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Fused pyrazino[2,3-*b*]indolizine and indolizino[2,3-*b*]quinoxaline derivatives; synthesis, structures, and properties

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ABSTRACT

The synthesis of six new compounds incorporating either a pyrazino[2,3-*b*]indolizine or indolizino[2,3-*b*]quinoxaline core are reported in good yield (58–87%). The intermediates for the key cyclization reaction for one set of compounds (**5a**–**c**), with a sterically demanding 3,5-dimethylpyrazole group in the 5-position of the core, were found to be mono-substituted. These intermediates could be isolated and cyclized by heating under acid-catalyzed conditions. To further demonstrate the versatility of the chemistry, compounds **6a**–**c** were synthesized in 58–68% yields. Compounds **5a**–**c** are non-planar in solution and the solid-state, while **6a**–**c** have close to planar conformations, pointing to weak hydrogen bonds between the acidic C–Hs and the adjacent azine nitrogen atoms. The cytotoxicity of the six newly synthesized and three previously prepared compounds was assessed against a human glioblastoma multiforme cell line.

1. Introduction

There is considerable interest in ruthenium(II) polypyridine complexes,[1–7] which have been investigated in the context of water splitting[8,9] and as sensitizers for dye-sensitized solar cells.[10–15] These investigations are particularly relevant as the planet's energy demands are an area of significant societal and scientific concern.[16,17] In exploring complexes for such applications, the stereochemical, electrochemical, and photophysical properties of ruthenium(II) polypyridine complexes are of particular interest.[3,5,7,18,19] These can be tailored by altering the nature of the ligands coordinated to the metal center.[2,7,20–26] These changes to the archetypal chelating biheterocyclic ligand structure have led to new complexes displaying modified electrochemical and photophysical properties, and in turn new candidates for the noted applications.

We have an interest in a group of planar, highly conjugated heterocyclic compounds (Fig. 1, (a)), 5-(2-pyridyl)pyrazino[2,3-*b*]indolizine (**1a**), 5-(2-pyridyl)indolizino[2,3-*b*]quinoxaline (**1b**), and 8,9-dimethyl-5-(2-pyridyl)indolizino[2,3-*b*]quinoxaline (**1c**), that are effective chelating ligands for transition metal ions.[27] Compounds **1a**–**c** are electrochemically active and display several distinct absorption features through the visible range; derivatives **1b** and **1c** give intensely purple colored solutions, while **1a** gives a red solution consistent with its shorter wavelength absorption in the visible range.[27] The complexes of the type $[RuL(bpy)_2]^{2+}$ and $[RuL(dmb)_2]^{2+}$ (where bpy=2,2′-bipyridine; dmb=4,4′-dimethyl-2,2′-bipyridine; L=**1a**–**c**) also show a number of characteristic redox potentials, and those complexes containing **1b** and **1c** are black dyes.

Other fused heterocyclic compounds with related cores (such as **2** and **3**) have also been studied due to their unique structures, synthetic challenges, and potentially interesting biological properties (Fig. 1, (b)).[28–30] For example, variolin B is a natural product isolated from the Antarctic sponge *Kirkpatrickia varialosai* by the group of Blunt and Munro.[31] Variolin B contains the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine skeleton **4**.[30] Synthetic approaches developed by one of us[32,33] allows the convergent synthesis of variolin B, while alternative linear synthetic pathways have been reported.[34–39] The chemistry and biological properties of variolin B and related derivatives have been reviewed.[30]

As part of our ongoing work on heterocyclic compounds as ligands,[26] we noted the structural similarities between the core of the variolins and compounds **1a**–**c**. This provoked us to study the biological properties of these fused heterocyclic compounds and to explore the synthesis of other derivatives. Herein we report the

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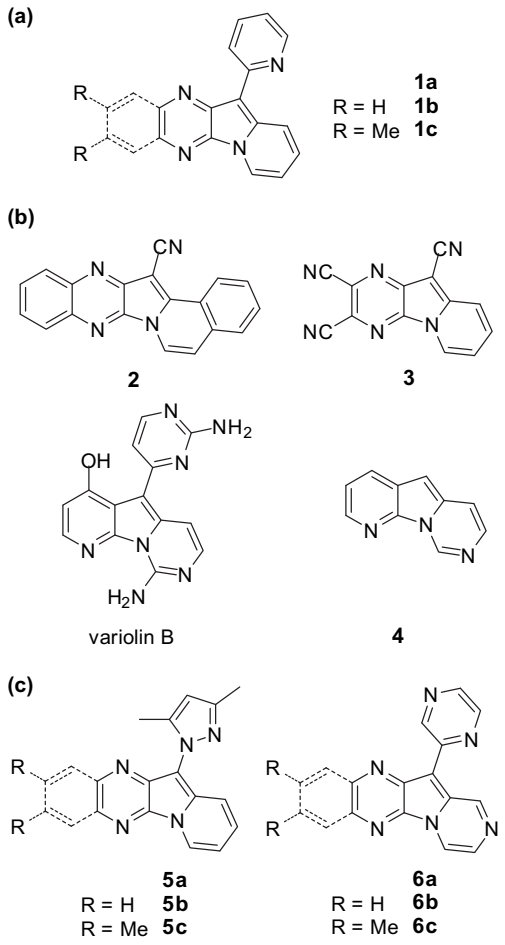


Fig. 1. (a) The structures of previously synthesized pyrazino[2,3-*b*]indolizine or indolizino[2,3-*b*]quinoxalines, **1a**–**c**; (b) 14-cyanobenzo[a]indolizino[2,3-*b*]quinoxaline, **2**; pyrazino[2,3-*b*]indolizine-2,3,10-tricarbonitrile, **3**; variolin B, and the pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine core of the variolins, **4**; and, (c) the structures of the new pyrazino[2,3-*b*]indolizine or indolizino[2,3-*b*]quinoxaline compounds prepared in this work (**5a**–**6c**).

synthesis of six new compounds containing a pyrazino[2,3-*b*]indolizine or indolizino[2,3-*b*]quinoxaline core (Fig. 1, (c)) and, for the first time, a comprehensive study into the intermediates involved in the synthesis. Three of the new compounds, 5-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrazino[2,3-*b*]indolizine (**5a**), 5-(3,5-dimethyl-1*H*-pyrazol-1-yl)indolizino[2,3-*b*]quinoxaline (**5b**), and 5-(3,5-dimethyl-1*H*-pyrazol-1-yl)-8,9-dimethylindolizino[2,3-*b*]quinoxaline (**5c**), have a 3,5-dimethylpyrazole substituent appended to the 5-position of the core, while the second set 5-(pyrazin-2-yl)-pyrrolo[1,2-*a*:4,5-*b*]dipyrazine (**6a**), 5-(pyrazin-2-yl)-pyrazino[1,2-*a*]pyrrolo[2,3-*b*]quinoxaline (**6b**), and 8,9-dimethyl-5-(pyrazin-2-yl)-pyrazino[1,2-*a*]pyrrolo[2,3-*b*]quinoxaline (**6c**), incorporate a pyrazine ring at this position. In addition to our synthetic studies, for the first time we evaluated the in vitro biological properties of **1a**–**c** and the six new derivatives **5a**–**6c**.

