A NEW GENERAL ROUTE TO NOVEL AZOMETHINE YLIDES FOR CYCLOADDITION REACTIONS

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Abstract - A general method providing access to stabilized azomethine ylides generated from substituted 1,3- and 3,1-aryloxazines was developed. A two-step sequence based on 1,3-dipolar cycloaddition reactions with N-arylmaleimides was elaborated to give a series of highly substituted pyrrolopyrrolidines in good yields.

The 1,3-dipolar cycloaddition reaction of azomethine ylides is a powerful method for the construction of pyrrolidine ring systems. Since the systematic studies by Huisgen1 in the 1960s, a large amount of literature has been devoted to this reaction.2 Azomethine ylides are unstable species which have to be prepared in situ. While the thermal ring opening of aziridines has been the only practical generation method known in the late 1970s, a great number of new methodologies has been since described. For example, the transformation of imine into azomethine ylide can be carried out under thermal activation or via catalysis with a wide range of metals and a tertiary base, as developed by Grigg3 and Tsuge.4 However the most fundamental ylde generation involves the elimination of a positively charged group at the α position of iminium salts. A proton (H⁺) sometimes accompanied by decarboxylation, or a silyl cation (R3Si⁺), may be abstracted to create the dipole. Indeed, the desilylation methodology investigated by Vedejs and Martinez5 in 1979 has become a general route to the generation of non-stabilized azomethine ylides, from various derivatives such as N-silylmethylamino ethers,6 N-silylmethylamidines,7 N-(disilylmethyl)pyrrolidines,8 N-silylmethyl-iminiums,9 -imidates,10 -imides,11 -amides,12 and -amines.13 The chiral non-racemic 1,3-dipolar cycloaddition was also investigated14,2e in the search of optically active proline derivatives or pyrrolidine systems. An efficient stereocontrol was obtained by the generation of chiral stabilized azomethine ylides from a chiral cyclic template as described by Harwood.15

A different methodology was adopted by our group by using optically active azomethine ylides derived from (-)-N-cyanomethyl- or (-)-N-alkyloxycarbonylmethyl-4-phenyl-1,3-oxazolidines (1) and (2) prepared
in one step from (R)-(-)-phenylglycinol.\textsuperscript{16} Reaction of 1 or 2 with trimethylsilyl triflate generated an intermediate iminium which was deprotonated by a base such as disopropylethylamine (Scheme 1). The cycloaddition of N-phenylmaleimide as dipolarophile and oxazolidine (1) under the previous conditions permitted the isolation of four cycloadducts (endo and exo) with a poor facial selectivity. In contrast, the use of 2a as an azomethine ylide precursor decreased the total yield of the reaction but afforded two diastereomers in equal amounts, resulting of an exo selectivity. Finally, a double induction using the ester of the chiral 8-phenylmenthol (2b) led to a single cycloadduct, as a consequence of an excellent diastereo and facial selectivity.\textsuperscript{16d}

![Scheme 1](image)

With the aim of synthesizing a great variety of highly substituted pyrrolidines as rigid proline analogs acting as conformationally constrained compounds, we became interested in cyclic amino-ether as depicted in formula (3) for providing a general access to stabilized azomethine ylides. To this end, we decided to investigate the reactivity of 1,3- and 3,1-benzoazaines as achiral azomethine ylide precursors.

**I-Reactivity of azomethine ylides derived from 1,3-aryl oxazines**

Four 1,3-aryloxazine derivatives have been synthesized with excellent yields. Preparation of naphthoxazines\textsuperscript{17} (4a) and (4b) was accomplished by a known method\textsuperscript{18} involving β-naphthol and two Mannich bases derived from formaldehyde, methyl glycinate and aminoacetonitrile, respectively. The new 1,3-benzoazaines (5a) and (5b) were conveniently obtained in three steps following a classical procedure:\textsuperscript{19} i) formation of a Schiff base with salicylaldehyde and methyl glycinate or aminoacetonitrile ii) reduction in situ with NaBH\textsubscript{4} iii) condensation with formaldehyde. Exposure of 4a and 5a to trimethylsilyl triflate, disopropylethylamine and N-benzylmaleimide in a one-pot procedure promoted the formation of cycloadducts (6) and (7) with modest yields (ca. 35 %) when the temperature of the reaction rose to 80-100 °C (Scheme 2). In contrast, no cycloaddition occurred when 4b and 5b were submitted to the same conditions. The formation of iminodiacetonitriles (8) and (9) was then observed, due to the elimination of the cyanide residue prior to the azomethine ylide generation.

Although the feasibility of forming reactive azomethine ylides from 1,3-aryloxazine precursors was verified by the characterization of cycloadducts (6) and (7), the rather drastic reaction conditions were inappropriate for the thermally unstable acetonitrile substituted compounds.

In the non-optimized reaction of 4a, two diastereomers (6a) epimeric at C-2, were obtained in a 55/45 ratio in favor of the 6a (H-2/H-3-cis). The stereoselectivity was increased in the case of compound (5a), leading to a major derivative (7b) (H-2/H-3, \textit{trans}), accompanied by its isomer (7a) (H-2/H-3, \textit{cis}) in an 80/20 ratio.\textsuperscript{20} The relative stereochemistry of the cycloadducts (6) and (7) was easily deduced from the \textit{3J} coupling
constant between H-2 and H-3 being respectively 2 Hz (trans relationship), 8 Hz (cis relationship).\textsuperscript{16,21}

![Chemical Structures]

\textbf{Scheme 2: Reagents: TMSOTf, i-Pr\textsubscript{2}NEt, toluene/Δ; N-benzylmaleimide.}

\section*{II-Reactivity of azomethine ylides derived from 3,1-benzoazazines}

Although the previous experiment demonstrated that 1,3-aryloxazine-derived azomethine ylides were accessible under certain conditions, the yields obtained in the cycloaddition reactions with maleimides were low. The lack of reactivity suggested that aminals of type (4) or (5), derived from phenolic compounds, are not convenient substrates in a general strategy because of their stability.

In contrast, the easily accessible 3,1-benzoazines (10), derived from 2-aminobenzyl alcohol should generate ylides in milder conditions, allowing subsequent 1,3-dipolar cycloaddition reactions.

We therefore decided to study the reactivity of a series 3,1-benzoazines and 2-substituted 3,1-benzoazines. Starting from the readily available 2-aminobenzyl alcohol, we prepared benzoazine (10a) as previously reported for similar compounds (Scheme 3).\textsuperscript{16a,16c} As an extension of our methodology we attempted to investigate the reactivity of ylides generated from 2-substituted 1,3-benzoazines (10b-d) obtained by the reaction of (2-hydroxymethylphenyl)aminoacetonitrile (11) with various aromatic aldehydes such as nicotinic, and isonicotinic aldehydes and furaldehyde (Scheme 3).

Under mild reaction conditions as previously described,\textsuperscript{16} two compounds (12a) and (13a) resulting from a cycloaddition to N-phenylmaleimide, were isolated in 48 and 16% yields respectively, after subsequent acidic treatment to remove the trimethylsilyl protective group. The relative stereochemistries were deduced as mentioned before from the value of the coupling constant between H-2 and H-3 being 8 Hz for 12a and 0 Hz for 13a.\textsuperscript{20} Since no conformation E or Z can be preferentially assigned to the intermediate iminium
bearing a cyano substituent, it is not possible to conclude if the observed stereochemistry is the result of either an exo addition to an E ylide or an endo addition to a Z ylide. Surprisingly, when the same reaction was repeated with N-benzylmaleimide, the ratio \(12b/13b = 40/60\) was inverted in favor of the cycloadduct \(13b\) isolated as the major compound.

