a fused cyclopropane ring involved synthesis of *N*-aziridinyl imines (Eschenmoser hydrazones)[3,4,10] and their subsequent thermolysis to diazomethines. Such reactive intermediates can undergo intramolecular 1,3-dipolar cycloaddition to give [3+2] pyrazoline cycloadducts.[3–5,11] The latter eliminate nitrogen on further heating to give the fused cyclopropane. Regitz et al.[12] reported 7-alkoxy-5-(diazomethyl)-5*H*-benzocycloheptenes, which gave pyrazoline cycloadducts that were homolyzed in xylene under reflux to the cyclopropane fused compounds. However, to the best of our knowledge, cycloaddition to give respective three-membered rings fused onto seven and eight membered alicyclic rings from the decomposition of arene-*N*-aziridinyl imines[3–5,11,13,14] or arenesulfonylhydrazones[5,6,9,11,13,15,16] has never been carried out. We now report thermolysis of Eschenmoser hydrazones to form new tetracyclic ring systems, azepino and azocino[1,2-*a*]benzimidazoles **4** and **5** containing a fused cyclopropane ring (Fig. 1).

2. Results and discussion

2.1. Synthesis of dimethyl substituted [1,2-a]alicyclic ring fused benzimidazoles

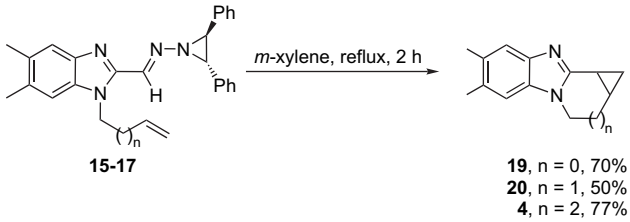
Synthesis of 5,6-dimethylbenzimidazole-2-hydrazone cycloaddition precursors involved N-alkylation of 5,6-dimethylbenzimidazole-2-methanol **6** using triethylamine and alkenyl halides in DMF. Although this reaction under optimised conditions only gave 5,6-dimethyl(*N*-alken-ω-enyl)-benzimidazole-2-methanols **7**–**10** in 35–46% yield, multigram syntheses of **7**–**10** were achieved (Scheme 1). Prior TBDMS protection of the alcohol substituent was found not to be viable, as previously reported on the unsubstituted benzimidazole-2-methanol[4] due to the insolubility of **6** in THF and nearly all common organic solvents. Oxidation of alcohols **7**–**10** to aldehydes **11**–**14** was efficiently carried out using manganese dioxide in CH_2Cl_2 in yields greater than 70%. Condensation with 1-amino-*trans*-2,3-diphenylaziridine gave 5,6-dimethyl-*N*-[(alk-ω-enylbenzimidazol-2-yl)-methylene]-*trans*-2,3-diphenylaziridin-1-amines (Eschenmoser hydrazones) **15**–**18** in good yields of 66–89%.



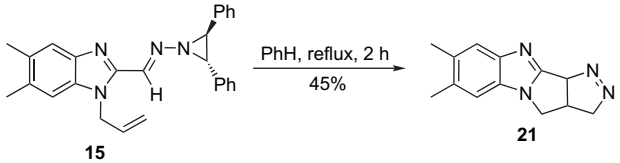
Scheme 1. Synthesis of Eschenmoser hydrazones: (a) Et_3N (2 equiv), $XCH_2(CH_2)_nCH{=}CH_2$ (1.2 equiv), DMF, reflux, 4 h, for compound **7**, *n*=0, X=I, yield=46%, for compound **8**, *n*=1, X=Br, yield=35%, for compound **9**, *n*=2, X=Br, yield=45% and for compound **10**, *n*=3, X=Br, yield=37%; (b) MnO_2 (~30 equiv), CH_2Cl_2, reflux, 30 min, for compound **11**, *n*=0, yield=75%, for compound **12**, *n*=1, yield=71%, for compound **13**, *n*=2, yield=76% and for compound **14**, *n*=3, yield=73%; (c) 1-amino-*trans*-2,3-diphenylaziridine (1 equiv), Et_2O, 0 °C, 8.5 h, for compound **15**, *n*=0, yield=84%, for compound **16**, *n*=1, yield=66%, for compound **17**, *n*=2, yield=72% and for compound **18**, *n*=3, yield=89%.

Thermolysis of Eschenmoser hydrazones **15** and **16** in xylene under reflux, respectively, gave cyclopropapyrrolo[1,2-*a*]benzimidazole **19** and cyclopropapyrido[1,2-*a*]benzimidazole **20** in yields of 70 and 50% (Scheme 2). In line with our previous observations into the thermolysis of benzimidazole-2-Eschenmoser hydrazones lacking aromatic methyl substituents,[3,4] thermolysis of **15** at lower temperatures (in benzene under reflux) resulted in the isolation of 1,3-dipolar [3+2] pyrazoline cycloadduct **21** in 45% yield (Scheme 3), which decomposed to the cyclopropane **19** at higher temperatures (xylene under reflux). However, possibly for reasons previously discussed,[4] hydrazone **16** decomposed to directly give cyclopropane **20** (in 50% yield) even under the mild conditions of boiling CH_2Cl_2.

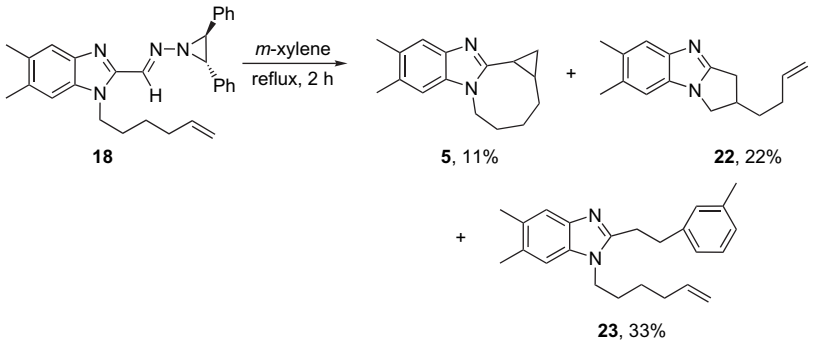
Recently, we reported[2] that cytotoxicity varies with ring size with respect to cyclopropapyrrolo[1,2-*a*]benzimidazolequinone **1** and the six-membered alicyclic ring fused analogue **2** under hypoxic conditions making the synthesis of further



Scheme 2. Isolated yields of cycloadducts from thermolysis of Eschenmoser hydrazones.



Scheme 3. [3+2] Pyrazoline cycloadduct isolated at lower temperature.