2. Results and discussion

2.1. Synthesis of 5a–c

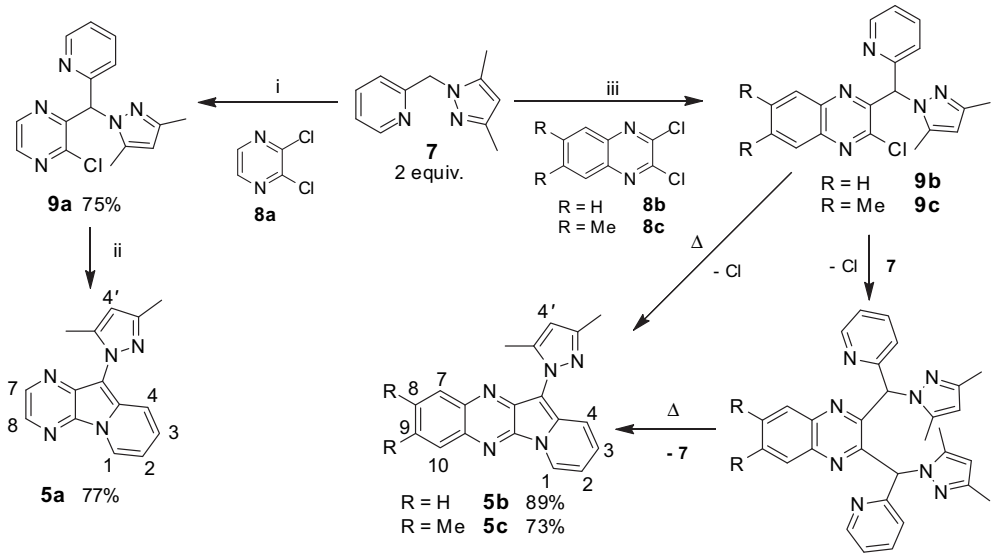
In previous work, we identified a one-pot synthesis that gives access to indolizino[2,3-*b*]quinoxaline or pyrazino[2,3-*b*]indolizine fused heterocycles **1a**–**c**.[27] To further develop this chemistry, we turned our attention to expanding the scope of this reaction. The first set of targets was the compounds bearing an electron-rich 3,5-dimethyl-1*H*-pyrazol-1-yl substituent in the 5-position of the core **5a**–**c**. The first target, compound **5a**, was ultimately synthesized in two steps from 2-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)pyridine (**7**)[40] and **8a**. Typically, 2 equivalents of the anion of the active methylene compound are used in these reactions because it is possible for two routes, via the mono- or di-substituted compounds, to be occurring in competition in the cyclization step to yield the final product (Scheme 1). However, in the case of compound **5a**, the normal conditions did not yield the expected final cyclized product but rather the mono-substituted intermediate **9a** as the major product in 75% yield (Scheme 1).

After the isolation of **9a**, we endeavored to find conditions to effect its cyclization to **5a**. Previously,[27] we had demonstrated that disubstituted intermediates could be cyclized under reflux conditions with trifluoroacetic acid (TFA) as a catalyst. In the case of **9a**, however, the conversion was found to be slow, and a ^{1}H NMR spectrum of the reaction mixture revealed only 80% conversion after 4 days. Hence, **9a** was heated in a microwave reactor, with TFA and acetonitrile as a solvent, at 140 °C for 90 min. The ^{1}H NMR spectrum of the reaction mixture revealed >99% conversion to product **5a**. The slow conversion of the mono-substituted compound **9a** can be attributed to the steric hindrance about the 3,5-dimethylpyrazolyl ring, which hinders cyclization and/or further substitution by a second equivalent of **7**. An X-ray crystal structure of **5a** shows a possible origin of this steric hindrance, whereby the methyl substituents on the pyrazole ring impede access to the adjacent position (C2) by incoming nucleophiles (Fig. 2).

The indolizino[2,3-*b*]quinoxaline compounds **5b** and **5c** were able to be synthesized successfully by the reaction of **7** with either **8b** or **8c**, in good yields of 89% and 73%, respectively. For both compounds, spontaneous cyclization of the respective intermediate compound to the product was observed during the course of the reaction. In both cases, a small portion of the reaction mixture was quenched at room temperature and analyzed by ^{1}H NMR spectroscopy. In the reaction of compound **7** with **8b**, the ^{1}H NMR spectrum revealed cyclized product **5b** as the major species, along with starting material **7**, and aromatic signals corresponding to very small quantities of the intermediates. However, in the case of the reaction of **7** with **8c**, the ^{1}H NMR spectrum revealed cyclized product **5c** as the minor species, with other peaks in the aromatic region corresponding to the proposed intermediates.

2.2. Investigations of the intermediates 9a–c

To obtain a better understanding of the nature of the intermediates present prior to heating, the reaction between **8c** and **7** was carried out in a 1:1 ratio, and the mixture was quenched at −78 °C after 30 min. The major compound in the reaction mixture was identified as the mono-substituted intermediate **9c**, which was isolated and characterized by X-ray crystallography (Fig. 3). Once again, the molecular structure confirms the presence of steric hindrance in **9c**, although it should be noted that the 3,5-dimethylpyrazole substituent can be directed away from the chlorine atom by rotation about the newly formed carbon–carbon bond. The ^{1}H NMR spectrum of **9c** is identical to the major intermediate species observed in the ^{1}H NMR spectrum of the reaction performed by using 1:2 equiv of compounds **8c** and **7**. Upon heating the solid **9c** above its melting point, a color change from colorless to purple was observed, indicating cyclization to product **5c**. In comparison to the pyrazine analogue **9a**, the mono-substituted quinoxaline compounds require less thermal energy to undergo the intermolecular cyclization reaction, and this can occur without the need of acid catalysis. Since the two sets of compounds (**9a** and **9b**/**9c**) possess the same degree of steric hindrance, the greater reactivity of compound **9b**/**9c** may be attributed



Scheme 1. (i) *n*-BuLi, THF, −78 °C, rt, **9a**; (ii) TFA, CH_3CN, **5a**; (iii) *n*-BuLi, THF, −78 °C, **5b** or **5c**, rt to reflux.

