

Structure–Activity Relationship Studies of Phenanthridine-Based Bcl-X<sub>L</sub> Inhibitors

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Received May 10, 2008

Despite their structural similarities, the natural products chelerythrine (**5**) and sanguinarine (**6**) target different binding sites on the pro-survival Bcl-X<sub>L</sub> protein. This paper details the synthesis of phenanthridine-based analogues of the natural products that were used to probe this difference in binding profiles. The inhibitory constants for these compounds were then measured in a fluorescence polarization assay against Bcl-X<sub>L</sub> and the tagged Bak-BH3 peptide. The results led to structure–activity relationship studies, which identified the structural motifs required for binding-site specificity as well as inhibitory activity. We also identified synthetic analogues of the natural products that display similar binding modes but with more potent IC<sub>50</sub> values.

## Introduction

Apoptosis, or programmed cell death, is a process by which unwanted or damaged cells undergo a series of regulated cellular events resulting in the safe destruction of the targeted cells. Many cancer cells, however, can prevent apoptosis from occurring by overproducing antiapoptotic proteins such as Bcl-2 and Bcl-X<sub>L</sub>.<sup>1</sup> One strategy for the development of therapeutics for cancer chemotherapy is to inhibit these antiapoptotic proteins and thus restore the potential to undergo apoptosis.<sup>2</sup> Several small molecule inhibitors of Bcl-X<sub>L</sub> have already been reported in the literature (Figure 1) including **1** (ABT-737),<sup>3</sup> **2** (BH3I-1),<sup>4,5</sup> gossypol (**3**),<sup>6,7</sup> and its analogue **4** (TW-37).<sup>8,9</sup> These compounds display good (nM to  $\mu$ M) binding affinities toward Bcl-X<sub>L</sub>, and in addition they are potent inducers of apoptosis in various cancer cell lines. Recently, Chan et al. identified the natural product chelerythrine (**5**) as an inhibitor of Bcl-X<sub>L</sub> through high-throughput screening of natural products.<sup>10</sup> Further investigations using NMR spectroscopy and computational methods show that despite their structural similarity, chelerythrine and its homologue sanguinarine (**6**) bind at different sites on the Bcl-X<sub>L</sub> protein.<sup>11</sup> To understand this difference in binding as well as to develop a structure–activity relationship study, a number of phenanthridine-based compounds that are structurally related to chelerythrine and sanguinarine were synthesized using complementary synthetic methods. These compounds were prepared in order to assess the structural motifs required for efficient binding of chelerythrine and sanguinarine analogues to Bcl-X<sub>L</sub>. The results can be used to optimize the structure of the chelerythrine and sanguinarine fragments to further enhance binding to the target protein.

## Synthesis

The compounds chosen for the study were phenanthridine-based analogues of chelerythrine and sanguinarine that contain the ABC-ring systems. The chelerythrine analogues are defined

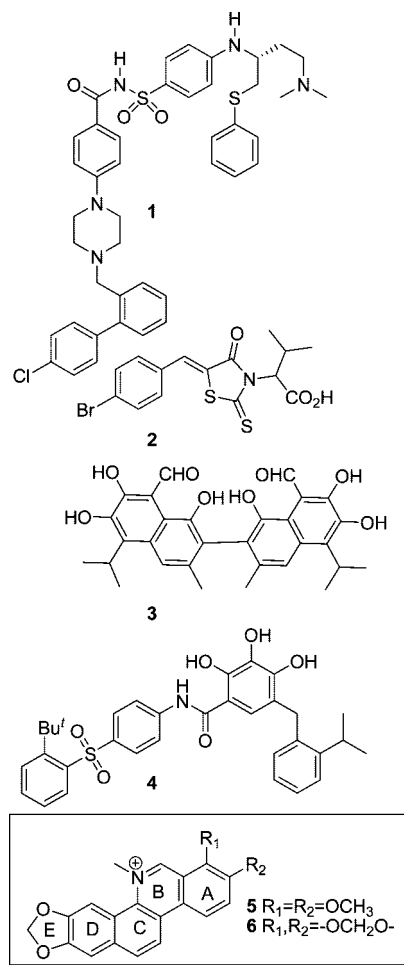


Figure 1. Structures of some small molecule inhibitors of Bcl-X<sub>L</sub>.

as the compounds whose structures contain freely rotating methoxy substituents at the 7- and 8-positions. The sanguinarine analogues are defined as the compounds with a fused dioxolo (–OCH<sub>2</sub>O–) group at the 7,8-positions. Previous studies have shown that chelerythrine binds to Bcl-X<sub>L</sub> through H-bonding interactions of the methoxy groups at an allosteric site known as the BH groove. Similarly, sanguinarine has been shown to

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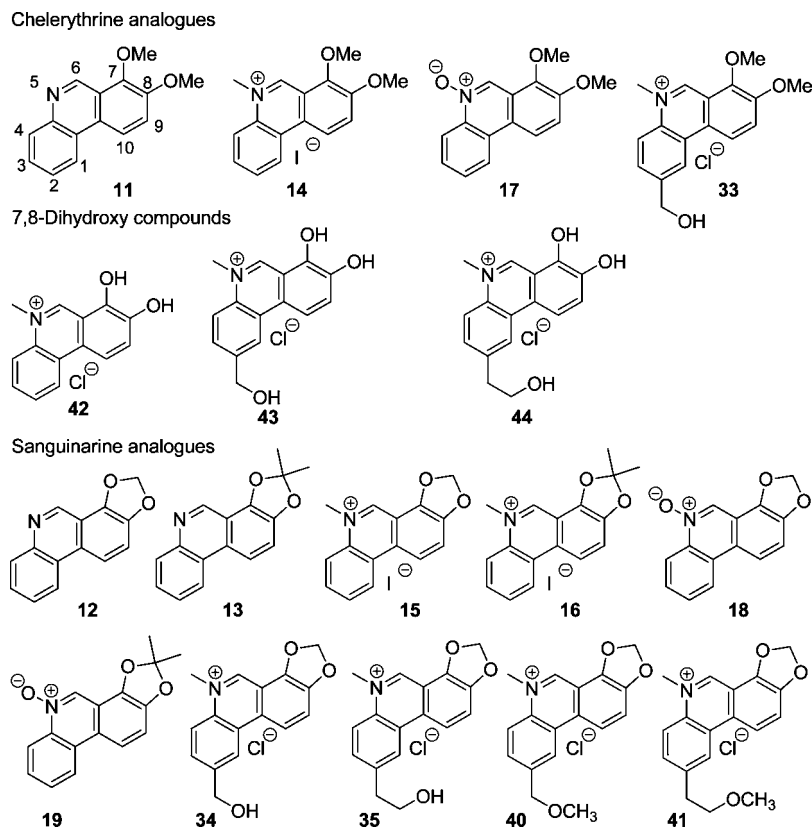
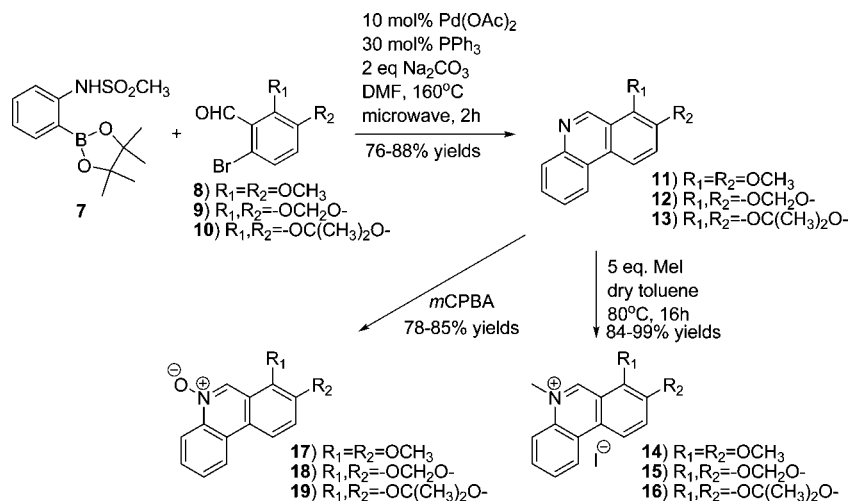


Figure 2. Structures of compounds synthesized for study.

#### Scheme 1



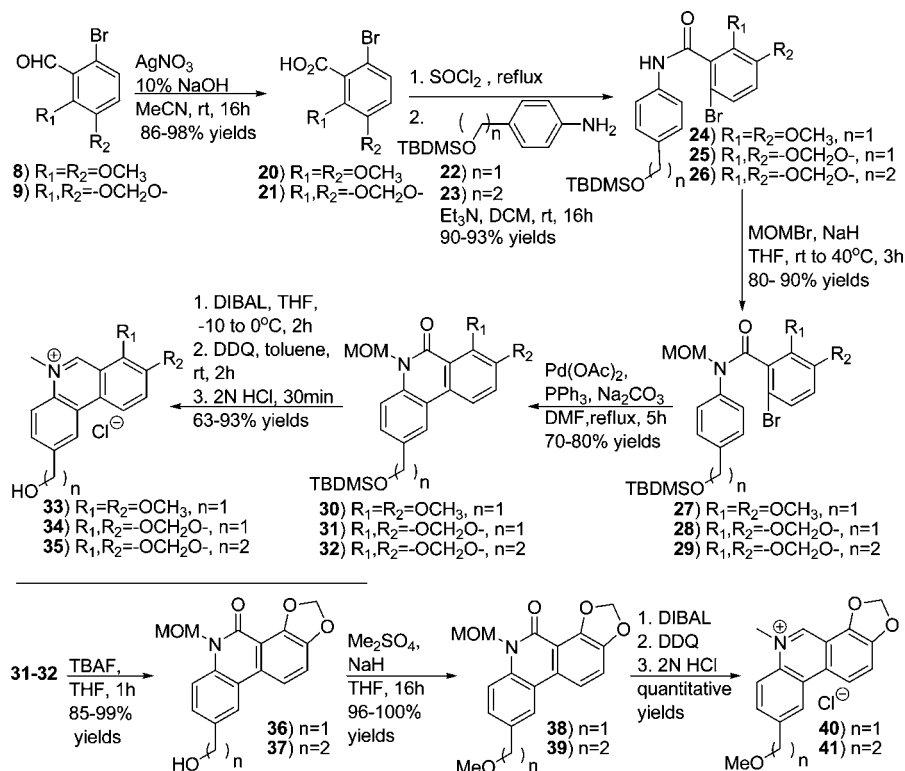
bind to a site on the BH1 region adjacent to the BH3 binding site, which can accommodate the constrained dioxolo group. We therefore prepared a number of 7,8-dimethoxy compounds, dioxolo compounds, and selected 7,8-dihydroxy compounds to probe their binding to the Bcl-X<sub>L</sub> protein (Figure 2). These structural analogues of chelerythrine and sanguinarine are then tested against Bcl-X<sub>L</sub> and the Bak-peptide to enable the measurement of the inhibition constants, and the most potent inhibitors will be studied by NMR methods to determine the binding sites on the protein.

Several A-ring substituted phenanthridines were synthesized using a one-pot Suzuki-Miyaura coupling between pinacol *N*-mesyl-2-aminophenylboronate (**7**) and the appropriate 2-bromobenzaldehydes **8–10** using a modification of the methodology reported by Snieckus.<sup>12</sup> This synthetic methodology is

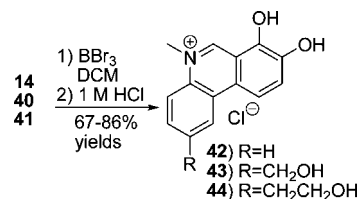
outlined in Scheme 1. Under the conditions utilized, the formation of a carbon-carbon bond between the bromobenzaldehyde and aminophenyl boronic acid occurred, followed by an in situ intramolecular Schiff base formation to yield the neutral phenanthridines **11–13** in good yields. To obtain the *N*-substituted species, these phenanthridines were treated with iodomethane to afford the desired *N*-methylphenanthridinium bromide salts **14–16** in 84–99% yields. Alternatively, the corresponding *N*-oxides were prepared by treating the phenanthridines **11–13** with *m*CPBA<sup>a</sup> to obtain the zwitterionic compounds **17–19** in high yields.

<sup>a</sup> Abbreviations: DDQ, 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone; DIBAL, diisobutylaluminum hydride; FPA, fluorescence polarization assay; *m*CPBA, *meta*-chloroperoxybenzoic acid; MOMBr, methoxymethyl bromide; TBAF, *tert*-butylammonium fluoride.

## Scheme 2



Scheme 3



The general synthetic methodology employed for the synthesis of 2-substituted phenanthridines is shown in Scheme 2. The appropriately substituted bromobenzaldehydes **8** and **9** were oxidized with AgNO<sub>3</sub> to obtain the bromobenzoic acids **20** and **21**. The bromobenzoic acids were then converted to the acid chlorides in situ using SOCl<sub>2</sub>, and these acid chlorides were then reacted with the anilines **22** and **23** to obtain the benzamides **24–26** in high yields.

To effect the intramolecular cyclization of the benzamides to the corresponding phenanthridinones, it is necessary to convert the secondary amides to the tertiary amides.<sup>13–16</sup> This transformation was accomplished by treating the benzamides with NaH and MOMBr in dry THF to give the corresponding *N*-MOM benzamides **27–29**. The *N*-MOM benzamides were then cyclized to the phenanthridinones **30–32** via an intramolecular Heck reaction using catalytic Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> in good yields.