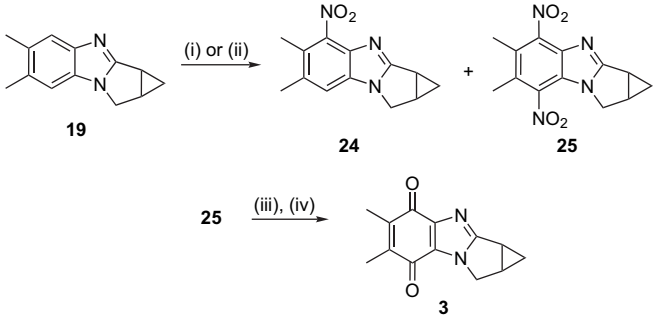


Scheme 4. Isolated yields of products formed from the thermolysis of *N*-hex-5-enyl Eschenmoser hydrazone **18**.

ring expanded [1,2-*a*]alicyclic ring fused benzimidazoles a worthwhile endeavour. This led us to prepare Eschenmoser hydrazones **17** and **18**, and to investigate their thermolysis in *m*-xylene under reflux. Scheme 2 shows that the formation of 7,8-dimethylcyclopropa[3,4]azepino[1,2-*a*]benzimidazole **4** occurred remarkably efficiently in higher yield (77%) than the formation of the respective 5:3 and 6:3 adducts **19** and **20**. Thermolysis of hydrazone **18** in *m*-xylene under reflux gave the impressive 8:3 macrocyclic system, cyclopropa-[3,4]azocino[1,2-*a*]benzimidazole **5** albeit in a poor yield of 11%, with products of intramolecular **22** and intermolecular **23** benzimidazolyl-2-carbenyl CH-insertion reactions formed in, respectively, higher yields of 22 and 33% (Scheme 4). Literature solvent CH-insertions are known, and occur when intramolecular diazomethine cycloaddition is less favoured,[13] which accounts for the formation of *m*-xylene adduct **23**. The formation of 1,5-CH-insertion adduct **22** is perhaps expected given that this reaction pathway accounts for the major products in the thermolysis of diazocyclooctane and diazocyclononane.[17]

2.2. Synthesis of 4,5-dimethylcyclopropa[3,4]pyrrolo-[1,2-a]benzimidazole-3,6-dione 3

The presence of 4,5-dimethyl substituents on the fused benzene part allowed conversion of **19** into benzimidazolequinone **3** by a nitration, reduction and oxidation sequence.[2]



Scheme 5. Preparation of benzimidazolequinone **3**: (i) 50:50 mixture of concd HNO_3 and concd H_2SO_4, 6 h, yield=14 and 46% for compounds **24** and **25**, respectively; (ii) 50:50 mixture of concd HNO_3 and concd H_2SO_4, 12 h, yield=0 and 79% for compounds **24** and **25**, respectively; (iii) PtO_2, H_2, 40 psi, EtOH, 17 h; (iv) $FeCl_3$ (aq), rt, 12 h, yield=76% for compound **3**.

Nitration for 6 h using mixtures of concd nitric and sulfuric acid gave a mixture of mono and dinitro derivatives **24** and **25** in 14 and 46% yield, respectively (Scheme 5). Increasing the reaction time to 12 h gave **25** selectively in 79% yield, which was reduced to the diamine in situ and oxidised with ferric chloride to **3** in good yield of 76%.

2.3. Influence of methyl substituents on cytotoxicity of benzimidazolequinones

4,5-Dimethylcyclopropapyrrolo[1,2-*a*]benzimidazolequinone **3** (IC_{50}=6.3 μmol dm^{-3}, ±0.7 μmol dm^{-3}) was found to be nearly one thousand times less cytotoxic than **1** (IC_{50}=0.0069 μmol dm^{-3}, ±0.0003 μmol dm^{-3})[2] towards human skin fibroblast GM00637 cells. The cytotoxicity of **3** was closer to that of MMC (IC_{50}=0.9 μmol dm^{-3}) using the same assay.[2] While, the potency of **1** almost tripled, the cytotoxicity of **3** did not vary significantly under hypoxic conditions (Fig. 2). The inductive donation of the methyl substituents into the oxidising quinone moiety of **3** will lead to a more negative reductive potential,[2] seemingly decreasing the rate of conversion of the prodrug quinone to the reductively activated biologically active forms. Similarly, the

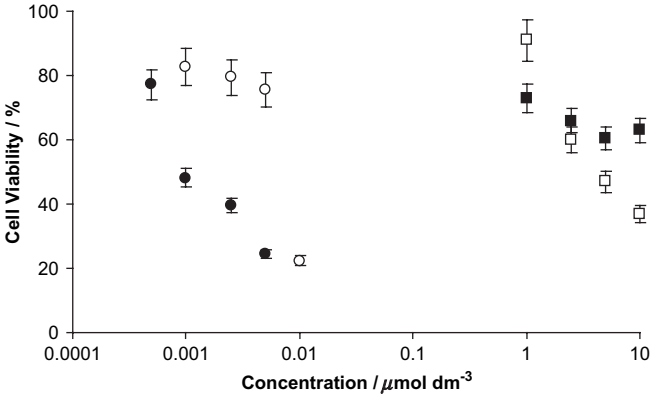


Figure 2. Cytotoxicity measurements using the MTT assay (shown using a logarithmic scale for concentration) on human skin fibroblast cells following treatment with cyclopropapyrrolo[1,2-*a*]benzimidazolequinone **1** (●, ○) and 4,5-dimethyl analogue **3** (■, □) under aerobic (open symbols) and hypoxic conditions (closed symbols) for 24 h at 37 °C. Each data point represents the mean of at least three independent experiments.

cytotoxicity and selectivity towards hypoxia of pyrido [1,2-*a*]benzimidazolequinones was previously found to be significantly decreased by the presence of 7,8-dimethyl substituents.[2] These results support the analogy of single electron reducing enzymes such as NADPH-cytochrome *c* reductase being involved in biological activity.[2,8,18]

3. Conclusion

5,6-Dimethyl-*N*-[(alk-ω-enylbenzimidazol-2-yl)-methylene]-*trans*-2,3-diphenylaziridin-1-amines (Eschenmoser hydrazones) are shown to be valuable precursors for the preparation of five, six and seven membered [1,2-*a*]alicyclic ring fused benzimidazoles containing a fused cyclopropane ring. Thermolysis of 5,6-dimethyl-*N*-[(hex-5-enyl-benzimidazol-2-yl)-methylene]-*trans*-2,3-diphenylaziridin-1-amine gave cyclopropane fused onto an eight membered [1,2-*a*]alicyclic ring as the minor product with the formation of benzimidazolyl-2-carbenyl CH-insertion products given in higher yields. Nitration, reduction and oxidation of 4,5-dimethylcyclopropapyrrolo[1,2-*a*]benzimidazole to the benzimidazolequinone is a facile process. Dimethyl substituents on the benzimidazolequinones were found to significantly reduce cytotoxicity towards human skin cells and selectivity to those grown under hypoxic conditions, which are found inside solid tumours.

