Anticancer Activity and Cisplatin Binding Ability of Bis-Quinoline and Bis-Isoquinoline Derived [Pd\(_2\)L\(_4\)]\(^{4+}\) Metallosupramolecular Cages

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New bis-quinoline (L\(_q\)) and bis-isoquinoline-based (L\(_{iq}\)) ligands have been synthesized, along with their respective homoleptic [Pd\(_2\)(L\(_q\))\(_4\)]\(^{4+}\) cages (C\(_q\)) and C\(_{iq}\)). The ligands and cages were characterized by \(^1\)H, \(^13\)C and diffusion ordered (DOSY) NMR spectroscopies, high resolution electrospray ionization mass spectrometry (HR-ESIMS) and in the case of the bis-quinoline cage, X-ray crystallography. The crystal structure of the C\(_q\) architecture showed that the [Pd\(_2\)(L\(_q\))\(_4\)]\(^{4+}\) cage formed a twisted meso isomer where the [Pd(quinoline)]\(_4\)]\(^{2+}\) units at either end of the cage architecture adopt the opposite twists (left and right handed). Conversely, Density Functional Theory (DFT) calculations on the C\(_{iq}\) cage architecture indicated that a lantern shaped conformation, similar to what has been observed before for related [Pd\(_2\)(L\(_{tripy}\))\(_4\)]\(^{4+}\) systems (where L\(_{tripy}\) = 2,6-bis(pyridin-3-yl ethynyl)pyridine), was generated. The different cage conformations manifest different properties for the isomeric cages. The C\(_q\) cage is able to bind, weakly in acetonitrile, the anticancer drug cisplatin whereas the C\(_{iq}\) architecture shows no interaction with the guest under the same conditions. The kinetic robustness of the two cages in the presence of Cl\(^-\) nucleophiles was also different. The C\(_{iq}\) cage was completely decomposed into free L\(_{iq}\) and [Pd(Cl)]\(_4\)]\(^{-}\) within 1 h. However, the C\(_q\) cage was more long lived and was only fully decomposed after 7 h. The new ligands (L\(_{iq}\) and L\(_q\)) and the Pd(II) cage architectures (C\(_{iq}\) and C\(_q\)) were assessed for their cytotoxic properties against two cancerous cell lines (A549 lung cancer and MDA-MB-231 breast cancer) and one non-cancerous cell line (HDFa skin cells). It was found that L\(_q\) and C\(_q\) were both reasonably cytotoxic (IC\(_{50}\) \(\approx\) 0.5 \(\mu\)M) against A549, while C\(_{iq}\) was slightly less active (IC\(_{50}\) = 7.4 \(\mu\)M). L\(_{iq}\) was not soluble enough to allow the IC\(_{50}\) to be determined against either of the two cancerous cell lines. However, none of the molecules showed any selectivity for the cancer cells, as they were all found to have similar cytotoxicities against HDFa skin cells (IC\(_{50}\) values ranged from 2.6 to 3.0 \(\mu\)M).

Keywords: palladium(II), anticancer, self-assembly, metallosupramolecular, quinoline
INTRODUCTION

Metalsupramolecular architectures (MSAs) (Cook and Stang, 2015) have been attracting increasing attention over the past two decades due to their many potential applications including catalysis (Yoshizawa et al., 2009; Yoshizawa and Fujita, 2010; Martí-Centelles et al., 2018), storage (Mal et al., 2009), and sensing (Wang et al., 2011). Inspired by the success of cisplatin and other metallodrugs (Mjós and Orvig, 2014) there is emerging interest in exploiting MSAs for biomedical purposes (Cook et al., 2013; Therrien, 2015; Casini et al., 2017; Zhou et al., 2017). Several groups have examined MSAs as drug delivery vectors (Therrien et al., 2008; Schmitt et al., 2012; Yi et al., 2012; Zheng et al., 2015; Samanta et al., 2016, 2017; Bhat et al., 2017; Xu et al., 2017; Wang J.-F. et al., 2018; Yue et al., 2018). Additionally, MSAs have been shown to bind DNA (Oleksy et al., 2006; Garci et al., 2017; Zhao et al., 2017) and RNA (Phongtongpasuk et al., 2013; Malina et al., 2015), interact with proteins (Li et al., 2014; Mitchell et al., 2017) and have anticancer (Hotze et al., 2008; Faulkner et al., 2014; Grishagin et al., 2014; Dubey et al., 2015; Zheng et al., 2016; Allison et al., 2018) and antibacterial (Richards et al., 2009; Howson et al., 2012; Wang H. et al., 2018) properties.

