Synthesis of Pyrrolo- and Pyrido-[1,2-α]benzimidazolequinone Anti-tumor Agents Containing a Fused Cyclopropane Ring

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Abstract: A cyclopropane ring has been fused onto tetrahydropyrrolo- and tetrahydropyrido-[1,2-α]-benzimidazoles and -benzimidazolequinones via the cycloaddition of diazomethines generated from the thermolysis of N-(allyl and but-3-enyl)benzimidazole-2-Eschenmoser hydrazones (aziridinyl imines). At lower temperatures, the 1,3-dipolar [3 + 2] cycloadduct was obtained for only the N-allylbenzimidazole-2-Eschenmoser hydrazones.

Key words: benzimidazoles, bioreductive, diazo-compounds, heterocycles, hydrazones

Many quinone derivatives are known to have anti-cancer activity, which is initiated by the reductive activation of the quinone moiety.1 In the case of mitomycin C (MMC 1) and aziridinomitosene 2 reductive activation leads to ring-opening of the aziridine ring and elimination of the urethane group to create reactive sites at C-1 and C-10, respectively for alkylation of DNA (Figure 1). Moody and coworkers have prepared analogues of the aziridinomitosene 2, in which the aziridine ring is replaced by a cyclopropane ring, and named these compounds cyclopropamitosene (CPM, 3).2–7 The reduced electrophilicity at C-1 in 3 resulted in selective alkylation of nucleophiles at C-10 under chemical reducing conditions.5 CPM 3 was also shown to undergo single-electron reduction; a process that is selective under bioreductive conditions to hypoxia, more toxic than under aerobic conditions and MMC under hypoxic conditions, respectively. 5,6 Bioreduction of 3 to the semiquinone radical anion was speculated to induce radical-ring opening of the cyclopropane ring to give a radical capable of abstracting the 4′-hydrogen from the deoxyribose part of DNA leading to strand cleavage.5,7 Therefore, the greater selectivity of CPM 3 toward hypoxic conditions, and the different mode of action to 1 and 2, makes the synthesis of structurally related heterocyclic compounds a worthwhile endeavor. Our interest has been in the preparation of benzimidazoles containing [1,2-α]-fused alicyclic rings,5 where literature synthetic methods have been limited to the preparation tricyclic fused systems8,10 until in a recent preliminary communication, we reported the preparation of new tetracyclic ring systems pyrrolo- and pyrido-[1,2-α]benzimidazoles containing a fused cyclopropane ring using benzimidazole-2-Eschenmoser hydrazones synthetic intermediates.11 The methodology was extended to the preparation of 1,1a,8,8a-tetrahydrocyclopropa[3,4]pyrrolo[1,2-α]benzimidazole-3,6-dione (4), which is the first prepared diazole analogue of indolequinone 3.

Figure 1

Benzimidazolequinone 4 was shown to have a lower reductive potential (–1.052 V, vs. ferrocene, Fe) than indolequinones 1 (–1.421 V, vs. Fe) and 3 (–1.395 V, vs. Fe) under analogous cyclic voltammetry conditions. A reversible one electron reduction was observed at low scan rates in contrast to other reported benzimidazolequinone anti-tumor agents that show cytotoxic activity via a two-electron reductive activation mediated by DT-diaphorase in an O2-independent pathway.10,11 A full account of the synthesis of anti-tumor agent 4 and analogues is given in the present paper, including a first report of the new benzimidazolequinone, 1a,2,3,9b-tetrahydro-1H-cyclopropa[3,4]pyrido[1,2-α]benzimidazole-5,8-dione (5).

The construction of the tetracyclic cyclopropapyrrolo- and cyclopropapyrido-[1,2-α]benzimidazole skeleton was accomplished by successful intramolecular cycloaddition of N-(allyl and but-3-enyl)benzimidazole-2-diazo-methines 6 and 7, respectively.