Finally, a single compound \(14a\) was obtained in a two-step procedure in good yield (81%) by modifying both the cycloaddition and work-up conditions. We reasoned that the yield of the cycloaddition should be appreciably increased by adjusting the temperature of the reaction (-30 °C to 0 °C). Furthermore, treatment of the crude reaction mixture with AgBF\(_4\) could allow in a one-pot reaction successively removal of the trimethylsilyl protective group, generation of an iminium ion by elimination of cyanide anion as previously reported,\(^{22}\) and oxazine ring closure. The same procedure was applied successfully to the cycloaddition products with N-benzylmaleimide, affording a single compound \(14b\) in 70% yield.

The excellent stereochemical control at C-2 of pyrrolopyrrolidines \(14\) can be rationalized by an approach of the nucleophilic hydroxyl group to the least-hindered face of the planar iminium ion created by elimination of the cyanide anion (Scheme 4).

This novel sequential combination provided an easy access to molecules possessing a high degree of complexity which would otherwise require a multistep synthesis. Therefore we focussed our work in applying this cascade methodology to 2-substituted 3,1-benzoazines.

The synthesis of 2,5-disubstituted pyrrolidines has attracted much interest in the past few years.\(^{23}\) The use of aromatic aldehydes such as benzaldehyde\(^{24}\) and furaldehyde\(^{25}\) for the synthesis of aryl imines activated by electron withdrawing groups as potential 1,3-dipoles has been investigated. In most cases, the
cycloaddition reactions of this type of stabilized azomethine ylides exhibited a poor selectivity at the newly created stereogenic center. This result presumably reflected the E:Z ratio of the stabilized ylide. In a detailed study, Harwood\textsuperscript{21} reported on the cycloaddition of a chiral non-racemic ylide generated from (3S,5R)-diphenylmorpholinone and benzaldehyde to maleimide leading to four diastereomers in 9, 11, 13, and 38% ratio. An \textit{exo}- or \textit{endo}-attack of the dipolarophile on the ylide in either a \textit{syn}- or \textit{anti}-configuration was suggested.

Therefore, the same sequential methodology as described before (ylide generation and cycloaddition followed by AgBF\textsubscript{4} reaction) was applied to the 3,1-benzoazines (10b-d). In each case, three final oxazines (15), (16), and (17) were obtained (Scheme 5). Again, the coupling constants between H-2/H-3 and H-5/H-4 allowed an unambiguous determination of the relative stereochemistry at C-2 and C-5 (Table) with the exception of compound (17b) which was shown to be H-2/H-3 \textit{trans} through its N-benzylpyridinium derivative.\textsuperscript{20}

![Scheme 5](image)

Taking into account the low yield of compounds (17) (Table), one can assume a good stereoselectivity (\textit{cis}) at the new C-5 stereogenic center. In contrast, the formation of C-2 diastereomers from the 2-substituted oxazines is quite confusing. Indeed, the introduction of an aromatic ring may stabilize the intermediate ylide in a preferential conformation allowing a good cycloaddition selectivity. On the other hand, the absence of stereoselectivity at C-2 resulting in the formation of compounds (15) and (16) in almost equal amount can be rationalized by a \(\pi\)-stacking effect of the two aromatic rings surrounding the intermediate iminium created by the elimination of the cyanide anion by AgBF\textsubscript{4}. This additional effect may allow an attack of the nucleophilic hydroxyl anion from both sides of the molecule.
Table: Yields of the three diastereomeric oxazines obtained by the cycloaddition of dipoles (10b-d) with N-substituted maleimides followed by treatment with AgBF₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>dipole</th>
<th>dipolarophile</th>
<th>oxazine</th>
<th>15 (%)</th>
<th>16 (%)</th>
<th>17 (%)</th>
<th>Yield %</th>
</tr>
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<tr>
<td>1</td>
<td>10b</td>
<td>R = phenyl</td>
<td>a Ar = 3-pyridinyl</td>
<td>32</td>
<td>29</td>
<td>8</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>R = benzyl</td>
<td>b Ar = 3-pyridinyl</td>
<td>20</td>
<td>11</td>
<td>-</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>R = phenyl</td>
<td>c Ar = 4-pyridinyl</td>
<td>23</td>
<td>10</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>R = benzyl</td>
<td>d Ar = 2-furanyl</td>
<td>26</td>
<td>32</td>
<td>10</td>
<td>68</td>
</tr>
</tbody>
</table>

In conclusion, we have demonstrated that various 3,1-benzoazaines may be successfully converted to stabilized azomethine ylides. A sequential methodology was developed for the synthesis in good to excellent yields of highly functionalized pyrrolopyrrolidines in a two-step procedure.

**EXPERIMENTAL**

**General Methods.** ¹H and ¹³C NMR spectra of CDCl₃, C₆D₆, DMSO-d₆, and acetone-d₆ solutions were recorded at 300 and 75 MHz (Bruker, AC-300) respectively. MS spectra (low resolution) were obtained in the chemical ionization mode with NH₃ on a Nermag/Sidar V 2.3. FTIR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Melting points were measured with a Leica Galen III apparatus. Starting materials and solvents were purchased from commercial sources. Tetrahydrofuran was dried via distillation from sodium-benzophenone ketyl. Other solvents were dried and distilled according to standard procedures immediately before use. Flash chromatography was carried out on silica gel (20-45 µm).

**Methyl N-[(2-hydroxyphenyl)methyl]glycinate:** To a solution of MeOH (500 mL) were added 6.28 g (50 mmol) of methyl glycinate hydrochloride and 2.8 g (50 mmol) of KOH (pellets). The mixture was refluxed until total dissolution and stirred for 1 h at rt after addition of salicylaldehyde (5.5 mL, 51.5 mmol). Sodium borohydride (1.89 g, 50 mmol) was added slowly and the reaction mixture was stirred for 30 min. The mixture was then poured into 300 mL of water and extracted with ethyl acetate (100 mL). The organic layer was washed with an aqueous saturated solution of NaCl and dried over Na₂SO₄. Evaporation to dryness yielded 6.72 g (69%) of methyl N-2-(hydroxyphenyl)methylglycinate.

**2H-1,3-Benzoxazine-3(4H)-acetic acid methyl ester (5a):** A solution of methanol (80 mL) containing methyl N-[(2-hydroxyphenyl)methyl]glycinate (5.975 g, 25.6 mmol), paraformaldehyde (0.920 g, 25.6 mmol), KOH (0.35 g, 0.6 mmol) was refluxed for 90 min and cooled to rt. A saturated aqueous solution of NaHCO₃ was then added to the reaction mixture which was extracted with ethyl acetate (2 x 100 mL). The organic layers were washed with brine, dried over Na₂SO₄ and evaporated to dryness under vacuum. Flash chromatography (silica, 250 g, cyclohexane/ethyl acetate 80/20) afforded 4.66 g (74%) of oxazine (5a) as a colorless oil. IR (ν cm⁻¹): 1746, 1225 (acetate); ¹H NMR (CDCl₃) δ: 3.61 (s, 2H, N-CH₂), 3.75 (s, 3H, Me), 4.10 (s, 2H, N-CH₂-Ph), 4.89 (s, 2H, N-CH₂-O), 6.7-7.2 (4H, H-aromatics); ¹³C NMR (CDCl₃) δ: 50.6 (N-CH₂CO), 51.9 (Me), 52.7 (N-CH₂-Ph), 82.5 (N-CH₂-O), 116.4, 120.8, 127.5, 127.8 (CH-aromatics), 119.2, 153.6 (C-aromatics), 171.0 (ester); m/z (Cl, NH₃), 208 (M+1); HRMS m/z [M]⁺, 207.0897, calc'd for C₁₁H₁₃NO₃ 207.0895.
**2H-1,3-Benzoxazine-3-(4H)-acetonitrile (5b):** Same procedure as for 5a using aminoacetonitrile hydrochloride (1 equiv) instead of methyl glycinate hydrochloride. Oxazine (5b) was obtained in 68 % yield and crystallized from ether.

mp 70-71 °C; IR (v cm⁻¹): 2234 (CN); ¹H NMR (CDCl₃) δ: 3.72 (s, 2H, N-CH₂-CN), 4.11 (s, 2H, N-CH₂-Ph), 4.87 (s, 2H, N-CH₂-O), 6.7-7.2 (4H, H-aromatics); ¹³C NMR (CDCl₃) δ: 40.1 (N-CH₂-CN), 50.1 (N-CH₂-Ph), 81.4 (N-CH₂-O), 116.3 (CN), 118.1 (C-aromatic), 121.4, 127.5, 128.2 (CH-aromatics), 153.1 (C-aromatic); m/z (IC, NH₃): 192 (M+1)⁺, 175 (M+1)⁺; Anal. Calcd for C₁₀H₁₀N₂O: C, 68.95; H 5.79 ; N 16.08. Found: C, 68.54; H 5.79; N 16.31.