Previous reports have shown that the reduction of the *N*-methoxymethylphenanthridinones such as **30–32** can be achieved using LiAlH<sub>4</sub> to obtain the corresponding neutral phenanthridines.<sup>13–16</sup> Although the reduction to obtain the neutral phenanthridines was successful, we found that the use of DIBAL as the reducing agent directly furnished the *N*-methyl 5,6-dihydrophenanthridines in one step. Subsequent dehydrogenation using DDQ and treatment with dilute HCl gave the desired phenanthridinium salts **33–35** in high yields. The structure of compound **35** was confirmed by X-ray analysis.

The phenanthridinones **31** and **32** were also used to prepare 2-substituted methyl ethers using a series of transformations. In the first step, the removal of the TBDMS protecting group was achieved by treating the phenanthridinones with TBAF to obtain the hydroxy compounds **36–37**. In the second step, these hydroxy compounds were methylated using dimethyl sulfate to obtain the methyl ethers **38–39**. Finally, the methyl ethers **38–39** were reduced with DIBAL and subsequently dehydro-

genated with DDQ to obtain the *N*-methylphenanthridinium methyl ethers **40–41** in quantitative yields.

To access the 7,8-dihydroxy compounds **42–44**, the compounds **14**, **40**, and **41** were treated with BBr<sub>3</sub> followed by workup with aqueous HCl to obtain the desired products in good yields (Scheme 3).

## Fluorescence Polarization Assay (FPA)

Several Bcl-X<sub>L</sub>/Bcl-2 inhibitors have been identified from high throughput screening based on fluorescence polarization.<sup>2,17</sup> To assess the binding activity of each synthesized compounds in Figure 2, a competitive binding assay based on fluorescence polarization was performed to test the ability of these compounds in disrupting the binding of the Bak-BH3 peptide to Bcl-X<sub>L</sub>.<sup>10,18,19</sup> In the fluorescence polarization assay, the Bcl-X<sub>L</sub> protein is incubated with a fluorescein-tagged Bak-BH3 peptide. The Bcl-X<sub>L</sub>:Bak-BH3 peptide complex is then titrated with the test compounds, and the displacement of the Bak-BH3 peptide is measured as a function of decreasing polarized fluorescence. In our assay, the concentrations of the test compounds ranged from 125 to 0.5 μM. The binding affinities are reported as the inhibitory concentration of the titrant required to displace 50% of the Bak-BH3 peptide (IC<sub>50</sub>). The results are summarized in Table 1. The results show that the benzophenanthridine **6** (IC<sub>50</sub> = 19 μM) has a much stronger binding affinity to the Bcl-X<sub>L</sub> protein than **5** (IC<sub>50</sub> = 100 μM). The chelerythrine analogue

**Table 1.** IC<sub>50</sub> Values From for the Displacement of Fluorescein-Tagged Bak Peptide From Bcl-X<sub>L</sub> as Measured By Fluorescence Polarization Assay<sup>a</sup>

compd	IC <sub>50</sub> ( $\mu$ M)	compd	IC <sub>50</sub> ( $\mu$ M)	compd	IC <sub>50</sub> ( $\mu$ M)	compd	IC <sub>50</sub> ( $\mu$ M)
<b>5</b>	100	<b>14</b>	>100	<b>19</b>	>100	<b>41</b>	6
<b>6</b>	19	<b>15</b>	12	<b>33</b>	>100	<b>42</b>	18
<b>11</b>	>100	<b>16</b>	>100	<b>34</b>	11	<b>43</b>	20
<b>12</b>	>100	<b>17</b>	>100	<b>35</b>	3	<b>44</b>	22
<b>13</b>	>100	<b>18</b>	>100	<b>40</b>	11		

<sup>a</sup> Note: IC<sub>50</sub> values >100  $\mu$ M Indicates Inactive.

**14**, which lacks the DE-rings, fails to displace the Bak-BH<sub>3</sub> peptide at the concentrations tested. Interestingly, none of the 7,8-dimethoxyphenanthridines (chelerythrine analogues **11**, **14**, **17**, **33**) displaced the Bak peptide at the concentrations tested. For the sanguinarine analogues, five compounds (**15**, **34–35**, **40–41**) display more potent binding activity than the parent compound with IC<sub>50</sub> values ranging from as low as 3 to 11  $\mu$ M. All three 7,8-dihydroxy phenanthridines (**42–44**) show improved inhibitory activity as compared to chelerythrine and equal potency to sanguinarine with IC<sub>50</sub> values ranging from 18–22  $\mu$ M. It is also noteworthy that none of the neutral phenanthridines nor the *N*-oxides displayed significant activity in the concentration range tested.

### Structure–Activity Relationship Study

Our studies show that none of the 7,8-dimethoxyphenanthridines (chelerythrine analogues) had IC<sub>50</sub> values below 100  $\mu$ M. However, it should also be noted that the parent compound chelerythrine itself shows poor binding activity against Bcl-X<sub>L</sub> and the Bak-peptide in FPA (IC<sub>50</sub>=100  $\mu$ M).<sup>11</sup> However, several 7,8-dihydroxy phenanthridines (**42–44**) showed lower  $\mu$ M inhibitory activity against Bcl-X<sub>L</sub>. The 7,8-dihydroxyphenanthridinium chloride (**42**) showed the greatest activity against Bcl-X<sub>L</sub> (IC<sub>50</sub>=18  $\mu$ M). The 2-substituted compounds **43** and **44** showed similar but slightly weaker activity than **42**. Interestingly, these compounds are equipotent to sanguinarine but more active than chelerythrine, suggesting that hydroxy groups improved the inhibitory toward Bcl-X<sub>L</sub> as compared to methoxy groups. It is also interesting to note that, despite the presence of C2 groups on compounds **43–44**, these compounds show similar binding activity as the simpler compound **42**. This suggests that C7 and C8 substituents have a greater impact on the inhibitory activity against Bcl-X<sub>L</sub> as compared to the C2 substituents.

With respect to the sanguinarine analogues, several compounds (**15**, **34–35**, **40–41**) exhibit better binding activity toward Bcl-X<sub>L</sub> than the parent compound **6** (IC<sub>50</sub> = 19  $\mu$ M). These results suggest that the DE-rings are not necessary for the binding of sanguinarine to Bcl-X<sub>L</sub>. For instance, the simplest sanguinarine analogue **15** has an IC<sub>50</sub> of 12  $\mu$ M. Furthermore, the compounds **34–35** have IC<sub>50</sub> values of 11 and 3  $\mu$ M respectively, and the methyl ethers **40–41** have IC<sub>50</sub> values of 11 and 6  $\mu$ M. Compounds **34** and **40** are the 2-substituted analogues that have a methylhydroxy and methylmethoxy group, respectively. These two compounds are only moderately more active than the analogue **15**, which suggests that the additional binding conferred by the short tail is weak. However, the longer tail of the ethylhydroxy and ethylmethoxy compounds **35** and **41** are 2–4 times more potent than the analogue **15**. This may be explained by an additional hydrogen bonding interaction between the oxygen atom on the 2-ethyloxy group and a protein residue that enhances binding.

A study of the sanguinarine-based analogues (**12**, **13**, and **18**) with variations at the 5-position (neutral nitrogen, *N*-methyl

and *N*-oxide) shows that the *N*-methyl compound **15** shows favorable binding to Bcl-X<sub>L</sub>. The neutral compound **12** and its *N*-oxide **18** however show poor binding activity toward Bcl-X<sub>L</sub>. These results indicate that the presence of the cationic *N*-methyl group is essential for efficient binding to the Bcl-X<sub>L</sub> protein. This increase in binding may be due to a charge–charge interaction of the cationic nitrogen with a negatively charged carboxylate residue on the Bcl-X<sub>L</sub> protein.

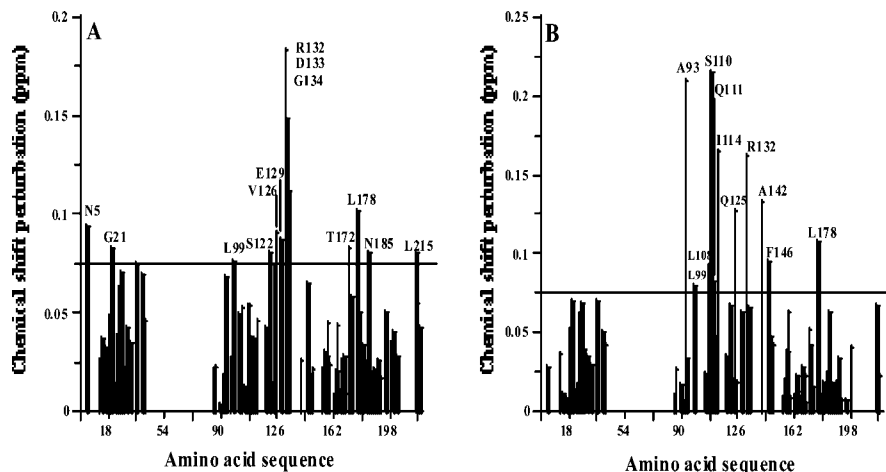
With respect to the substituents on the A-ring for the sanguinarine analogues, it is interesting to note that the dimethyldioxolo compound **16** is inactive. This compound differs from the highly active compound **15** due to the presence of an acetonide group (OC(CH<sub>3</sub>)<sub>2</sub>O) rather than a dioxolo group (OCH<sub>2</sub>O). It is possible that the additional steric bulk provided by the methyl groups, as opposed to the smaller hydrogen groups, is sufficient to prevent the compound from binding. This suggests that these compounds may bind at a site with a small pocket, which can accommodate the constrained dioxolo group, and bulkier groups such as the acetonide group, which is present in compound **16**, or the dimethoxy groups of the chelerythrine analogues may prevent these compounds from binding effectively.

In summary, the SAR study shows that the 7,8-dimethoxy chelerythrine analogues including the parent compound display very poor binding activity. The 7,8-dihydroxy compounds, on the other hand, are more potent than chelerythrine and equipotent with sanguinarine toward Bcl-X<sub>L</sub>. With respect to the sanguinarine analogues, several compounds show better promise as inhibitors of Bcl-X<sub>L</sub>. This study also shows that the presence of a quaternary nitrogen is also essential for the binding activity of these phenanthridines. The constrained dioxolo ring system also enhances the binding activity of these compounds. Furthermore, the DE rings are not required for good binding activity. Elaboration of the C-ring using ethylhydroxy and its methyl ether (i.e., compounds **35** and **41**) also significantly improve the binding activity of these compounds to Bcl-X<sub>L</sub>. To understand and study the binding of selected active compounds from the SAR studies obtained from the FPA, we turned our attention to NMR studies and docking simulations.

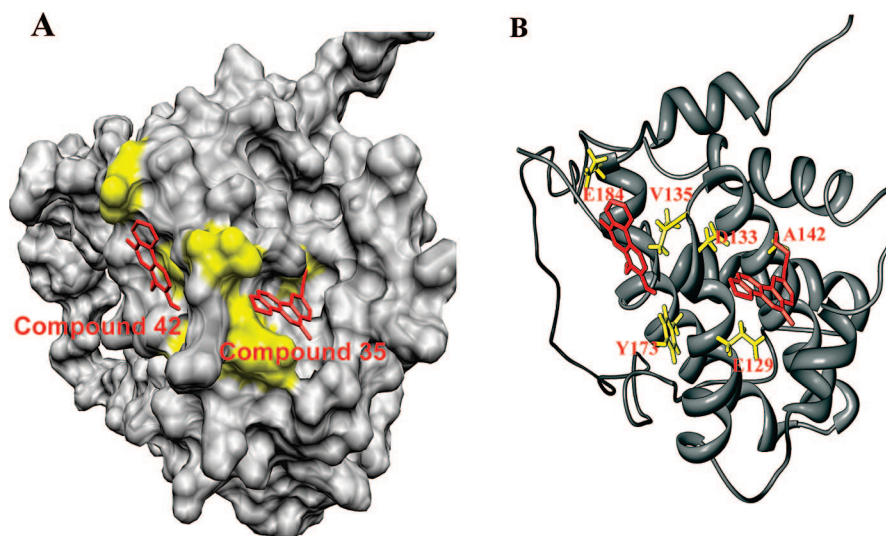
### NMR Studies and Docking Simulations

NMR titration studies were carried out to determine the binding site of the ligands **35** and **42** to the Bcl-X<sub>L</sub> proteins. This was carried out by first preparing <sup>15</sup>N-labeled human Bcl-X<sub>L</sub> as described previously.<sup>11</sup> The labeled proteins were then titrated with the test compounds, and the chemical shift perturbations of the amide cross-peaks in the ligand:protein complex relative to the unbound protein were determined using <sup>1</sup>H–<sup>15</sup>N heteronuclear single quantum correlation (HSQC) experiments. The results of the NMR titration studies with human Bcl-X<sub>L</sub> are shown in Figure 3. The results show that compound **42** strongly perturbs the 11 different residues on the protein by more than 0.075 ppm. Similarly, compound **35** causes significant chemical shifts perturbations for 13 protein residues over the same threshold. One striking observation is that chemical shift perturbation for each ligand–protein complex is very different in terms of the residues affected as well as the magnitude of the shifts. The results show that the two complexes have only three shifted residues in common: L99, R132, and L178. However, both complexes share a common perturbed region at the BH1 domain where residues are disturbed by compound **42** (Q125, R132, A142, F146), while six residues are disturbed by compound **35** (S122, V126, E129, R132, D133, G134). These results indicate that the binding sites of the two compounds are not identical, but they are likely to share a





**Figure 3.** Combined amide proton and nitrogen chemical shift perturbations of Bcl-X<sub>L</sub> derived from the <sup>1</sup>H–<sup>15</sup>N HSQC spectra after titration with compounds **35** (A) and **42** (B) are plotted against the residual number of the protein. The molar ratio of ligand to protein was 10:1 in both titrations. Residues that are perturbed by more than an arbitrary threshold value of 0.075 ppm are labeled.