Synthetic pathways toward the preparation of benzimidazole-2-hydrazone precursors of 6 and 7 began with the N-alkylation of 1H-benzimidazol-2-ylmethanol 8, rather than 1H-benzimidazole-2-carbaldehyde. N-Alkylation of

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the aldehyde could not be carried out owing to its insolubility in organic solvents, which has been attributed to the formation of the dimeric hemiaminal.\(^\text{13}\) \(N\)-Allyl and (3-butenyl)-1H-benzimidazole-2-methanols 9 and 10 were prepared selectively on gram scale, but in only reasonable poor yields of 41% and 30%, respectively, by treatment of alcohol \(8\) with a large excess of triethylamine followed by an equal excess of allyl bromide and 4-bromo-1-butene in refluxing THF (Scheme 1). Nevertheless, our alkylations of 8 using triethylamine compared favourably with literature alkylations, which under basic conditions were not selective leading to both \(N\) and \(O\)-alkylation.\(^\text{14}\)

Improved yields of 10 of 44% overall, were achieved when TBDMS-protection of the 2-hydroxymethyl group of 8 was first carried out to allow alkylation using sodium hydride and 4-bromo-1-butene with subsequent deprotection using TBAF (Scheme 2), as previously reported for other benzimidazole-2-methanol alkylations.\(^\text{15}\) Alcohols 9 and 10 were oxidized in half an hour to the required aldehydes 11 and 12 in 77% and 55% yield, respectively, using a large excess of manganese dioxide in refluxing dichloromethane (Scheme 1).

The preparation 2-tosylhydrazone 15 as the diazomethine precursor was unsuccessful, and led to the isolation of aduct 16 from the attempted reaction of tosyl hydrazide with benzimidazole-2-carbaldehyde 11 in methanol (Scheme 3). In contrast the literature preparations of \(N\)-(\(\omega\)-alkenyl)indole-2-tosylhydrazones were reported to be facile, and efficient intramolecular cycloadditions to form cyclopropapyrrolo[1,2-\(a\)]indoles,\(^\text{2}\) and precursors of CPM aziridine\(^\text{16}\) (Scheme 4). Hydrazones 17 and 18 upon thermolysis in refluxing xylene for 2 hours gave novel tetracyclic systems, cyclopropapyrrolo- and cyclopropapyrido-[1,2-\(a\)]benzimidazoles 19 and 20 in 85% and 53% yields, respectively.

Therefore, alternative precursors for reactive intermediates 6 and 7 were required, and we turned our attention to the preparation of Eschenmoser hydrazones or aziridinyl imines. Jones and Moody reported the thermolysis of \(N\)-allylindole-2-Eschenmoser hydrazone to cyclopropapyrrolo[1,2-\(a\)]indole in reasonable yield.\(^\text{2}\) Benzimidazole-2-Eschenmoser hydrazones 17 and 18 proved to be effective isolable precursors for 6 and 7, which were obtained in yields of 77% and 98% from the condensation of aldehydes 11 and 12 with \(trans\)-1-amino-2,3-diphenylaziridine\(^\text{16}\) (Scheme 4). Hydrazones 17 and 18 upon thermolysis in refluxing xylene for 2 hours gave novel tetra cyclic systems, cyclopropapyrrolo- and cyclopropapyrido-[1,2-\(a\)]benzimidazoles 19 and 20 in 85% and 53% yields, respectively.

### Scheme 1

\textbf{Reagents and conditions:} (i) \(\text{Et}_3\text{~N, CH}_3=\text{CH(CH}_3)_2\text{Br, THF, reflux, 4 h, 41% for } 9\) and 30% for 10; (ii) MnO\(_2\), CH\(_3\)Cl\(_2\), reflux, 30 min, 77% for 11 and 55% for 12.

### Scheme 2

\textbf{Reagents and conditions:} (i) TBDMSCl, pyridine, r.t., 4 h, 100% for 13; (ii) NaH, \(\text{CH}_3=\text{CH(CH}_3)_2\text{Br, THF, reflux, 8.5 h, 58% for 14; (iii) TBAF, THF, r.t., 15 min, 75% for 10.}

### Scheme 3

\textbf{Reagents and conditions:} H\(_2\)N–NHTs, MeOH, r.t., 18 h, 29% for 16.

### Scheme 4

\textbf{Reagents and conditions:} (i) \(E\)-1-Amino-2,3-diphenyl-aziridine, Et\(_2\)O, 0 °C, 8 h, 77% for 17 and 98% for 18; (ii) xylene, reflux, 2 h, 85% for 19 and 53% for 20.