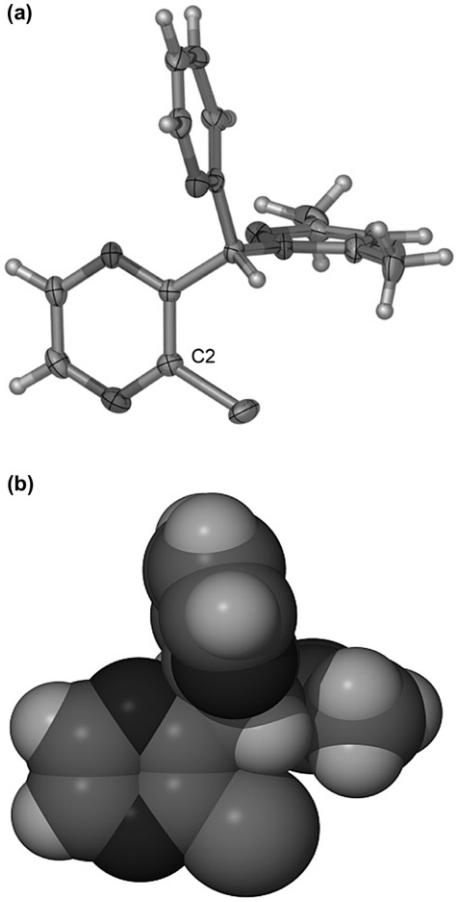


Fig. 2. (a) A perspective view of the X-ray molecular structure of compound **9a** showing the possible origin of the steric hindrance. Thermal ellipsoids are shown at the 50% probability level. (b) A space-filling representation of the structure.

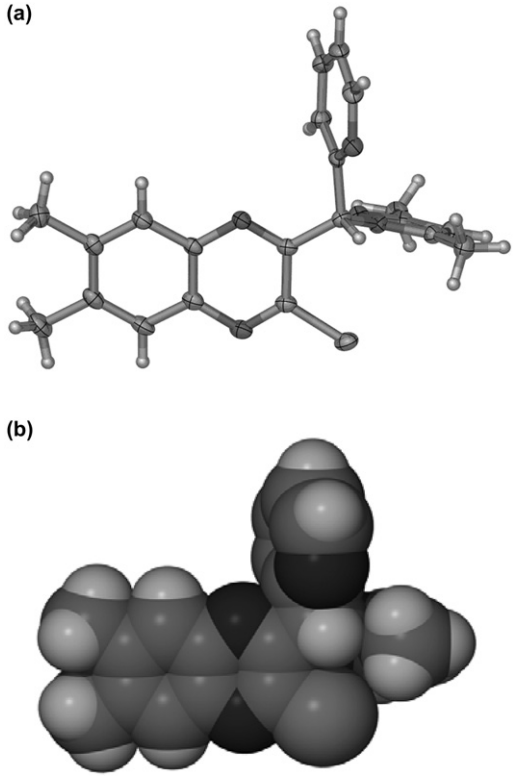


Fig. 3. (a) A perspective view of the solid-state molecular structure of **9c**. Thermal ellipsoids are shown at the 50% probability level. (b) A space-filling representation alludes to the possibility that the pyrazole ring hinders the approach of nucleophiles to C2 of **9c**.

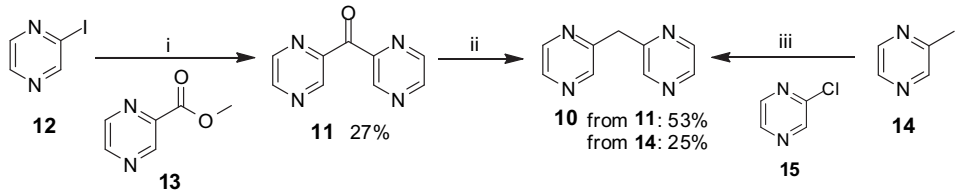
to greater resonance stabilization of the reaction intermediates provided by the quinoxaline ring with respect to the pyrazine ring during cyclization.

In summary, the three compounds **5a**, **5b**, and **5c** were isolated as red (**5a**) and purple (**5b**, and **5c**) solids, and gave intense red-orange and purple solutions, respectively, upon dissolution in dichloromethane, which is indicative of the conjugated indolizino [2,3-*b*]quinoxaline core.

2.3. Synthesis of 6a–c

The synthesis of compounds **6a–c** required the identification of a reliable procedure to prepare di-2-pyrazinylmethane (**10**). A

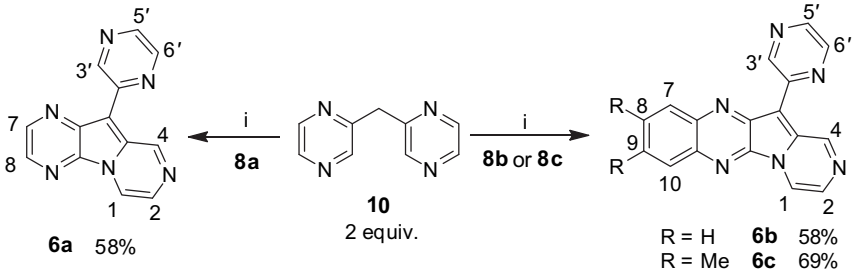
potential precursor, di-2-pyrazinylketone (**11**), is known[41] and could be synthesized from 2-iodopyrazine (**12**) using *n*-BuLi in a lithium–halogen exchange protocol.[42] In order to avoid the unwanted nucleophilic substitution of 2-iodopyrazine with the butyl anion, we attempted the preparation of ketone **11** by metalation of **12** using commercially-available *i*-PrMgCl or *n*-BuMgCl[43] (Scheme 2) and reacting the newly-formed Grignard reagent with methyl ester **13**. With *i*-PrMgCl only trace amounts of the desired ketone **11** were obtained, while performing the reaction with *n*-BuMgCl gave the ketone in 27% yield, with a major portion of the Grignard material isolated as 2-butylpyrazine. A Wolff–Kishner reduction on **11** gave diarylmethane **10** in 53% isolated yield.



Scheme 2. (i) *n*-BuMgCl, THF, 0 °C; (ii) ethylene glycol, KOH, $NH_2NH_2 \cdot H_2O$; (iii) LDA, THF, −78 °C.

An alternative route to **10** involving a one-step reaction, which proceeds via a lithiation of 2-methylpyrazine was also investigated. Based on the synthesis of di-2-pyridylmethane,[44] metalation of 2-methylpyrazine (**14**) by using LDA,[45] and its subsequent reaction with 2-chloropyrazine (**15**), gave **10** directly in 25% yield. The isolated yield of 25% is an improvement on the synthesis of **10** by means of the ketone method (ca. 14% overall).

