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Article

Structure−Activity Relationships of Highly Cytotoxic Copper(II) Complexes with Modified Indolo[3,2-*c*]quinoline Ligands

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A number of indolo[3,2-*c*]quinolines were synthesized and modified at the lactam unit to provide a peripheral binding site able to accommodate metal ions. Potentially tridentate ligands **HL^{1a}**−**HL^{4a}** and **HL^{1b}**−**HL^{4b}** were reacted with copper(II) chloride in isopropanol/methanol to give novel five-coordinate copper(II) complexes [Cu(**HL^{1a-4a}**)Cl_2] and [Cu(**HL^{1b-4b}**)Cl_2]. In addition, a new complex [Cu(**HL^{5b}**)Cl_2] and two previously reported compounds [Cu(**HL^{6a}**)Cl_2] and [Cu(**HL^{6b}**)Cl_2] with modified paullone ligands **HL^{5b}**, **HL^{6a}**, and **HL^{6b}**, which can be regarded as close analogues of indoloquinolines **HL^{1b}**, **HL^{4a}**, and **HL^{4b}**, in which the pyridine ring was formally substituted by a seven-membered azepine ring, were synthesized for comparison. The new ligands and copper(II) complexes were characterized by ^{1}H and ^{13}C NMR, IR and electronic absorption spectroscopy, ESI mass spectrometry, magnetic susceptibility measurements in solution at 298 K ([Cu(**HL^{1a}**)Cl_2] and [Cu(**HL^{4b}**)Cl_2]), and X-ray crystallography ([Cu(**HL^{3b}**)Cl_2]·3DMF, [Cu(**HL^{4b}**)Cl_2]·2.4DMF, **HL^{5b}** and [Cu(**HL^{5b}**)Cl_2]·0.5CH_3OH). All complexes were tested for cytotoxicity in the human cancer cell lines CH1 (ovarian carcinoma), A549 (non-small cell lung cancer), and SW480 (colon carcinoma). The compounds are highly cytotoxic, with IC_{50} values ranging from nanomolar to very low micromolar concentrations. Substitution of the seven-membered azepine ring in paullones by a pyridine ring resulted in a six- to nine-fold increase of cytotoxicity in SW480 cells. Electron-releasing or electron-withdrawing substituents in position 8 of the indoloquinoline backbone do not exert any effect on cytotoxicity of copper(II) complexes, whereas copper(II) compounds with Schiff bases obtained from 2-acetylpyridine and indoloquinoline hydrazines are 10 to 50 times more cytotoxic than those with ligands prepared from 2-formylpyridine and indoloquinoline hydrazines.

Introduction

In recent years, metal complexes which are able to interfere with cellular structures have attracted great interest as potential anticancer drugs. Complexes with biologically active ligands are particularly attractive, as they combine qualities of classic non-targeted coordination compounds and organic ligands with selectivity for cellular targets (e.g., enzymes).[1−10] Indolo-[3,2-*d*]benzazepines, also named paullones, have been reported as potent inhibitors of intracellular proteins, for example, cyclin-dependent kinases (CDKs), glycogen synthase kinase-3β and mitochondrial malate dehydrogenase.[11−13] Since the original paullones do not possess suitable binding sites for metal ions, novel derivatives able to coordinate to gallium(III), ruthenium(II), osmium(II), and copper(II) have been designed and synthesized.[14−18] All complexes exhibit remarkable cytotoxicity in vitro, whereby the complexes with copper(II), the only physiologically relevant metal ion used, showed IC_{50}