**Figure 4.** Docking models of compounds **35** and **42** bound to Bcl-X<sub>L</sub>. The protein is represented as a surface diagram (A) and ribbon diagram (B), and the docked ligands on the protein are shown as sticks. Compounds **35** and **42** bind at the BH1 domain and BH groove of the protein respectively. Residues such as E129, D133, V135, A142, Y173, and E184 that play an essential role for binding of compound **35** or **42** are colored in yellow.

common region on the protein that is likely to be the BH1 domain. This BH1 domain is comprised of a portion of helices 4–5 and its connecting loop and is located between the BH groove (chelerythrine binding site) and the BH3 binding groove (sanguinarine binding site).

It should be noted however that the chemical shift perturbations can be caused by direct protein–ligand interactions or by indirect protein conformational changes induced by the ligand. Docking studies using AutoDockSuite 4.0.1 were thus employed using a rigid protein structure to determine if the observed chemical shift perturbations are likely to arise from direct ligand–protein interactions.

The NMR structure of the human Bcl-X<sub>L</sub><sup>20</sup> was used as the rigid protein for docking studies, and the ligand structures of **35** and **42** were generated using Sybyl. The Autodock 4.0.1 program equipped with ADT was used for generating docking models by employing a Genetic Algorithm–Local Search (GA-LS) method for the docking of the flexible ligands to the rigid protein.<sup>21</sup> A grid box was selected to cover the residues in the regions of interest (BH groove, BH3 binding groove, and BH1 region) for AutoDock calculations. For each docking job, 100

hybrid GA-LS runs were carried out. A total of 100 possible binding conformations were generated and grouped into clusters based on a 1.0 Å cluster tolerance.

The docking results for the compound **42** show 98 out of 100 possible conformers in a single cluster when the cluster tolerance is set to 1.0 Å. The cluster is located at the top portion of the BH groove (Figure 4 A). It was found that the hydrophilic sidechains from residues H177 and Y173 are in close proximity to the hydroxy groups of compound **42**. The sidechains of residues V135, L178, and W181 are also shown to interact with compound **42** via hydrophobic interactions. The docking model suggests that compound **42** binds selectively at the BH groove, the region where chelerythrine has been shown to bind.

The docking results for compound **35** in Figure 4 yielded two clusters with a cluster tolerance of 1.0 Å. The major cluster contains 72 conformers docked at the BH1 region (Figure 4A). Furthermore, a single cluster is obtained when the tolerance is adjusted to 1.1 Å. The docking results show that the side chain of the residues L108, L130, F131, A142, and F143 interact with the sanguinarine analogue by hydrophobic interactions, while E129 is in close contact to the cationic nitrogen atom of

**Table 2.** Degree of Overall Chemical Shift Perturbation Caused By Compounds **42** and **35** on the Backbone NHs of Various Human Bcl-X<sub>L</sub> Mutants as Examined by <sup>1</sup>H-<sup>15</sup>N HSQC Spectra

mutant	structural context	compd <b>35</b>	compd <b>42</b>
E129A	BH1	+++	++++
L130A	BH3 groove	+++	+++
D133K	BH1	+++	++++
V135A	BH groove	++++	++
R139A	BH3 groove	++++	++++
A142G	BH1	+	++
Y173F	BH groove	++++	+
E184A	BH groove	++++	+++

compound **35** (Figure 4B). These results suggest that compound **35** binds at the same region where sanguinarine binds.

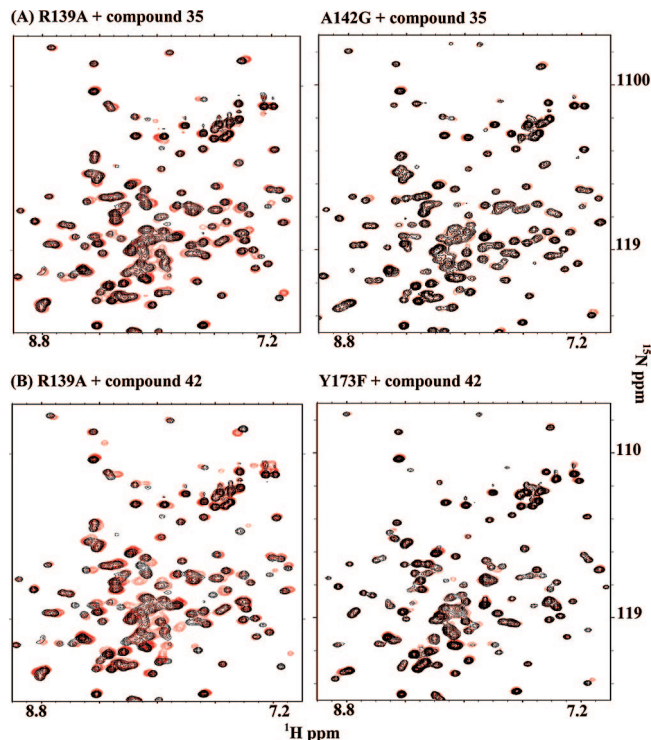
To verify the binding sites predicted by docking studies, further NMR studies were conducted in which mutants of the Bcl-X<sub>L</sub> protein were employed. The point mutations were based on the residues predicted by the model to be essential for binding (E129A, L130A, D133K, V135A, R139A, A142G, Y173F, and E184A). These mutations correspond to residues from three different regions of the protein (R139A and L130A from the BH3 binding groove, E129A, D133K, and A142G from the BH1 domain, and V135A, Y173F, and E184A from the BH groove). The mutants were then titrated with compounds **35** or **42** and analyzed by HSQC. The qualitative results are shown in Table 2.

The overall chemical shift perturbation showed that A142G mutation, which is in the BH1 region, drastically inhibited the binding of compound **35** to Bcl-X<sub>L</sub> (Figure 5). The binding of **35** to Bcl-X<sub>L</sub> was moderately inhibited by mutations such as E129A and D133K, which are also in the BH1 domain. However, mutation on the BH groove such as V135A, Y173F, and E184A showed little effect on the binding of **35** to Bcl-X<sub>L</sub> (Table 2).

In contrast, mutations on the BH groove such as V135A, Y173F, and E184A inhibited significantly the binding of compound **42** to Bcl-X<sub>L</sub> (Figure 5). It was also noted that the mutations on the BH1 region such as E129A and D133K showed little effect on the binding of **42** (Table 2). Taken together, the extent of chemical shift perturbation obtained for human Bcl-X<sub>L</sub> mutants upon titration as well as the docking models for these compounds on the protein demonstrates that compounds **35** and **42** bind at different binding sites, the BH1 domain, and the BH groove of human Bcl-X<sub>L</sub>, respectively. Furthermore, these experiments provide strong evidence that the analogue **42** binds to the same site as chelerythrine and, similarly, the analogue **35** binds to the same site as sanguinarine.

## Conclusion

We have thus synthesized a number of chelerythrine and sanguinarine analogues and tested them in FPA assays for their inhibitory activity against Bcl-X<sub>L</sub> and the Bak-peptide. We have shown that three dihydroxy compounds show greater potency against Bcl-X<sub>L</sub> than the natural product chelerythrine. We have also identified five sanguinarine analogues that are more potent than the corresponding natural product. A combination of NMR titration studies and in silico docking studies have shown that our most potent compounds, the sanguinarine analogue **35** and compound **42**, bind at the BH1 domain and BH groove respectively, similar to the binding preference of their natural parent compounds. Further work is underway to link these

**Figure 5.** Effect of mutations at different sites of human Bcl-X<sub>L</sub> on the binding of the analogue **35** and the analogue **42** based on the extent of chemical shift perturbation. (A) The <sup>1</sup>H-<sup>15</sup>N HSQC spectra of R139A and A142G mutant before and after titration with **35**. (B) The <sup>1</sup>H-<sup>15</sup>N HSQC spectra of R139A and Y173F mutant before and after titration with **42**. In all spectra, the cross peaks are colored black for free Bcl-X<sub>L</sub> mutant protein and red for protein in the presence of **42** or **35**.

analogues together to see determine if a more potent bidentate compound can be obtained.

## Experimental Section

**Chemistry. General Experimental Section.** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were acquired on a Bruker 400 UltraShield spectrometer operating at 400 and 100 MHz, respectively. All the proton spectra were referenced to the respective residual solvent peaks (MeOH-*d*<sub>4</sub>: 3.20; DMSO-*d*<sub>6</sub>: 2.50; D<sub>2</sub>O: 4.79; CD<sub>2</sub>Cl<sub>2</sub>: 5.31 ppm), except for those recorded in CDCl<sub>3</sub>, were referenced to TMS. Carbon spectra were referenced to the central peak of the respective residual solvents (MeOH-*d*<sub>4</sub>: 49.0; DMSO-*d*<sub>6</sub>: 39.5; CDCl<sub>3</sub>: 77.0; CD<sub>2</sub>Cl<sub>2</sub>: 53.7 ppm). Low-resolution and high-resolution electron impact mass spectra (EIMS) were measured using a Finnigan MAT95XP double-focusing mass spectrometer. Low-resolution electrospray ionization (ESI) mass spectra were recorded using Waters Quattro Micro API, and high resolution mass spectra were obtained using the Agilent 6210 time-of-flight LC/MS. Infrared (IR) spectra were measured on a BioRad FTIR spectrophotometer with samples analyzed as KBr discs or thin films on a KBr plate. Elemental analysis was performed using a EuroEA3000 series CHNS Analyzer. X-ray analysis data was obtained using a Rigaku single crystal X-ray diffraction system with Saturn-70 CCD detector. Preparative HPLC was carried out using either on a Waters 600 controller and 2996 detector with an Xterra C<sub>18</sub> 19 mm × 50 mm column, or a Waters 2545 binary gradient module and 2996 detector with a Luna C<sub>18</sub> 21.2 mm × 250 mm column.

**Experimental Details. Preparation of 2-Bromo-5,6-dimethoxybenzaldehyde (8).** A mixture of 2-bromo-5-methoxy-6-hydroxybenzaldehyde (4.62 g, 20 mmol), dimethyl sulfate (3 mL, 32 mmol), and potassium carbonate (8.28 g, 60 mmol) in acetone (300 mL) was refluxed for 5 h and then cooled down. The solvent was removed in vacuo, and the residue was partitioned between water

and ether, then further extracted with ether (3 × 200 mL). The ether extract was washed successively with saturated NaHCO<sub>3</sub>, water, and brine and then dried with MgSO<sub>4</sub>. Concentration of the organic layer left a solid, which was then recrystallized from ether as pale-yellow needles (4.4 g, 90% yield). *R<sub>f</sub>* (1:4 EtOAc/hexanes): 0.34; mp: 75–77 °C (lit.<sup>22</sup> 76–77 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.34 (s, 1H), 7.34 (d, *J* = 9 Hz, 1H), 6.96 (d, *J* = 9 Hz, 1H), 3.93 (s, 3H, OMe), 3.89 (s, 3H, OMe). HRMS (ESI<sup>+</sup>): calcd 243.9769 for C<sub>9</sub>H<sub>9</sub><sup>79</sup>BrO<sub>3</sub> [M]<sup>+</sup> and 245.9715 for C<sub>9</sub>H<sub>9</sub><sup>81</sup>BrO<sub>3</sub> [M]<sup>+</sup>; found, 243.9730 and 245.9709, respectively.

**5-Bromobenzo[d][1,3]dioxole-4-carbaldehyde (9).** This compound was purchased from Sigma-Aldrich (product no. 597376).

**Preparation of 5-Bromo-2,2-dimethylbenzo[d][1,3]dioxole-4-carbaldehyde (10).** To a solution of 5-bromo-2,2-dimethylbenzo[d][1,3]dioxole (1.2 g, 5.24 mmol) in dry THF (15 mL) was added *N,N*-diisopropylamine (0.812 mL, 5.76 mmol) and *n*-BuLi (1.3 M in hexanes, 4.44 mL, 5.76 mmol). The mixture was stirred at –78 °C for 15 min and then DMF (0.51 mL, 6.55 mmol) was added and the resulting mixture was stirred at –78 °C for a further 15 min. The resulting mixture was then warmed to rt and stirred for a further 4 h. The reaction was quenched by the addition of saturated Na<sub>2</sub>CO<sub>3</sub>. The crude product was extracted with ethyl acetate (3 × 150 mL), and the organic layer was washed with brine, dried with MgSO<sub>4</sub>, and then filtered. The solvent was removed under reduced pressure, and the resulting crude mixture was subjected to column chromatography on silica to give the product as pale-yellow crystals in 74% yield. *R<sub>f</sub>* (1:10, EtOAc/hexane): 0.2; mp: 92 °C (lit. 91–92 °C).<sup>23</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.22 (s, 1H), 6.99 (d, *J* = 8 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 1.68 (s, 6H).