Deprotonation of **10** and subsequent reaction with either **8a**, **8b** or **8c** gave three new compounds (Scheme 3) possessing either an pyrrolo[1,2-*a*:4,5-*b*]dipyrazine (**6a**) or pyrazino[1,2-*a*]pyrrolo[2,3-*b*]quinoxaline (**6b** and **6c**) core, respectively. The propensity of *n*-BuLi to act as a nucleophile in the presence of pyrazine derivatives[46] led us to first examine the use of LDA as the base. LDA has been widely used on pyrazine derivatives,[45,47,48] however, the isolated yields of **6b** and **6c** using LDA were 35% and 36%, respectively. In contrast, when *n*-BuLi was used as the base, the compounds **6a**, **6b**, and **6c** were isolated in much improved yields of 58%, 67%, and 69%, respectively. Like compounds **5a**–**c**, these heterocycles were isolated as red and purple solids that gave intense orange and purple solutions upon dissolution in chloroform.



Scheme 3. (i) *n*-BuLi, THF, −78 °C, rt to reflux.

2.4. Solution and solid-state structures

The structures and purity of compounds **5a**–**c** and **6a**–**c** were confirmed by 2D NMR spectroscopy, mass spectrometry, and elemental analysis. In the ^{1}H NMR spectrum of compounds **5a**, **5b** and **5c**, H4 appears significantly upfield relative to **1a**–**c**.[27] Therefore, it was deduced that the 3,5-dimethylpyrazolyl ring in the 5-position is in a significantly twisted conformation, with the π-system of the pyrazolyl ring shielding the H4 atom. This differs significantly from what we propose occurs in solution for **1a**–**c** and **6a**–**c** where the heterocyclic ring in the 5-position of the core is close to planar and involved in two H-bonding interactions.

A single crystal of compound **5b**, suitable for X-ray crystallography, was obtained by slow evaporation of a dichloromethane/diethyl ether solution of **5b**. Compound **5b** crystallizes in the monoclinic space group $P2_1/c$ with one complete molecule in the asymmetric unit (Fig. 4). As observed for other closely related compounds,[27] the core of **5b** is planar. The conformation of the 3,5-dimethylpyrazolyl ring in the solid-state is in agreement with that observed in solution by ^{1}H NMR spectroscopy. The twisted conformation, where the torsion angle is 58.4°, can be attributed to a steric hindrance between the 5′-methyl group of the 3,5-dimethylpyrazolyl ring and H4.

For the compounds **6a**, **6b**, and **6c**, it was expected that the pyrazine ring in the 5-position would be close to planar with respect to the core, as the position of the H4 atom in the ^{1}H NMR spectrum was relatively downfield due to deshielding by the adjacent nitrogen atom. A single crystal X-ray structure confirmed this conformation to be present in the solid-state of **6a** (Fig. 5) and **6b** (Fig. 6). In the structure of **6a** the torsion angle for the pendent pyrazine ring is 17.6°, while in the structure of **6b** the torsion angle is 5.6°. These conformations are consistent with an H-bonding interaction between the acidic C–Hs (H4 and H3′) and the adjacent nitrogen atoms in both structures.

2.5. Biological activity

Due to the promising biological activity of the variolin family of compounds,[30] we assessed the biological activity of selected compounds against the T98G (human glioblastoma multiforme) cell line. Variolin B has an IC_{50} of 0.716 μM against the P388 murine leukemia cell line,[30] and both variolin B and deoxyvariolin B have been observed to affect cell-cycle progression. The cytotoxicity of our compounds was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay[49] and cell viability was determined by measuring the absorbance of the purple formazan solution at 600 nm using a microplate reader. The results are shown below in Table 1, with no determination being possible for compound **5c**, which was found to be poorly soluble in the cell culture medium.

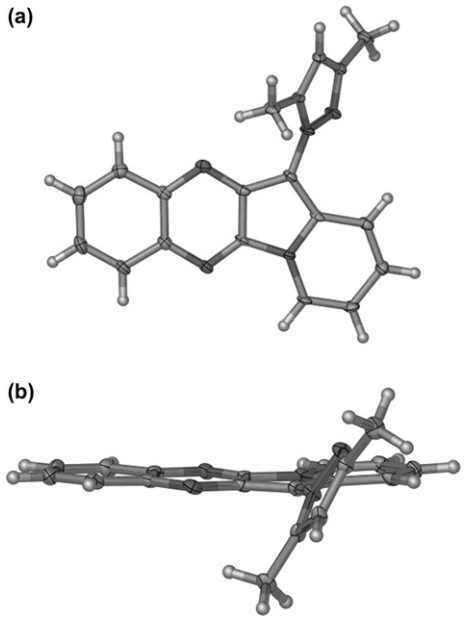


Fig. 4. (a) A perspective view of the molecular structure of **5b** showing the planar indolizino[2,3-*b*]quinoxaline core with thermal ellipsoids at the 50% probability level. (b) A view of **5b** perpendicular to the core showing the out-of-plane twist of the pyrazole ring.

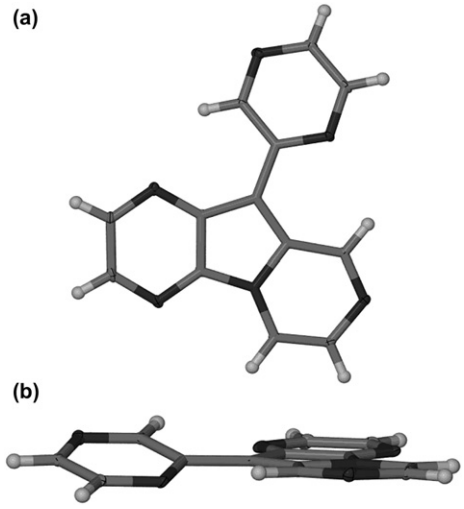


Fig. 5. (a) A perspective view of **6a**, with thermal ellipsoids at the 50% probability level. (b) A view of **6a** perpendicular to the core showing the near planar conformation of the pyrazine ring.

None of the compounds tested exhibited marked cytotoxic activity against the T98G cell line, although the pyrrolo[1,2-*a*:4,5-*b*]dipyrazine (**6a**) and pyrazino[1,2-*a*]pyrrolo[2,3-*b*]quinoxaline (**6b** and **6c**) derived compounds were found to be the most active compounds. The least active compound, **5a**, is the one with the smallest core aromatic surface area, and consequently might point to some type of DNA intercalation being important in the cytotoxicity of this particular set of compounds.