Thermolysis of hydrazone 17 and 4,7-dimethoxy analogue 21 at lower temperatures (refluxing benzene) for three hours selectively gave the 1,3-dipolar [3+2] cycloadducts 22 and 24 in 56% and 44% yield respectively (Scheme 5), and an X-ray crystal structure of 22 was obtained.\(^\text{11}\) Under the latter lower decomposition temperatures, hydrazone 18 also decomposed to cyclopropane 20, and no evidence of the formation of the 1,3-dipolar [3+2] pyrazoline cycloadduct 23 was obtained. The instability of 23 may be due to steric interactions between the 4,5-hydrogens on the [1,2-\(a\)]-fused six-membered ring and the fused pyrazoline 1,2-azo nitrogen atoms. 1-Pyrazoline fused onto six membered alicyclic rings in tricyclic sys-
tems have been previously isolated, however the aromatic ring was benzene in these cases.\textsuperscript{17}

Once the methodology for the incorporation of the fused cyclopropane ring onto pyrrolo- and pyrido[1,2-\textit{a}]benzimidazoles had been established, we turned our attention to functionalising the benzene part in order to form target benzimidazolequinones \textit{4} and \textit{5}. \textit{(4,7-Dimethoxybenzimidazol-2-yl)methanol} (\textit{25}) was prepared according to the procedure of Weinberger and Day\textsuperscript{18} on a multi-gram scale in \textit{46\%} yield by a modification of the Phillips condensation\textsuperscript{19} between 3,6-dimethoxybenzene-1,2-diones and \textit{aryl} amines and glycolic acid. We decided to carry out alkylation on benzimidazole by the protection of the 2-hydroxymethyl group of \textit{25} with TBDMSCl, which allowed us to carry out the N-alkylation using sodium hydride (Scheme 6). N-Alkylation with allyl bromide and 4-bromo-1-butene, TBAF deprotection and manganese dioxide oxidation gave aldehydes \textit{31} and \textit{32} in overall yields of \textit{43\%} and \textit{39\%}, respectively, for the four synthetic steps from \textit{25}. Condensation with \textit{trans-1-amino-2,3-diphenylaziridine} gave the 4,7-dimethoxybenzimidazole-2-Eschmenoser hydrazones \textit{21} and \textit{33} in excellent yields of \textit{83\%} and \textit{86\%}, and thermolysis in refluxing xylene gave cycloadducts \textit{34} and \textit{35} in yields of \textit{68\%} and \textit{58\%}, respectively. Hydrobromic acid induced demethylation of \textit{34} and \textit{35} gave the reactive hydroquinones \textit{36} and \textit{37} in situ, which underwent oxidation almost immediately at room temperature to give novel tetracyclic target benzimidazolequinones \textit{4} and \textit{5} using ferric chloride in identical yields of \textit{64\%}.

It is interesting to compare our clean synthesis of \textit{5} with the approach by Moody and co-workers to the \textit{1,2-\textit{a}}indolequinone analogue also containing cyclopropane fused onto a six-membered alicyclic ring, in which oxidation of the phenol to the quinone by the free radical, Fremy’s salt, resulted in isolation of significant quantities of the by-product due to ring-opening of the cyclopropane ring.\textsuperscript{7} This was not observed in our ferric chloride oxidations of \textit{5} under the same conditions as for \textit{4}\textsuperscript{11} gave a similar redox potential of \textit{−1.074} vs ferrocene, and showed at low scan rates an analogous reversible single electron transfer process. This indicated a negligible effect on reductive activation of the increase in size by one CH\textsubscript{2} of the fused alicyclic ring. Cytotoxicity and selectivity of \textit{4}, \textit{5} and related \textit{[1,2-\textit{a}]} fused benzimidazolequinones toward hypoxic conditions will be reported in a subsequent paper.