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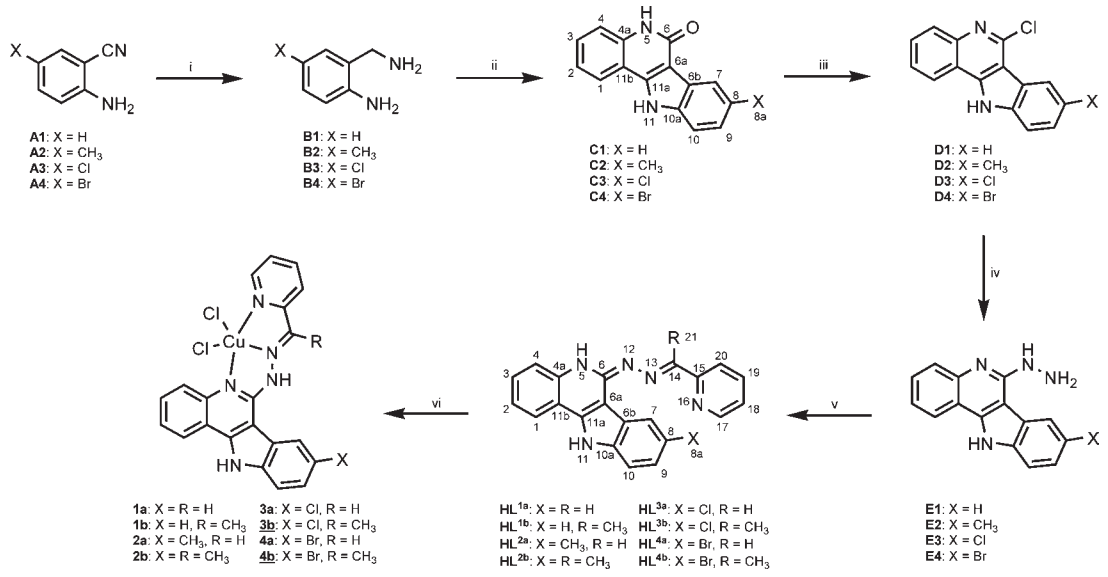
Scheme 1. Synthesis of **1a**−**4b**[a] and Numbering Schemes for Original and Modified Indoloquinolines[b]



[a] Reagents and conditions: (i) borane, 1.0 M in THF, THF, Ar, rt, 48 h (**B2**, 61%), 24 h (**B3**, 96%), 72 h (**B4**, 83%); (ii) glacial AcOH, reflux, 4 h [(**C1**, 80%), (**C2**, 56%), (**C3**, 60%), (**C4**, 64%)]; (iii) $POCl_3$, reflux, 24 h/NaOH, extraction with ethyl acetate [(**D1**, 97%), (**D2**, 72%), (**D3**, 86%), (**D4**, 90%)]; (iv) $N_2H_4 \cdot H_2O$, reflux, 24 h [(**E1**, 95%), (**E2**, 86%), (**E3**, 92%), (**E4**, 86%)]; (v) 2-formylpyridine, ethanol, reflux, 24 h [(**HL**^{1a}, 89%), (**HL**^{2a}, 82%), (**HL**^{3a}, 90%), (**HL**^{4a}, 78%)] or 2-acetylpyridine, ethanol, reflux, 24 h [(**HL**^{1b}, 89%), (**HL**^{2b}, 83%), (**HL**^{3b}, 94%), (**HL**^{4b}, 84%)]; (vi) $CuCl_2 \cdot 2H_2O$, isopropanol, reflux, 30 min [(**1a**, 82%), (**1b**, 90%), (**2a**, 86%), (**2b**, 94%), (**3a**, 83%), (**3b**, 86%), (**4a**, 85%), (**4b**, 91%)]. [b] Underlined compounds have been characterized by X-ray crystallography.

values in the low micromolar and high nanomolar concentration range.[18] Furthermore, the effect of metal coordination on solubility in aqueous media and on the impact on cell cycle progression have been reported as well.[14−18]

As an extension to this previous work, we were interested in studying the effect of substitution of the folded seven-membered azepine ring in indolo[3,2-*d*]benzazepines by a flat six-membered pyridine ring, prompting us to prepare the corresponding indolo[3,2-*c*]quinolines. Quite recently, the first ruthenium(II) and osmium(II) complexes with indolo[3,2-*c*]quinolines have been reported.[19] The modified indolo[3,2-*c*]quinoline ligands as well as their ruthenium(II) and osmium-(II) complexes were all more cytotoxic than the corresponding modified paullone ligands and their complexes.[19] Furthermore, the indoloquinolines and their complexes readily intercalate into DNA as evidenced by 90% replacement of methyl green in a competitive replacement assay.[19] These results are in accord with the previous suggestion of other authors that DNA is a possible intracellular target of indoloquinolines.[20]