**2-Bromo-5,6-dimethoxybenzoic Acid (20).** To 2-bromo-5,6-dimethoxybenzaldehyde (**8**) (300 mg, 1.22 mmol) in MeCN (5 mL) was added AgNO<sub>3</sub> solution (0.1 M, 24 mL) and 10% NaOH solution (6 mL). The mixture was stirred at room temperature for 16 h and then filtered through Celite 545. MeCN was removed in vacuo. The aqueous phase was acidified with 4 M HCl until the pH = 5, and then the organic acid was extracted with EtOAc (20 mL). The organic layer was washed with 1 M HCl, dried with MgSO<sub>4</sub>, and concentrated in vacuo to afford the product (274 mg, 86% yield) as a colorless oil. *R<sub>f</sub>* (1:9 MeOH/CH<sub>2</sub>Cl<sub>2</sub>): 0.18. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.27 (d, *J* = 9 Hz, 1H), 6.86 (d, *J* = 9 Hz, 1H), 3.92 (s, 3H, OMe), 3.88 (s, 3H, OMe). MS (CI<sup>–</sup>) (*m/z*, %): 259 (95), 261 [M – H]<sup>–</sup> 100).

**5-Bromobenzo[d][1,3]dioxole-4-carboxylic Acid (21).** The title compound was obtained in 98% yield as a white solid from commercially available 5-bromobenzo[d][1,3]dioxole-4-carbaldehyde (**9**) following the same procedure for the preparation of **20**; mp: 167–168 °C (lit. 166–168 °C).<sup>24</sup> <sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 7.09 (d, *J* = 8 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 6.06 (s, 2H). HRMS (ESI<sup>+</sup>): calcd for 266.9263 for C<sub>8</sub>H<sub>5</sub><sup>79</sup>BrO<sub>4</sub>Na [M + Na]<sup>+</sup> and 268.9248 for C<sub>8</sub>H<sub>5</sub><sup>81</sup>BrO<sub>4</sub>Na [M + Na]<sup>+</sup>; found, 266.9269 and 268.9250.

**(4-Aminophenyl)methyl-*tert*-butyldimethylsilyl Ether (22).** To a solution of (4-aminophenyl)methanol (3.69 g, 30 mmol) in anhydrous DMF (60 mL) under argon was added imidazole (4.08 g, 60 mmol). The mixture was stirred at room temperature for 30 min, and then TBDMSCl (4.6 g, 30.5 mmol) in DMF (40 mL) was slowly added via syringe. The reaction mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica (15% ethyl acetate in hexane) to give the desired product (4.32 g, 61% yield) as a colorless oil. *R<sub>f</sub>* (1:4 EtOAc/hexane): 0.25. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.10 (d, *J* = 8 Hz, 2H), 6.65 (d, *J* = 8 Hz, 2H), 4.62 (s, 2H), 0.91 (s, 9H, 3 × CH<sub>3</sub>), 0.08 (s, 6H, 2 × CH<sub>3</sub>). HRMS (CI<sup>+</sup>): calcd 238.1622 for C<sub>13</sub>H<sub>24</sub>NOSi [M + H]<sup>+</sup>; found, 238.1684.

**(4-Aminophenyl)ethyl-*tert*-butyldimethylsilyl Ether (23).** (4-Aminophenyl)ethyl-*tert*-butyldimethylsilyl ether was obtained as a colorless oil from 2-(4-aminophenyl)ethanol in 95% yield following the general procedure as above. *R<sub>f</sub>* (1:4 EtOAc/hexane): 0.27. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 6.99 (d, *J* = 8 Hz, 2H), 6.62 (d, *J* = 8 Hz, 2H), 3.74 (app. t, *J* = 7 Hz, 2H), 2.71 (app. t, *J* = 7 Hz, 2H),

0.88 (s, 9H, 3 × CH<sub>3</sub>), 0.00 (s, 6H, 2 × CH<sub>3</sub>). HRMS (ESI<sup>+</sup>): calcd 252.1778 for C<sub>14</sub>H<sub>25</sub>NOSi [M + H]<sup>+</sup>; found, 252.1795.

**Synthesis of Phenanthridines via Suzuki Coupling. 7,8-Dimethoxyphenanthridine (11).** To a solution of 2-bromo-5,6-dimethoxybenzaldehyde (500 mg, 2 mmol) and pinacol 2-aminophenylboronate (608 mg, 2 mmol) in DMF (15 mL) under nitrogen was added anhydrous Na<sub>2</sub>CO<sub>3</sub> (0.4 g, 3.9 mmol), Pd(OAc)<sub>2</sub> (43 mg, 0.20 mmol), and PPh<sub>3</sub> (0.2 g, 0.78 mmol). The mixture was thrice degassed and flushed with nitrogen, then heated in a sealed tube for 2 h at 160 degrees under microwave conditions (Biotage initiator). The reaction mixture was filtered through Celite, and the DMF solvent was removed under reduced pressure. The crude product was extracted with CHCl<sub>3</sub> (3 × 150 mL), and the organic layer was washed with brine, dried with MgSO<sub>4</sub>, and then filtered. The solvent was removed under reduced pressure, and the resulting crude mixture was subjected to column chromatography on silica to give the desired phenanthridine as yellow crystals in 76% yield.

Pale-yellow solid; mp: 111–113 °C from EtOAc/hexane (lit. 121–122 °C, petroleum ether).<sup>25</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.64 (s, 1H), 8.49 (br d, *J* = 8 Hz, 1H), 8.33 (d, *J* = 9 Hz, 1H), 8.20 (br d, *J* = 8 Hz, 1H), 7.68 (m, 2H), 7.59 (d, *J* = 9 Hz, 1H), 4.11 (s, 3H, OMe), 4.05 (s, 3H, OMe). HRMS (ESI<sup>+</sup>): calcd 240.1019 for C<sub>15</sub>H<sub>14</sub>NO<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup>; found, 240.1014.

**[1,3]Dioxolo[4,5-*i*]phenanthridine (12).** Pale-yellow solid; mp: 148–149 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.34 (s, 1H), 8.44 (br d, *J* = 8 Hz, 1H), 8.14 (br d, *J* = 8 Hz, 1H), 8.11 (d, *J* = 9 Hz, 1H), 7.66 (m, 2H), 7.42 (d, *J* = 9 Hz, 1H), 6.27 (s, 2H, OCH<sub>2</sub>O). HRMS (ESI<sup>+</sup>): calcd 223.0633 for C<sub>14</sub>H<sub>8</sub>NO<sub>2</sub> [M]<sup>+</sup>; found, 223.0637.

**Preparation of 2,2-Dimethyl-[1,3]dioxolo[4,5-*i*]phenanthridine (13).** *R<sub>f</sub>* (1:5 EtOAc/hexanes): 0.4; mp: 118–120 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.25 (s, 1H), 8.34 (d, *J* = 8 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 7.98 (d, *J* = 9 Hz, 1H), 7.56 (m, 2H), 7.27 (d, *J* = 9 Hz, 1H), 1.75 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 146.8, 145.9, 143.9, 142.5, 129.9, 127.8, 127.6, 126.8, 124.5, 122.0, 120.7, 114.6, 113.7, 112.0, 26.05. IR (KBr): 3469, 2933, 1641, 1469, 1379, 1290, 1255, 1236, 1222, 1109, 1022, 951, 916, 826, 760 cm<sup>–1</sup>. HRMS (EI<sup>+</sup>): calcd 251.0946 for C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub> [M]<sup>+</sup>; found: 251.0940.

**General Procedure for the *N*-Methylation of the Phenanthridines.** To a suspension of the phenanthridine (typically 50 mg) in dry toluene was added iodomethane (5 eq). The reaction mixture was heated at 80 °C for 16 h in a sealed tube. The resulting precipitate was then filtered and washed with cold toluene (5 mL) and diethyl ether (5 mL) and then dried in vacuo.

**7,8-Dimethoxy-5-methylphenanthridinium Iodide (14).** Obtained as an orange solid from **11** (79 mg, 99% yield); mp: 202–208 °C (dec). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.18 (s, 1H), 9.07 (m, 1H), 8.82 (d, *J* = 9 Hz, 1H), 8.47 (m, 1H), 8.25 (d, *J* = 9 Hz, 1H), 8.06 (m, 2H), 4.71 (s, 3H, NCH<sub>3</sub>), 4.15 (s, 3H, OMe), 4.10 (s, 3H, OMe). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 151.3, 151.0, 146.7, 133.1, 130.8, 130.3, 127.4, 125.5, 125.3, 124.3, 119.9, 119.1, 119.0, 62.3, 57.0, 45.8.

HRMS (ESI<sup>+</sup>): calcd 254.1181 for C<sub>16</sub>H<sub>16</sub>NO<sub>2</sub> [M]<sup>+</sup>; found, 254.1176.

**[1,3]Dioxolo-5-methyl-[4,5-*i*]phenanthridinium Iodide (15).** Prepared from **12**. The product was further purified by preparative HPLC (Luna C<sub>18</sub>, 21.2 × 250 mm, flow rate: 20 mL/min, mobile phase: acetonitrile in water with 0.1% formic acid, gradient: 10–70% over 15 min, retention time (*R<sub>t</sub>*) 9.1 min) to afford the pure product as an orange solid (68 mg, 84% yield). mp: 125–127 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.17 (s, 1H), 8.95 (m, 1H), 8.56 (d, *J* = 9 Hz, 1H), 8.42 (m, 1H), 8.04 (d, *J* = 9 Hz, 1H), 8.01 (m, 2H), 6.58 (s, 2H, OCH<sub>2</sub>O), 4.63 (s, 3H, NCH<sub>3</sub>). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 150.3, 147.8, 147.6, 133.0, 130.7, 130.6, 126.5, 125.7, 124.4, 120.2, 119.3, 116.9, 109.0, 104.9, 45.5. HRMS (ESI<sup>+</sup>): calcd 238.0868 for C<sub>15</sub>H<sub>12</sub>NO<sub>2</sub> [M]<sup>+</sup>; found, 238.0861.

**Preparation of 2,2-Dimethyl-[1,3]dioxolo-5-methyl-[4,5-*i*]phenanthridinium Iodide (16).** Prepared from **13**. Recrystallization from CHCl<sub>3</sub>/hexane yielded the desired product as orange crystals in quantitative yield; mp: 192–195 °C (dec). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.55 (s, 1H), 8.65 (m, 1H), 8.25 (m, 1H), 8.20 (d, *J* = 9 Hz, 1H), 7.93 (m, 2H), 7.68 (d, *J* = 9 Hz, 1H), 4.90 (s, 3H), 1.93 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 150.2, 148.5, 148.0, 133.0, 130.8, 130.7,



126.6, 126.4, 124.7, 124.1, 119.41, 119.38, 115.3, 109.3, 47.2, 26.28. IR (KBr,  $\text{cm}^{-1}$ ): 3450, 3050, 2991, 1641, 1617, 1489, 1347, 1297, 1251, 1213, 1156, 762. HRMS ( $\text{EI}^+$ ): calcd 266.1177 for  $\text{C}_{17}\text{H}_{16}\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ ; found, 266.1179.

**General Procedure for the N-Oxidation of Phenanthridines.** To a solution of the phenanthridine (typically 90 mg) in DCM (1 mL) was added *m*CPBA (177 mg). The mixture was stirred at rt for 16 h, and then saturated  $\text{NaHCO}_3$  was added, followed by addition of more DCM (15 mL). The DCM layer was washed with water and then brine and dried over  $\text{Na}_2\text{SO}_4$ . After removal of DCM in vacuo, the crude product was purified by column chromatography on silica (1:9 *i*-PrOH/hexanes) to give desired product.

**7,8-Dimethoxy-5-methylphenanthridine-5-oxide (17).** Yellow solid; mp: 144–162 °C (dec).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  9.17 (s, 1H), 8.87 (m, 1H), 8.45 (m, 1H), 8.20 (d,  $J = 9$  Hz, 1H), 7.76 (m, 2H), 7.44 (d,  $J = 9$  Hz, 1H), 4.05 (s, 3H,  $\text{OCH}_3$ ), 4.04 (s, 3H,  $\text{OCH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  151.0, 142.5, 138.2, 130.6, 129.3, 128.7, 126.6, 122.4, 122.1, 121.5, 120.7, 118.1, 116.3, 61.7, 56.5. HRMS ( $\text{ESI}^+$ ): calcd 256.0968 for  $\text{C}_{15}\text{H}_{14}\text{NO}_3$  [ $\text{M} + \text{H}$ ] $^+$ ; found, 256.0967.