Since the pioneering work of McMorran and Steel (McMorran and Steel, 1998) interest in [M2(L)4]n+ cage-type structures has burgeoned (Schmidt et al., 2014). Some time ago now we reported that a [Pd2(Itripy)(L)4]+ cage (where Itripy = 2,6-bis(pyridin-3-yl)ethynyl)pyridine) could host two molecules of the anticancer drug cisplatin within the cavity of the cage (Lewis et al., 2012), and thus had potential as a drug delivery vector. Disappointingly, the binding event, which was governed mainly by hydrogen bonding interactions, was weak (Preston et al., 2015). The host-guest complex formed in acetonitrile (CH3CN) and dimethylformamide (DMF) but unfortunately, in more hydrogen bond competitive solvents such as water and dimethyl sulfoxide (DMSO) no host-guest interaction was observed. Additionally, the parent Pd(II) based cage decomposed rapidly in the presence of nucleophiles (Lewis et al., 2012; McNeill et al., 2015). Thus, in order to exploit these [Pd2(L)4]+ cages as cisplatin delivery vehicles these issues need to be addressed. We and others have examined a range of modifications to the parent [Pd2(L)4]+ cage system in order to improve the solubility (Lewis and Crowley, 2014; Preston et al., 2015; Han et al., 2017) and other properties (Lewis et al., 2013, 2014; Kaiser et al., 2016; Schmidt et al., 2016a) of the cage. Efforts have also been made to enhance the strength of the host-guest interaction (Kim et al., 2015) and the stability of the cages in the presence of biologically relevant nucleophiles (Preston et al., 2016). However, while some improvements have been made these [Pd2(L)4]+ cages still require further modifications in order to be useful drug delivery vectors.

The [Pd2(L)4]+ cages have also been examined for their cytotoxic properties. We showed that the parent [Pd2(Itripy)(L)4]+ was modestly cytotoxic (IC50 values range from 40 to 70 μM) against a range of cancer cell lines but was less active than related bis-1,2,3-triazole [Pd2(L)4]14+ helicates (McNeill et al., 2015). We also examined the cytotoxicity of related amino substituted [Pd2(L)4]14+ cages against the same panel of cancer cells and found that they exhibited similar cytotoxic properties as the parent systems (Preston et al., 2016). Casini, Kühn and co-workers (Kaiser et al., 2016; Schmidt et al., 2016b) have measured the cytotoxicity of a series of related [Pd2(L)4]+ cages and observed similar IC50 values (10–70 μM). Additionally, they have measured the cytotoxicity of mixtures of the cages and cisplatin and unsurprisingly have found that those mixtures are more cytotoxic than cage alone (IC50 = 2–13 μM). Yoshizawa, Ahmedova and co-workers have also found that [M2(L)4]+ (M = Pd2+ or Pt2+) cages with similar, but more hydrophobic, dipyridyl anthracenyl ligands (Lanthracene) display high anticancer activity (IC50 values range from 0.9 to 37.4 μM against HL-60, HL-60/Dox, HT-29, T-24, SKW-3 cancer cell lines) (Ahmedova et al., 2016; Anife et al., 2016).

The majority of the [Pd2(L)4]+ cages examined to date feature pyridyl donors, as part of our efforts to improve the biological properties of these systems herein we describe the use of isoquinoline and quinoline-derived ligands for the assembly of two new [Pd2(L)4]+ cages. While is well-known that isoquinoline and quinoline ligands can bind with palladium(II) and platinum(II) (Bondy et al., 2004) their use as donor systems in ligands for the generation MSAs has not been extensively explored (Bloch et al., 2016, 2017). These quinoline derived systems feature different electronic and steric properties compared to the parent pyridyl systems thus we also examine the effect these changes have on the host-guest chemistry with cisplatin, the stability of the cages in the presence of nucleophiles and the anti proliferative properties of the cages.