**Pyrrolopyrrolidines (6a)** (H₂/H₃ cis; (±)- (1α,3αβ,6αβ) -octahydro-2[2-hydroxy-1-naphthalenyl]methyl)-4,6-dioxo-5-phenylmethyl-1-pyrrolo[3,4-c]pyrrole-carboxylic acid methyl ester) and (6b) (H₂/H₃ trans; (±)-(1α,3αα,6αα)-octahydro-2[2-hydroxy-1-naphthalenyl]methyl]-4,6-dioxo-5-phenylmethyl-1-pyrrolo[3,4-c]pyrrole-carboxylic acid methyl ester): In a typical procedure, N,N-diisopropylethylamine (2.45 mL, 14 mmol) and trimethylsilyl triflate (2.8 mL, 15.4 mmol) were added dropwise to a solution of 7 mmol of oxazine and 9.1 mmol of N-benzylmaleimide in dry toluene (250 mL) under an argon atmosphere. The reaction mixture was refluxed for 3 h. Trimethylsilyl triflate (0.63 mL, 3.5 mmol) was added dropwise and the reaction mixture refluxed under an argon atmosphere for 90 min. It was then quenched with 100 mL of an aqueous saturated solution of NaHCO₃ and extracted with ethyl acetate (2 x 100 mL). The organic layers were washed with water (300 mL) and brine (250 mL), dried over Na₂SO₄ and evaporated to dryness. Flash chromatography (silica 150 g, cyclohexane/ethyl acetate 75/25) afforded 271 mg (9 %) of 6a (H₂/H₃ cis) and 232 mg (7 %) of 6b (H₂/H₃ trans).

6a: mp 199-202 °C (ether); IR (v cm⁻¹): 3367 (OH), 1774 (imide), 1728 (ester), 1698 (imide), 1218 (acetate); ¹H NMR (C₆D₆) δ: 1.64 (dd, J = 10 and 8 Hz, 1H, H-5), 2.10 (t, J = 8 Hz, 1H, H-4); 2.69 (t, J = 8 Hz, 1H, H-3), 2.85 (d, J = 8 Hz, 1H, H-2), 3.15 (d, J = 10 Hz, 1H, H-5), 3.38, 3.42, (AB, J = 13 Hz, 1H, N-CH₂-Ar), 3.54 (s, 3H, Me), 3.88, 3.92 (AB, J = 13 Hz, 1H, N-CH₂-Ar), 4.45 (s, 2H, N-CH₂-Ph), 7.0-7.8 (m, 11H, H-aromatics); ¹³C NMR (CDCl₃) δ: 42.7 (N-CH₂-Ph), 43.1 (C-4), 47.1 (C-3), 49.1 (C-5), 52.8 (Me), 54.8 (N-CH₂-Ph), 68.1 (C-2), 112.0, 119.0, 120.7, 122.5, 126.3, 127.7, 127.9, 128.6, 129.7 (CH-aromatics), 132.4, 134.8, 155.3, 170.2 (ester), 175.0, 176.9 (imide); m/z (Cl, NH₃): 445 (M+1)⁺; Anal. Calcd for C₂₆H₂₄N₂O₅: C 68.15; H 5.61; N 6.11. Found: C, 67.93; H 5.35; N 6.06.

6b: amorphous; IR (v cm⁻¹): 3345 (OH), 1734 (ester), 1700 (imide), 1227 (acetate); ¹H NMR (C₆D₆) δ: 2.65 (td, J = 9 and 3 Hz, 1H, H-4), 2.72 (dd, J = 9 and 2 Hz, 1H, H-3), 2.89 (dd, J = 10 and 3 Hz, 1H, H-5), 3.09 (dd, J = 10 and 3 Hz, 1H, H-5), 3.14 (s, 3H, Me), 3.90 (d, J = 2 Hz, 1H, H-2), 3.91, 3.95, 4.00, 4.04 (AB, J = 15 Hz, 2H, N-CH₂-Ar), 4.57 (s, 2H, N-CH₂-Ph), 7.0-7.7 (m, 11H, H-aromatics); ¹³C NMR (C₆D₆) δ: 43.5 (N-CH₂-Ph), 44.6 (C-4), 48.4 (C-5), 49.5 (C-3), 52.2 (Me), 54.2 (N-CH₂-Ar), 65.7 (C-2), 112.4, 119.7 (C-aromatics), 122.2, 123.4, 127.1, 128.2, 128.5, 128.8, 129.5, 129.6, 130.6 (CH-aromatics), 156.6 (C-aromatic), 171.1 (ester), 176.5, 177.5 (imide); m/z (Cl, NH₃): 445 (M+1)⁺.
Pyrrolidines (7a) (H₂/H₃ cis; (±)-1α,3αβ,6αβ)-octahydro-2-(2-hydroxyphenylmethyl)-4,6-dioxo-5-phenylmethyl-1-pyrrolo[3,4-c]pyrrolecarboxylic acid methyl ester) and (7b) (H₂/H₃ trans; (±)-1α,3αα,6αα)-octahydro-2-(2-hydroxyphenylmethyl)-4,6-dioxo-5-phenylmethyl-1-pyrrolo[3,4-c]pyrrolecarboxylic acid methyl ester): Same procedure as for 6a and 6b with benzoazine (5a) (3.10 g, 15 mmol).

7a: (0.347 g, 6 %); crystallized from chloroform; mp 160-162 °C; IR (v cm⁻¹): 3380 (OH), 1770 (imide), 1734 (ester), 1704 (imide), 1220 (acetate); ¹H NMR (CDCl₃) δ: 2.53 (dd, J = 10 and 8 Hz, 1H, H-5), 3.03, 3.08, 4.16, 4.65 (AB, J = 13 Hz, 2H, N-CH₂-Ar), 3.26 (t, J = 8 Hz, 1H, H-4), 3.40 (d, J = 10 Hz, 1H, H-5), 3.50 (d, J = 8 Hz, 1H, H-2), 3.57 (t, J = 8 Hz, 1H, H-3), 3.76 (s, 3H, Me), 4.65 (s, 2H, N-CH₂-Ph), 6.5-7.4 (m, 12H, H-aromatics), 8.15 (s, 1H, OH); ¹³C NMR (CDCl₃) δ: 42.7 (N-CH₂-Ph), 43.2 (C-4), 47.1 (C-3), 51.9 (Me), 54.8 (C-5), 55.8 (N-CH₂-Ar), 67.9 (C-2), 116.5, 119.1, 121.2 (C-aromatics), 127.7, 127.9, 128.7, 129.5 (CH-aromatics), 134.8, 156.6 (C-aromatics), 170.1 (ester), 175.0, 176.9 (imide); m/z (CI, NH₃): 395 (M+1)⁺; Anal. Calcd for C₉₂H₸₂N₂O₅, CHCl₃: C 53.77; H 4.51; N 5.45. Found: C 54.21; H 4.81; N 5.61.