3. Conclusions

The syntheses of six fused heterocyclic compounds **5a**–**6c** have been accomplished in good yield. Due to steric hindrance caused by the 3,5-dimethylpyrazole ring, the synthesis of the series of compounds **5a**–**c** proceeded via cyclization of the corresponding

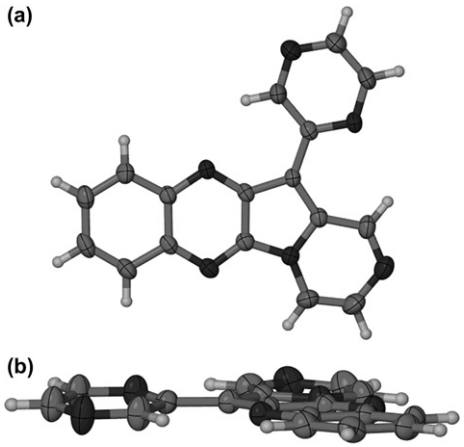


Fig. 6. (a) A perspective view of the molecular structure of **6b** showing the planar core, with thermal ellipsoids at the 50% probability level. (b) A view of **6b** perpendicular to the core showing the near planar conformation of the pyrazine ring.

Table 1
In vitro cytotoxicity of compounds **1a**–**c**, **5a**, **5b**, and **6a**–**c** in an MTT cytotoxicity assay using the human glioblastoma multiforme (T98G) cell line

Compound	1a	2a	3a	5a	5b	5c	6a	6b	6c
Average (μM)	88.8	66.7	72.7	324.0	62.1	ND[c]	33.8	46.0	36.4
SE[a]	8.5	6.2	4.9	34.6	6.7	ND[c]	5.8	6.5	1.6
N[b]	5	5	5	4	3		3	5	4

[a] SE=standard error.
[b] N=number of cytotoxicity assays run.
[c] ND=not determined due to solubility limitations.

isolable mono-substituted intermediates **9a** and **9c** under forcing conditions. The intermediate **9b** cyclizes upon warming to room temperature and it was not isolated from the reaction mixture. The synthesis of **6a**–**c** required the preparation of di-2-pyrazinylmethane (**7**), which after some investigation, was accomplished in 25% isolated yield. Thereafter, the synthesis of **6a**–**c** proceeded in a facile manner to generate the three new compounds in good yields (58–68%).

Due to steric hindrance, compounds **5a**–**c** are non-planar in solution and the solid-state, while **6a**–**c** have close to planar conformations, pointing to H-bonding interactions between the acidic C–H groups (H4 and H3′) and the adjacent nitrogen atoms in these compounds, as confirmed by NMR spectroscopy and X-ray crystallography. The cytotoxicity of these newly synthesized compounds and three previously synthesized compounds was also assessed. Despite their structural similarity to variolin B, there was no significant cytotoxic activity observed for any of the compounds, with **6a**, **6b**, and **6c** being the most active of the series. In future studies, we will utilize their bidentate chelating motifs to prepare transition metal complexes, which should have improved aqueous solubility and cytotoxicity. Our work on the coordination chemistry of these compounds and investigation into applications in dye-sensitized solar cells is ongoing and will be reported in due course.

4. Experimental details

4.1. General experimental

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed by the Campbell Microanalytical Laboratory at the University of Otago. Unless otherwise stated, NMR spectra were recorded on a Varian 600 MHz spectrometer at 23 °C using a 5-mm probe. ^{1}H

NMR spectra recorded in $CDCl_3$ were referenced relative to the internal standard Me_4Si. When required, one-dimensional nuclear Overhauser effect correlation spectroscopy (1D NOESY), total correlation spectroscopy (TOCSY), rotating frame Overhauser effect spectroscopy (ROESY), two-dimensional correlation spectroscopy (2D COSY), 2D NOESY, 2D ROESY, heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond correlation (HMBC) experiments were performed using standard pulse sequences. Electrospray (ES) mass spectra were recorded using a Finnigan LCQ mass spectrometer. Infrared spectra were collected on a Perkin–Elmer Spectrum 100 using a UATR sampling accessory. UV/vis absorption spectra were recorded on a Varian Cary 5000 UV/vis/NIR spectrometer in dichloromethane solutions with concentrations of ~0.25 mM.

Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. Tetrahydrofuran was dried by standard literature procedures and distilled fresh from sodium/benzophenone, and diisopropylamine was freshly distilled from potassium hydroxide. 1,4-Dihydro-2,3-quinoxalinedione,[50] 1,4-dihydro-6,7-dimethyl-2,3-quinoxalinedione,[50] 2,3-dichloroquinoxaline,[51] 2,3-dichloro-6,7-dimethylquinoxaline,[51] 2-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)pyridine (**7**),[40] 2-iodopyrazine (**12**),[42] and 2-pyrazinecarboxylate methyl ester (**13**)[52] were prepared according to the methods described in the literature.

4.2. Synthesis

*4.2.1. Di-2-pyrazinylmethane (**10**).* A solution of 2-methylpyrazine (2.31 mL, 25.2 mmol) in THF (50 mL) was added dropwise to freshly prepared LDA (26.0 mmol) in THF (15 mL) at −78 °C under an atmosphere of argon. The resulting dark red solution was stirred for 1 h at −78 °C, then cooled to −95 °C. 2-Chloropyrazine (1.00 mL, 11.4 mmol) in THF (50 mL) was cooled to −78 °C and transferred via cannula to the solution of the anion. Once the addition was complete the dark mixture was stirred at −95 °C for 5 min, then the cooling was removed and the reaction vessel was allowed to warm to room temperature, during which a color change to deep purple was observed. After stirring for 15 min, water (50 mL) was added and the mixture was stirred for a period of 2 h during which a color change to dark brown was observed. The mixture was concentrated under reduced pressure, and repeatedly extracted with dichloromethane (5×50 mL) until the extracts were almost colorless. The organic extracts were combined and dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The dark residue was twice extracted by adding hexane to the residue and refluxing for a period of 1.5 h. The extracts were combined and evaporated under reduced pressure, yielding a yellow crystalline solid, which was sublimed under reduced pressure at 110–120 °C (bath temperature) to afford **10** as a pale yellow crystalline solid. (0.49 g, 25%), mp: 61–63 °C; ν_{max} (neat, cm^{-1}) 3010, 1579, 1520, 1479, 1405; ^1H NMR (300 MHz/$CDCl_3$): δ 8.64 (d, 2H, H3), 8.52 (dd, 2H, J=2.5 Hz, H5), 8.47 (d, 2H, J=2.5 Hz, H6), 4.39 (s, 2H, CH_2); ^{13}C NMR (75.4 MHz/$CDCl_3$): δ 41.8, 143.1, 144.43, 145.2, 154.0; Found: C 62.8, H 4.9, N 32.3, $C_9H_8N_4$ requires: C 62.8, H 4.7, N 32.5%.

*4.2.2. General procedure for the synthesis of **5a**–**c** and **6a**–**c**.* *n*-BuLi (1.05 equiv) was added dropwise to a solution of the diarylmethane (1 equiv) in dry THF at −78 °C under an argon atmosphere. The solution was stirred for 0.5 h, followed by the dropwise addition of the electrophile (0.49 equiv) in THF. The reaction mixture was slowly allowed to warm to room temperature overnight, followed by heating at reflux (16 h). The reaction mixture was quenched with H_2O (2 mL) and the solvent was removed under reduced pressure. The residue was taken up into chloroform or dichloromethane (3×50 mL) and washed with water (3×50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure.