4. Experimental

4.1. General

All Chemicals were purchased from Sigma–Aldrich and reactions were carried out in freshly dried and distilled solvents. Flash column and thin layer chromatography were, respectively, carried out using Merck silica gel 60, 234–40 mesh as absorbent and aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}).

Melting points were determined on a Stuart melting point apparatus and are uncorrected. IR spectra were determined on a Perkin–Elmer Spectrum 1000 FT-IR spectrophotometer with ATR accessory. ^{1}H NMR (399.8 Hz) and ^{13}C NMR (100.5 Hz) spectra were recorded in $CDCl_3$, unless otherwise stated and measured on a JEOL GXFT 400 MHz instrument. Data are expressed in parts per million downfield from $SiMe_4$ as internal standard or relative to $CHCl_3$. All *J* values are given in hertz. Assignments were supported by HMQC ^{1}H–^{13}C NMR 2D spectra for compounds **3**–**5**, **21** and **22** and DEPT for compounds **4**–**8**, **13**, **15**, **18** and **20**–**25**. NMR assignments for compounds **19** and **24** are based on those previously reported for 1,1a,8,8a-tetrahydrocyclopropa[3,4]-pyrrolo[1,2-*a*]benzimidazole[4] and 7,8-dimethyl-6-nitro-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole,[2] respectively. X-ray crystal data for 3,3a,4,10b-tetrahydropyrazolo[3′,4′:3,4]-pyrrlo[1,2-*a*]benzimidazole was used to support the structure of **21**.[3] High resolution mass spectra were obtained on the Finnigan MAT 900 XLT with accurate mass obtained by manual peak matching using electrospray ionisation (ESI, ES^{+}) from the EPSRC National Mass Spectrometry Service (University of Swansea). Electron impact (EI, EI^{+}) and chemical ionisation (CI, CI^{+}) mass spectra for compounds **11**–**14** and **20** were obtained on a Micro Mass GTC spectrometer and all elemental analyses were carried out on Perkin–Elmer 2400 Series II analyzer at NUI, Galway. Hydrazones **15**–**18** were stable when stored in a freezer, but degraded within hours at room temperature hence elemental analysis or HRMS were not obtained.

4.2. 5,6-Dimethylbenzimidazole-2-methanol **6**

4,5-Diamino-*o*-xylene (10.00 g, 73 mmol) and glycolic acid (8.32 g, 0.109 mol) in 4 M HCl (150 mL) were heated under reflux for 1 h. The reaction mixture was filtered, and basified with 6 M NH_4OH until a precipitate was formed, which was recrystallised twice from MeOH to give **6** (7.76 g, 60%), as a buff solid; mp 244–246 °C, dec (mp[19] 244 °C, dec); δ_H (CD_3OD) 2.43 (s, 6H, CH_3), 5.15 (s, 2H, CH_2), 7.54 (s, 2H, Ar–H), OH and NH not observed; δ_C (CD_3OD) 20.4 (2×CH_3), 56.6 (CH_2), 114.5, 131.0, 137.3.

4.3. General procedure for the synthesis of 5,6-dimethyl-(*N*-alken-ω-enyl)benzimidazole-2-methanols

4.3.1. (1-Allyl-5,6-dimethyl-1*H*-benzimidazol-2-yl)-methanol **7**

Triethylamine (7.8 mL, 56 mmol) was added to a stirring solution of **6** (5.00 g, 28 mmol) in DMF (60 mL) and the mixture heated under reflux for 1 h. Allyl iodide (3.1 mL, 34 mmol) was added and the solution heated under reflux for 3 h. The reaction mixture was cooled and H_2O added (7 mL). The aqueous mixture was extracted into EtOAc (3×20 mL), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography using silica gel as absorbent with gradient elution using hexane and EtOAc as eluent to give **7** (2.78 g, 46%), as a pale brown solid; R_f 0.16 (EtOAc); mp 156–157 °C. ν_{max}/cm^{-1} 3126 (OH), 2855, 1477, 1411, 1341, 1036, 1000; δ_H 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.78–4.82 (m, 4H, NCH_2 and CH_2OH), 4.97 (d, 1H, *J* 17.0, 3′-*trans*-H), 5.17 (d, 1H, *J* 11.2, 3′-*cis*-H), 5.91–6.00 (m, 1H, 2′-H), 7.01 (s, 1H, 7-H), 7.42 (s, 1H, 4-H), OH not observed; δ_C 20.3 (CH_3), 20.7 (CH_3), 45.9 (NCH_2), 56.9 (CH_2OH), 110.1 (7-CH), 117.3 (3′-CH_2), 119.5 (4-CH), 131.3 (C), 132.0 (C), 132.2 (2′-CH), 133.3 (C), 139.6 (C), 153.0 (Im-2-C). Anal. Calcd for $C_{13}H_{16}N_2O$ (%): C, 72.2; H, 7.5; N, 12.9. Found (%): C, 71.9; H, 7.6; N, 12.8.

4.3.2. (1-But-3-enyl-5,6-dimethyl-1*H*-benzimidazol-2-yl)methanol **8**

Triethylamine (7.8 mL, 56 mmol), **6** (5.00 g, 28 mmol) and 4-bromo-1-butene (3.5 mL, 34 mmol) in DMF (60 mL) gave **8** (2.30 g, 35%), as a pale brown solid; R_f 0.25 (EtOAc); mp 126–127 °C. ν_{max}/cm^{-1} 3079 (OH), 2847, 1479, 1413, 1354, 1330, 1052; δ_H 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.54–2.59 (m, 2H, 2′-CH_2), 4.23 (t, *J* 7.5, 2H, NCH_2), 4.80 (s, 2H, CH_2OH), 5.03–5.07 (m, 2H, 4′-CH_2), 5.75–5.83 (m, 1H, 3′-H), 7.05 (s, 1H, 7-H), 7.42 (s, 1H, 4-H), OH not

observed; δ_C 20.3 (CH_3), 20.7 (CH_3), 34.1 (2′-CH_2), 43.4 (NCH_2), 56.8 (CH_2OH), 110.0 (7-CH), 118.1 (4′-CH_2), 119.4 (4-CH), 131.2 (C), 132.1 (C), 133.5 (3′-CH), 134.0 (C), 140.2 (C), 153.1 (Im-2-C). Anal. Calcd for $C_{14}H_{18}N_2O$ (%): C, 73.0; H, 7.8; N, 12.1. Found (%): C, 73.1; H, 7.8; N 12.1.