7b: (1.44 g, 24 %), colorless oil; IR (v cm⁻¹): 3363 (OH), 1775 (imide), 1737 (ester), 1706 (imide), 1244 (acetate); ¹H NMR (CDCl₃) δ: 3.13 (dd, J = 10 and 2 Hz, 1H, H-5), 3.30 (dd, J = 10 and 8 Hz, 1H, H-5), 3.39 (td, J = 8 and 2 Hz, 1H, H-4), 3.48 (dd, J = 8 and 2 Hz, 1H, H-3), 3.76 (s, 2H, N-CH₂-Ar), 3.77 (s, 3H, Me), 3.99 (d, J = 2 Hz, 1H, H-2), 4.68 (s, 2H, N-CH₂-Ph), 7.2-7.5 (m, 9H, H-aromatics); ¹³C NMR (CDCl₃) δ: 42.9 (N-CH₂-Ph), 43.9 (C-4), 48.6 (C-3), 52.3 (Me), 53.4 (C-5), 54.2 (N-CH₂-Ar), 65.4 (C-2), 116.2, 119.5, 120.7 (CH-aromatics), 128.0, 128.7, 129.3, 134.0 (CH-aromatics), 135.0, 156.7 (C-aromatics), 170.2 (ester), 177.3 (imide); m/z (CI, NH₃): 395 (M+1)⁺; HRMS m/z [M]+, 394.1532, calcd for C₉₂H₸₂N₂O₅ 394.1529.

[(2-Hydroxy-1-naphthalenyl) methyl]iminodiacetonitrile (8): obtained from 1H-naphtho[1,2-e]-[1,3]oxazine-2(3H)-acetonitrile (4b) (2.35 g, 10.5 mmol) as crystals from CHCl₃ (0.960 g, 36 %); mp 151-153 °C; ¹H NMR (acetone-d₆) δ: 3.93 (s, 4H, N-CH₂-CN), 4.39 (s, 2H, N-CH₂-Ar), 7.30 (d, J = 9 Hz, 1H, H-3), 7.38 (ddd, J = 8, 7, and 1 Hz, 1H, H-aromatic), 7.54 (ddd, J = 8, 7, and 1 Hz, H-aromatic), 7.85 (d, J = 9 Hz, 1H, H-4), 8.85 (d, J = 8 Hz, 1H, H-aromatic), 8.13 (d, J = 8 Hz, 1H, H-aromatic), 9.11 (s, 1H, OH); ¹³C NMR (Acetone-d₆) δ: 42.4 (N-CH₂-CN), 48.7 (N-CH₂-Ar), 113.9 (CN), 116.7 (C-1), 119.2 (C-3), 124.4, 124.7, 128.0, 129.8 (CH-aromatics), 130.4 (C-aromatic), 131.7 (CH-aromatic), 135.5 (C-aromatic), 155.7 (C-2); m/z (CI, NH₃): 269 (M+1)⁺, 252 (M+1)⁺.

([(2-Hydroxyphenyl)methyl]iminodiacetonitrile (9): Same procedure as above from benzoazine-3-acetonitrile (5b): (522 mg, 3 mmol) as a colorless oil (0.255 g, 42 %); IR (v cm⁻¹): 3376 (OH), 2240 (CN); ¹H NMR (CDCl₃) δ: 3.70 (s, 4H, N-CH₂-CN), 3.94 (s, 2H, N-CH₂-Ar), 6.9-7.4 (m, 4H, H-aromatics); ¹³C NMR (CDCl₃) δ: 41.1 (N-CH₂-CN), 56.1 (N-CH₂-Ar), 113.3 (CN), 116.7 (C-3), 118.5 (C-1), 120.7 (C-5), 130.0, 130.6 (CH-aromatics), 156.0 (C-2); m/z (CI, NH₃): 219 (M+1)⁺, 202 (M+1)⁺; HRMS m/z [M]+, 201.0899, calcd for C₁₁H₁₁N₁O₂ 201.0902.
**2H-3,1-Benzoxazine-1-(4H)-acetonitrile (10a):** Citric acid (15 g, 78 mmol) was dissolved in 165 mL of an aqueous solution of formaldehyde (15 % in water). An aqueous solution (200 mL) of KCN (5.85 g, 90 mmol), 400 mL of an aqueous solution of citric acid (13 g, 68 mmol), and 2-aminobenzyl alcohol (10 g, 81 mmol) were added simultaneously over 90 min. The reaction mixture was stirred for 2 h at rt. It was quenched with an aqueous saturated solution of NaHCO₃ (pH = 8) and extracted with ethyl acetate. The organic layers were washed with water (750 mL) and brine (750 mL), dried over Na₂SO₄ and evaporated to dryness. Crystallization from ether afforded 5.77 g of benzoxazine (10a). The mother liquors were purified by flash chromatography to give 3.7 g of 10a (yield 67 %).

mp 45-48 °C; IR (ν cm⁻¹), 2239 (CN); ¹H NMR (CDCl₃) δ: 4.10 (s, 2H, CH₂-CN), 4.70 (s, 2H, H-4), 4.88 (s, 2H, H-2), 6.9-7.3 (m, 4H, H-aromatics); ¹³C NMR (CDCl₃) δ: 40.9 (CH₂-CN), 67.3 (C-4), 81.0 (C-2), 116.2 (CN), 118.4 (C-8), 122.5 (C-6), 125.2 (C-5), 128.8 (C-4a), 127.6 (C-7), 141.8 (C-8a); m/z (Cl, NH₃): 192 (M+18)⁺, 175 (M+1)⁺; Anal. Calcd for C₁₀H₁₀N₂O: C 68.95; H 5.79; N 16.08. Found: C 68.89; H 5.78; N 16.31.

**2-Substituted 3,1-benzoxazines (10b-d):**

**General procedure :**

**a) (2-Hydroxymethylphenyl) aminoacetonitrile (11):** To a solution of 2-aminobenzyl alcohol (2.9 g, 23.6 mmol) in anhydrous THF (75 mL) were added N,N-diisopropylethylamine (4.9 mL, 28.3 mmol) and bromoacetonitrile (2 mL, 28.3 mmol). The reaction mixture was refluxed under an argon atmosphere for 24 h. After cooling the precipitate was filtered and the solution was evaporated to dryness under vacuum. The acetonitrile was crystallized from ethyl acetate (3.8 g, 100 %). mp 96-98 °C; IR (ν cm⁻¹): 3473 (NH), 3332 (OH), 2248 (CN); ¹H NMR (CDCl₃) δ: 1.95 (s, 1H, OH), 4.13 (d, J = 7 Hz, 2H, N-CH₂-CN), 4.66 (s, 2H, Ph-CH₂-OH), 5.37 (t, J = 7 Hz, 1H, NH), 6.77 (d, J = 8 Hz, 1H, H-2), 6.87 (t, J = 8 Hz, 1H, H-4), 7.10 (d, J = 8 Hz, 1H, H-5), 7.30 (t, J = 8 Hz, 1H, H-3); ¹³C NMR (CDCl₃) δ: 31.9 (N-CH₂-CN), 64.4 (O-CH₂), 111.0 (C-2), 117.0 (CN), 119.0 (C-4), 125.6 (C-6), 129.2, 129.6 (CH-aromatics), 144.7 (C-1); m/z (Cl, NH₃): 180 (M+18)⁺, 163 (M+1)⁺; Anal. Calcd for C₉H₁₇NO₂: C 66.65; H 6.21; N 17.27. Found: C 66.74; H 6.37; N 17.25.