RESULTS AND DISCUSSION

The synthesis of the new quinoline (Lq) and isoquinoline (Liq) based ligands was facile (Supplementary Material). Using sequential Sonogashira carbon-carbon cross coupling reactions from commercially available building blocks the ligands were generated in good yields (Lq = 86% and Liq = 78%). 1H and 13C NMR spectroscopic data were consistent with the formation of the ligands which was supported by high-resolution electrospray mass spectrometry (HR-ESIMS) (Figure 1 and Supplementary Material). Peaks corresponding to protonated and sodiated ligand were observed at m/z = 382.1320 and 404.1132, respectively, for Lq and similar peaks were observed for Liq (Supplementary Material).

With the ligands in hand, the complexation with [Pd(CH3CN)4][BF4]2 in acetonitrile was examined (Figure 1). The cage formation was monitored using 1H NMR spectroscopy (CD3CN, 298 K) and showed that mixing [Pd(CH3CN)4][BF4]2 and the Liq ligand at room temperature (RT) in a 1:2 ratio led to the rapid (<2 min) and quantitative formation of the expected Ciq cage (Figure 1), similar to what was observed with the parent Itripy system (Lewis et al., 2012). Interestingly, the behavior of Liq with [Pd(CH3CN)4][BF4]2 at room temperature was very different. After 5 min at RT the reaction mixture displayed multiple proton resonances, none of which were due to free ligand, consistent with the formation of a mixture of different cage isomers. The reaction was monitored using 1H NMR spectroscopy for 24 h at RT however little to no changes were
The assembly reaction between Lq with [Pd(CH3CN)4][BF4]2 was then carried out at 65°C in CD3CN and again monitored using 1H NMR spectroscopy (Figure 2). After 5 min the same complicated series of proton resonances were observed. However, with continued heating this slowly resolved into a single series of resonances (after 7 h), consistent with the formation of a single cage isomer (Supplementary Material).

The calculated Pd – N bond lengths (Pd1-N2 2.045 Å) were similar to what have been previously observed for the [Pd2(Ltripy)4]4+ cages where the Pd-N bond lengths range from 2.016 to 2.027 Å (Lewis et al., 2012; Lewis and Crowley, 2014). The Lq ligands of the cage are twisted giving a V-shaped conformation where the terminal quinoline and central pyridyl heterocyclic units are not co-planar which is quite different to what was observed with the [Pd2(Ltripy)4]4+ cages. In X-ray structures of the parent [Pd2(Ltripy)4]4+ cages the Ltripy ligands were found in a linear conformation with the heterocyclic units coplanar. The twisting also alters the Pd1-Pd1’ distance within Cq related to the [Pd2(Ltripy)4]4+ cages. The Pd1-Pd1’ distances for the parent [Pd2(Ltripy)4]4+ cages range from 11.49 to 12.24 Å, whereas the Pd1-Pd1’ distance was found to be longer (12.506 Å) suggesting that the Cq cage has a larger cavity despite featuring the same 2,6-diethylpyridine linker units. The [Pd(quinoline)]4+ units at the top and bottom of Cq are twisted in opposite directions, the top cationic unit has a right handed twist while the bottom cationic unit has a left handed twist giving an overall meso structure (Figures 3B,C and Supplementary Material). Despite extensive efforts we were unable to obtain X-ray diffraction quality single crystals of Cq. Thus, to gain further insight into the structure of Cq we modeled the cage using Density Functional Theory (DFT) calculations (Figures 3D,E). Energy minimization of Cq (DFT, BP86 de2-SVP, acetonitrile solvation, Supplementary Material) showed that the cage adopted a lantern shape similar to what was previously observed for [Pd2(Ltripy)4]4+ cages (Lewis et al., 2012; Lewis and Crowley, 2014). The calculated Pd – N bond distances (2.049 Å) and the Pd-Pd bond lengths range from 2.016 to 2.027 Å (Lewis et al., 2012; Schmidt et al., 2016b, 2016, 2017; Kaiser et al., 2016; Preston et al., 2016, 2017; Schmidt et al., 2016b). Therefore, we examined the ability of Cq and Ciq to interact with cisplatin in CH3CN using 1H NMR spectroscopy. Addition of an excess of cisplatin to a
CD$_3$CN solution of the C$_{iq}$ cage resulted in a downfield shift and broadening ($\Delta\delta = 0.03$ ppm) of the internally directed cage proton H$_a$ (Figures 4A,B) indicative of cisplatin binding within the cage cavity, albeit weakly. A similar $^1$H NMR experiment was carried out with the C$_q$ cage (Figures 4C,D). However, with the C$_q$ cage no shifts were observed for any of the cage proton resonances in the presence of an excess of cisplatin suggesting that the more twisted C$_q$ cage does not interact with the anticancer agent. The behavior was similar to what has been observed with a related twisted $[\text{Pd}_2(\text{L}_2\text{Atripy})_4]^{4+}$ cage (where $\text{L}_2\text{Atripy} = 2.6$-bis[2-(6-amino-3-pyridinyl)ethynyl]-4-pyridinemethanol) (Preston et al., 2016). The $[\text{Pd}_2(\text{L}_2\text{Atripy})_4]^{4+}$ cage did not bind cisplatin in DMF solvent and the lack of binding was ascribed to the twisted cage cavity which was not as preorganised as those of the related lantern shaped $[\text{Pd}_2(\text{L}_{\text{tripy}})_4]^{4+}$ cages. Presumably the different cavity and different spatial arrangement of the hydrogen bond donors and acceptors caused by the twisting observed in the crystal structure of C$_q$ impedes the cisplatin-C$_q$ interaction in this case.