The pharmacological relevance of indoloquinolines is also demonstrated by the fact that isocryptolepine, a derivative of indolo[3,2-*c*]quinoline, and the closely related cryptolepine, a derivative of indolo[3,2-*b*]quinoline, could be isolated from the roots of *Cryptolepis sanguinolenta*, an African plant used in traditional medicine to fight malaria.[21−23] Whereas cryptolepine was extensively studied for its medicinal applicability, isocryptolepine and further indolo-[3,2-*c*]quinolines were only explored by researchers to a limited extent, although their antiproliferative activity in vitro has been confirmed.[24−29]

Herein we report on the synthesis of the first copper(II) complexes with tridentate modified indolo[3,2-*c*]quinoline ligands (Scheme 1), related to the quite recently published copper(II) complexes with indolo[3,2-*d*]benzazepine-based ligands.[18] To directly compare the two classes of heterocycles, one novel copper(II) complex with a *N*-(7,12-dihydroindolo-[3,2-*d*][1]benzazepin-6-yliden)-*N*′-(1-pyridin-2-yl-ethyliden) azine ligand and two complexes reported previously have been synthesized (Chart 1), and their cytotoxicity was compared to those of indoloquinolines. Effects of the substitution of the seven-membered azepine ring by the six-membered

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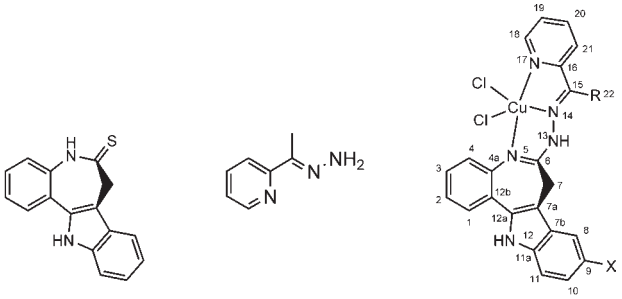
Chart 1. Starting Materials for the Synthesis of Complex **5b** and Numbering Scheme for Complexes **5b**, **6a**, and **6b** with Paullone-Based Tridentate Ligands[a]



[a] The underlined compound has been characterized by X-ray crystallography. Compounds **6a** and **6b** were prepared as described recently.[18]

pyridine ring and other structure−activity relationships are discussed.

Experimental Section

Starting Materials. 2-Aminobenzonitrile (**A1**), 2-amino-5-methylbenzonitrile (**A2**), borane tetrahydrofuran complex solution, 2-aminobenzylamine (**B1**), isatin, glacial acetic acid, phosphorus oxychloride, hydrazine hydrate, 2-formylpyridine, 2-acetylpyridine, copper(II) chloride dihydrate and dimethylformamide were all purchased from Sigma-Aldrich and used without further purification. 2-Amino-5-chlorobenzonitrile (**A3**) and isopropanol (analytical reagent grade) were purchased from Acros Organics. Tetrahydrofuran (THF, analytical reagent grade) was purchased from Fisher Scientific and dried using standard protocols. Ethanol (96%) and diethyl ether were purchased from Brenntag and Donauchem, correspondingly. 2-Amino-5-bromobenzonitrile (**A4**) was synthesized according to Roche et al.[30] The substituted benzylamines (**B2**−**B4**), were obtained by reduction of compounds **A2**−**A4** with borane in dry THF, according to the procedure reported by Giordani et al.[31] The syntheses of compounds **C1**,[32] **D1**,[20] **E1**,[33] **HL**^{1a}, and **HL**^{1b} [34] were performed following the literature procedures. 7,12-Dihydroindolo[3,2-*d*][1]benzazepine-6(5*H*)-thione (Chart 1) was prepared following a published protocol.[35] 2-Acetylpyridine hydrazone was obtained by reacting 2-acetylpyridine with excess hydrazine hydrate as the reagent and solvent at room temperature for 24 h.