**b) Cyclodehydration reaction**

To a solution of (2-hydroxymethylphenyl)aminoacetonitrile (11) (6.78 g, 41.8 mmol) in toluene (100 mL) were added pyridinium p-toluenesulfonate (2.3 g, 9.2 mmol) and 3-pyridinylcarboxaldehyde (35 mL, 0.37 mol). The reaction mixture was refluxed in a Dean-Stark apparatus for 30 min. Evaporation of toluene followed by distillation under reduced pressure (1.5 mm/8 °C) of the remaining 3-pyridinylcarboxaldehyde left a crude residue which was treated with an aqueous saturated solution of NaHSO₃ (150 mL) for 1 h. After filtration of the precipitate, the organic solution was washed with brine (100 mL), dried and evaporated to dryness. The pyridinylbenzoxazine (10b) crystallized from ether (5 g). Further flash chromatography of the mother liquors over silica (eluent: cyclohexane/ethyl acetate 40/60) afforded 2.83 g of 10b (total yield 7.83 g, 75 %).

mp 90-92 °C, IR (ν cm⁻¹): 2238 (CN); ¹H NMR (CDCl₃) δ: 3.76, 3.82, 3.98, 4.05 (AB, J = 18 Hz, 2H,
N-CH<sub>2</sub>-CN), 4.75, 4.80, 4.91, 4.96 (AB, J = 15 Hz, 2H, H-4), 5.65 (s, 1H, H-2), 6.9-7.3 (m, 4H, aromatics), 7.36 (dd, J = 8 and 5 Hz, H-aromatic), 7.88 (dt, J = 8 and 2 Hz, 1H, H-aromatic), 8.64 (dd, J = 5 and 2 Hz, 1H, H-aromatic); $^{13}$C NMR (CDCl<sub>3</sub>) δ: 38.7 (N-CH<sub>2</sub>-CN), 65.4 (C-4), 87.2 (C-2), 115.8 (CN), 118.5, 122.8, 123.6, 125.1 (CH-aromatics), 125.5 (C-aromatics), 128.0 (CH-aromatics), 132.2, 135.1, 141.6, 149.2, 150.5 (C-aromatics); m/z (Cl, NH<sub>3</sub>): 252 (M+1)<sup>+</sup>; Anal. Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O: C 71.70; H 5.21; N 16.72. Found: C 71.53; H 5.48; N 16.77.

(±)-2-(4-Pyridinyl)-(2H)-3,1-benzoazinone-(4H)-acetanitrile (10c): Obtained with 4-pyridinylcarboxaldehyde. Yield 82%; mp 119-121 °C (ether, ethyl acetate); IR (ν cm<sup>-1</sup>): 2238 (CN); $^1$H NMR (CDCl<sub>3</sub>) δ: 3.84, 3.90, 3.98, 4.04, (AB-system, J = 15 Hz, 2H, N-CH<sub>2</sub>-CN), 4.84, 4.89, 4.97, 5.02 (AB J = 15 Hz, 2H, N-CH<sub>2</sub>-O), 5.66 (s, 1H, H-2), 6.9-7.3 (m, 4H, H-aromatics), 7.46 (d, J = 6 Hz, 2H, H-aromatics) 8.67 (d, J = 6 Hz, 2H, H-aromatics); $^{13}$C NMR (CDCl<sub>3</sub>) δ: 39.4 (N-CH<sub>2</sub>-CN), 6.52 (C-4), 87.6 (C-2), 115.7 (CN), 119.3, 122.0, 123.2, 125.2, 128.0 (CH-aromatics), 121.6, 125.9, 145.0 (C-aromatics), 150.4 (CH-aromatics); m/z (Cl, NH<sub>3</sub>): 252 (M+1)<sup>+</sup>; Anal. Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O: C 71.70; H 5.21; N 16.72. Found: C 71.42; H 5.48; N 16.86.

(±)-2-(3-Furanyl)-(2H)-3,1-benzoazinone-(4H)-acetanitrile (10d): Obtained with 2-furanylcarboxaldehyde as a colorless oil (yield 71%); $^1$H NMR (CDCl<sub>3</sub>) δ: 3.93, 3.99, 4.08, 4.14 (AB, J = 18 Hz, 2H, N-CH<sub>2</sub>-CN), 4.81, 4.86, 4.94, 4.99 (AB, J = 15 Hz, 2H, N-CH<sub>2</sub>-O), 5.73 (s, 1H, H-2), 6.40 (dd, J = 3 and 1 Hz, 1H, H-4, H-furanyl), 6.50 (dd, J = 3 and 1 Hz, 1H, H-3, H-furanyl), 6.9-7.3 (m, 4H, H-aromatics), 7.49 (dd, J = 2 and 1 Hz, 1H, H-5, H-furanyl); $^{13}$C NMR (CDCl<sub>3</sub>) δ: 37.9 (N-CH<sub>2</sub>-CN), 65.2 (C-4), 83.4 (C-2), 110.5, 110.8 (CH-furanyl), 115.8 (CN), 116.0, 121.5 (CH-aromatics), 145.3 (C-5-furanyl), 149.1 (C-2-furanyl); m/z (Cl, NH<sub>3</sub>): 241 (M+1)<sup>+</sup>; HRMS m/z [M]+, 240.0901, calcd for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> 240.0899.

Pyrollopyrrolidines (12a) [(±)-(1α,3αβ,6αβ)-octahydro-2-(2-hydroxymethylphenyl)-4,6-dioxo-5-phenyl-pyrrolo[3,4-c]pyrrolocarbonitrile] and (13a) [(±)-(1β,3αα,6αα)-octahydro-2-(2-hydroxymethylphenyl)-4,6-dioxo-5-phenyl-pyrrolo[3,4-c]pyrrolocarbonitrile]: In a typical procedure, to a stirred solution of 10a (1.48 g, 8.5 mmol) and N-phenylmaleimide (1.9 g, 11 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (80 mL) was added N,N-diisopropylethylamine (3 mL, 17.2 mmol) under an argon atmosphere. The solution was then cooled to −78 °C. Trimethylsilyl triflate (2 mL, 10.4 mmol) was added dropwise in 15 min. The reaction mixture was stirred at −78 °C for 4 h and left at rt for 12 h. After concentration under vacuum the crude residue was dissolved in methanol (90 mL) and treated with a saturated aqueous solution of citric acid (pH = 3.5) during 18 h at rt. The resulting solution was made alkaline with a saturated aqueous solution of NaHCO<sub>3</sub> and extracted with ethyl acetate (250 mL). The organic layers were washed with water (250 mL) and brine (250 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness under vacuum. Flash chromatography of the residue (cyclohexane/ethyl acetate 80/20) afforded 12a (1.38 g, 47%) and 13a (495 mg, 17%).

12a: mp 169-172 °C (colorless crystals from methanol); IR ν cm<sup>-1</sup>: 3483 (OH), 2250 (CN), 1780, 1775
Pyroropyrroldinides (12b) [(±)-(1α,3αα,6αα)-octahydro-2-(2-hydroxymethylphenyl)-4,6-dioxo-5-phenylmethyl-1-pyrrolo[3,4-c]pyrrolcarbonitrile] and (13b) [(±)-(1α,3αα,6αα)-octahydro-2-(2-hydroxymethylphenyl)-4,6-dioxo-5-phenyl-1-pyrrolo[3,4-c]pyrrolcarbonitrile]: Same procedure as for compounds (12a) and (13a) with N-benzylmaleimide.