*4.2.3. 2-Chloro-3-[(3,5-dimethyl-1H-pyrazol-1-yl)(pyridin-2-yl) methyl]pyrazine (**9a**).* 2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl] pyridine (**7**) (1.05 g, 5.61 mmol), *n*-BuLi (2.48 mL, 5.71 mmol) and 2,3-dichloropyrazine (**8a**) (0.284 mL g, 2.72 mmol) were combined according to the general procedure. The reaction mixture was stirred at room temperature for 4 h and then quenched. The solvent was removed under reduced pressure and the dark oil was left to stand for 24 h, during which time the product crystallized. The crystals were separated from the oily residue by decanting, and the remainder of the product was isolated by adding diethyl ether to the oily mixture and cooling to −20 °C, which induced further crystallization of **9a**. The crystalline samples were combined and recrystallized from diethyl ether to yield the product as an off-white crystalline solid (0.62 g, 75%). Mp 147–149 °C; ν_{max} (neat, cm^{-1}) 1590, 1557, 1439, 1381; ^1H NMR (600 MHz/$CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 5.92 (s, 1H, H4′), 7.02 (d, 1H, J=7.7 Hz, H3″), 7.05 (s, 1H, CH), 7.24 (dd, 1H, J=4.8, 7.7 Hz, H5″), 7.70 (t, 1H, J=7.7 Hz, H4″), 8.31 (d, 1H, J=2.5 Hz, H5/H6), 8.44 (d, 1H, J=2.5 Hz, H5/H6), 8.54 (d, 1H, J=4.8 Hz, H6″); ^{13}C NMR (151 MHz/$CDCl_3$): δ 11.3, 13.7, 65.2, 106.0, 122.8, 123.0, 137.1, 140.6, 141.9, 142.7, 148.8, 148.9, 149.4, 152.3, 157.6; *m*/*z* 264.0 (MH^+) (cyclizes); Found: C 60.1, H 4.7, N 23.5, $C_{15}H_{14}ClN_5$ requires: C 60.1, H 4.7, N 23.4%.

*4.2.4. 5-(3,5-Dimethyl-1H-pyrazol-1-yl)pyrazino[2,3-b]indolizine (**5a**).* 2-Chloro-3-((3,5-dimethyl-1*H*-pyrazol-1-yl)(pyridin-2-yl) methyl)pyrazine (0.132 g, 0.440 mmol) was dissolved in acetonitrile (9 mL) and TFA (0.5 mL) in a sealed vessel and reacted in a CEM Discover S microwave reactor at 145 °C for 1.5 h with stirring. The microwave settings were 150 W, with a maximum pressure of 250 psi. During the course of the reaction the pressure was stable at around 50 psi. The resulting dark red mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (4×15 mL). The solvent was dried over $MgSO_4$ and removed under reduced pressure. The red solid obtained was recrystallized from diethyl ether to yield **5a** as a bright red fluffy solid (0.09 g, 77%) mp: 134–136 °C; ν_{max} (neat, cm^{-1}) 2914, 1633, 1578, 1558, 1487; ^1H NMR (600 MHz/$CDCl_3$) δ 2.22 (s, 3H, Me), 2.34 (s, 3H, Me), 6.08 (s, 1H, H4′), 6.77 (t, 1H, J=6.8 Hz, H2), 7.22 (dd, 1H, J=6.8, 9.3 Hz, H3), 7.52 (d, 1H, J=9.3 Hz, H4), 8.37 (d, 1H, J=2.4 Hz, H8), 8.75 (d, 1H, J=2.4 Hz, H7), δ 8.82 (d, 1H, J=6.8 Hz, H1); ^{13}C NMR (151 MHz/$CDCl_3$): δ 11.5, 13.8, 103.4, 105.7, 110.4, 116.9, 123.8, 127.5, 132.8, 134.3, 134.8, 135.5, 142.5, 143.2, 149.9; *m*/*z* 264.1 (MH^+); Found: C 68.6, H 4.9, N 26.8, $C_{15}H_{13}N_5$ requires: C 68.4, H 5.0, N 26.6%; λ_{max}/nm: 452 (ε/M^{-1} cm^{-1} 4010).

*4.2.5. 5-(3,5-Dimethyl-1H-pyrazol-1-yl)indolizino[3,2-b]quinoxaline (**5b**).* 2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)methyl]pyridine (**7**) (0.459 g, 2.45 mmol), *n*-BuLi (1.11 mL, 2.50 mmol), and 2,3-dichloroquinoxaline (**8b**) (0.238 g, 1.20 mmol) were combined and reacted as described in the general procedure. The crude reaction mixture was subject to a standard work-up with dichloromethane. The crude solid obtained was suspended in cold hexane, isolated under reduced pressure, and thoroughly washed with cold hexane (4×25 mL), to afford the product **5b** as a purple solid (0.33 g, 89%). Mp: 214–216 °C; ν_{max} (neat, cm^{-1}) 2917, 1636, 1589, 1540, 1518, 1485; ^1H NMR (600 MHz/$CDCl_3$): δ 2.28 (s, 3H, Me), 2.38 (s, 3H, Me), 6.13 (s, 1H, H4′), 6.71 (t, 1H, J=6.8 Hz, H2), 7.28 (dd, 1H, J=9.2, 6.8 Hz, H3), 7.49 (d, 1H, J=9.2 Hz, H4), 7.71–7.81 (m, 2H, H7/H10), 8.27 (d, 1H, J=8.2 Hz, H8/H9), 8.31 (d, 1H, J=8.2 Hz, H8/H9), 8.94 (d, 1H, J=6.8 Hz, H1); ^{13}C NMR (151 MHz/$CDCl_3$): δ 11.6, 13.7, 101.9, 105.8, 109.5, 116.8, 125.2, 127.1, 128.6, 128.7, 128.9, 130.4, 134.6, 136.0, 137.1, 140.8, 142.8, 143.3, 149.9; *m*/*z*: 314.3 (MH^+);

Found: C 68.8, H 4.8, N 21.5, $C_{19}H_{15}N_5 \cdot H_2O$ requires: 68.85, 5.2, 21.1%; λ_{max}/nm: 527 (ε/M^{-1} cm^{-1} 4620).