General Procedure for the Synthesis of Substituted Benzylamines (B2, B3). To a solution of substituted benzonitrile in dry THF at 0 °C under an argon atmosphere was slowly added borane (1.0 M in THF). The reaction mixture was stirred for 10 min at 0 °C and further 48 h (**B2**), or 24 h (**B3**) at room temperature. The reaction mixture was cooled to 0 °C and quenched by addition of ethanol (96%). The resulting solution was saturated with gaseous HCl. The precipitated dihydrochloride was filtered off and then treated with an aqueous solution of ammonia. The resulting suspension was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over sodium sulfate. Ethyl acetate was completely removed under reduced pressure and the product further dried in vacuo.

2-Amino-5-methylbenzylamine (B2). 2-Amino-5-methylbenzonitrile (0.95 g, 7.2 mmol), freshly dried THF (20 mL), borane (1.0 M in THF, 9 mL), 48 h. Yield: 0.59 g, 61%. $C_8H_{12}N_2$, M_r = 136.91 g/mol. ^{1}H NMR ($CDCl_3$, δ_H): 6.91 (d, 1H, $^3J(H_{C3})$ = 7.9 Hz, C4), 6.90 (s, 1H, C6), 6.63 (d, 1H, $^3J(H_{C4})$ = 7.3 Hz, C3), 4.36 (bs, 2H, N(C2)), 3.88 (s, 2H, C7), 2.25 (s, 3H, C8), 1.41 (bs, 2H, N(C7)). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ_C): 143.63 (C2), 129.70 (C6), 128.59 (C4), 127.21 (C1), 126.40 (C6), 115.99 (C3), 44.93 (C7), 20.39 (C8).

2-Amino-5-chlorobenzylamine (B3). 2-Amino-5-chlorobenzonitrile (3.01 g, 19.76 mmol), freshly dried THF (50 mL), borane (1.0 M in THF, 24 mL), 24 h. Yield: 2.93 g, 96%. $C_7H_9ClN_2$, M_r = 156.61 g/mol. ^{1}H NMR (DMSO-d_6, δ_H): 7.08 (s, 1H, $^4J(H_{C4})$ = 2.4 Hz, C6), 6.93 (d, 1H, $^3J(H_{C3})$ = 8.5 Hz, $^4J(H_{C6})$ = 2.4 Hz, C4), 6.61 (d, 1H, $^3J(H_{C4})$ = 8.0 Hz, C3), 5.21 (s, 2H, N(C2)), 3.58 (s, 2H, C7), 1.80 (s, 2H, N(C7)). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 145.94 (C2), 129.09 (C1), 127.67 (C6), 126.87 (C4), 119.57 (C5), 116.17 (C3), 42.97 (C7).

General Procedure for the Synthesis of 8-Substituted 5,11-Dihydroindolo[3,2-*c*]quinolin-6-ones. A mixture of isatin and the respective benzylamine in glacial acetic acid was refluxed for 4 h under argon atmosphere. After cooling to room temperature the light-brown precipitate was filtered off, washed with acetic acid (2 × 5 mL), water, and diethyl ether and dried in vacuo.

8-Methyl-5,11-dihydroindolo[3,2-*c*]quinolin-6-one (C2). Isatin (0.58 g, 3.94 mmol), 2-amino-5-methylbenzylamine (0.56 g, 4.04 mmol), glacial acetic acid (10 mL). Yield: 0.54 g, 56%. Anal. Calcd for $C_{16}H_{12}N_2O$ (M_r = 248.28 g/mol) (%): C, 77.40; H, 4.87; N, 11.28. Found: C, 77.19; H, 4.78; N, 11.12. ^{1}H NMR (DMSO-d_6, δ_H): 12.41 (s, 1H, N11), 11.38 (s, 1H, N5), 8.16 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 8.01 (s, 1H, C7), 7.51−7.47 (m, 2H, C3, C10), 7.44 (d, 1H, $^3J(H_{C3})$ = 7.6 Hz, C2), 7.26 (dd, 1H, $^3J(H_{C1})$ = 7.6 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2), 7.18 (d, 1H, $^3J(H_{C10})$ = 8.2 Hz, C9), 2.47 (s, 3H, C8a). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 160.35 (C6), 141.15 (C11a), 138.34 (C4a), 136.42 (C10a), 130.28 (C8), 129.48 (C3), 125.86 (C9), 125.09 (6b), 122.49 (C1), 121.89 (C2), 121.01 (C7), 116.44 (C4), 112.51 (C11b), 111.77 (C10), 106.57 (C6a), 21.70 (C8a).