12b: colorless oil (yield 19%); IR (ν cm⁻¹): 3472 (OH), 2253 (CN), 1777, 1706 (imide); ¹H NMR (CDCl₃) δ: 2.25 (dd, J = 10 and 8 Hz, 1H, H-5), 2.38 (td, J = 8 and 2 Hz, 1H, H-4), 2.77 (t, J = 8 Hz, 1H, H-3), 3.39 (dd, J = 10 and 2 Hz, 1H, H-5), 3.73 (d, J = 8 Hz, 1H, H-2), 4.26 (s, 2H, N-CH₂-Ph), 4.44, 4.49, 4.62, 4.67 (AB, J = 14 Hz, 2H, CH₂OH), 7.1-7.6 (m, 9H, H-aromatics); ¹³C NMR (CDCl₃) δ: 42.7 (N-CH₂-Ph), 43.5 (C-4), 46.3 (C-3), 54.4 (C-2), 55.3 (C-5), 60.4 (CH₂OH), 114.9 (CN), 120.3, 126.5, 127.3, 127.6, 127.9, 128.7, 129.2 (CH-aromatics), 135.7, 138.3, 141.9 (C-aromatics), 173.3, 176.4 (C=O); m/z (CI, NH₃): 379 (M+18)⁺, 362 (M+1)⁺, 335 (M-HCN+1)⁺; HRMS m/z [M⁺], 361.1424, calcd for C₂₁H₁₄N₂O₃ 361.1426.

13b: colorless oil (yield 29%); IR (ν cm⁻¹): 3474 (OH), 2231 (CN), 1777, 1704 (imide); ¹H NMR (CDCl₃) δ: 3.47 (t, J = 8 Hz, 1H, H-4), 3.52 (d, J = 10 Hz, 1H, H-5), 3.60 (d, J = 8 Hz, 1H, H-3), 3.78 (dd, J = 10, 8 Hz, 1H, H-5), 3.91, 3.95, 3.99, 4.03 (AB-system, J = 12 Hz, 2H, N-CH₂-Ph), 4.63, 4.68, 4.74, 4.78 (AB, J = 12 Hz, 2H, N-CH₂-Ph), 4.63, 4.68, 4.74, 4.78 (AB, J = 14 Hz, 2H, O-CH₂-Ar), 5.13 (s, 1H, H-2), 7.1-7.6 (m, 9H, H-aromatics); ¹³C NMR (CDCl₃) δ: 42.5 (C-4), 43.2 (N-CH₂-Ph), 49.5 (C-3), 51.8 (C-5), 57.7 (C-2), 6.13 (CH₂OH), 115.5 (CN), 121.2, 126.4, 128.2, 128.7, 129.1, 130.2 (CH-aromatics), 135.1, 135.6, 141.4 (C-aromatics), 174.9, 177.0 (C=O); m/z (EI): 361 (M⁺), 343 (M-H₂O)⁺, 334 (M-HCN)⁺.
for 12 h. After concentration under vacuum the crude residue was dissolved in dry THF (500 mL). Silver tetrafluoroborate (7.43 g, 38.2 mmol) was added and the reaction mixture was stirred under nitrogen atmosphere at rt for 5 h. It was then quenched with an aqueous saturated NaHCO₃ solution (pH = 8), and extracted with ethyl acetate (350 mL). The organic layers were washed with water and brine, dried over Na₂SO₄ and evaporated to dryness. Flash chromatography of the residue (silica, cyclohexane/ethyl acetate 75/25) afforded 7.5 g (81 %) of pyrrolidine (14a); mp 174-177 °C (cyclohexane/ethyl acetate 60/40); IR (v cm⁻¹): 1783, 1715 (imide); ¹H NMR (CD₂Cl₂) δ: 2.66 (td, J = 8 and 1 Hz, 1H, H-4), 3.09 (d, J = 8 Hz, 1H, H-3), 3.17 (dd, J = 9 and 8 Hz, 1H, H-5), 3.85 (dd, J = 9 and 1 Hz, 1H, H-5), 4.37 (s, 2H, O-CH₂), 4.83 (s, 1H, H-2), 6.4-7.4 (m, 9H, H-aromatics); ¹³C NMR (CD₂Cl₂) δ: 44.4 (C-4), 52.9 (C-3), 56.2 (C-5), 68.0 (O-CH₂), 92.4 (C-2), 123.4, 125.6 (CH-aromatics), 126.6, 127.0, 128.2, 128.5, 128.8, 129.5 (CH-aromatics), 133.3, 143.3 (C-aromatics), 174.7, 177.6 (C=O); m/z (CI, NH₃): 321 (M+1)⁺; Anal. Calcd for C₁₉H₁₈N₂O₃: C 71.24; H 5.03; N 8.74. Found: C 71.15; H 5.20; N 8.40.

Pyrrolobenzoazine (14b) [(±)-(6α,6β,9αβ,9aβ)-9a,10-dihydro-8-phenylmethyl-(5H,6aH)-1-pyrrolo[3',4';3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9(6bH,8H)-dione]: The same procedure as for compound (14a) was employed with N-benzylmaleimide to give pyrrolidine (14b) as an amorphous compound (70 %). IR (v cm⁻¹): 1778, 1707 (imide); ¹H NMR (CD₂Cl₂) δ: 2.63 (td, J = 8 and 1 Hz, 1H, H-4), 3.03 (d, J = 8 Hz, 1H, H-3), 3.17 (dd, J = 9 and 8 Hz, 1H, H-5), 3.84 (dd, J = 9 and 1 Hz, 1H, H-5), 4.43 (s, 2H, (N-CH₂-Ph), 4.53 (s, 2H, O-CH₂), 4.80 (s, 1H, H-2), 6.5-7.5 (m, 9H, H-aromatics); ¹³C NMR (CD₂Cl₂) δ: 42.4 (N-CH₂-Ph), 43.5 (C-4), 52.0 (C-3), 54.9 (C-5), 67.0 (O-CH₂), 91.0 (C-2), 122.4, 124.7, 127.3, 127.6, 127.9, 128.5 (CH-aromatics), 125.8, 136.0, 142.4 (C-aromatics), 174.7, 177.5 (C=O); m/z (CI, NH₃): 669 (2M+1)⁺; HRMS m/z [M]⁺, 334.1320, calcd for C₂₅H₂₆N₂O₃ 334.1317.

Pyrrolobenzoazines (15a) [(±)-(6α,6α,9α,10α)-9a,10-dihydro-8-phenyl-10-(3-pyridinyl)-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH,8H)-dione], (16a) [(±)-(6α,6β,9αβ,10β)-9a,10-dihydro-8-phenyl-10-(3-pyridinyl)-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH,8H)-dione] and (17a) [(±)-(6α,6β,9α,10α)-9a,10-dihydro-8-phenyl-10-(3-pyridinyl)-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(8H,6bH)-dione]: The same procedure as for the synthesis of 14a was employed with a solution of (3-pyridinyl)benzoxazine (10b) in toluene, to give a crude mixture of diastereomers (69 %). Flash chromatography (silica, 150 g, ethyl acetate/cyclohexane 70/30) afforded 15a (32 %), 16a (29 %), 17a (8 %).

15a: mp 250-265 °C (acetone); IR (v cm⁻¹): 1784, 1718 (imide); ¹H NMR (CDCl₃) δ: 3.44 (dd, J = 9 and 3 Hz, 1H, H-4), 3.98 (dd, J = 9 and 7 Hz, 1H, H-3), 4.89, 4.94, 5.03, 5.08 (AB, J = 15 Hz, 2H, O-CH₂), 5.15 (d, J = 3 Hz, 1H, H-5), 5.47 (d, J = 7 Hz, 1H, H-2), 6.3-7.5 (m, 10H, H-aromatics), 7.79 (dt, J = 8 and 2 Hz, 1H, H-aromatic), 8.61 (dd, J = 5 and 1.5 Hz, 1H, H-aromatic), 8.72 (d, J = 2 Hz, 1H, H-aromatic); ¹³C NMR (CDCl₃) δ: 49.1 (C-3), 54.0 (C-4), 66.1 (C-5), 67.9 (O-CH₂), 89.3 (C-2), 118.5,
121.9, 123.9, 124.8, 126.5 127.4, 128.7, 129.1 (CH-aromatics), 123.3, 131.7, 138.4, 141.0 (CH-aromatics), 134.5, 148.3, 149.2 (CH-aromatics), 172.2, 175.5 (C=O); m/z (CI, NH3): 398 (M+1)^+; HRMS m/z [M]^+, 397.1424, calcd for C_{23}H_{19}N_{3}O_{3} 397.1426.