The kinetic robustness of the related $[\text{Pd}_2(\text{L}_{\text{tripy}})_4]^{4+}$ architectures in the presence of common biological nucleophiles (chloride (Cl$^-$), histidine and cysteine) has been determined using $^1$H NMR competition experiments. When the parent $[\text{Pd}_2(\text{L}_{\text{tripy}})_4]^{4+}$ architectures were treated with 8 equivalents of tetrabutylammonium chloride the pyridyl substituted cages were rapidly and quantitatively decomposed (in <5 min). To examine the effect of substituting the pyridyl donor units for quinoline heterocycles time-course $^1$H NMR competition experiments were carried out in d$_6$-DMSO where 2mM solutions of each cage (C$_q$ or C$_{iq}$) were treated with 8 equivalents of tetrabutylammonium chloride at 298 K (Figure 5 and Supplementary Material). Within 30 s of adding Cl$^-$ to the C$_{iq}$ cage, there were multiple species observed in the $^1$H NMR spectrum. These were attributed to the C$_{iq}$ cage, [Cl$\subset$C$_{iq}$]$^{13+}$, the $[\text{Pd}_2(\text{L}_4)_2\text{Cl}_4]$ macrocycle and free ligand based on our own previous results (Preston et al., 2015) and related literature. After 50 min, only uncoordinated ligand was visible in the $^1$H NMR spectrum (Supplementary Material).

Under the same conditions, C$_q$ was stable for 1 h before showing signs of decomposition (Figure 5). After 3 h, there was no evidence of the C$_q$ cage, and the $^1$H NMR spectrum displayed peaks corresponding to free ligand and a second metal-containing species, which based on the observed chemical shifts was most likely the neutral $[\text{Pd}_2(\text{L}_4)_2\text{Cl}_4]$ macrocycle (Figure 5H). This degradation behavior has been seen before with the $[\text{Pd}_2(\text{L}_{\text{tripy}})_4]^{4+}$ system in DMF (Preston et al., 2015). After 7 h, only free ligand could observed in the $^1$H NMR spectrum indicating that all the ligand containing metal complexes had been completely decomposed into $[\text{Pd}(\text{Cl})_4]^{2-}$ (Figure 5J).

In comparison to the previously reported $[\text{Pd}_2(\text{L}_{\text{tripy}})_4]^{4+}$ cage ($\tau_{1/2} = 2$ min), the isoquinoline cage displayed an identical half-life ($\tau_{1/2} = 2$ min), whereas the quinoline system was considerably more robust ($\tau_{1/2} = 2$ h). Presumably the observed results reflect the different steric profiles of the two quinoline substituted cages (C$_q$ or C$_{iq}$). The C$_q$ cage has the quinoline moieties protecting the external face of the palladium, providing more impediment to nucleophilic attack from that face (Figure 6). The C$_{iq}$ does not feature the same steric impediment as the benzene units of the isoquinoline heterocycles do not block the top face of the C$_{iq}$ cage as much as they do in the quinoline C$_q$ (Figure 6).
FIGURE 3 | Molecular structures of $C_q$ and $C_{iq}$. X-ray structure of $C_q$: (A) ellipsoid side view, (B) tube side view, and (C) tube top view showing paddle-like array of quinoline panels over palladium(II) center. Solvent molecules and counterions have been omitted for clarity. Ellipsoids are shown at 50% probability. DFT optimized (BP86 def2-SVP) model of $C_{iq}$; (D) side view and (E) top view showing lantern-shaped structure. Colors: carbon gray, nitrogen blue, palladium magenta, hydrogen white.