In conclusion, new tetracyclic diazole ring systems based on pyrrolo- and pyrido-[1,2-\textit{a}]benzimidazoles containing a fused cyclopropane ring were accessible using cycloaddition reactions of diazomethines derived from the thermolysis of benzimidazole-2-Eschmenoser hydrazones or aziridinyl imines in refluxing xylene. At lower temperatures of refluxing benzene, the \textit{3 + 2} pyrazoline cycloadduct was obtained for the \textit{N}-allyl-benzimidazole-2-diazomethines, and not for the \textit{N}-but-3-ethyl-benzimidazole-2-diazomethine. The synthesis of bioreductive benzimidazolequinones \textit{1a,1b,8a-tetrahydrocyclopropapyrido[1,2-\textit{a}]benzimidazole-3,6-dione (4)} and \textit{1a,2,3,9b-tetrahydro-1H-cyclopropa[3,4]pyrido[1,2-\textit{a}]benzimidazole-5,8-dione (5)} is described in full. The

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme5}
\caption{Scheme 5 Reagents and conditions: PhH, reflux, 3 h, 56\%, 0\% and 44\% for \textit{22, 23} and \textit{24}, respectively. Adduct \textit{20} isolated in 23\% from the reaction using \textit{19}.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme6}
\caption{Scheme 6 Reagents and conditions: (i) TBDMSCl, pyridine, r.t., 4 h, 90\% for \textit{26}; (ii) NaH, CH\textsubscript{2}=CH(CH\textsubscript{2})\textsubscript{3}Br, THF, reflux, 8.5 h, 86\% for \textit{27} and 70\% for \textit{28}; (iii) TBAF, THF, r.t., 15 min, 85\% for \textit{29} and \textit{30}; (iv) MnO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, reflux, 30 min, 65\% for \textit{31} and 73\% for \textit{32}; (v) \textit{E}-1-Amino-2,3-diphenylaziridine, EtO\textsubscript{2}, 0 °C, 8 h, 83\% for \textit{21} and 86\% for \textit{33}; (vi) xylene, reflux, 2 h, 68\% for \textit{34} and 58\% for \textit{35}; (vii) 48\% HBr (aq), reflux, 3 h; (viii) FeCl\textsubscript{3} (aq), r.t., 5 min, 64\% for \textit{4} and \textit{5} after steps (vii) and (viii).}
\end{figure}
former compound is a diazole analogue of the indole-quinone anti-tumor agent, cyclopropamitosene 3.

Melting points were measured on a Stuart Scientific melting point apparatus SMP3, and are uncorrected. IR spectra were determined using neat samples on a Perkin-Elmer Spectrum 1000 FT-IR with an UATR accessory attached. 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded in CDC13 on a Jeol GXFT 400 instrument with a DEC AXP 300 computer work station. Chemical shifts are given in ppm, and J values are given in Hz. Electronic impact (EI) and chemical ionization (CI) mass spectra were recorded on a Micro Mass GTC GC-MS spectrometer. EPSRC National Mass Spectrometry Service carried out low resolution EI and CI on a Micromass Quattro II, and high resolution mass spectrometry using peak-matching techniques on the Finnigan MAT 900 XLT in CI mode for compounds 1 and 2. 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded in CDCl3 on a Jeol GXFT 400 instrument equipped with a DEC AXP 300 computer work station. Chemical shifts are given in ppm, and J values are given in Hz. 

EcoChemie Autolab with PEGSTAT12 potentiostat controlled by EcoChemie Autolab with PEGSTAT12 potentiostat controlled by ECS 600 software at scan rates 20, 50, 100 and 200 mV s–1. Quinones 4 and 5 were dissolved in DMF, containing 0.1 M tetrabutylammonium perchlorate and 1 M mmol Fe(C) as reference. Cyclic voltammetry was recorded at a platinum disk electrode in a single compartment electrochemical cell (2 mL volume) containing Ag/AgCl reference electrode and a platinum wire counter electrode. Cyclic voltammetry was recorded at a platinum disk electrode in 0.1 M tetrabutylammonium perchlorate as electrolyte and 1 mM ferrocene (Fc) as reference. Column chromatography was carried out using Merck silica gel 60, 234–400 mesh or using Aldrich aluminium oxide, activated neutral, Brockmann grade 3, STD Grade, 150 mesh size. Cyclic voltammetry was performed on an EcoChemie Autolab with PEGSTAT12 potentiostat controlled by GPES software at scan rates 20, 50, 100 and 200 mV s–1. All anhydrous reactions were carried under an inert atmosphere using distilled and anhydrous solvents. TBAF was a 1 M solution in THF, and was used as purchased from Aldrich. Benzimidazole-2-methanols 8th and 25th were prepared in 57% and 46% yield by condensation of 1,2-phenylenediamine and 3,6-dimethoxybenzene-1,2-diamine respectively with glycolic acid in refluxing 4 M hydrochloric acid. trans-1-Amino-2,3-dihydroazine was prepared according to Eschenmoser’s two step procedure 29 in 71% yield starting from N-anilinophthalimide and trans-stilbene and used immediately. We have previously reported the procedure for the conversion of N-[3-Butenyl-1H]-benzimidazol-2-yl)methylene)-E-2,3-diphenylavridin-1-amine (18) to 1a,2,3,9b-tetraydrocyclo-