16a: mp 177-180 °C (ethyl acetate/cyclohexane 60/40); IR (ν cm⁻¹): 1783, 1716 (imide); ^1H NMR (CDCl₃) δ: 3.61 (dd, J = 9 and 1.5 Hz, 1H, H-4), 3.84 (dd, J = 9 and 2 Hz, 1H, H-3), 4.79, 4.84, 5.08, 5.13 (AB, J = 15 Hz, 2H, O-CH₂), 5.22 (d, J = 2 Hz, 1H, H-2), 5.46 (d, J = 1.5 Hz, 1H, H-5), 6.7-7.5 (m, 10H, aromatics), 7.78 (d, J = 8 Hz, 1H, H-aromatic), 8.38 (d, J = 5 Hz, 1H, H-aromatic), 8.64 (s, 1H, H-aromatic), ^13C NMR (CDCl₃) δ: 51.3 (C-3), 52.0 (C-4), 66.0 (C-5), 67.6 (O-CH₂), 91.5 (C-2), 119.6, 121.3, 123.4 (CH-aromatics), 124.1 (C-aromatic), 124.8, 126.2, 127.3, 128.8, 129.1 (CH-aromatics), 131.4 (C-aromatic), 133.5 (C-aromatic), 135.5, 139.0 (C-aromatics), 148.9, 149.4 (CH-aromatics), 174.2, 176.1 (C=O); m/z (CI, NH₃): 398 (M+1)^+; HRMS m/z [M]^+, 397.1432, calcd for C_{23}H_{19}N_{3}O_{3} 397.1426.

Pyrolobenzoxazines (15b) [(±)-(6α,6bα,9α,10α)-9a,10-dihydro-8-phenylmethyl-10-(3-pyridinyl)-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH,8H)-dione] and (16b) [(±)-(6α,6bβ,9aβ,10β)-9a,10-dihydro-8-phenylmethyl-10-(3-pyridinyl)-5H,6aH-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH,8H)-dione]: The same procedure as above was employed with (3-pyridinyl)benzoxazine (10b) and N-benzylmaleimide to give crystalline compounds (15b) (23 %) and (16b) (10 %).

15b: mp 204 °C (ethyl acetate/cyclohexane 70/30); IR (ν cm⁻¹): 1777, 1709 (C=O); ^1H NMR (CDCl₃) δ: 3.30 (dd, J = 9 and 3 Hz, 1H, H-4), 3.87 (dd, J = 9 and 7 Hz, 1H, H-3), 4.69 (s, 2H, N-CH₂-Ph), 4.73, 4.78, 4.95, 5.00 (AB, J = 15 Hz, 2H, O-CH₂), 5.02 (d, J = 3 Hz, 1H, H-5), 6.2-7.4 (m, 10H, H-aromatics), 7.74 (dd, J = 8, 2, and 1.5 Hz, 1H, H-aromatic), 8.60 (dd, J = 5 and 1.5 Hz, 1H, H-aromatic), 8.70 (d, J = 2 Hz, 1H, H-aromatic); ^13C NMR (CDCl₃) δ: 42.7 (N-CH₂-Ph), 49.1 (C-3), 53.9 (C-4), 65.7 (C-5), 67.5 (O-CH₂), 88.8 (C-2), 118.7, 122.0 (CH-aromatics), 123.4 (C-aromatic), 123.8, 124.7, 127.3, 127.7, 128.4 134.4 (CH-aromatics), 135.2, 138.2, 140.9 (C-aromatics), 148.5, 149.4 (CH-aromatics), 172.6, 176.1 (C=O); m/z (CI, NH₃): 412 (M+1)^+; HRMS m/z [M]^+ 411.1577, calcd for C_{23}H_{19}N_{3}O_{3} 411.1583

16b: mp 192 °C (ethyl acetate/cyclohexane 60/40); IR (ν cm⁻¹): 1780, 1707 (C=O); ^1H NMR (CDCl₃) δ: 3.49 (d, J = 9 Hz, 1H, H-3), 3.72 (dd, J = 9 and 2 Hz, 1H, H-4), 4.72 (s, 2H, N-CH₂-Ph), 4.79, 4.84, 5.01, 5.06 (AB, J = 15 Hz, 2H, O-CH₂), 5.09 (d, J = 2 Hz, 1H, H-5), 5.38 (s, 1H, H-2), 6.6-7.0 (m, 4H, H-aromatics), 7.13 (dd, J = 8 and 5 Hz, 1H, H-aromatic), 7.2-7.4 (m, 5H, H-aromatics), 7.74 (ddd, J = 8, 2, and 1.5 Hz, 1H, H-aromatic), 8.4 (d, J = 5; 1.5 Hz, 1H, H-aromatic), 8.63 (d, J = 2 Hz, 1H,
H-aromatic); $^{13}$C NMR (CDCl$_3$) $\delta$: 42.9 (N-CH$_2$-Ph), 51.2 (C-4), 52.0 (C-3), 65.7 (C-5), 67.6 (O-CH$_3$), 91.2 (C-2), 119.5, 121.2, 123.4 (CH-aromatics), 124.1 (C-aromatic), 124.7, 127.2, 128.0, 128.4, 128.7 (CH-aromatics), 135.1, 139.1 (C-aromatics), 149.1, 149.5 (CH-aromatics), 174.7, 176.6 (C=O); m/z (Cl, NH$_3$): 412 (M+1)$^+$.

**Pyrrolobenzoxazines (15c) [(±)-(6α,6β,9α,10α)-9a,10-dihydro-8-phenylmethyl-10-(4-pyridinyl)-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH8H)-dione] and (16c) [(±)-(6α,6β,9α,10β)-9a,10-dihydro-8-phenylmethyl-10-(4-pyridinyl)-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH8H)-dione]: The same procedure as above was employed with (4-pyridinyl)benzoxazine (10c) and N-phenylmaleimide to give compounds (15c) (23 %) and (16c) (10 %).

**15c**: mp 233-236 °C (methanol); IR (ν cm$^{-1}$): 1784, 1716 (C=O); $^1$H NMR (CDCl$_3$) $\delta$: 3.44 (dd, J = 9 and 3 Hz, 1H, H-4), 3.98 (dd, J = 9 and 7 Hz, 1H, H-3), 4.91, 4.96, 5.07, 5.12 (AB, J = 15 Hz, 2H, O-CH$_2$), 5.16 (d, J = 3 Hz, 1H, H-5), 5.52 (d, J = 7 Hz, 1H, H-2), 6.3-7.5 (m, 11H, H-aromatics), 8.69 (d, J = 6 Hz, 2H, H-aromatics); $^{13}$C NMR (CDCl$_3$) $\delta$: 49.1 (C-3), 53.7 (C-4), 67.0 (C-5), 68.0 (O-CH$_2$), 89.3 (C-2), 117.9, 121.4, 121.7, 124.8, 126.5, 127.6, 128.8, 129.1 (CH-aromatics), 122.8, 131.6, 140.9, 151.9 (C-aromatics), 150.5 (CH-aromatics), 172.0, 175.4 (C=O); m/z (Cl, NH$_3$): 398 (M+1)$^+$; Anal. Calcd for C$_2$H$_{19}$N$_3$O$_3$: C 72.53; H 4.82; N 10.57. Found: C 72.03; H 4.80; N 10.31.