**[1,3]Dioxolo[4,5-*i*]phenanthridine-5-oxide (18).** Yellow solid; mp: 178–197 °C (dec).  $^1\text{H}$  NMR ( $\text{CDCl}_3 + \text{MeOH}-d_4$ ):  $\delta$  8.87 (s, 1H), 8.79 (d,  $J = 3$  Hz, 1H), 8.42 (d,  $J = 5$  Hz, 1H), 8.01 (d,  $J = 8$  Hz, 1H), 7.76 (m, 2H), 7.31 (d,  $J = 5$  Hz, 1H), 6.25 (s, 2H,  $\text{OCH}_2\text{O}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3 + \text{MeOH}-d_4$ ):  $\delta$  146.9, 142.1, 138.0, 129.9, 129.4, 129.0, 127.0, 122.8, 121.9, 120.6, 116.0, 112.2, 111.7, 103.1. HRMS ( $\text{ESI}^+$ ): calcd 240.0655 for  $\text{C}_{14}\text{H}_{10}\text{NO}_3$  [ $\text{M} + \text{H}$ ] $^+$ ; found, 240.0648.

**2,2-Dimethyl-[1,3]dioxolo[4,5-*i*]phenanthridine-5-oxide (19).** Pale-yellow solid (75 mg, 78% yield); mp: 156–158 °C.  $R_f$  (1:9, IPA/hexane) 0.21.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.85 (s, 1H), 8.83 (m, 1H), 8.38 (m, 1H), 7.94 (d,  $J = 8$  Hz, 1H), 7.71 (m, 2H), 7.19 (d,  $J = 8$  Hz, 1H), 1.81 (s, 6H,  $2 \times \text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  146.3, 141.4, 138.2, 129.5, 128.8, 128.4, 127.1, 122.5, 121.0, 120.8, 115.1, 111.9, 111.6, 26.0. ESI-MS ( $m/z$ , %): 268 ([ $\text{M} + \text{H}$ ] $^+$ , 100), 290 ([ $\text{M} + \text{Na}$ ] $^+$ , 20).

#### General Procedure for the Synthesis of the Benzamides.

**2-Bromo-*N*-(4-(*tert*-butyldimethylsilyloxymethyl)phenyl)-5,6-dimethoxybenzamide (24).** The benzoic acid **20** (1.51 g, 5.79 mmol) was refluxed in neat thionyl chloride (2 mL) for 2 h then allowed to cool to rt. The excess thionyl chloride was removed under reduced pressure to yield the crude acid chloride. A solution of (4-aminophenyl)methyl-*tert*-butyldimethylsilyl ether (**22**) in DCM (5 mL) was added to a solution of the crude acid chloride in DCM (15 mL), followed by triethylamine (1.62 mL, 11.65 mmol). The mixture was stirred at room temperature under argon for 3 h, after which the solvent was removed. The residue was purified by column chromatography on silica to afford the product (2.24 g, 90% yield) as a pale-yellow solid.  $R_f$  (1:4 EtOAc/hexane): 0.15; mp: 121–122 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.61 (br s, 1H, NH), 7.59 (d,  $J = 8$  Hz, 2H), 7.32 (d,  $J = 8$  Hz, 2H), 7.25 (d,  $J = 8$  Hz, 1H), 6.79 (d,  $J = 8$  Hz, 1H), 4.72 (s, 2H,  $\text{CH}_2\text{O}$ ), 3.87 (s, 3H, OMe), 3.86 (s, 3H, OMe), 0.94 (s, 9H,  $3 \times \text{CH}_3$ ), 0.10 (s, 6H,  $2 \times \text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  163.5, 152.2, 146.9, 138.0, 136.4, 133.8, 128.3, 126.8, 120.1, 114.3, 109.9, 64.6, 62.2, 56.1, 26.0, 18.4, –5.2. FTIR (KBr,  $\text{cm}^{-1}$ ): 3262, 2931, 2857, 1659, 1604, 1542, 1414, 1280, 1092, 1060, 1006, 838, 776. HRMS ( $\text{EI}^+$ ): calcd 479.1122 for  $\text{C}_{22}\text{H}_{30}^{79}\text{BrNO}_4\text{Si}$  [ $\text{M}$ ] $^+$  and 481.1102 for  $\text{C}_{22}\text{H}_{30}^{81}\text{BrNO}_4\text{Si}$  [ $\text{M}$ ] $^+$ ; found, 479.1120 and 481.1106, respectively. Anal. ( $\text{C}_{22}\text{H}_{30}\text{BrNO}_4\text{Si}$ ) C, H, N.

**5-Bromo-*N*-(4-(*tert*-butyldimethylsilyloxymethyl)phenyl)benzo[d][1,3]dioxole-4-carboxamide (25).** The product was obtained as white needles in 86% yield following the procedure for compound **24** using benzoic acid **21**.  $R_f$  (3:7 EtOAc/hexanes): 0.4; mp: 125–126 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.78 (br s, NH, 1H), 7.60 (d,  $J = 8$  Hz, 2H), 7.31 (d,  $J = 8$  Hz, 2H), 7.09 (d,  $J = 8$  Hz, 1H), 6.73 (d,  $J = 8$  Hz, 1H), 6.06 (s, 2H,  $\text{OCH}_2\text{O}$ ), 4.72 (s, 2H,  $\text{CH}_2\text{O}$ ), 0.94 (s, 9H,  $3 \times \text{CH}_3$ ), 0.10 (s, 6H,  $2 \times \text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  161.1, 147.5, 146.5, 138.2, 136.2, 126.8, 126.5, 120.0, 119.5, 110.9, 110.8, 102.5, 64.6, 26.0, 18.4, –5.2. FTIR (KBr,  $\text{cm}^{-1}$ ): 3300, 2955, 2855, 1662, 1611, 1548, 1452, 1248, 1092, 1043, 838, 774. HRMS

( $\text{ESI}^+$ ): calcd 486.0707 for  $\text{C}_{21}\text{H}_{26}^{79}\text{BrNO}_4\text{SiNa}$  [ $\text{M} + \text{Na}$ ] $^+$ ; found, 486.0699. Anal. ( $\text{C}_{21}\text{H}_{26}\text{BrNO}_4\text{Si}$ ) C, H, N.

**5-Bromo-*N*-(4-(2-*tert*-butyldimethylsilyloxyethyl)phenyl)benzo[d][1,3]dioxole-4-carboxamide (26).** The product was obtained as a white solid in 93% yield from **21** and **23** using the same reaction conditions for the preparation of **24**.  $R_f$  (1:4 EtOAc/hexanes): 0.24; mp: 103–104 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.68 (br s, 1H, NH), 7.55 (d,  $J = 8$  Hz, 2H), 7.20 (d,  $J = 8$  Hz, 2H), 7.10 (d,  $J = 8$  Hz, 1H), 6.75 (d,  $J = 8$  Hz, 1H), 6.07 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.79 (app. t,  $J = 7$  Hz, 2H), 2.81 (app. t,  $J = 7$  Hz, 2H), 0.88 (s, 9H,  $3 \times \text{CH}_3$ ), 0.00 (s, 6H,  $2 \times \text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  161.0, 147.5, 146.5, 136.0, 135.5, 129.7, 126.5, 120.0, 119.5, 111.0, 110.8, 102.5, 64.5, 39.1, 25.9, 18.3, –5.4. FTIR (KBr,  $\text{cm}^{-1}$ ): 3289, 2929, 2857, 1657, 1605, 1542, 1411, 1325, 1247, 1110, 1046, 834, 775. HRMS ( $\text{ESI}^+$ ): calcd 478.1044 for  $\text{C}_{22}\text{H}_{29}^{79}\text{BrNO}_4\text{Si}$  [ $\text{M} + \text{H}$ ] $^+$  and 480.1029 for  $\text{C}_{22}\text{H}_{29}^{81}\text{BrNO}_4\text{Si}$  [ $\text{M} + \text{H}$ ] $^+$ ; found, 478.1041 and 480.1024, respectively. Anal. ( $\text{C}_{22}\text{H}_{28}\text{BrNO}_4\text{Si}$ ) C, H, N.

**General Procedure for the N-MOM Protection of Benzamides.** **2-Bromo-*N*-(4-(*tert*-butyldimethylsilyloxymethyl)phenyl)-*N*-(methoxymethyl)-5,6-dimethoxybenzamide (27).** To the benzamide **24** (100 mg, 0.208 mmol) in THF (5 mL) under argon was added portionwise NaH (50 mg, 1.25 mmol). The mixture was stirred at room temperature for 20 min, and then MOMBr (37.8  $\mu\text{L}$ , 0.42 mmol) was added via syringe to the reaction mixture. The mixture was warmed to 40 °C and stirred for a further 3 h. The reaction was quenched by the addition of saturated  $\text{NaHCO}_3$ . The crude product was extracted with diethyl ether ( $3 \times 50$  mL), and the organic layer was washed with brine. The organic layer was separated and dried with  $\text{MgSO}_4$  and then filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica to afford **27** as a colorless wax (98 mg, 90% yield).  $R_f$  (1:4 EtOAc/hexanes): 0.22; mp: 77–79 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.33 (d,  $J = 8$  Hz, 2H), 7.13 (d,  $J = 8$  Hz, 2H), 7.00 (d,  $J = 8$  Hz, 1H), 6.59 (d,  $J = 8$  Hz, 1H), 5.29 (d,  $J = 10$  Hz, 1H,  $\text{OCH}_2\text{N}$ ), 5.21 (d,  $J = 10$  Hz, 1H,  $\text{OCH}_2\text{N}$ ), 4.62 (s, 2H,  $\text{CH}_2\text{O}$ ), 3.90 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.62 (s, 3H, OMe), 0.88 (s, 9H,  $3 \times \text{CH}_3$ ), 0.01 (s, 6H,  $2 \times \text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  167.4, 151.7, 145.7, 141.3, 139.1, 134.1, 127.8, 127.3, 126.2, 113.7, 108.9, 78.8, 64.4, 61.8, 56.8, 55.9, 25.9, 18.3, –5.3. FTIR (KBr,  $\text{cm}^{-1}$ ): 2932, 2857, 1660, 1473, 1301, 1266, 1063, 1009, 837, 778. HRMS ( $\text{EI}^+$ ): calcd 523.1384 for  $\text{C}_{24}\text{H}_{34}^{79}\text{BrNO}_5\text{Si}$  [ $\text{M}$ ] $^+$  and 525.1364 for  $\text{C}_{24}\text{H}_{34}^{81}\text{BrNO}_5\text{Si}$  [ $\text{M}$ ] $^+$ ; found, 523.1395 and 525.1383 respectively.

**5-Bromo-*N*-(4-(*tert*-butyldimethylsilyloxymethyl)phenyl)-*N*-(methoxymethyl)benzo[d][1,3]dioxole-4-carboxamide (28).** The product was obtained as a colorless gum in 84% yield from **25** following a procedure similar to that used for the preparation of **27** above.  $R_f$  (3:7 EtOAc/hexanes): 0.43.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.26 (d,  $J = 8$  Hz, 2H), 7.16 (d,  $J = 8$  Hz, 2H), 6.85 (d,  $J = 8$  Hz, 1H), 6.47 (d,  $J = 8$  Hz, 1H), 5.93 (d,  $J = 1$  Hz, 1H), 5.72 (d,  $J = 1$  Hz, 1H), s, 2H,  $\text{CH}_2\text{O}$ ), 3.525 (d,  $J = 10$  Hz, 1H,  $\text{OCH}_2\text{H}_b\text{O}$ ), 5.22 (d,  $J = 10$  Hz, 1H,  $\text{OCH}_2\text{H}_b\text{O}$ ), 4.64 (s, 3H, OMe), 0.89 (s, 9H,  $3 \times \text{CH}_3$ ), 0.02 (d,  $J = 1$  Hz, 6H,  $2 \times \text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  165.7, 146.7, 144.2, 141.6, 139.0, 127.2, 126.2, 125.3, 120.8, 110.3, 109.7, 101.9, 78.7, 64.4, 56.9, 25.9, 18.3, –5.3. FTIR (KBr,  $\text{cm}^{-1}$ ): 2932, 1665, 1513, 1450, 1302, 1241, 1042, 924, 873, 801. HRMS ( $\text{ESI}^+$ ): calcd 530.0969 for  $\text{C}_{23}\text{H}_{30}^{79}\text{BrNO}_5\text{SiNa}$  [ $\text{M} + \text{Na}$ ] $^+$ ; found, 530.0951.