Propano[3,4]pyrido[1,2-a]benzimidazole (20) in 53% yield and the characterization of 18 and 1,1a,8a-tetraydrocyclopropano[3,4]pyrrolo[1,2-a]benzimidazole-3,6-dione 4 in a preliminary communication.61

Synthesis of N-allyl-1H-benzimidazol-2-ethanol (9)

Et3N (23.5 mL, 0.169 mol) and 8 (5.000 g, 33.78 mmol) in THF (100 mL) were refluxed for 1 h. Allylm bromide (14.6 mL, 0.169 mol) was added and the solution refluxed for a further 3 h. Water (30 mL) was added to the cooled reaction mixture which was extracted with Et2O (3 × 40 mL), dried (MgSO4) and evaporated to dryness. The residue was purified by column chromatography using silica gel as absorbent with CH2Cl2 and EtOAc (gradient elution) to yield 9 as a pale yellow solid (2.610 g, 41%); mp 97–98 °C (lit. 41 mp 96 °C).

IR: 3054 (OH) 2833, 2719, 1463, 1410, 1330, 1011, 964, 934, 855 cm–1.

1H NMR: δ = 4.85–4.90 (4 H, m, NCH2 and CH2OH), 4.97–5.02 (1 H, d, J = 17.1 Hz, 3′-trans-H), 5.17–5.19 (1 H, d, J = 10.3 Hz, 3′-cis-H), 5.90–5.99 (1 H, m, 2′-H), 7.21–7.27 (3 H, m, ArH), 7.66–7.68 (1 H, m, ArH), OH peak not observed.

13C NMR: δ = 45.9 (NCH3), 56.6 (CH2OH), 109.0 (ArCH), 171.4 (3′-CH3), 119.2 (ArCH), 122.3 (ArCH), 122.9 (ArCH), 131.9 (2′-CH), 135.0 (C), 141.4 (C), 153.9 (Im-2-C).


HRMS (EI): m/z calcd for C12H14N2O [M + H]+ 203.1108; found, 203.1109.

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N-(3-Butenyl)-1H-benzimidazole-2-thanol (10); TBDMS-Deprotection of 14
TBDMS-protected alcohol 14 (0.460 g, 1.45 mmol) and TBAF (1.46 mL, 1.46 mmol) in THF (20 mL) were stirred at r.t. for 15 min. The solution was evaporated to dryness to yield a brown residue, which was purified by column chromatography using silica gel as absorbent with hexane and EtOAc (gradient elution) to yield 10 (0.227 g, 75%).

IR: 2823, 1615, 1511, 1462, 1409, 1332, 1157, 1088 cm⁻¹.

N- Allyl-1H-benzimidazole-2-carbaldehyde (11)
Alcohol 9 (40 mg, 0.21 mmol) and activated MnO₂ (0.540 g, 6.21 mmol) were refluxed in CH₂Cl₂ (50 mL) for 30 min. The cooled reaction mixture was filtered through celite, and evaporated to dryness to yield 11, as a yellow solid (30 mg, 77%); mp 38–39 °C.

IR: 1688 (C=O), 1479, 1468, 1413, 1327, 1240, 1161, 994, 928 cm⁻¹.

HRMS (CI): m/z calcd for C₁₁H₁₀N₂O₁, 186.0793; found, 186.0789.

HRMS (EI): m/z calcd for C₁₁H₁₀N₂O, 186.0930; found, 186.0789.