8-Chloro-5,11-dihydroindolo[3,2-*c*]quinolin-6-one (C3). Isatin (0.66 g, 4.50 mmol), 2-amino-5-chlorobenzylamine (0.80 g, 5.11 mmol), glacial acetic acid (10 mL). Yield: 0.72 g, 60%. Anal. Calcd for $C_{15}H_9ClN_2O$ (M_r = 268.70 g/mol) (%): C, 67.05; H, 3.38; N, 10.43. Found: C, 66.67; H, 3.14; N, 10.29. ^{1}H NMR (DMSO-d_6, δ_H): 12.74 (s, 1H, N11), 11.51 (s, 1H, N5), 8.18 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 8.14 (s, 1H, C7), 7.63 (d, 1H, $^3J(H_{C9})$ = 8.5 Hz, C10), 7.53 (dd, 1H, $^3J(H_{C2})$ = 7.6 Hz, $^3J(H_{C4})$ = 7.6 Hz, C3), 7.46 (d, 1H, $^3J(H_{C3})$ = 7.6 Hz, C4), 7.37 (d, 1H, $^3J(H_{C10})$ = 8.5 Hz, C9), 7.31 (dd, 1H, $^3J(H_{C1})$ = 7.6 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 160.05 (C6), 142.32 (C11a), 138.65 (C4a), 136.69 (C10a), 130.13 (C3), 126.00 (C6b), 125.99 (C8), 124.36 (C9), 122.75 (C1), 122.16 (C2), 120.15 (C7), 116.65 (C4), 113.78 (C10), 112.17 (C11b), 106.40 (C6a).

8-Bromo-5,11-dihydroindolo[3,2-*c*]quinolin-6-one (C4). Isatin (0.37 g, 2.51 mmol), 2-amino-5-bromobenzylamine (0.56 g, 2.76 mmol), glacial acetic acid (3.5 mL). Yield: 0.50 g, 64%. Anal. Calcd for $C_{15}H_9BrN_2O$ (M_r = 313.15 g/mol) (%): C, 57.53; H, 2.90; N, 8.95. Found: C, 57.22; H, 2.71; N, 8.62. ^{1}H NMR (DMSO-d_6, δ_H): 12.75 (s, 1H, N11), 11.52 (s, 1H, N5), 8.29 (s, 1H, C7), 8.18 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 7.59 (d, 1H, $^3J(H_{C9})$ = 8.5 Hz, C10), 7.54 (dd, 1H, $^3J(H_{C2})$ = 7.6 Hz, $^3J(H_{C4})$ = 7.6 Hz, C3), 7.50 (d, 1H, $^3J(H_{C10})$ = 8.5 Hz, C9), 7.48 (d, 1H, $^3J(H_{C3})$ = 7.6 Hz, C4), 7.31 (dd, 1H, $^3J(H_{C1})$ = 7.9 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 160.04 (C6), 142.14 (C11a), 138.66 (C4a), 136.96 (C10a), 130.14 (C3), 126.92 (C9), 126.62 (C6b), 123.17 (C7), 122.76 (C1), 122.17

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(C2), 116.65 (C4), 114.23 (C10), 113.89 (C8), 112.14 (C11b), 106.27 (C6a).

General Procedure for the Synthesis of 8-Substituted 6-Chloro-11*H*-indolo[3,2-*c*]quinolines. To 8-substituted 5,11-dihydroindolo-[3,2-*c*]quinolin-6-one was added $POCl_3$ as a reagent and solvent under argon atmosphere. The reaction mixture was refluxed for 24 h. After cooling to room temperature the reaction mixture was poured onto ice (200 mL) and slowly neutralized with solid sodium hydroxide until a pH of 6−7 was reached. The resulting aqueous suspension was extracted with ethyl acetate (5 × 200 mL). The combined organic layers were washed with 5% $NaHCO_3$ aqueous solution (2 × 250 mL) and dried over Na_2SO_4. Ethyl acetate was evaporated under reduced pressure to yield the product as a beige solid, which was dried in vacuo.