**5-Bromo-*N*-(4-(2-*tert*-butyldimethylsilyloxyethyl)phenyl)-*N*-(methoxymethyl)benzo[d][1,3]dioxole-4-carboxamide (29).** The compound **29** was obtained as a colorless gum in 80% yield from **26** using the same procedure as that used for the preparation of **27**. The  $^1\text{H}$  NMR spectrum reveals two rotamers as evidenced by two distinct singlet resonances for the dioxolane ring at  $\delta$  5.96 and 5.76 ppm.  $R_f$  (1:1.8 EtOAc/acetone/hexanes): 0.40.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.22 (d,  $J = 8$  Hz, 2H), 7.06 (d,  $J = 8$  Hz, 2H), 6.86 (d,  $J = 8$  Hz, 1H), 6.48 (d,  $J = 8$  Hz, 1H), 5.96 (s, 1H,  $\text{OCH}_2\text{O}$ ), 5.76 (s, 1H,  $\text{OCH}_2\text{O}$ ), 5.22 (d,  $J = 12$  Hz, 1H,  $\text{NCH}_2\text{H}_b\text{O}$ ), 5.21 (d,  $J = 12$  Hz, 1H,  $\text{NCH}_2\text{H}_b\text{O}$ ), 3.73 (app. t,  $J = 6$  Hz, 2H), 3.58 (s, 3H, OMe), 2.71 (app. t,  $J = 6$  Hz, 2H), 0.82 (s, 9H,  $3 \times \text{CH}_3$ ), –0.13 (s, 3H,  $\text{CH}_3$ ), –0.14 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  165.6, 146.7,



144.2, 139.7, 138.5, 129.6, 127.1, 125.3, 120.9, 110.3, 109.7, 101.9, 78.9, 63.9, 56.9, 39.0, 25.9, 18.2, -5.50, -5.53. FTIR (KBr, cm<sup>-1</sup>): 2930, 2857, 1670, 1451, 1301, 1241, 1110, 1043, 836, 778. HRMS (ESI<sup>+</sup>): calcd 544.1131 for C<sub>24</sub>H<sub>32</sub><sup>79</sup>BrNO<sub>5</sub>SiNa [M + Na]<sup>+</sup> and 546.1110 for C<sub>24</sub>H<sub>32</sub><sup>81</sup>BrNO<sub>5</sub>SiNa [M + Na]<sup>+</sup>; found, 544.1088 and 546.1112, respectively.

**Procedure for the Palladium Catalyzed Aryl-Aryl Coupling. Synthesis of 2-(*tert*-butyldimethylsilyloxymethyl)-7,8-dimethoxy-5-(methoxymethyl) Phenanthridin-6(5*H*)-one (30).** To a solution of the compound **27** (4 g, 7.63 mmol) in dry DMF (200 mL) was added anhydrous Na<sub>2</sub>CO<sub>3</sub> (1.62 g, 15.28 mmol), Pd(OAc)<sub>2</sub> (171 mg, 0.76 mmol), and PPh<sub>3</sub> (0.5 g, 1.91 mmol) under argon. The mixture was thrice degassed under reduced pressure and then filled with argon and then refluxed under argon for 7 h. The reaction mixture was cooled to rt and then diluted with diethyl ether and filtered through Celite 545 to remove the precipitated Pd. Concentration of the solution under reduced pressure gave a residue, which was subjected to purification via column chromatography on silica (EtOAc/hexanes, gradient 20–100%) to afford the title compound as a white amorphous solid (2.37 g, 70% yield). *R*<sub>f</sub> (1:1 EtOAc/hexanes): 0.51; mp: 107–108 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.12 (br s, 1H), 8.03 (d, *J* = 9 Hz, 1H), 7.50 (d, *J* = 9 Hz, 1H), 7.41 (d, *J* = 9 Hz, 1H), 7.40 (dd, *J* = 9 and 2 Hz, 1H), 5.79 (s, 2H, NCH<sub>2</sub>O), 4.84 (s, 2H, CH<sub>2</sub>O), 4.00 (s, 3H, OMe), 3.98 (s, 3H, OMe), 3.49 (s, 3H, OMe), 0.98 (s, 9H, 3 × CH<sub>3</sub>), 0.14 (s, 6H, 2 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 160.4, 153.2, 150.7, 135.9, 135.4, 128.9, 126.8, 120.2, 119.9, 118.8, 118.1, 118.0, 115.8, 73.7, 64.7, 61.4, 56.6, 56.6, 26.0, 18.5, -5.1. FTIR (KBr, cm<sup>-1</sup>): 2927, 2854, 1655, 1499, 1458, 1318, 1278, 1103, 1080, 836, 774. HRMS (EI<sup>+</sup>): calcd 443.2123 for C<sub>24</sub>H<sub>33</sub>NO<sub>5</sub>Si [M]<sup>+</sup>; found, 443.2144.

**8-(*tert*-Butyldimethylsilyloxymethyl)-5-(methoxymethyl)-[1,3]dioxolo[4,5-*i*]phenanthridin-4(5*H*)-one (31).** The product was obtained as a white solid in 71% yield from **28** following the procedure outlined for compound **30**. *R*<sub>f</sub> (1:1 EtOAc/hexanes): 0.39; mp: 128–129 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.98 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 6.19 (s, 2H, OCH<sub>2</sub>O), 5.70 (s, 2H, NCH<sub>2</sub>O), 4.78 (s, 2H, CH<sub>2</sub>O), 3.43 (s, 3H, OMe), 0.95 (s, 9H, 3 × CH<sub>3</sub>), 0.12 (s, 6H, 2 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 160.2, 148.3, 147.9, 136.2, 135.1, 128.5, 126.8, 120.3, 119.1, 116.1, 115.2, 113.3, 110.6, 102.9, 73.3, 64.5, 56.7, 26.0, 18.4, -5.2. FTIR (KBr, cm<sup>-1</sup>): 2929, 2856, 1659, 1459, 1369, 1306, 1253, 1064, 1912, 838, 775. HRMS (ESI<sup>+</sup>): calcd 428.1888 for C<sub>23</sub>H<sub>30</sub>NO<sub>5</sub>Si [M + H]<sup>+</sup>; found, 428.1878. Anal. (C<sub>23</sub>H<sub>29</sub>NO<sub>5</sub>Si) C, H, N.

**8-(2-*tert*-Butyldimethylsilyloxyethyl)-5-(methoxymethyl)-[1,3]dioxolo[4,5-*i*]phenanthridin-4(5*H*)-one (32).** Compound **32** was synthesized from **29** using the procedure for the preparation of **30**. The desired product was obtained as a white solid in 80% yield. *R*<sub>f</sub> (1:1 EtOAc/hexanes): 0.45; mp: 128–129 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.94 (s, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.48 (d, *J* = 9 Hz, 1H), 7.29 (d, *J* = 9 Hz, 1H), 7.22 (d, *J* = 8 Hz, 1H), 6.24 (s, 2H, OCH<sub>2</sub>O), 5.77 (s, 2H, NCH<sub>2</sub>O), 3.86 (app. t, *J* = 6 Hz, 2H), 3.47 (s, 3H, OMe), 2.90 (app. t, *J* = 6 Hz, 2H), 0.88 (s, 9H, 3 × CH<sub>3</sub>), 0.00 (s, 6H, 2 × CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 160.3, 148.4, 147.9, 134.6, 134.2, 129.8, 128.6, 123.5, 119.2, 116.1, 115.3, 113.3, 110.8, 102.9, 73.3, 64.4, 56.7, 39.1, 25.9, 18.3, -5.4. FTIR (KBr, cm<sup>-1</sup>): 2954, 2857, 1657, 1461, 1307, 1256, 1057, 912, 833, 775. HRMS (ESI<sup>+</sup>): calcd 442.2044 for C<sub>24</sub>H<sub>32</sub>NO<sub>5</sub>Si [M + H]<sup>+</sup>; found, 442.2056. Anal. (C<sub>24</sub>H<sub>31</sub>BrNO<sub>5</sub>Si) C, H, N.

**General Procedure for the Deprotection of the TBDMS Group.** To a stirred solution of TBS-protected ethers **31** or **32** (typically 500 mg) in dry THF (50 mL) was added *tetra-n*-butylammonium fluoride (1 M in THF, 2.84 mL) slowly under argon. The mixture was stirred for 1 h at rt and quenched by adding saturated NH<sub>4</sub>Cl. The reaction mixture was partitioned between water (50 mL) and EtOAc (50 mL) and then further extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine, dried with MgSO<sub>4</sub>, and concentrated in vacuo to yield a crude product, which was then purified by column chromatography to give the desired product as a white solid.

**8-(Hydroxymethyl)-5-(methoxymethyl)-[1,3]dioxolo[4,5-*i*]phenan-**

**thridin-4(5*H*)-one (36).** White solid (yield 99%). *R*<sub>f</sub> (1:1 EtOAc/hexanes): 0.07; mp: 202–204 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.08 (s, *J* = 9 Hz, 1H), 7.77 (d, *J* = 9 Hz, 1H), 7.48 (d, *J* = 9 Hz, 1H), 7.40 (dd, *J* = 9 and 2 Hz, 1H), 7.22 (d, *J* = 9 Hz, 1H), 6.25 (s, 2H, NCH<sub>2</sub>O), 5.74 (s, 2H, OCH<sub>2</sub>O), 4.74 (s, 2H, CH<sub>2</sub>OH), 3.46 (s, 3H, OMe). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 160.4, 148.3, 148.0, 136.2, 135.1, 128.3, 127.5, 121.3, 119.3, 116.2, 115.4, 113.5, 110.4, 102.9, 73.3, 64.1, 56.6. FTIR (KBr, cm<sup>-1</sup>): 3445, 3318, 2939, 1656, 1456, 1316, 1263, 1086, 1032, 951, 804. HRMS (ESI<sup>+</sup>): calcd 336.0842 for C<sub>17</sub>H<sub>15</sub>NO<sub>5</sub>Na [M + Na]<sup>+</sup>; found, 336.0836. Anal. C<sub>17</sub>H<sub>15</sub>NO<sub>5</sub> C, H, N.

**8-(2-Hydroxyethyl)-5-(methoxymethyl)-[1,3]dioxolo[4,5-*i*]phenanthridin-4(5*H*)-one (37).** Compound **37** was synthesized from **32** following the general procedure. As the product is polar and poorly soluble in most organic solvents, the crude product was obtained by vacuum filtration. The precipitate was washed with small portions of DCM, followed by acetone and then water. The precipitate was dried in vacuo to yield the desired product as white amorphous solid (685 mg, 85% yield). *R*<sub>f</sub> (100% EtOAc): 0.36; mp: 216–217 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.97 (br s, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 9 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.40 (d, *J* = 9 Hz, 1H), 6.26 (s, 2H, OCH<sub>2</sub>O), 5.77 (s, 2H, OCH<sub>2</sub>N), 3.94 (app. t, *J* = 6 Hz, 2H, CH<sub>2</sub>O), 2.97 (app. t, *J* = 6 Hz, 2H, ArCH<sub>2</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 160.3, 148.4, 148.1, 134.9, 133.5, 129.6, 128.3, 123.4, 119.5, 116.5, 115.4, 113.4, 110.7, 102.9, 73.4, 63.6, 56.8, 38.7. FTIR (KBr, cm<sup>-1</sup>): 3420, 2919, 2863, 1654, 1458, 1307, 1266, 1060, 808. MS-ESI<sup>+</sup> (*m/z*, %): 350 ([M + Na]<sup>+</sup>, 100). HRMS (ESI<sup>+</sup>): calcd 328.1180 for C<sub>18</sub>H<sub>18</sub>NO<sub>5</sub> [M + H]<sup>+</sup>, and 350.0999 for C<sub>18</sub>H<sub>17</sub>NO<sub>5</sub>Na [M + Na]<sup>+</sup>; found, 328.1175 and 350.0983, respectively.

**O-Methylation of 2-Substituted Phenanthridinones. 5,8-Bis-(methoxymethyl)-[1,3]dioxolo[4,5-*i*]phenanthridin-4(5*H*)-one (38).** To a suspension of compound **36** (30 mg, 0.0958 mmol) in THF (5 mL) was added NaH (60% in mineral oil, 19 mg, 0.475 mmol). The mixture was stirred for 20 min at rt, and then dimethyl sulfate (27 μL, 0.285 mmol) was added slowly by syringe. The reaction mixture was refluxed for 6 h, after which the mixture was cooled to rt and water was added slowly to quench the excess NaH. The mixture was diluted with EtOAc (20 mL) and water (20 mL), and the EtOAc layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvent in vacuo gave a white residue, which was subjected to silica gel chromatography (70% EtOAc in hexanes). The product was obtained as a white solid in 96% yield. *R*<sub>f</sub> (7:3 EtOAc/hexane): 0.29; mp: 193–194 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.08 (d, *J* = 2 Hz, 1H), 7.81 (d, *J* = 9 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.40 (dd, *J* = 8 and 2 Hz, 1H), 7.24 (d, *J* = 9 Hz, 1H), 6.26 (s, 2H, OCH<sub>2</sub>O), 5.78 (s, 2H, OCH<sub>2</sub>N), 4.54 (s, 2H, CH<sub>2</sub>OH), 3.48 (s, 3H, OMe), 3.44 (s, 3H, OMe). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 160.4, 148.4, 148.1, 135.7, 133.1, 128.4, 122.2, 119.5, 116.3, 115.5, 113.5, 110.7, 102.9, 74.2, 73.4, 58.2, 56.8. MS-ESI<sup>+</sup> (*m/z*, %): 350 ([M + Na]<sup>+</sup>, 100). HRMS (ESI<sup>+</sup>): calcd 328.1180 for C<sub>18</sub>H<sub>18</sub>NO<sub>5</sub> [M + H]<sup>+</sup>, and 350.0999 for C<sub>18</sub>H<sub>18</sub>NO<sub>5</sub>Na [M + Na]<sup>+</sup>; found, 328.1179 and 350.0997 respectively.