4.3.3. (1-Pent-4-enyl-5,6-dimethyl-1H-benzimidazol-2-yl)methanol ***9***

Triethylamine (7.8 mL, 56 mmol), **6** (5.00 g, 28 mmol) and 5-bromo-1-pentene (4.0 mL, 34 mmol) in DMF (60 mL) gave **9** (3.10 g, 45%), as a pale brown solid; R_f 0.21 (EtOAc); mp 121–122 °C. ν_{max}/cm^{-1} 3137 (OH), 2923, 2853, 1482, 1465, 1430, 1349, 1211, 998, 972; δ_H 1.89–1.96 (m, 2H, CH_2), 2.10–2.16 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.17 (t, 2H, *J* 7.5, NCH_2), 4.79 (s, 2H, CH_2OH), 5.02–5.08 (m, 2H, 5′-CH_2), 5.76–5.86 (m, 1H, 4′-H), 7.03 (s, 1H, 7-H), 7.39 (s, 1H, 4-H), OH not observed; δ_C 20.3 (CH_3), 20.7 (CH_3), 28.9, 30.9 (both CH_2), 43.4 (NCH_2), 56.9 (CH_2OH), 110.0 (7-CH), 115.9 (5′-CH_2), 119.5 (4-CH), 131.2, 132.1, 133.8 (all C), 137.1 (4′-CH), 140.3 (C), 152.9 (Im-2-C). Anal. Calcd for $C_{15}H_{20}N_2O$ (%): C, 73.7; H, 8.2; N, 11.4. Found (%): C, 73.6; H, 8.2; N, 11.1.

4.3.4. (1-Hex-5-enyl-5,6-dimethyl-1H-benzimidazol-2-yl)methanol ***10***

Triethylamine (7.8 mL, 56 mmol), **6** (5.00 g, 28 mmol) and 6-bromo-1-hexene (4.5 mL, 34 mmol) in DMF (6 mL) gave **10** (2.70 g, 37%), as a pale brown solid; R_f 0.43 (EtOAc/10%MeOH); mp 88–89 °C. ν_{max}/cm^{-1} 3144, 2917, 2853, 1512, 1481, 1432, 1356, 1327, 1228, 998; δ_H 1.43–1.50 (m, 2H, 3′-CH_2), 1.81–1.85 (m, 2H, 2′-CH_2), 2.05–2.15 (m, 2H, 4′-CH_2), 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.17 (t, *J* 7.5, 2H, NCH_2), 4.79 (s, 2H, CH_2OH), 4.97–5.02 (m, 2H, 6′-CH_2), 5.72–5.79 (m, 1H, 5′-H), 7.03 (s, 1H, 7-H), 7.40 (s, 1H, 4-H), OH peak not observed; δ_C 20.1 (CH_3), 20.5 (CH_3), 26.1, 29.3, 33.2 (all CH_2), 43.7 (NCH_2), 56.0 (CH_2OH), 110.0 (7-CH), 115.0 (6′-CH_2), 119.1 (4-CH), 131.0, 132.0, 133.4 (all C), 138.0 (5′-CH), 140.0 (C), 153.0 (Im-2-C). Anal. Calcd for $C_{16}H_{22}N_2O$ (%): C, 74.4; H, 8.6; N, 10.8. Found (%): C, 74.2; H, 8.8; N, 10.5.

4.4. General procedure for the synthesis of 5,6-dimethyl-(N-alken-ω-enyl)benzimidazole-2-carbaldehydes

4.4.1. 1-Allyl-5,6-dimethyl-1H-benzimidazole-2-carbaldehyde ***11***

Alcohol **7** (1.20 g, 5.5 mmol) and activated MnO_2 (14.50 g, 0.166 mol) were stirred and heated under reflux in CH_2Cl_2 (1000 mL) for 0.5 h. The cooled reaction mixture was filtered and the filtrate was evaporated to dryness to give **11** (0.91 g, 75%), as a yellow solid; R_f 0.49 (CH_2Cl_2); mp 87–88 °C. ν_{max}/cm^{-1} 1682 (CHO), 1483, 1454, 1412, 1327, 1235, 1008, 964, 920; δ_H 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.97 (d, 1H, *J* 16.2, 3′-*trans*-H), 5.12–5.16 (m, 3H, 3′-*cis*-H and NCH_2), 5.90–5.95 (m, 1H, 2′-H), 7.17 (s, 1H, 7-H), 7.63 (s, 1H, 4-H), 10.02 (s, 1H, CHO); δ_C 20.5 (CH_3), 21.2 (CH_3), 46.8 (NCH_2), 110.8 (7-CH), 117.4 (3′-CH_2), 121.9 (4-CH), 132.2 (C), 133.9 (2′-CH), 135.2 (C), 137.4 (C), 141.8 (C), 145.3 (Im-2-C), 184.6 (CHO); *m/z* (EI) 214 (M^+, 20%), 185 (100), 121 (42); HRMS (EI): found M^+, 214.1102. $C_{13}H_{14}N_2O$ requires, 214.1106.

4.4.2. 1-But-3-enyl-5,6-dimethyl-1H-benzimidazole-2-carbaldehyde ***12***

Alcohol **8** (0.150 g, 0.65 mmol) and activated MnO_2 (1.69 g, 19.5 mmol) in CH_2Cl_2 (150 mL) gave **12** (0.105 g, 71%), as a yellow solid; R_f 0.64 (EtOAc); mp 88–90 °C. ν_{max}/cm^{-1} 1696 (C=O), 1484, 1467, 1440, 1413, 1364, 1221, 999, 930; δ_H 2.41 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.56–2.60 (m, 2H, 2′-CH_2), 4.64 (t, *J* 7.2, 2H, NCH_2), 4.99–5.02 (m, 2H, 4′-CH_2), 5.74–5.82 (m, 1H, 3′-H), 7.22 (s, 1H, 7-H), 7.66 (s, 1H, 4-H), 10.05 (s, 1H, CHO); δ_C 20.4 (CH_3), 21.1 (CH_3), 34.5 (2′-CH_2), 44.0 (NCH_2), 110.6 (7-CH), 118.0, 121.8, 133.7 (3′-CH and C), 135.1, 137.2, 141.7 (all C), 145.5 (Im-2-C), 184.7 (CHO); *m/z* (EI) 228 (M^+, 100%); HRMS (EI): found M^+, 228.1267. $C_{14}H_{16}N_2O$ requires, 228.1263.