N-(3-Butenyl)-1H-benzimidazole-2-carbaldehyde (12)
The same procedure used for the synthesis of 11 yielded 12 as a yellow oil (55%).

IR: 1691 (C=O), 1479, 1468, 1413, 1327, 1240, 913 cm⁻¹.

HRMS (EI): m/z calcd for C₁₁H₁₁N₂O, 187.0873; found, 186.0789.

N-(3-Butenyl)-1H-benzimidazole-2-carbaldehyde (12)
The same procedure used for the synthesis of 11 yielded 12 as a yellow oil (55%).

IR: 1691 (C=O), 1479, 1468, 1413, 1327, 1240, 913 cm⁻¹.

HRMS (EI): m/z calcd for C₁₁H₁₁N₂O, 187.0873; found, 186.0789.

N- Allyl-2-(methoxymethyl)-1H-benzimidazole (16)
p-Tosyl hydrazide (0.420 g, 2.25 mmol) and 11 (0.430 g, 2.31 mmol) in MeOH (20 mL) were stirred at r.t. for 18 h. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography using silica gel as absorbent with hexane and CH₂Cl₂ (gradient elution) to yield 16 as a clear oil (0.134 g, 29%).

IR: 2823, 1615, 1511, 1462, 1409, 1332, 1157, 1088 cm⁻¹.

HRMS (EI): m/z calcd for C₁₁H₁₂N₂O₂, 202.1106; found, 202.1101.

N-[1-Allyl-1H-benzimidazol-2-ylmethylene]-(E)-2,3-diphenylaziridin-1-amine (17)
(E)-1-Amino-2,3-diphenylaziridine (0.105 g, 0.48 mmol) and 11 (0.370 g, 1.99 mmol) in Et₂O (5 mL) were stirred at 0 °C for 8 h. The solution was evaporated to dryness and the residue was purified by column chromatography using neutral alumina as absorbent with hexane and CH₂Cl₂ (gradient elution) to yield 17 as a yellow oil (0.146 g, 77%).

IR: 3030, 2087, 1602, 1452, 1408, 1333, 1283, 1161, 1010, 922 cm⁻¹.

1H NMR: δ = 3.81 (2 H, s, aziridine-H), 4.75–4.80 (1 H, d, J = 16.1 Hz, 3'-trans-H), 4.85–4.91 (2 H, m, NCH₂), 5.58–5.66 (1 H, m, 2'-H), 7.22–7.28 (13 H, m, ArH), 7.73–7.76 (1 H, m, ArH), 8.46 (1 H, s, CH=N).

13C NMR: δ = 46.9 (NCH₂ and aziridine-CH), 110.5 (ArCH), 116.5 (3'-CH₃), 120.5 (ArCH), 122.7 (ArCH), 124.2 (ArCH), 127.8 (ArCH), 128.4 (ArCH), 132.5 (2'-CH), 136.2 (C), 142.9 (CH=N), 145.9 (C), 151.3 (Im-2-C).

HRMS (EI): m/z calcd for C₁₁H₁₀N₄, 198.0937; found, 198.0910.

3,3a,4,10b-Tetrahydrocyclopenta[3,4]pyrrolo[1,2-a]benzimidazole (19)
Aziridinamine 17 (0.112 g, 0.29 mmol) in xylene (20 mL) was refluxed for 2 h. The solution was evaporated to dryness to yield a residue which was purified by column chromatography using neutral alumina as absorbent with hexane and CH₂Cl₂ (gradient elution) to yield 19 as a yellow oil (43 mg, 85%).

IR: 3380, 3055, 2893, 1624, 1538, 1453, 1404, 1268, 1214, 1151, 1032, 931 cm⁻¹.

1H NMR: δ = 0.76–0.79 (1 H, m, 1-H), 1.36–1.42 (1 H, m, 1-H), 2.48–2.50 (2 H, m, 1a and 8a-H), 4.03–4.13 (2 H, m, 8-CH₂), 7.16–7.18 (3 H, m, ArH), 7.64–7.66 (1 H, m, ArH).

13C NMR: δ = 14.5 (1a-CH), 16.0 (1-CH₂), 20.6 (8a-CH), 45.3 (8-CH₂), 108.8 (ArCH), 119.3 (ArCH), 121.3 (ArCH), 127.1 (ArCH), 132.3 (C), 148.0 (C), 161.3 (Im-1b-C).