**8-(2-Methoxyethyl)-5-(methoxymethyl)-[1,3]dioxolo[4,5-*i*]phenanthridin-4(5*H*)-one (39).** Compound **39** was prepared from **37** following the general procedure for the preparation of **38**. The product was a white solid (quantitative yield). *R*<sub>f</sub> (1:1 EtOAc/hexanes): 0.23. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.94 (d, *J* = 2 Hz, 1H), 7.77 (d, *J* = 9 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.31 (dd, *J* = 9 and 2 Hz, 1H), 7.23 (d, *J* = 8 Hz, 1H), 6.25 (s, 2H), 5.77 (s, 2H), 3.66 (app. t, *J* = 7 Hz, 2H), 3.47 (s, 3H, OMe), 3.38 (s, 3H, OCH<sub>3</sub>), 2.97 (app. t, *J* = 7 Hz, 2H). HRMS (ESI<sup>+</sup>): calcd 364.1155 for C<sub>19</sub>H<sub>19</sub>NO<sub>5</sub>Na [M + Na]<sup>+</sup>; found, 364.1144.

**Procedure for the Synthesis of *N*-Methyl Phenanthridinium Chlorides. 2-(Hydroxymethyl)-7,8-dimethoxy-5-methylphenanthridinium Chloride (33).** To a solution of compound **30** (300 mg, 0.68 mmol) in dry THF (20 mL) was slowly added a solution of diisobutylaluminum hydride (DIBAL, 1 M in toluene, 2.71 mL) at -10 °C under argon. The mixture was stirred at -10 °C for 1 h and then warmed to rt. Saturated MgSO<sub>4</sub> was added dropwise until a colorless precipitate was formed, and the mixture was stirred

vigorously for an additional 30 min. The mixture was diluted with diether ether and filtered through Celite. Removal of solvents gave a colorless residue. The residue was dissolved in toluene (10 mL), and a solution of 2,3-dicyano-5,6-dichloro-parabenzoquinone (DDQ, 227 mg in 10 mL toluene, 1 mmol) was then added slowly. The reaction mixture was stirred for 2 h prior to acidification with 2 M HCl (15 mL). The acidic solution was stirred for an additional 15 min, during which a yellow aqueous layer was formed. This aqueous layer was separated then washed with ether (15 mL) and then chloroform (2 × 15 mL), and the organic layers were discarded. Removal of water under reduced pressure gave an orange residue, which was recrystallized from MeOH-ether to afford **33** as yellow needles (200 mg, 93% yield). mp: 187–189 °C (dec). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.15 (s, 1H), 8.93 (s, 1H), 8.77 (d, *J* = 9 Hz, 1H), 8.43 (d, *J* = 8 Hz, 1H), 8.24 (d, *J* = 9 Hz, 1H), 8.00 ((d, *J* = 8 Hz, 1H), 4.85 (s, 2H, CH<sub>2</sub>OH), 4.70 (s, 3H, NMe), 4.14 (s, 3H, OMe), 4.10 (s, 3H, OMe). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 151.5, 150.9, 147.1, 146.0, 132.5, 129.7, 127.8, 125.8, 125.6, 121.3, 120.2, 119.6, 119.5, 62.7, 62.6, 57.4, 46.3. FTIR (KBr, cm<sup>-1</sup>): 3371, 3214, 3022, 2957, 1596, 1509, 1447, 1335, 1292, 1252, 1067, 957, 809, 781. MS-ESI<sup>+</sup> (*m/z*, %): 284 ([M]<sup>+</sup>, 100), 269 ([M-Me]<sup>+</sup>, 37). HRMS (ESI<sup>+</sup>): calcd 284.1287 for C<sub>17</sub>H<sub>18</sub>NO<sub>3</sub> [M]<sup>+</sup>; found, 284.1283.

**8-(Hydroxymethyl)-5-methyl-[1,3]dioxolo[4,5-*i*]phenanthridinium Chloride (34).** Compound **34** was prepared from **31** following the procedure used for the preparation of compound **33**. Orange solid, 90% yield; mp: 230–236 °C (dec). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 9.77 (s, 1H), 8.67 (br s, 1H), 8.33 (d, *J* = 10 Hz, 1H), 8.25 (d, *J* = 10 Hz, 1H), 7.93 (dd, *J* = 9 and 2 Hz, 1H), 7.83 (d, *J* = 9 Hz, 1H), 6.44 (s, 2H), 4.94 (s, 2H), 4.58 (s, 3H, N-Me). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 148.0, 147.6, 147.4, 143.8, 131.3, 129.2, 125.9, 125.2, 120.6, 119.3, 119.2, 115.9, 108.3, 105.1, 62.6, 45.4. FTIR (KBr, cm<sup>-1</sup>): 3333, 2977, 1615, 1500, 1472, 1293, 1062, 1030, 903, 832. HRMS (ESI<sup>+</sup>): calcd 268.0968 for C<sub>16</sub>H<sub>14</sub>NO<sub>3</sub> [M]<sup>+</sup>; found, 268.0975.

**8-(2-Hydroxyethyl)-5-methyl-[1,3]dioxolo[4,5-*i*]phenanthridinium Chloride (35).** Compound **35** was prepared from **32** following the general procedure. The crude product was recrystallized from methanol to afford yellow prism crystals (45 mg, 92% yield); mp: 243–246 °C (dec). <sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 9.94 (s, 1H, *N* = CH), 8.77 (s, 1H), 8.55 (d, *J* = 8 Hz, 1H), 8.34 (d, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8 Hz, 1H), 4.67 (s, 3H, NMe), 3.96 (app. t, *J* = 6 Hz, 2H, CH<sub>2</sub>O), 3.17 (app. t, *J* = 6 Hz, 2H, ArCH<sub>2</sub>). <sup>13</sup>C NMR (MeOH-*d*<sub>4</sub>): δ 150.4, 149.8, 149.5, 145.0, 133.4, 128.6, 127.8, 125.4, 120.7, 120.6, 118.0, 110.9, 106.5, 63.4, 46.5, 40.0. FTIR (KBr, cm<sup>-1</sup>): 3384, 3232, 3070, 2920, 1614, 1502, 1472, 1293, 1275, 1064, 1029, 841, 812. HRMS (ESI<sup>+</sup>): calcd 282.1125 for C<sub>17</sub>H<sub>16</sub>NO<sub>3</sub> [M]<sup>+</sup>; found, 282.1124.

**8-(Methoxymethyl)-5-methyl-[1,3]dioxolo[4,5-*i*]phenanthridinium Chloride (40).** Compound **40** was prepared from **38** following the procedure for compound **33**. Purification via reverse phase HPLC (Luna 21.2 mm × 250 mm; flow rate: 20 mL/min; mobile phase: acetonitrile in water with 0.1% formic acid; gradient: 10% (10 min), 10–70% (10 min), 70% (5 min), *R*<sub>t</sub> 7.9 min) afforded the product, which was obtained as an orange solid in quantitative yield; mp: 199–202 °C (dec). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 9.53 (s, 1H), 8.14 (s, 1H), 8.01 (d, *J* = 9 Hz, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.77 (dd, *J* = 8 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 6.38 (s, 2H, OCH<sub>2</sub>O), 4.66 (s, 2H, CH<sub>2</sub>O), 4.40 (s, 3H, NMe), 3.54 (s, 3H, OMe). <sup>13</sup>C NMR (D<sub>2</sub>O): δ 148.3, 147.7, 147.5, 140.9, 131.5, 129.9, 125.8, 125.1, 121.6, 119.4, 119.3, 115.9, 108.3, 105.2, 72.8, 58.3, 45.4. FTIR (KBr, cm<sup>-1</sup>): 3442, 3045, 1619, 1471, 1445, 1295, 1274, 1105, 1061, 900, 831. HRMS (ESI<sup>+</sup>): calcd 282.1125 for C<sub>17</sub>H<sub>16</sub>NO<sub>3</sub> [M]<sup>+</sup>; found, 282.1122.

**8-(2-Methoxyethyl)-5-methyl-[1,3]dioxolo[4,5-*i*]phenanthridinium Chloride (41).** Compound **41** was prepared from **39** following the general procedure for preparing **33**. Reverse phase HPLC (Luna 21.2 mm × 250 mm, flow rate: 20 mL/min; mobile phase: acetonitrile in water with 0.1% formic acid; gradient: 10% (10 min), 10–70% (10 min), 70% (5 min), *R*<sub>t</sub> 10.6 min) yielded the product as an orange solid in quantitative yields; mp: 146–147 °C (dec). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 9.28 (s, 1H), 7.99 (d, *J* = 1 Hz, 1H), 7.85 (d,

*J* = 9 Hz, 1H), 7.72 (d, *J* = 9 Hz, 1H), 7.69 (dd, *J* = 9 and 1 Hz, 1H), 7.48 (d, *J* = 9 Hz, 1H), 6.28 (s, 2H, OCH<sub>2</sub>O), 4.24 (s, 3H, NMe), 3.80 (app. t, *J* = 7 Hz, 2H), 3.36 (s, 3H, OCH<sub>3</sub>), 3.02 (app. t, *J* = 7 Hz, 2H). <sup>13</sup>C NMR (D<sub>2</sub>O): δ 147.5, 147.3, 147.2, 143.1, 131.8, 130.5, 125.4, 124.8, 123.0, 119.2, 119.1, 115.8, 107.9, 105.2, 72.0, 57.9, 45.4, 34.8. FTIR (KBr, cm<sup>-1</sup>): 3400, 2948, 1615, 1498, 1475, 1301, 1248, 1104, 1067, 892, 839. HRMS (ESI<sup>+</sup>): calcd 296.1281 for C<sub>18</sub>H<sub>18</sub>NO<sub>3</sub> [M]<sup>+</sup>; found, 296.1279.

**Procedure for Cleavage of Methyl Ethers. 7,8-Dihydroxy-5-methylphenanthridinium Chloride (42).** To the suspension of **14** (20 mg, 0.052 mmol) in dry DCM (5 mL) under argon was slowly added an excess amount of BBr<sub>3</sub> (1 M in DCM, 0.2 mL) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C and quenched with dry MeOH. The solvent was removed in vacuo to yield an orange crude product, which was acidified with dilute HCl and purified by reverse phase HPLC (Luna C<sub>18</sub>, 21.2 mm × 250 mm, flow rate: 20 mL/min; mobile phase: acetonitrile in water with 0.1% formic acid; gradient: 10–70%, 15 min, *R*<sub>t</sub> 6.6 min) to afford pure product **42** as a beige solid in 86% yield; mp: 263–266 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.00 (s, 1H), 8.83 (br s, 1H), 8.30 (br s, 1H), 8.20 (br s, 1H), 7.92 (m, 3H), 4.57 (s, 3H, NMe). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 150.6, 147.6, 145.3, 132.7, 129.9, 129.7, 126.8, 125.9, 125.7, 123.9, 119.6, 115.1, 112.5, 45.1. FTIR (KBr): 3421 (br), 3093 (br), 1613, 1543, 1491, 1458, 1359, 1339, 1240, 1175, 1005, 838, 765, 710 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd 226.0863 for C<sub>14</sub>H<sub>12</sub>NO<sub>2</sub><sup>+</sup> [M]<sup>+</sup>; found, 226.0860.

**7,8-Dihydroxy-2-(hydroxymethyl)-5-methylphenanthridinium Chloride (43).** The title compound was prepared following the previous procedure for compound **42**. The crude product was stirred at 80 °C for 5 h in the presence of a few drops of 1 M HCl to convert any 2-methylbromo-5-methyl-7,8-dihydroxyphenanthridinium byproduct to the title compound **43**. The solvent was then removed in vacuo, and the crude product was recrystallized from MeOH to afford the desired product as an orange solid (67% yield). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 9.19 (s, 1H), 7.99 (s, 1H), 7.88 (d, *J* = 9 Hz, 1H), 7.72 (d, *J* = 9 Hz, 1H), 7.40 (d, *J* = 9 Hz, 1H), 7.22 (d, *J* = 9 Hz, 1H), 4.79 (s, 2H, CH<sub>2</sub>OH), 4.27 (s, 3H, NMe). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 150.1, 145.4, 144.9, 144.7, 131.7, 128.6, 127.5, 126.2, 125.5, 120.6, 119.7, 115.3, 113.7, 62.3, 45.5. ESI-MS (*m/z*, %): 256 ([M]<sup>+</sup>, 100). HRMS (ESI<sup>+</sup>): calcd 256.0968 for C<sub>15</sub>H<sub>14</sub>NO<sub>3</sub><sup>+</sup> [M]<sup>+</sup>; found, 256.0960.

**7,8-Dihydroxy-2-(2-hydroxyethyl)-5-methylphenanthridinium (44).** The reaction of compound **41** with BBr<sub>3</sub> for 16 h afforded the desired product, which was purified by preparative HPLC. HPLC condition: Luna C<sub>18</sub> 21.2 mm × 250 mm, flow rate: 20 mL/min; mobile phase: acetonitrile in water; gradient: 20% (5 min), 20–80% (20 min), 80% (5 min), *R*<sub>t</sub> 3.0 min. Yellow solid, 84% yield. <sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 9.98 (s, 1H), 8.72 (s, 1H), 8.30 (d, *J* = 9 Hz, 1H), 8.29 (d, *J* = 9 Hz, 1H), 7.89 (d, *J* = 9 Hz, 1H), 7.82 (d, *J* = 9 Hz, 1H), 4.65 (s, 3H, NMe), 3.95 (app. t, *J* = 6 Hz), 3.16 (app. t, *J* = 6 Hz). ESI-MS (*m/z*, %): 270 ([M]<sup>+</sup>, 95). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 149.8, 145.3, 144.6, 142.4, 131.4, 131.3, 127.4, 126.1, 125.5, 123.7, 119.4, 115.2, 113.8, 61.7, 45.2, 38.6. ESI-MS (*m/z*, %): 270 ([M]<sup>+</sup>, 95). HRMS (ESI<sup>+</sup>): calcd 270.1125 for C<sub>16</sub>H<sub>16</sub>NO<sub>3</sub><sup>+</sup> [M]<sup>+</sup>; found, 270.1143.