6-Chloro-8-methyl-11*H*-indolo[3,2-*c*]quinoline (D2). C2 (0.51 g, 2.05 mmol), $POCl_3$ (20 mL). Yield: 0.40 g, 72%. Anal. Calcd for $C_{16}H_{11}ClN_2 \cdot 0.25C_4H_8O_2$ (M_r = 288.75 g/mol) (%): C, 70.71; H, 4.54; N, 9.70. Found: C, 70.85; H, 4.35; N, 9.85. ^{1}H NMR (DMSO-d_6, δ_H): 12.99 (s, 1H, N11), 8.52 (d, 1H, $^3J(H_{C2})$ = 8.2 Hz, C1), 8.23 (s, 1H, C7), 8.03 (d, 1H, $^3J(H_{C3})$ = 8.2 Hz, C4), 7.77 (dd, 1H, $^3J(H_{C2})$ = 8.2 Hz, $^3J(H_{C4})$ = 8.4 Hz, C3), 7.71 (dd, 1H, $^3J(H_{C1})$ = 8.1 Hz, $^3J(H_{C3})$ = 8.1 Hz, C2), 7.65 (d, 1H, $^3J(H_{C9})$ = 8.4 Hz, C10), 7.38 (d, 1H, $^3J(H_{C10})$ = 8.4 Hz, C9), 2.54 (s, 3H, C8a). ^{13}C{^{1}H} NMR (DMSO-d_6, δ_C): 144.92 (C6), 144.76 (C4a), 142.46 (C11a), 137.54 (C10a), 130.70 (C6b), 129.56 (C3), 128.83 (C4), 127.96 (C9), 126.70 (C2), 122.64 (C1), 121.47 (C8), 121.41 (C7), 117.03 (C11b), 112.32 (C10), 111.62 (C6a), 21.81 (C8a). ESI-MS in methanol (positive): 267 $[(D2)H]^+$, 289 $[(D2)Na]^+$, 555 $[(D2)_2Na]^+$.

6,8-Dichloro-11*H*-indolo[3,2-*c*]quinoline (D3). C3 (0.72 g, 2.66 mmol), $POCl_3$ (20 mL). Yield: 0.66 g, 86%. Anal. Calcd for $C_{15}H_8Cl_2N_2$ (M_r = 287.14 g/mol) (%): C, 62.74; H, 2.81; N, 9.76. Found: C, 62.40; H, 2.86; N, 9.51. ^{1}H NMR (DMSO-d_6, δ_H): 13.26 (s, 1H, N11), 8.51 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 8.34 (s, 1H, C7), 8.04 (d, 1H, $^3J(H_{C3})$ = 8.2 Hz, C4), 7.80 (dd, 1H, $^3J(H_{C2})$ = 7.6 Hz, $^3J(H_{C4})$ = 7.9 Hz, C3), 7.77 (d, 1H, $^3J(H_{C9})$ = 8.5 Hz, C10), 7.73 (dd, 1H, $^3J(H_{C1})$ = 7.9 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2), 7.56 (d, 1H, $^3J(H_{C10})$ = 8.5 Hz, C9). ^{13}C{^{1}H} NMR (DMSO-d_6, δ_C): 145.03 (C4a), 144.71 (C6), 143.19 (C11a), 137.75 (C10a), 130.10 (C3), 128.91 (C4), 127.03 (C2), 126.47 (C9), 126.14 (C8), 122.76 (C1), 122.42 (C6b), 120.76 (C7), 116.89 (C11b), 114.28 (C10), 111.14 (C6a). ESI-MS in methanol (positive): 287 $[(D3)H]^+$, 309 $[(D3)Na]^+$.