4.4.3. 1-Pent-4-en-1-yl-5,6-dimethyl-1H-benzimidazole-2-carbaldehyde ***13***

Alcohol **9** (0.200 g, 0.81 mmol) and activated MnO_2 (2.11 g, 24.3 mmol) in CH_2Cl_2 (160 mL) gave **13** (0.150 g, 76%), as a yellow solid; R_f 0.28 (CH_2Cl_2); mp 89–90 °C. ν_{max}/cm^{-1} 2845, 1690 (C=O), 1486, 1468, 1413, 1360, 1264, 1003, 917; δ_H 1.89–1.95 (m, 2H, 2′-CH_2), 2.09–2.14 (m, 2H, 3′-CH_2), 2.39 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.55 (t, *J* 7.5, 2H, NCH_2), 5.00–5.06 (m, 2H, 5′-CH_2), 5.77–5.84 (m, 1H, 4′-H), 7.21 (s, 1H, 7-H), 7.65 (s, 1H, 4-H), 10.04 (s, 1H, CHO); δ_C 20.3 (CH_3), 21.1 (CH_3), 29.3, 30.7 (both CH_2), 44.2 (NCH_2), 110.5 (7-CH), 115.6 (5′-CH_2), 121.7 (4-CH), 133.6, 135.1, 137.0 (all C), 137.1 (4′-CH), 141.7 (C), 145.4 (Im-2-C), 184.5 (CHO); *m/z* (EI) 242 (M^+, 100%), 227 (8); HRMS (EI): found M^+, 242.1417. $C_{15}H_{18}N_2O$ requires, 242.1419.

4.4.4. 1-Hex-5-en-1-yl-5,6-dimethyl-1H-benzimidazole-2-carbaldehyde ***14***

Alcohol **10** (0.250 g, 0.97 mmol) and activated manganese dioxide (2.61 g, 30.0 mmol) in CH_2Cl_2 (180 mL) gave **14** (0.180 g, 73%), as a yellow solid; R_f 0.37 (50:50 hexane/Et_2O); mp 95–96 °C. ν_{max}/cm^{-1} 2939, 2859, 1678 (C=O), 1485, 1468, 1413, 1248, 1184, 998; δ_H 1.39–1.46 (m, 2H, 3′-CH_2), 1.78–1.85 (m, 2H, 2′-CH_2), 2.02–2.08 (m, 2H, 4′-CH_2), 2.43 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.57 (t, *J* 7.4, 2H, NCH_2), 4.96–5.02 (m, 2H, 6′-CH_2), 5.70–5.80 (m, 1H, 5′-H), 7.22 (s, 1H, 7-H), 7.66 (s, 1H, 4-H), 10.05 (s, 1H, CHO); δ_C 20.1 (CH_3), 21.1 (CH_3), 25.9, 29.7, 33.2 (all CH_2), 44.6 (NCH_2), 110.6 (7-CH), 115.0 (6′-CH_2), 121.8 (4-CH), 133.7, 135.2, 137.2 (all C), 138.0 (5′-CH), 141.1 (C), 145.8 (Im-2-C), 184.6 (CHO); *m/z* (EI) 256 (M^+, 100%); HRMS (EI): found M^+, 256.1574. $C_{16}H_{20}N_2O$ requires, 256.1576.

4.5. General procedure for the synthesis of 5,6-dimethyl-N-[(alk-ω-enyl-benzimidazol-2-yl)-methylene]-trans-2,3-diphenylaziridin-1-amines (Eschenmoser hydrazones)

4.5.1. N-[(Allyl-5,6-dimethyl-1H-benzimidazol-2-yl)-methylene]-(trans)-2,3-diphenylaziridin-1-amine **15**

1-Amino-*trans*-2,3-diphenylaziridine (97 mg, 0.46 mmol) was added to a solution of aldehyde **11** (0.100 g, 0.46 mmol) in Et_2O (7 mL), and the mixture was stirred at 0 °C for 8.5 h. The solution was evaporated to dryness and the residue was purified by column chromatography using silica gel as absorbent with hexane and Et_2O as eluent to give **15** (0.160 g, 84%), as a white solid; R_f 0.43 (60:40 hexane/Et_2O); mp 126–127 °C. ν_{max}/cm^{-1} 2972, 1618, 1492, 1449, 1411, 1327, 1155, 1008, 964, 920; δ_H 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.79 (s, 2H, aziridine-H), 4.75 (d, *J* 17.1, 1H, 3′-*trans*-H), 4.82–4.86 (m, 2H, NCH_2), 5.00 (d, *J* 10.3, 1H, 3′-*cis*-H), 5.56–5.68 (m, 1H, 2′-H), 7.02 (s, 1H, 7-H), 7.27–7.48 (m, 10H, Ph–H), 7.51 (s, 1H, 4-H), 8.43 (s, 1H, CH=N); δ_C 20.2 (CH_3), 20.9 (CH_3), 47.0 (NCH_2 and aziridine-CH), 110.3 (7-CH), 116.4 (3′-CH_2), 120.4 (4-CH), 126.4, 127.7, 127.9, 128.5, 128.8 (all CH), 132.3 (C), 132.8 (2′-CH), 134.2, 135.1, 141.8 (all C), 145.4 (Im-2-C), 151.7 (CH=N).

4.5.2. N-[(But-3-enyl-5,6-dimethyl-1H-benzimidazol-2-yl)-methylene]-trans-2,3-diphenylaziridin-1-amine **16**

1-Amino-*trans*-2,3-diphenylaziridine (0.130 g, 0.61 mmol) and aldehyde **12** (0.140 g, 0.61 mmol) in Et_2O (10 mL) gave **16** (0.170 g, 66%), as a white solid; R_f 0.80 (EtOAc); mp 114–115 °C. ν_{max}/cm^{-1} 2925, 1617, 1604, 1496, 1450, 1429, 1331, 1006, 957, 915; δ_H 2.18–2.23 (m, 2H, 2′-CH_2), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.83 (s, 2H, aziridine-H), 4.21 (t, *J* 7.5, 2H, NCH_2), 4.87–4.95 (m, 2H, 4′-CH_2), 5.48–5.57 (m, 1H, 3′-H), 7.05 (s, 1H, 7-H), 7.25–7.40 (m, 10H, Ph–H), 7.49 (s, 1H, 4-H), 8.50 (s, 1H, CH=N); δ_C 20.3 (CH_3), 20.8 (CH_3), 33.8 (2′-CH_2), 43.9 (NCH_2), 110.0 (7-CH), 116.9 (4′-CH_2), 120.3 (4-CH), 127.8, 128.4, 131.8, 133.8, 134.4, 134.9, 141.5, 145.2 (Im-2-C), 151.6 (CH=N).