**Biology. Fluorescence Polarization Assay.** The Bak-BH3 peptide labeled with fluorescein at the N terminus was synthesized by Mimotopes (Clayton, Victoria, Australia) and purified by HPLC. The peptide was dissolved in DMSO at 1 mM, and stock solutions of the test compounds (4 mM in DMSO) were used for serial dilutions (250–0.65 μM final concentrations). The reaction was carried out in a total volume of 100 μL/well containing 3 μg glutathione S-transferase (GST)-Bcl<sub>XL</sub>ΔC19 and 60 nM labeled peptide in assay buffer (50 mM Tris, pH 8, 150 mM NaCl and 0.1% bovine serum albumin). To each well was added 10 μL of the test compounds, and the reaction mixture was incubated at rt for 1 h. The fluorescence polarization values were determined using a Tecan GeniosPro plate reader using the excitation/emission wavelengths 485/535 nm.

**Protein Expression, Purification and NMR Titration.** A vector modified from pET-32a containing the construct for human Bcl-



X<sub>L</sub> (from residues 1–218 with the flexible loop from residues 45–84 removed) as described by Zhang et al.<sup>11</sup> was used for expression of wild-type Bcl-X<sub>L</sub> and its mutants (E129A, L130A, D133K, V135A, R139A, A142G, Y173F, and E184A). The DNA sequences of all the constructs were confirmed by Big Dye sequencing. The expression, purification, and thrombin cleavage of His-tagged Bcl-X<sub>L</sub> protein were performed as described previously.<sup>11</sup> The purified proteins were concentrated to around 0.25 mM and buffer exchanged to 20 mM sodium phosphate buffer (pH 7.0) using Amicon Centrprep-10 (Millipore) for NMR experiments. For NMR titrations, both compounds **35** and **42** (stock solutions of 50 mM in DMSO) were titrated into wild-type and mutant Bcl-X<sub>L</sub> at inhibitor to protein molar ratio of 10:1. <sup>1</sup>H–<sup>15</sup>N HSQC spectrum of each titrated sample (~0.25 mM protein in 20 mM phosphate buffer containing 10% D<sub>2</sub>O v/v) was recorded on a 500 MHz Bruker DRX spectrometer equipped with cryoprobe at 298 K. All spectra were acquired with 1024 complex data points in *t*<sub>2</sub> and 128 points in *t*<sub>1</sub> with spectral widths of 26.4 ppm and 16 ppm in the <sup>15</sup>N and <sup>1</sup>H dimensions, respectively, using 16 scans. All NMR data were processed using NMR Pipe/NMRDraw suite<sup>26</sup> and analyzed by Sparky.<sup>27</sup> The combined amide proton and nitrogen chemical shift perturbation from the <sup>1</sup>H–<sup>15</sup>N HSQC spectra of Bcl-X<sub>L</sub> after titration with the test compounds were calculated using the following relation:

$$\text{chemical shift perturbation} = \{(\Delta H)^2 + [(\Delta N)^2 \times 0.2]\}^{1/2}$$

where  $\Delta H$  and  $\Delta N$  are change in chemical shift in <sup>1</sup>H and <sup>15</sup>N dimensions, respectively.

**Molecular Docking.** The NMR structure of human Bcl-X<sub>L</sub> (Bcl-X<sub>L</sub>; PDB ID: 1LXL)<sup>20</sup> was used for docking of the test compounds. The 3D structures of the inhibitors were generated using Sybyl7.3 followed by Powell energy minimization. Autodock 4.0.1 program equipped with ADT was used for generating docking models. Autogrids covering residues that were perturbed more than the threshold value of 0.075 ppm in the BH groove, BH3 binding groove, and BH1 region were defined for both compounds **35** and **42** in the AutoDock calculations using a grid spacing of 0.375 Å. The GA-LS algorithm was adopted using default settings except the number of individuals in the population was changed to 500 and maximum number of energy evolutions was increased to 15000000. For each docking job, 100 hybrid GA-LS runs were carried out. A total of 100 possible binding conformations were generated and grouped into clusters based on a 1.0 Å cluster tolerance.

**Acknowledgment.** We thank the Agency for Science, Technology, and Research (A\*STAR), Singapore, for the research funding for this project. The authors also thank Mr. Janarthanan Krishnamoorthy (NUS) for providing assistance on aspects of this project.

**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>C NMR spectra, elemental analysis, and HPLC traces. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Dai, Y.; Grant, S. Targeting Multiple Arms of the Apoptotic Regulatory Machinery. *Cancer Res.* **2007**, *67* (7), 2908–2911.
- (2) Qian, J.; Voorbach, M. J.; Huth, J. R.; Coen, M. L.; Zhang, H.; Ng, S.-C.; Comess, K. M.; Petros, A. M.; Rosenberg, S. H.; Warrior, U.; Burns, D. J. Discovery of novel inhibitors of Bcl-xL using multiple high-throughput screening platforms. *Anal. Biochem.* **2004**, *328* (2), 131–138.
- (3) Oltsersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, D. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J.; Joseph, M. K.; Kitada, S.; Korsmeyer, S. J.; Kunzer, A. R.; Letai, A.; Li, C.; Mitten, M. J.; Nettesheim, D. G.; Ng, S. C.; Nimmer, P. M.; O'Connor, J. M.; Oleksijew, A.; Petros, A. M.; Reed, J. C.; Shen, W.; Tahir, S. K.; Thompson, C. B.; Tomaselli, K. J.; Wang, B.; Wendt, M. D.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. *Nature* **2005**, *435* (7042), 677–681.
- (4) Lugovskoy, A. A. D.; Alexei, I.; Fahmy, A. F.; Zhou, P.; Gross, J. D.; Yuan, J.; Wagner, G. A Novel Approach for Characterizing Protein Ligand Complexes: Molecular Basis for Specificity of Small-Molecule Bcl-2 Inhibitors. *J. Am. Chem. Soc.* **2002**, *124* (7), 1234–1240.
- (5) Milanese, E.; Costantini, P.; Gambalunga, A.; Colonna, R.; Petronilli, V.; Cabrelle, A.; Semenzato, G.; Cesura, A. M.; Pinard, E.; Bernardi, P. The mitochondrial effects of small organic ligands of BCL-2: sensitization of BCL-2-overexpressing cells to apoptosis by a pyrimidine-2,4,6-trione derivative. *J. Biol. Chem.* **2006**, *281* (15), 10066–10072.
- (6) Wang, S.; Yang, D. Small molecule gossypol-related antagonists of Bcl-2 family proteins and inhibit the anti-apoptotic effects of Bcl-2 family proteins in cancer cells. 2002-US17206 2002097053, 20020530, 2002.
- (7) Khorchid, A.; Beauparlant, P. Bcl-2-targeted cancer therapeutics. *Expert Opin. Ther. Pat.* **2004**, *14* (6), 805–818.
- (8) Wang, G.; Nikolovska-Coleska, Z.; Yang, C.-Y.; Wang, R.; Tang, G.; Guo, J.; Shangary, S.; Qiu, S.; Gao, W.; Yang, D.; Meagher, J.; Stuckey, J.; Krajewski, K.; Jiang, S.; Roller, P. P.; Abaan, H. O.; Tomita, Y.; Wang, S. Structure-Based Design of Potent Small-Molecule Inhibitors of Anti-Apoptotic Bcl-2 Proteins. *J. Med. Chem.* **2006**, *49* (21), 6139–6142.
- (9) Zeitlin, B. D.; Joo, E.; Dong, Z.; Warner, K.; Wang, G.; Nikolovska-Coleska, Z.; Wang, S.; Noer, J. E. Antiangiogenic Effect of TW37, a Small-Molecule Inhibitor of Bcl-2. *Cancer Res.* **2006**, *66* (17), 8698–8706.
- (10) Chan, S.-L.; Lee, M. C.; Tan, K. O.; Yang, L.-K.; Lee, A. S. Y.; Flotow, H.; Fu, N. Y.; Butler, M. S.; Soejarto, D. D.; Buss, A. D.; Yu, V. C. Identification of Chelerythrine as an Inhibitor of BclXL Function. *J. Biol. Chem.* **2003**, *278* (23), 20453–20456.
- (11) Zhang, Y.-H.; Bhunia, A.; Wan Kah, F.; Lee Mei, C.; Chan, S.-L.; Yu Victor, C. K.; Mok, Y.-K. Chelerythrine and sanguinarine dock at distinct sites on BclXL that are not the classic BH3 binding cleft. *J. Mol. Biol.* **2006**, *364* (3), 536–549.
- (12) Chamoins, S.; Houldsworth, S.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. The Suzuki–Miyaura cross coupling reactions on solid support. Link to solution phase directed ortho metalation. The Leznoff acetal linker approach to biaryl and heterobiaryl aldehydes. *Tetrahedron Lett.* **1998**, *39* (24), 4179–4182.
- (13) Harayama, T. Synthesis of benzo[c]phenanthridine alkaloids using a palladium-catalyzed aryl–aryl coupling reaction. *Heterocycles* **2005**, *65* (3), 697–713.
- (14) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. Total synthesis of benzo[c]phenanthridine alkaloids, chelerythrine and 12-methoxydihydrochelerythrine, by a palladium-assisted internal biaryl coupling reaction. *Synthesis* **2001**, (3), 444–450.
- (15) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. Synthesis of trisphaeridine and norchelerythrine through palladium-catalyzed aryl–aryl coupling reaction. *J. Chem. Soc., Perkin Trans. I* **2001**, (5), 523–528.
- (16) Bernardo, P. H.; Fitriyanto, W.; Chai, C. L. L. Palladium-mediated synthesis of calothrixin B. *Synlett* **2007**, (12), 1935–1939.
- (17) Zhai, D.; Jin, C.; Satterthwait, A. C.; Reed, J. C. Comparison of chemical inhibitors of antiapoptotic Bcl-2-family proteins. *Cell Death Differ.* **2006**, *13* (8), 1419–1421.
- (18) Enyedy, I. J. L.; Y.; Nacro, K.; Tomita, Y.; Wu, X.; Cao, Y.; Guo, R.; Li, B.; Zhu, X.; Huang, Y.; Long, Y. Q.; Roller, P. P.; Yang, D.; Wang, S. Discovery of small-molecule inhibitors of Bcl-2 through structure-based computer screening. *J. Med. Chem.* **2001**, *44* (25), 4313–4324.
- (19) Xing, C.; Wang, L.; Tang, X.; Sham, Y. Y. Development of selective inhibitors for anti-apoptotic Bcl-2 proteins from BHI-1. *Bioorg. Med. Chem.* **2007**, *15* (5), 2167–2176.
- (20) Muchmore, S. W.; Sattler, M.; Liang, H.; Meadows, R. P.; Harlan, J. E.; Yoon, H. S.; Nettesheim, D.; Chang, B. S.; Thompson, C. B.; Wong, S. L.; Ng, S. L.; Fesik, S. W. X-ray and NMR structure of human Bcl-xL, an inhibitor of programmed cell death. *Nature* **1996**, *381* (6580), 335–341.
- (21) Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *J. Comput. Chem.* **1998**, *19* (14), 1639–1662.
- (22) Kessar, S. V. Benzene cyclization route to benzo[c]phenanthridine alkaloids. Synthesis of chelerythrine, decarine, and nitidine. *J. Org. Chem.* **1988**, *53* (8), 1708–1713.
- (23) Mattson, R. J.; Sloan, C. P.; Lockhart, C. C.; Catt, J. D.; Gao, Q.; Huang, S. Ortho-directed lithiation of 3,4-(alkylenedioxy)halobenzenes with LDA and LiTMP. The first ortho lithiation of an iodobenzene. *J. Org. Chem.* **1999**, *64* (21), 8004–8007.



- (24) Sit, S.-Y.; Kai, X.; Jacutin-Porte, S.; Boy, K. M.; Seanz, J.; Taber, M. T.; Gulwadi, A. G.; Korpinen, C. D.; Burris, K. D.; Molski, T. F.; Ryan, E.; Xu, C.; Verdoorn, T.; Johnson, G.; Nichols, D. E.; Mailman, R. B. Synthesis and SAR exploration of dinapsoline analogues. *Bioorg. Med. Chem.* **2004**, *12* (4), 715–734.
- (25) Kessar, S. V.; Pal, D.; Singh, M. New routes to condensed polynuclear compounds. VIII. Phenanthridine synthesis through cyclization of haloanils. *Tetrahedron* **1973**, *29* (1), 177–184.
- (26) Delaglio, F.; Grzesiek, S.; Vuister, G. W.; Zhu, G.; Pfeifer, J.; Bax, A. NMRPipe: a multidimensional spectral processing system based on UNIX pipes. *J. Biomol. NMR* **1995**, *6* (3), 277–293.
- (27) Goddard, T. D.; Kneller, D. G. *SPARKY 3*; University of California: San Francisco.

JM8005433