FIGURE 4 | Partial $^1$H NMR (500 MHz, CD$_3$CN, 298 K) stacked plot of (A) $C_{iq}$ (B) $C_{iq}$ + cisplatin (10 eq.) (C) $C_q$, and (D) $C_q$ + cisplatin (10 eq.).
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FIGURE 5 | Partial 1H NMR (500 MHz, d6-DMSO, 298 K) spectra showing the stability of Cq in the presence of 8 eq. Cl− anions. (A) Lq, (B) Cq, (C) Cq with 8 eq. Cl− (t = 2 min), (D) t = 10 min, (E) t = 20 min, (F) t = 30 min, (G) t = 1 h, (H) t = 3 h, (I) t = 5 h, (J) t = 7 h.

FIGURE 6 | Top down views of (A) and (B) the DFT optimized model of Ciq, and (C) and (D) the X-ray structure of Cq.

To assess biological activity, the cytotoxic effect (as half-maximal inhibitory concentrations (IC50)) of the ligands and cages were determined against three different cell lines: cisplatin resistant MDA-MB-231 (breast cancer) (Lehmann et al., 2011), A549 (lung cancer) and non-cancerous primary cells: adult human dermal fibroblasts (HDFa) (Table 1 and Supplementary Material). The ligands Lq and Liq exhibited limited solubility, and so data above the concentration of 1 µM was unattainable. Below this threshold, Liq displayed minimal cytotoxic activity against both cell lines, while Lq was shown to be cytotoxic against A549 (IC50 = 0.5 µM). Both cages were observed to be cytotoxic against the malignant cell lines, with Cq showing the same level of toxicity as its ligand against lung cancer cells (IC50 = 0.5 µM). Cq was slightly less cytotoxic against MDA-MB-231 (IC50 = 1.7 µM), whereas Ciq was less cytotoxic than the quinoline analog, with the IC50 values ranging from 4.0 to 7.4 µM against the cancer cells. Both quinoline cages were found to be considerably more active than the related parent [Pd2(Ltripy)4]4+ cage system (IC50 = 41.4 and 56.7 µM against A549 and MDA-MB-231, respectively) (McNeill et al., 2015). The quinoline cages were also more active than cisplatin against the two cancer lines examined (cisplatin IC50 values = 41.2 and 9.4 µM, against MDA-MB-231 and A549, respectively) (Lo et al., 2015; McNeill et al., 2015). The quinoline cages Cq and Ciq were more cytotoxic than all the [Pd2(Ltripy)4]4+ cage systems reported in the literature (IC50 values for the Ltripy based systems ranged from 10 to 100 µM) (McNeill et al., 2015; Kaiser et al., 2016; Schmidt et al., 2016b). Additionally, Cq was also more active, albeit against different cancer cell lines (HL-60, HL-60/Dox, HT-29, T-24, SKW-3), than the hydrophobic [Pd2(Lanthracene)4]4+ cages of Yoshizawa and Ahmedova (IC50 values ranged from 0.9 to 37.4 µM) (Ahmedova et al., 2016; Anife et al., 2016).
C₃ was also more cytotoxic than a hydrophobic bis-hexyl-1,2,3-triazole substituted [Pd₂(Lhextrz)₄]⁴⁺ helicate, C₃hextrz, we developed previously (IC₅₀ values = 6.9 and 6.0 μM against A549 and MDA-MB-231, respectively) (McNeill et al., 2015). We presume that the favorable combination of high hydrophobicity and the kinetic robustness against biological nucleophiles leads to the higher observed activity of C₃ relative to the other [Pd₂(L₄)⁴⁺] architectures. Disappointingly, neither of the cages (C₃ and C₄q) showed any selectivity for the cancer cells, they were all found to have similar cytotoxicity against HDFa skin cells (IC₅₀ values ranged from 2.6 to 3.0 μM).