*4.2.6. 5-(3,5-Dimethyl-1H-pyrazol-1-yl)-8,9-dimethylindolizino[2,3-b]quinoxaline (**5c**).* 2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)methyl]pyridine (**7**) (0.647 g, 3.46 mmol), *n*-BuLi (1.50 mL, 3.50 mmol), and 2,3-dichloro-6,7-dimethylquinoxaline (**8c**) (0.383 g, 1.69 mmol) were combined and reacted in the manner described in the general procedure. The crude reaction mixture was subjected to a standard work-up with dichloromethane. The solid obtained was suspended in cold hexane, isolated by filtration, and thoroughly washed with cold hexane (4×25 mL) to afford **5c** as a purple solid (0.42 g, 73%). Mp: 201–203 °C; ν_{max} (neat, cm^{-1}) 2910, 1634, 1587, 1536, 1511, 1488; ^{1}H NMR (600 MHz/$CDCl_3$): δ 2.28 (s, 3H, Me′), 2.35 (s, 3H, Me′), 2.53 (s, 3H, Me), 2.55 (s, 3H, Me), 6.10 (s, 1H, H4′), 6.67 (t, 1H, *J*=6.8 Hz, H2), 7.22 (dd, 1H, *J*=9.3, 6.8 Hz, H3), 7.45 (d, 1H, *J*=9.3 Hz, H4), 7.98 (s, 1H, H7/H10), 8.04 (s, 1H, H7/H8), 8.88 (d, 1H, *J*=6.8 Hz, H1); ^{13}C NMR (151 MHz/$CDCl_3$): δ 11.6, 13.8, 20.3, 20.4, 102.1, 105.7, 109.1, 116.7, 125.0, 127.4, 127.9, 129.5, 134.2, 135.5, 136.2, 137.8, 139.2, 139.6, 142.4, 142.6, 149.7; *m*/*z*: 342.2 (MH^+); Found: C 73.0, H 5.8, N 20.1. $C_{21}H_{19}N_5 \cdot ¼H_2O$ requires: C 72.9, H 5.7, N 20.25%; λ_{max}/nm: 524 (ε/M^{-1} cm^{-1} 4800).

*4.2.7. 2-Chloro-3-[(3,5-dimethyl-1H-pyrazol-1-yl)(pyridin-2-yl)methyl]-6,7-dimethylquinoxaline (**9c**).* 2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)methyl]pyridine (**7**) (0.397 g, 2.12 mmol), *n*-BuLi (0.962 mL, 2.10 mmol), and 2,3-dichloro-6,7-dimethylquinoxaline (0.438 g, 1.93 mmol) were combined as described in the general procedure. The reaction mixture was allowed to stir at −78 °C for 0.5 h, and then quenched with EtOH (20 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography eluting with 9:1 dichloromethane/ethyl acetate to afford a white solid (0.25 g, 34%). Mp: 176–179 °C; ν_{max} (neat, cm^{-1}) 1590, 1555, 1474, 1436; ^{1}H NMR (600 MHz/$CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 5.93 (s, 1H, H4′), 7.13 (d, 1H, *J*=7.7 Hz, H3″), 7.18 (s, 1H, CH), 7.25 (dd, 1H, *J*=4.8, 7.7 Hz, H5″), 7.67 (s, 1H, H5/H10), 7.70–7.75 (m, 3H, H4″, H5/H10), 8.55 (d, 1H, *J*=4.8 Hz, H6″); ^{13}C NMR (151 MHz/$CDCl_3$): δ 11.4, 13.7, 20.1, 20.4, 66.2, 106.1, 122.7, 123.4, 127.0, 128.8, 136.9, 139.4, 140.2, 140.4, 140.6, 141.7, 146.3, 148.5 148.7, 149.9, 157.9; *m*/*z* 342.0 (MH^+) (cyclizes); Found: C 66.8, H 5.3, N 18.6. $C_{21}H_{20}ClN_5$ requires: C 66.7, H 5.4, N 18.5%.

*4.2.8. 5-(Pyrazin-2-yl)-pyrrolo[1,2-a:4,5-b]pyrazine (**6a**).* Di-2-pyrazinylmethane (**10**) (0.244 g, 1.41 mmol) in THF (20 mL), *n*-BuLi (0.740 mL, 1.43 mmol), and 2,3-dichloropyrazine (**8a**) (0.0730 mL, 0.698 mmol) in THF (20 mL) were combined and reacted in the manner described. The reaction mixture was stirred at room temperature for 16 h then heated at reflux for 20 h. The reaction mixture was quenched with methanol (2 mL). Upon cooling to room temperature a red precipitate formed. The solvent was removed under reduced pressure and the crude product was isolated as described in the general procedure using $CHCl_3$ as the extracting solvent. The isolated product was recrystallized from THF to afford the title compound **6a** as an orange solid (0.10 g, 58%). Mp: 262 °C; ν_{max} (neat, cm^{-1}) 3098, 1576, 1542, 1504, 1482, 1467; ^{1}H NMR (300 MHz/$CDCl_3$): δ 7.97 (d, *J*=4.8 Hz, 1H, H6′), 8.47 (d, *J*=2.4 Hz, 1H, H1), 8.59 (d, *J*=2.3 Hz, 1H, H8), 8.65–8.68 (m, 2H, H2/H5′), 9.00 (d, *J*=2.3 Hz, 1H, H7), 10.18 (d, *J*=1.5 Hz, 1H, H4), 10.45 (d, *J*=1.7 Hz, 1H, H3′); ^{13}C NMR (151 MHz/$CDCl_3$): 102.7, 115.9, 128.0, 130.6, 134.3, 136.3, 137.9, 141.4, 143.7, 144.4, 144.6, 149.4, 149.4; *m*/*z* 249.2 (MH^+); Found: C 61.9, H 3.4, N 33.3. $C_{13}H_8N_6 \cdot ¼H_2O$ requires: C 61.8, H 3.4, N 33.3%; λ_{max}/nm: 464 (ε/M^{-1} cm^{-1} 4200).