**16c**: amorphous; IR (ν cm$^{-1}$): 1781, 1711 (C=O); $^1$H NMR (DMSO-d$_6$) $\delta$: 3.70 (d, J = 9 Hz, 1H, H-4), 3.85 (d, J = 8 Hz, 1H, H-3), 4.89, 4.94, 5.05, 5.10 (AB, J = 15 Hz, 2H, O-CH$_2$), 5.29 (s, 1H, H-5), 5.46 (s, 1H, H-2), 6.6-7.6 (m, 11H, H-aromatics), 8.48 (d, J = 4.5 Hz, 2H, H-aromatics); $^{13}$C NMR (DMSO-d$_6$) $\delta$: 51.9 (C-4), 53.3 (C-3), 65.6 (C-5), 68.5 (O-CH$_2$), 91.7 (C-2), 118.9, 121.0, 123.7, 128.1, 129.7, 130.1 (CH-aromatics), 124.4, 133.1, 140.7, 150.8 (C-aromatics), 151.0 (CH-aromatics), 175.5, 177.2 (C=O); m/z (Cl, NH$_3$): 398 (M+1)$^+$; Anal. Calcd for C$_2$H$_{19}$N$_3$O$_3$I/2H$_2$O: C 70.92; H 4.6; N 10.34. Found: C 70.71; H 5.04; N 10.35.

**Pyrrolobenzoxazines (15d) [(±)-(6α,6β,9α,10α)-9a,10-dihydro-8-phenylmethyl-10-(2-furanyl)-8-phenylmethyl-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH8H)-dione], (16d) [(±)-(6α,6β,9α,10β)-9a,10-dihydro-8-phenylmethyl-10-(2-furanyl)-8-phenylmethyl-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(8H,6bH)-dione] and (17d) [(±)-(6α,6β,9α,10β)-9a,10-dihydro-8-phenylmethyl-10-(2-furanyl)-8-phenylmethyl-(5H,6aH)-pyrrolo[3',4':3,4]pyrrolo[1,2-a][3,1]benzoxazine-7,9-(6bH8H)-dione]: The same procedure as above was employed with (2-furanyl)benzoxazine and N-benzylmaleimide to yield compounds (15d) (26 %), (16d) (32 %) and (17d) (10 %).

**15d**: mp 148-150 °C (methanol); IR (ν cm$^{-1}$): 1780, 1710 (imide); $^1$H NMR (CDCl$_3$) $\delta$: 3.56 (dd, J = 9 and 3 Hz, 1H, H-4), 3.90 (dd, J = 9 and 7 Hz, 1H, H-3), 4.70 (s, 2H, N-CH$_2$-Ph), 4.77, 4.82, 4.98, 5.03 (AB, J = 15 Hz, 2H, O-CH$_2$), 5.05 (d, J = 3 Hz, 1H, H-5- furanyl), 5.33 (d, J = 7 Hz, 1H, H-2), 6.30 (d, J = 3 Hz, 1H, H-5-furanyl), 6.35 (dd, J = 3 and 2 Hz, 1H, H-3-furanyl), 6.4-7.4 (m, 9H, H-
aromatics), 7.43 (d, J = 2 Hz, 1H, H-5-furanyl); $^{13}$C NMR (CDCl$_3$) δ: 42.6 (N-CH$_2$-Ph), 48.5 (C-3), 49.7 (C-4), 59.3 (C-5), 67.7 (O-CH$_2$), 87.6 (C-2), 108.7, 110.4 (CH-furanyl), 117.8, 121.3 (CH-aromatics), 124.5, 127.2, 127.7, 128.4 (CH-aromatics), 135.3, 140.5 (C-aromatics), 142.7 (C-5-furanyl), 152.5 (C-2-furanyl), 173.0, 176.2 (C=O); $m/z$ (CI, NH$_3$): 401 (M+1)$^+$; Anal. Calcd for C$_{24}$H$_{20}$N$_2$O$_4$: C 71.99; H 5.03; N 7.00. Found: C 71.91; H 5.08; N 7.01.

16d: mp 158-159 °C (methanol/chloroform 90/10); IR (ν cm$^{-1}$): 1780, 1714 (imide); $^1$H NMR (CD$_3$D$_6$) δ: 2.93 (d, J = 8 Hz, 1H, H-4), 3.30 (dd, J = 8 and 1 Hz, 1H, H-3), 4.41 (s, 2H, O-CH$_2$), 4.56 (s, 2H, N-CH$_2$-Ph), 4.85 (d, J = 1 Hz, 1H, H-2), 5.54 (s, 1H, H-5), 5.86 (dd, J = 3 and 2 Hz, 1H, H-4-furanyl), 5.91 (d, J = 3 Hz, H-3-furanyl), 6.3-6.9 (m, 4H, H-aromatics), 6.93 (d, J = 2 Hz, 1H, H-5-furanyl), 7.0-7.6 (m, 5H, H-aromatics); $^{13}$C NMR (CD$_3$D$_6$) δ: 42.4 (N-CH$_2$-Ph), 49.5 (C-4), 51.6 (C-3), 61.1 (C-5), 67.1 (O-CH$_2$), 91.1 (C-2), 108.4 (C-3-furanyl), 110.0 (C-4-furanyl), 120.9, 121.4, 124.4 (CH-aromatics), 125.2 (C-aromatic), 126.7, 127.3, 127.6, 127.9, 128.5, 128.7 (CH-aromatics), 136.0, 139.7 (C-aromatics), 141.4 (C-5-furanyl), 152.8 (C-2-furanyl), 174.5, 176.2 (C=O); $m/z$ (CI, NH$_3$): 401 (M+1)$^+$; Anal. Calcd for C$_{24}$H$_{20}$N$_2$O$_4$: C 71.99; H 5.03; N 7.00. Found: C 72.16; H 5.25; N 6.97.

17d: mp 161-163 °C (methanol); IR (ν cm$^{-1}$): 1779, 1709 (imide); $^1$H NMR (CDCl$_3$) δ: 3.52 (d, J = 9 Hz, 1H, H-3), 3.68 (t, J = 9 Hz, H-4), 4.66 (s, 2H, N-CH$_2$-Ph), 4.84 (d, J = 9 Hz, 1H, H-5), 4.86, 4.91, 5.04, 5.09 (AB, J = 15 Hz, 2H, O-CH$_2$), 5.27 (s, 1H, H-2), 6.05 (d, J = 7 Hz, 1H, H-aromatic), 6.20 (d, J = 3 Hz, 1H, H-3-furanyl), 6.30 (dd, J = 3 and 2 Hz, 1H, H-4-furanyl), 6.9-7.0 (m, 3H, H-aromatics), 7.15 (d, J = 2 Hz, 1H, H-5-furanyl), 7.2-7.5 (m, 6H, H-aromatics); $^{13}$C NMR (CDCl$_3$) δ: 42.8 (N-CH$_2$-Ph), 47.1 (C-4), 51.2 (C-3), 62.7 (C-5), 67.2 (O-CH$_2$), 89.9 (C-2), 110.5 (C-4-furanyl), 110.7 (C-3-furanyl), 122.0, 123.3, 124.7 (CH-aromatics), 125.8 (C-aromatic), 126.9, 127.7, 128.4, 129.0 (C-aromatics), 135.2, 140.8 (C-aromatics), 142.7 (C-5-furanyl), 149.1 (C-2-furanyl), 174.9 (C=O); $m/z$ (CI, NH$_3$): 401 (M+1)$^+$; Anal. Calcd for C$_{24}$H$_{20}$N$_2$O$_4$1/2H$_2$O: C 70.40; H 5.17; N 6.84. Found: C 70.38; H 5.23; N 6.79.

REFERENCES


2. For a review, see:


For simplicity, the numbering system adopted for the cycloadducts throughout this manuscript does not follow official nomenclature rules. However the CAS nomenclature is given in the experimental section.