8-Bromo-6-chloro-11*H*-indolo[3,2-*c*]quinoline (D4). C4 (0.48 g, 1.55 mmol), $POCl_3$ (20 mL). Yield: 0.05 g, 90%. $C_{15}H_8BrClN_2$, M_r = 331.59 g/mol. ^{1}H NMR (DMSO-d_6, δ_H): 13.28 (s, 1H, N11), 8.52 (d, 1H, $^3J(H_{C2})$ = 8.2 Hz, C1), 8.50 (s, 1H, C7), 8.05 (d, 1H, $^3J(H_{C3})$ = 8.2 Hz, C4), 7.82 (dd, 1H, $^3J(H_{C2})$ = 8.2 Hz, $^3J(H_{C4})$ = 8.2 Hz, C3), 7.76 (dd, 1H, $^3J(H_{C1})$ = 7.9 Hz, $^3J(H_{C3})$ = 8.1 Hz, C2), 7.73 (d, 1H, $^3J(H_{C9})$ = 8.7 Hz, C10), 7.68 (d, 1H, $^3J(H_{C10})$ = 8.7 Hz, C9). ^{13}C{^{1}H} NMR (DMSO-d_6, δ_C): 145.04 (C4a), 144.70 (C6), 143.03 (C11a), 138.04 (C10a), 130.13 (C9), 129.07 (C3), 128.92 (C4), 127.07 (C2), 123.72 (C7), 123.03 (C6b), 122.79 (C1), 116.87 (C11b), 114.72 (C10), 113.98 (C8), 111.01 (C6a). ESI-MS in methanol (positive): 331 $[(D4)H]^+$, 353 $[(D4)Na]^+$.

General Procedure for the Synthesis of 8-Substituted 5,11-Dihydroindolo[3,2-*c*]quinolin-6-ylhydrazines. To 8-substituted 6-chloro-11*H*-indolo[3,2-*c*]quinoline hydrazine hydrate as reagent and solvent was added and the reaction mixture heated at 115 °C for 24 h under argon atmosphere. After cooling to room temperature, the resulting beige precipitate was filtered off, washed with water (2 × 10 mL), ethyl acetate and dried in vacuo.

8-Methyl-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylhydrazine (E2). D2 (0.37 g, 1.4 mmol), hydrazine hydrate (10 mL). Yield: 0.31 g, 86%. Anal. Calcd for $C_{16}H_{14}N_4 \cdot 0.1H_2O$ (M_r = 264.11 g/mol): C, 72.76; H, 5.42; N, 21.21. Found: C, 73.13; H, 5.17; N, 20.91. ^{1}H NMR (DMSO-d_6, δ_H): 12.35 (s, 1H, N11), 8.25 (d, 1H, $^3J(H_{C2})$ = 7.3 Hz, C1), 8.19 (s, 1H, C7), 7.94 (s, 1H, N12), 7.74 (d, 1H, $^3J(H_{C3})$ = 7.0 Hz, C4), 7.56−7.50 (m, 2H, C3, C10), 7.36−7.28 (m, 1H, C2), 7.22 (d, 1H, $^3J(H_{C10})$ = 8.2 Hz, C9), 4.68 (s, 2H, N13), 2.50 (s, 3H, C8a). ESI-MS in methanol (positive): 263 $[(E2)H]^+$.

8-Chloro-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylhydrazine (E3). D3 (0.64 g, 2.2 mmol), hydrazine hydrate (10 mL). Yield: 0.58 g, 92%. Anal. Calcd for $C_{15}H_{11}ClN_4 \cdot 0.1C_4H_8O_2$ (M_r = 291.54 g/mol): C, 63.44; H, 4.08; N, 19.22. Found: C, 63.69; H, 3.74; N, 19.15. ^{1}H NMR (DMSO-d_6, δ_H): 12.66 (s, 1H, N11), 8.49 (bs, 1H, N12), 8.26 (d, 1H, $^3J(H_{C2})$ = 6.3 Hz, C1), 8.20 (s, 1H, C7), 7.75 (d, 1H, $^3J(H_{C3})$ = 6.3 Hz, C4), 7.63 (d, 1H, $^3J(H_{C9})$ = 8.2 Hz, C10), 7.60−7.54 (m, 1H, C3), 7.39 (d, 1H, $^3J(H_{C10})$ = 7.9 Hz, C9), 7.37−7.31 (m, 1H, C2), 4.69 (s, 2H, N13). ESI-MS in methanol (positive): 283 $[(E3)H]^+$.