**CONCLUSION**

We have herein reported the synthesis, characterization, cisplatin binding, kinetic robustness and cytotoxicity of two new bis-isouquinoline and bis-quinoiline derived [Pd₂L₄]⁴⁺ cage complexes. The crystal structure of C₄q architecture showed that the [Pd₂L₄]⁴⁺ cage formed a twisted meso isomer where the [Pd₂(quinoiline)L₄]²⁺ units at either end of the cage architecture adopt the opposite twists (left and right handed). Conversely, Density Functional Theory (DFT) calculations on the C₄q cage architecture indicated that a lanthanum shaped conformation similar to what has been observed before for related [Pd₂(Ltripy)₄]⁴⁺ systems was generated. The different cage conformations resulted in different properties for the isomeric cages. The C₄q cage is able to bind, weakly in acetonitrile, the anticancer drug cisplatin whereas the C₃q architecture shows no interaction with the guest under the same conditions. The kinetic robustness of the two cages in the presence of Cl⁻ nucleophiles was also different. The C₄q cage was completely decomposed into free L₄ and [Pd(Cl)L]²⁻ within 1 h. However, the C₃q cage was more long lived and was only fully decomposed after 7 h. The ligands (L₄q and L₄q) and cages (C₄q and C₃q) were assessed for their cytotoxic properties against two cancerous cell lines (A549 lung cancer cells and MDA-MB-231 breast cancer cells) and one non-cancerous cell line (HDFa skin cells). It was found that L₄q and C₃q were both reasonably cytotoxic against A549, while C₄q was slightly less active. The higher observed cytotoxicity of C₃q relative to the other [Pd₂(L₄)⁴⁺]⁴⁺ architectures was presumed to be due the favorable combination of high hydrophobicity and the kinetic robustness against biological nucleophiles. However, none of the new molecules showed any selectivity for cancer cells, they were all found to have similar cytotoxicity against HDFa skin cells. A range of [Pd₂(L₄q)]⁴⁺ cage systems have now been shown to be cytotoxic. However, in order to advance this class of MSA as anticancer agents more in depth mode of action/mechanistic studies on the origins of the cytotoxic activity are required. Studies to this effect are now underway.

**AUTHOR CONTRIBUTIONS**

RV and JC conceived the idea, analyzed the data and wrote the manuscript. RV and LG conducted the synthesis. RV and DP conducted stability studies. RV, DP and JJ conducted cytotoxicity studies. GG oversaw the cytotoxicity studies and analyzed the data. All authors provided feedback on the manuscript drafts and approved the submission.

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**TABLE 1** | Half-maximal inhibitory concentrations (IC₅₀) of ligands L₄q and L₄q, and cages C₃q and C₄q architectures at 24 h.

| Compound                        | MDA-MB-231 | A549   | HDFa   | MCF-10A  |
|---------------------------------|------------|--------|--------|----------|
|                                 | IC₅₀ (μM)  |        |        |          |
|                                 | L₄q        | C₃q    | L₄q    | C₄q      |
|                                 | >1⁰        | 0.5 ± 0.1 | >1⁰    | –        |
|                                 | 1.7 ± 0.1  | 0.5 ± 0.1 | 2.6 ± 0.4 | –        |
|                                 | >1⁰        | >1⁰    | >1⁰    | –        |
|                                 | 4.0 ± 0.3  | 7.4 ± 1.0 | 3.0 ± 0.4 | –        |
| L₄hextrz (McNeill et al., 2015)| 89.8 ± 10.7 | 28.5 ± 2.6 | –      | 18.1 ± 3.1 |
| L₄tripy (McNeill et al., 2015) | 6.0 ± 0.6  | 6.9 ± 0.9  | –      | 8.1 ± 1.2  |
|                                 | >100       | 95.3 ± 9.7  | –      | >100     |
| C₄tripy (McNeill et al., 2015)  | 56.7 ± 2.2 | 41.4 ± 3.9  | –      | 71.4 ± 3.9 |
| cisplatin (Lo et al., 2015)     | 41.2 ± 3.9 | 9.4 ± 0.3  | –      | –        |

⁰IC₅₀ values are given as mean ± SE.
¹The L₄tripy and C₄hextrz cages were tested against MCF-10A as a non-cancerous control.
²Solubility limited the range of concentrations to below 1 μM. * – * Not determined.

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RV and JC conceived the idea, analyzed the data and wrote the manuscript. RV and LG conducted the synthesis. RV and DP conducted stability studies. RV, DP and JJ conducted cytotoxicity studies. GG oversaw the cytotoxicity studies and analyzed the data. All authors provided feedback on the manuscript drafts and approved the submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2018.00563/full#supplementary-material

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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