HRMS (EI): m/z calcd for C₁₁H₁₂N₂O₂, 207.0844; found, 207.0838.

3,3a,4,10b-Tetrahydroazepino[3',4':3,4]pyrrolo[1,2-a]benzimidazole (22)
Aziridinone 17 (0.260 g, 0.68 mmol) in benzene (20 mL) was refluxed for 3 h. The solution was evaporated to dryness and the crude residue was purified by column chromatography using neutral alumina as absorbent with hexane and CH₂Cl₂ (gradient elution) to yield 22 as a white solid (76 mg, 56%); mp 189–190 °C.

IR: 1621, 1552, 1483, 1452, 1416, 1324, 1219, 990 cm⁻¹.

1H NMR: δ = 3.58–3.64 (1 H, m, 3a-H), 3.72–3.76 (1 H, m, 3'-CH), 4.34–4.38 (1 H, m, 3'-CH₂), 4.78–4.92 (2 H, m, NCH₂), 6.13–6.15 (1 H, d, J = 8.3 Hz, 10b-H), 7.26–7.28 (3 H, m, ArH), 7.81–7.83 (1 H, d, J = 8.1 Hz, ArH).

13C NMR: δ = 36.8 (3a-CH), 48.8 (3'-CH₂), 84.3 (3-CH), 90.8 (10b-CH), 109.9 (ArCH), 120.9 (ArCH), 122.6 (ArCH), 122.9 (ArCH), 131.9 (C), 149.3 (C), 154.4 (10a-C).

HRMS (EI): m/z calcd for C₁₁H₁₂N₂O₂, 207.0844; found, 207.0838.

The same procedure as for 22 yielded 24 as a white solid (44%); mp 180–181 °C.

IR: 1523, 1257, 1108, 1078 cm⁻¹.

1H NMR: δ = 3.45–3.51 (1 H, m, 1H), 3.75 (3 H, s, OCH3), 3.99 (3 H, s, OCH3), 4.39–4.45 (1 H, m, 4-CH2), 4.65–4.79 (2 H, m, 3-CH2), 5.95–5.97 (1 H, m, 10b-H), 6.44–6.45 (2 H, ABq, J = 8.3 Hz, ArH).

13C NMR: δ = 47.3 (NCH2), 55.7 (OCH3), 55.9 (CH2O), 102.1 (ArCH), 124.6 (C), 134.0 (2'-CH), 141.5 (C), 151.2 (1m-2-C).

MS (CI): m/z (%) = 263 (M + H+, 100), 322 (25), 236 (23), 78 (15), 55 (4).

HRMS (CI): m/z c Calc for C13H17N2O3 [M + H]+, 246.1003; found, 246.1002.

HRMS (CI): m/z c Calc for C18H23N3O4Si, 363.1422; found, 363.1420.

(1 H, m, 3'-H), 6.55–6.71 (2 H, ABq, J = 10.4 Hz, ArH), 7.28–7.49 (10 H, m, ArH), 8.51 (1 H, s, ArCH=N).

13C NMR: δ = 111.1–111.5 (1 H, m, 1-H), 123–129 (1 H, m, 1-H), 1.85–1.88 (1 H, m, 1a-H), 2.05–2.16 (1 H, m, 2’-CH2), 2.29–2.34 (1 H, m, 2’-CH), 2.42–2.47 (1 H, m, 9b-H), 3.59–3.68 (1 H, 3’-CH), 4.81–8.46 (1 H, 3’-CH)), 6.48–6.62 (2 H, ABq, J = 10 Hz, 6 and 7-H).

13C NMR: δ = 9.9 (3-H), 10.9 (9b-H), 13.7 (1a-CH), 19.7 (2’-CH), 39.7 (3’-CH), 129.5 (C), 135.9 (67’-CH), 136.9 (67’-CH), 141.1 (C), 153.7 (9a-C), 178.2 (C=O), 181.0 (C=O).

MS (CI): m/z (%) = 215 (13, M + H+), 213 (19), 188 (100), 139 (53).

HRMS (CI): m/z calcd for C12H16N2O2 [M + H+]2+, 213.0659; found, 213.0661.

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References