4.5.3. N-[(Pent-4-enyl-5,6-dimethyl-1H-benzimidazol-2-yl)-methylene]-trans-2,3-diphenylaziridin-1-amine **17**

1-Amino-*trans*-2,3-diphenylaziridine (0.120 g, 0.58 mmol) and aldehyde **13** (0.140 g, 0.58 mmol) in Et_2O (10 mL) gave **17** (0.180 g, 72%) as a yellow oil; R_f 0.75 (Et_2O). ν_{max}/cm^{-1} (neat) 3028, 2926, 1602, 1497, 1450, 1416, 1328, 1165, 999; δ_H 1.53–1.62 (m, 2H, 2′-CH_2), 1.82–1.90 (m, 2H, 3′-CH_2), 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.82 (s, 2H, aziridine-H), 4.14 (t, *J* 7.4, 2H, N–CH_2), 4.94–4.98 (m, 2H, 5′-CH_2), 5.65–5.72 (m, 1H, 4′-H), 7.04 (s, 1H, 7-H), 7.27–7.39 (m, 10H, ArH), 7.53 (s, 1H, 4-H), 8.52 (s, 1H, CH=N); δ_C 20.4 (CH_3), 20.9 (CH_3), 33.4 (2×CH_2), 44.6 (NCH_2), 110.1 (7-CH), 114.8 (5′-CH_2), 120.4 (4-CH), 126.6–128.7 (Ar–CH), 131.8, 133.8, 135.1, 138.5 (CH), 141.9 (C), 145.4 (Im-2-C), 151.6 (CH=N).

4.5.4. N-[(Hex-5-enyl-5,6-dimethyl-1H-benzimidazol-2-yl)-methylene]-(trans)-2,3-diphenylaziridin-1-amine **18**

1-Amino-*trans*-2,3-diphenylaziridine (0.100 g, 0.47 mmol) and aldehyde **14** (90 mg, 0.35 mmol) in Et_2O (9 mL) gave **18** (0.140 g, 89%), as a yellow solid; R_f 0.31 (60:40 hexane/EtO_2); mp 113–114 °C. ν_{max}/cm^{-1} 2915, 2856, 1601, 1484, 1449, 1430, 1330, 1157, 1000, 908; δ_H 1.15–1.20 (m, 2H, 3′-CH_2), 1.46–1.51 (m, 2H, 2′-CH_2), 1.90–1.95 (m, 2H, 4′-CH_2), 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.80 (s, 2H, aziridine-H), 4.13–4.17 (m, 2H, NCH_2), 4.96–5.00 (m, 2H, 6′-CH_2), 5.70–5.77 (m, 1H, 5′-H), 7.05 (s, 1H, 7-H), 7.26–7.39 (m, 10H, Ar–H), 7.49 (s, 1H, 4-H), 8.47 (s, 1H, CH=N); δ_C 20.3 (CH_3), 20.9 (CH_3), 25.9, 29.7, 33.4, 44.6 (all CH_2), 110.1 (7-CH), 114.9 (6′-CH_2), 120.4 (4-CH), 126.6–128.9 (Ar–CH), 131.8, 133.8, 135.1 (all C), 138.5 (5′-CH), 141.9, 145.4 (both C), 151.7 (CH=N).

4.6. General procedure for thermolysis of Eschenmoser hydrazones

4.6.1. 4,5-Dimethyl-1,1a,8,8a-tetrahydrocyclopropa[3,4]-pyrrolo[1,2-a]benzimidazole **19**

Hydrazone **15** (0.120 g, 0.295 mmol) in *m*-xylene (20 mL) was heated under reflux for 2 h. The solution was evaporated to dryness to give a residue, which was purified by column chromatography using silica gel as absorbent with hexane and EtOAc as eluent to give **19** (41 mg, 70%), as a brown solid; R_f 0.51 (EtOAc/10%MeOH); mp 130–131 °C. ν_{max}/cm^{-1} 2920, 1628, 1535, 1459, 1410, 1357, 1311, 1271, 1141, 1031, 955; δ_H 0.73–0.75 (m, 1H, 1-H), 1.35–1.37 (m, 1H, 1-H), 2.32 (s, 6H, CH_3), 2.43–2.48 (m, 2H, 1a and 8a-H), 4.02–4.08 (m, 2H, 8-CH_2), 6.95 (s, 1H, 6-H), 7.40 (s, 1H, 3-H); δ_C 14.7 (1a or 8a-CH), 16.2 (1-CH_2), 20.3 (CH_3), 20.4 (CH_3), 20.7 (1a or 8a-CH), 45.5 (8-CH_2), 109.5 (6-CH), 119.8 (3-CH), 130.1, 130.8, 131.0, 146.8 (all C), 161.4 (Im-1b-C); *m/z* (ESI) 199 ($[M+H]^+$, 100%), 185 (3), 52 (16); HRMS (ESI): found MH^+, 199.1231. $C_{13}H_{15}N_2$ requires, 199.1230.

4.6.2. 6,7-Dimethyl-1a,2,3,9b-tetrahydro-1H-cyclopropa-[3,4]pyrido[1,2-a]benzimidazole **20**

Hydrazone **16** (0.150 g, 0.36 mmol) in *m*-xylene (20 mL) gave **20** (38 mg, 50%), as a brown solid; R_f 0.24 (EtOAc); mp 136–137 °C. ν_{max}/cm^{-1} 2922, 2854, 1524, 1457, 1402, 1363, 1315, 1027, 998; δ_H 1.01–1.05 (m, 1H, 1-H), 1.15–1.21 (m, 1H, 1-H), 1.78–1.83 (m, 1H, 2-H), 2.10–2.19 (m, 1H, 2-H), 2.29–2.43 (s, 8H, CH_3 and 1a and 9b-H), 3.52–3.60 (m, 1H, 3-H), 4.12–4.17 (m, 1H, 3-H), 6.98 (s, 1H, 5-H), 7.42 (s, 1H, 8-H); δ_C 9.3 (CH_2), 11.3 (1a-CH), 13.3 (9b-CH), 20.2 (CH_3), 20.4 (CH_3), 20.5 (CH_2), 37.3 (3-CH_2), 108.5 (5-CH), 118.8 (8-CH), 130.2, 130.3, 132.9, 141.4, 152.5 (all C); *m/z* (CI) 213 ($[M+H]^+$, 100%), 114 (25); HRMS (ESI): found MH^+, 213.1388. $C_{14}H_{17}N_2$ requires, 213.1386.