*4.2.9. 5-(Pyrazin-2-yl)-pyrazino[1,2-a]pyrrolo[2,3-b]quinoxaline (**6b**).* Di-2-pyrazinylmethane (**10**) (0.220 g, 1.27 mmol) in THF (20 mL), *n*-BuLi (0.674 mL, 1.28 mmol), and 2,3-dichloroquinoxaline (**8b**) (0.123 g, 0.618 mmol) in THF (15 mL) and reacted in the manner described. After stirring at room temperature, the reaction mixture was warmed to 50 °C for 1 h and then quenched. The purple reaction mixture was subjected to the standard work-up (using $CHCl_3$) and yielded a dark solid, which was isolated by filtration and repeatedly washed with diethyl ether until the washings were clear. This afforded the title compound as a purple solid (0.11 g, 58%). Sublimes 280–283 °C; ν_{max} (neat, cm^{-1}) 3074, 1577, 1546, 1521, 1509, 1466; ^{1}H NMR (600 MHz/$CDCl_3$): δ 7.86 (dd, *J*=7.4, 7.8 Hz, 1H, H8/H9), 7.91 (dd, *J*=7.4, 7.8 Hz, 1H, H8/H9), 7.95 (d, *J*=4.7 Hz, 1H, H1), 8.29 (d, *J*=8.4 Hz, 1H, H7/H10), 8.43 (d, *J*=8.4 Hz, 1H, H7/H10), 8.48 (s, 1H, H6′), 8.67 (s, 1H, H5′), 8.76 (d, *J*=4.7 Hz, 1H, H2), 10.48 (s, 1H, H3′), δ 10.50 (s, 1H, H4); ^{13}C NMR (151 MHz/$CDCl_3$): 101.1, 116.8, 127.2, 128.9, 129.0, 129.5, 129.7, 134.6, 135.4, 138.2, 138.5, 141.1, 143.7, 144.0, 144.5, 149.5, 149.6; *m*/*z*: 298.9 (MH^+); Found: C 67.9, H 3.4, N 28.4. $C_{17}H_{10}N_6$ requires: C 68.4, H 3.4, N 28.2%; λ_{max}/nm: 536, 570 (ε/M^{-1} cm^{-1} 4760, 4200).

*4.2.10. 8,9-Dimethyl-5-(pyrazin-2-yl)-pyrazino[1,2-a]pyrrolo[2,3-b]quinoxaline (**6c**).* Di-2-pyrazinylmethane (**10**) (0.224 g, 1.30 mmol) in THF (20 mL), *n*-BuLi (0.576 mL, 1.32 mmol), and 6,7-dimethyl-2,3-dichloroquinoxaline (**8c**) (0.140 g, 0.616 mmol) in THF (15 mL) were combined and reacted in the manner described. The purple reaction mixture was worked-up as described in the general procedure, yielding a dark solid, which was isolated by filtration and repeatedly washed with diethyl ether until the washings were clear. This afforded the title compound as a purple solid (0.14 g, 69%). Sublimes 278–280 °C; ν_{max} (neat, cm^{-1}) 2919, 1577, 1540, 1507, 1491, 1464; ^{1}H NMR (600 MHz/$CDCl_3$) 2.57 (s, 3H, Me), 2.58 (s, 3H, Me), 7.89 (d, 1H, *J*=4.8 Hz, H1), 7.94 (s, 1H, H7/H10), 8.08 (s, 1H, H7/H10), 8.45 (d, 1H, *J*=2.5 Hz, H6′), 8.64 (s, 1H, H5′), 8.67 (d, 1H, *J*=4.8 Hz, H2), 10.40 (s, 1H, H3′), 10.41 (s, 1H, H4); ^{13}C NMR (151 MHz/$CDCl_3$): δ 20.5, 20.6, 100.9, 116.7, 127.0, 127.4, 128.2, 133.7, 134.9, 137.3, 137.5, 140.0, 140.4, 140.9, 143.1, 143.6, 144.4, 149,4, 149.6; Found: C 66.2, H 4.3, N 24.6. $C_{19}H_{14}N_6 \cdot H_2O$ requires: C 66.3, H 4.3, N 24.6; *m*/*z*: 327.0 (MH^+); λ_{max}/nm: 531, 564 (ε/M^{-1} cm^{-1} 4680, 3800).

4.3. Cell line

T98G human glioblastoma multiforme cells were purchased from the ATCC. The cells were maintained as a monolayer in minimum essential medium (MEM), supplemented with 10% fetal bovine serum, penicillin (100 units/mL), streptomycin (100 g/mL), and L-glutamine (2.5 mM), at 37 °C in a humidified 5% CO_2 atmosphere.

4.4. Cytotoxicity assays

Cytotoxicity was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[49] Cells were harvested with trypsin (0.1% v/v), and cell pellets were isolated by centrifugation. Cells were then re-suspended to single cells suspension, cell numbers counted using a Hemocytometer counter (Weber) and then seeded at a density of 1×10^4 cells/well in 96-well plates, in 100 μL growth medium and allowed to adhere overnight at 37 °C. Cells were incubated at 37 °C in a humidified atmosphere of 5% CO_2 in the presence of compounds **1a**–**c**, **5a**, **5b**, and **6a**–**c**, and vehicle (control). Serial dilutions (1:2 and 1:10) of compound solution in cell medium were added to wells in triplicate. Compounds were tested at a concentration range prescribed by the limits of compound solubility and that produced a sigmoidal cytotoxic response. After 72 h of drug exposure, MTT solution in PBS (20 μL, 0.25% w/v) was added to each well and the incubation continued for 4 h. Culture medium and excess MTT solution were removed and the resulting reduced formazan crystals dissolved by addition of 150 μL DMSO.

Cell viability was determined by measuring the absorbance of the purple formazan solution at 600 nm using a Victor$_3$V microplate reader (Perkin–Elmer). All readings were corrected for absorbance from negative control and wells containing medium alone. The level of purple intensity was expressed relative to the corresponding control as percent viability. Corresponding IC_{50} values for each of the compounds tested were then determined at the dose required to induce a 50% decrease in cell viability from sigmoidal dose–response curves produced in GraphPad Prism 5 (Version 5.04). Experiments were repeated at least three times for each compound and all IC_{50} values are reported with standard errors.

4.5. Crystallography

Crystals were mounted under paratone-N oil on a plastic loop. X-ray diffraction data were collected with (i) Mo Kα radiation (λ=0.7107 Å) using an Oxford Diffraction X-calibur single crystal X-ray diffractometer at 150(2) K (structures **9a**, **9c**, and **6b**), or (ii) synchrotron radiation (λ=0.7107 Å) at 150(2) K using the Protein Micro-crystal and Small Molecule X-ray Diffraction beam line (MX2) at the Australian Synchrotron (structures of **5b**, and **6a**).[53] Data sets were corrected for absorption using a multi-scan method, and structures were solved by direct methods using SHELXS-97[54] and refined by full-matrix least squares on F^2 by SHELXL-97,[55] interfaced through the program X-Seed.[56] In general, all non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as invariants at geometrically estimated positions, unless specified otherwise in additional details below. Figures were produced using the program POV-Ray,[57] interfaced through the program X-Seed. Publication materials were prepared using the program CIFTAB.[58] Details of data collections and structure refinements are given below. CCDC 818294–818298 contain the supplementary crystallographic data for this structure. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A summary of the crystallographic data and structure refinements are given in Table 2.

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Supplementary data

Electronic Supplementary data (ESD) available: ^{1}H and ^{13}C NMR spectra for all new compounds, crystallographic information files for **9a**, **9c**, **5b**, **6a**, and **6b**. The following are the Supplementary data related to this article: doi:10.1016/j.tet.2011.09.133.

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