4.6.3. 7,8-Dimethyl-3,3a,4,10b-tetrahydropyrazolo-[3′,4′:3,4]pyrrolo[1,2-a]benzimidazole **21**

Hydrazone **15** (0.120 g, 0.295 mmol) in PhH (20 mL) gave **21** (30 mg, 45%), as a yellow solid; R_f 0.43

(EtOAc/10%MeOH); mp 186–187 °C; ν_{max}/cm^{-1} 2922, 2852, 1521, 1459, 1415, 1356, 1287, 1009, 984; δ_H 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.53–3.61 (m, 1H, 3a-H), 3.66–3.70 (m, 1H, 4-H), 4.27–4.31 (m, 1H, 4-H), 4.74–4.88 (m, 2H, 3-CH_2), 6.09 (d, *J* 8.4, 1H, 10b-H), 7.03 (s, 1H, 6-H), 7.54 (s, 1H, 9-H); δ_C 20.5 (CH_3), 20.6 (CH_3), 36.9 (3a-CH), 48.8 (4-CH_2), 84.2 (3-CH_2), 90.9 (10b-CH), 110.1 (6-CH), 120.9 (9-CH), 130.2, 131.5, 132.2, 147.9, 153.3 (all C).

*4.6.4. 7,8-Dimethyl-1,1a,2,3,4,10b-hexahydrocyclopropa-[3,4]azepino[1,2-a]benzimidazole **4***

Hydrazone **17** (0.150 g, 0.35 mmol) in *m*-xylene (20 mL) gave **4** (61 mg, 77%), as yellow oil; R_f 0.56 (EtOAc/10%MeOH). ν_{max}/cm^{-1} 2919, 1524, 1456, 1403, 1364, 1314, 1026; δ_H 0.40–0.45 (m, 1H, 1a-H), 0.70–0.74 (m, 1H, 1-H), 1.23–1.28 (m, 2H, 1-H, 10b-H), 1.78–1.83 (m, 2H, 2-CH_2), 2.14–2.23 (m, 2H, 3-CH_2), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.24–4.30 (m, 1H, 4-H), 4.36–4.44 (m, 1H, 4-H), 7.03 (s, 1H, 6-H), 7.46 (s, 1H, 9-H); δ_C 11.9, 12.2 (1a-CH or 10b-CH), 13.4 (1-CH_2), 20.3 (CH_3), 20.6 (CH_3), 23.6 (CH_2), 27.0 (CH_2), 40.8 (4-CH_2), 109.0 (6-CH), 119.5 (9-CH), 130.3, 131.2, 132.6, 141.6 (all C), 153.5 (Im-10a-C); *m/z* (ESI) 227 ($[M+H]^+$, 100%), 213 (3), 52 (18); HRMS (ESI): found MH^+, 227.1541. $C_{15}H_{19}N_2$ requires, 227.1543.

*4.6.5. 8,9-Dimethyl-1a,2,3,4,5,11b-hexahydro-1H-cyclopropa[3,4]azocino[1,2-a]benzimidazole **5***

Hydrazone **18** (0.170 g, 0.38 mmol) in *m*-xylene (30 mL) gave after column chromatography using silica gel as absorbent with pentane and EtOAc as eluent in order of elution *1-hex-5-en-1-yl-5,6-dimethyl-2-(3-phenylethyl)-1H-benzimidazole **23*** (43 mg, 33%), as a yellow oil; R_f 0.59 (80:20 pentane/EtOAc); ν_{max}/cm^{-1} 2924, 2857, 1511, 1478, 1465, 1412, 1321, 998; δ_H 1.38–1.44 (m, 2H, 3′-CH_2), 1.65–1.71 (m, 2H, 2′-CH_2), 2.02–2.07 (m, 2H, 4′-CH_2), 2.32 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.07–3.11 (m, 2H, C*H*$_2$CH$_2$), 3.16–3.20 (m, 2H, CH$_2$C*H*$_2$), 3.92 (t, *J* 7.5, 2H, NCH$_2$), 4.93–5.00 (m, 2H, 6′-CH_2), 5.69–5.77 (m, 1H, 5′-CH), 7.01–7.19 (m, 5H, 7-H and xylene-H), 7.55 (s, 1H, 4-H); δ_C 20.3, 20.6, 21.4 (all CH_3), 26.1, 29.2, 29.7, 33.2, 34.1 (all CH_2), 43.3 (NCH$_2$), 109.6 (7-CH), 115.2 (6′-CH_2), 119.3 (4-CH), 125.4, 127.1, 128.3, 128.6, 129.2, 130.5, 131.1, 133.5, 137.9, 141.1, 153.2 (Im-2-C); *m/z* (ESI) 347 ($[M+H]^+$, 100%), 74 (3), 60 (4); HRMS (ESI): found MH^+, 347.2476. $C_{24}H_{31}N_2$ requires, 347.2482. The second product eluted was *2-but-3-enyl-6,7-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole **22*** (20 mg, 22%), as a yellow solid, R_f 0.30 (50:50 pentane/EtOAc); mp 117–118 °C. ν_{max}/cm^{-1}; 2922, 2851, 1513, 1465, 1241, 1374, 1321, 1264, 1148, 997; δ_H 0.81–0.97 (m, 1H, 2-H), 1.66–1.76 (m, 2H), 2.06–2.10 (m, 2H), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.89–2.95 (dd, *J* 14.8, 11, 1H, 3-C*H*H), 3.29 (d, *J* 14.8, 1H, 3-CH*H*), 3.91–3.98 (dd, *J* 14.5, 10.3, 1H, 1-C*H*H), 4.26–4.30 (m, 1H, 1-CH*H*), 5.01 (d, *J* 10.5, 1H, 4′-*cis*-H), 5.10 (d, *J* 17.1, 1H, 4′-*trans*-H), 5.77–5.86 (m, 1H, 3′-H), 7.04 (s, 1H, 8-H), 7.45 (s, 1H, 5-H); δ_C 20.2 (CH_3), 20.3 (CH_3), 27.2, 35.0, 36.5 (all CH_2), 39.7 (2-CH), 44.1 (1-CH_2), 109.3 (8-CH), 113.7 (4′-CH_2), 119.2 (5-CH), 130.1, 131.0, 140.6 (all C), 141.6 (3′-CH), 154.8 (Im-3a-C); *m/z* (ESI) 241 ($[M+H]^+$, 100%), 60 (4); HRMS (ESI): found MH^+, 241.1702. $C_{16}H_{21}N_2$ requires, 241.1699. The third product eluted was **5** (10 mg, 11%), as a white solid; R_f 0.37 (EtOAc); mp 120–122 °C. ν_{max}/cm^{-1} 2920, 1526, 1478, 1464, 1407, 1354, 1312, 1136, 1023, 996; δ_H 0.20–0.26 (m, 1H), 0.91–0.93 (m, 1H), 1.16–1.23 (m, 2H), 1.53–1.59 (m, 2H), 1.80–1.86 (m, 2H), 2.05–2.12 (m, 2H, 4-CH_2), 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.24–4.38 (m, 2H, 5-CH_2), 7.03 (s, 1H, 7-H), 7.47 (s, 1H, 10-H); δ_C 10.3 (1a-CH), 13.5 (1-CH_2), 19.9 (3-CH_2), 20.3 (CH_3), 20.6 (CH_3), 28.4 (11b-CH), 29.0 (4-CH_2), 30.2 (2-CH_2), 43.6 (5-CH_2), 109.3 (7-CH), 119.6 (10-CH), 130.4 (C), 131.1 (C), 137.6 (C), 140.9 (C), 153.9 (11a-C); *m/z* (ESI) 241 ($[M+H]^+$, 100%), 217 (4), 60 (4); HRMS (ESI): found MH^+, 241.1700. $C_{16}H_{21}N_2$ requires, 241.1699.

4.7. General procedure for nitration

Mixture of concd H_2SO_4 and fuming HNO_3 (50:50 5 mL) was added to **19** (50 mg, 0.25 mmol), and the mixture stirred at 0 °C for 6 h. The reaction was basified using NH_4OH to pH 12 and extracted into $CHCl_3$ (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography using silica gel as absorbent with hexane and EtOAc as eluent to give in order elution *4,5-dimethyl-3,6-dinitro-1,1a,8,8a-tetrahydrocyclopropa[3,4]pyrrolo[1,2-a]benzimidazole **25*** (33 mg, 46%), as a yellow solid; R_f 0.81 (EtOAc); mp 212–213 °C. ν_{max}/cm^{-1} 2919, 1523 (NO_2), 1445, 1417, 1391, 1366 (NO_2), 1340, 1291, 1243, 1073, 910; δ_H 0.87–0.90 (m, 1H, 1-H), 1.47–1.53 (m, 1H, 1-H), 2.36 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.56–2.62 (m, 2H, 1a and 8a-H), 4.12–4.26 (m, 2H, 8-CH_2); δ_C 14.7 (8a-CH), 15.1 (CH_3), 15.8 (CH_3), 16.3 (1-CH_2), 21.6 (1a-CH), 48.5 (8-CH_2), 122.9, 125.6, 125.9, 136.0, 140.4, 144.0 (all-C), 166.0 (Im-1b-C); *m/z* (ESI) 289 ($[M+H]^+$, 100%), 104 (4), 74.1 (4); HRMS (ESI): found MH^+, 289.0934. $C_{13}H_{13}N_4O_4$ requires, 289.0931. The second product eluted was *4,5-dimethyl-3-nitro-1,1a,8,8a-tetrahydrocyclopropa[3,4]pyrrolo[1,2-a]benzimidazole **24*** (9 mg, 14%), as a brown solid; R_f 0.46 (EtOAc); mp 160–161 °C. ν_{max}/cm^{-1} 2920, 1521 (NO_2), 1455, 1375, 1359 (NO_2), 1310, 1274, 1202, 1040; δ_H 0.84–0.88 (m, 1H, 1-H), 1.45–1.48 (m, 1H, 1-H), 2.33 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.54–2.59 (m, 2H, 1a and 8a-H), 4.09–4.17 (m, 2H, 8-CH_2), 7.15 (s, 1H, 6-H); *m/z* (ESI) 244 ($[M+H]^+$, 100%), 215 (3), 111 (4), 105 (4), 68 (7), 60 (17); HRMS (ESI): found MH^+, 244.1080. $C_{13}H_{14}N_3O_2$ requires, 244.1081.

*4.8. 4,5-Dimethyl-1,1a,8,8a-tetrahydrocyclopropa[3,4]-pyrrolo[1,2-a]benzimidazole-3,6-dione **3***

Dinitrobenzimidazole **25** (0.100 g, 0.35 mmol) and Pd–C (27 mg) in EtOH (60 mL) were shaken under 40 psi H_2 using a Parr apparatus for 17 h. $FeCl_3$ (aq) (0.7 M, 20 mL) was added and stirring continued for 12 h. The mixture was filtered through Celite and evaporated to dryness. Saturated NaOAc (aq) was

added and the mixture extracted with $CHCl_3$ (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The resultant residue was purified by column chromatography using silica gel as absorbent with gradient elution of pentane and EtOAc as eluent to give **3** (60 mg, 76%), as an orange solid; R_f 0.41 (EtOAc); mp 224–225 °C. ν_{max}/cm^{-1} 2923, 1638 (C=O), 1524, 1475, 1454, 1372, 1306, 1274, 1239, 1179, 1037; δ_H 0.73–0.77 (m, 1H, 1-H), 1.37–1.43 (m, 1H, 1-H), 1.98 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.45–2.51 (m, 2H, 1a-H and 8a-H), 4.19–4.29 (m, 2H, 8-CH_2); δ_C 11.9 (CH_3), 12.6 (CH_3), 14.2 (1a-CH or 8a-CH), 15.6 (1-CH_2), 21.1 (1a-CH or 8a-CH), 47.9 (8-CH_2), 129.0, 138.7, 141.0, 145.2, 161.4, 178.1 (C=O), 181.0 (C=O); *m/z* (ESI) 229 ($[M+H]^+$, 100%), 68 (3), 60 (5); HRMS (ESI): found MH^+, 229.0973, $C_{13}H_{13}N_2O_2$ requires, 229.0972.

4.9. Biological studies

Cell culture of normal human skin fibroblast cell line (GM00637I) was described in our previous publication, along with the cytotoxicity assays of MMC, benzimidazolequinones **1** and **2**.[2] The same procedure for the MTT assay was used to measure the cytotoxicity of **3** under aerobic and hypoxic conditions,[2] except cells were treated in parallel with 0.1, 0.5 and 1.0 μmol dm^{-3} of MMC (aerobic and hypoxic conditions) and 0.01 μmol dm^{-3} (under aerobic conditions) of benzimidazolequinone **1** as a positive control for cytotoxicity in the MTT assay.

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