8-Bromo-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylhydrazine (E4). D4 (1.0 g, 3.0 mmol), hydrazine hydrate (25 mL). Yield: 0.90 g, 86%. $C_{15}H_{11}BrN_4$, M_r = 327.18 g/mol. ^{1}H NMR (DMSO-d_6, δ_H): 12.57 (bs, 1H, N11), 8.60 (bs, 1H), 8.36−8.16 (m, 2H), 7.79−7.70 (m, 1H), 7.64−7.45 (m, 3H), 7.41−7.24 (m, 1H), 4.58 (bs, 2H, N13). ESI-MS in methanol (positive): 327 $[(E4)H]^+$.

General Procedure for the Synthesis of Ligands (HL^{2a-4b}). To a suspension of 8-substituted 5,11-dihydroindolo[3,2-*c*]quinolin-6-ylhydrazine in ethanol (96%, 10 mL) was added 2-formylpyridine or 2-acetylpyridine at 50 °C and the reaction mixture heated at reflux for 24 h, and then cooled to room temperature. The brightly yellow precipitate formed was filtered off and dried in vacuo.

***N*-(8-Methyl-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-methylidene)azine (HL^{2a}). E2** (0.10 g, 0.38 mmol), 2-formylpyridine (40.1 μL, 0.42 mmol). Yield: 0.12 g, 86%. Anal. Calcd for $C_{22}H_{17}N_5$ (M_r = 351.40 g/mol) (%): C, 75.19; H, 4.88; N, 19.93. Found: C, 74.97; H, 4.80; N, 19.60. ^{1}H NMR (DMSO-d_6, δ_H): 12.44 (s, 1H, N11), 10.88 (s, 1H, N5), 8.62 (d, 1H, $^3J(H_{C18})$ = 4.9 Hz, C17), 8.58 (d, 1H, $^3J(H_{C19})$ = 7.9 Hz, C20), 8.52 (s, 1H, C14), 8.25 (s, 1H, C7), 8.13 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 7.92−7.87 (m, 2H, C4, C19), 7.51 (d, 1H, $^3J(H_{C9})$ = 8.4 Hz, C10), 7.49 (dd, 1H, $^3J(H_{C2})$ = 7.7 Hz, $^3J(H_{C4})$ = 7.7 Hz, C3), 7.36 (dd, 1H, $^3J(H_{C17})$ = 7.4 Hz, $^3J(H_{C19})$ = 7.4 Hz, C18), 7.26 (dd, 1H, $^3J(H_{C1})$ = 7.6 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2), 7.20 (d, 1H, $^3J(H_{C10})$ = 8.4 Hz, C9), 2.50 (s, 3H, C8a). ^{13}C{^{1}H} NMR (DMSO-d_6, δ_C): 155.52 (C15), 152.37 (C6), 150.85 (C14), 149.76 (C17), 139.05 (C11a), 137.92 (C4a), 136.97 (C10a), 136.57 (C19), 130.14 (C8), 129.53 (C3), 125.99 (C9), 124.33 (C6b), 123.71 (C18), 122.78 (C7), 122.32 (C1), 122.06 (C2), 121.42 (C20), 117.13 (C4), 113.67 (C11b), 111.69 (C10), 104.79 (C6a), 21.86 (C8a). The chemical shift of methyl group protons 8a was determined by a HSQC experiment, as the δ-value coincides with that of DMSO-d_6 solvent residual signal (see Supporting Information, Figure S1). ESI-MS in methanol (positive): 352 $[(HL^{2a})H]^+$, 374 $[(HL^{2a})Na]^+$. UV−vis (isopropanol), λ_{max} (ε, M^{-1} cm^{-1}): 230 (36900), 266 (27100), 330 (13750), 357 (13300), 410 (18500), 425 (18700).

***N*-(8-Methyl-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-ethylidene)azine (HL^{2b}). E2** (0.16 g, 0.59 mmol), 2-acetylpyridine (73 μL, 0.65 mmol). Yield: 0.18 g, 83%. Anal. Calcd for $C_{23}H_{19}N_5 \cdot H_2O$ (M_r = 383.45 g/mol) (%): C, 72.04; H, 5.52; N, 18.26. Found: C, 71.82; H, 5.31; N, 17.98. ^{1}H NMR (DMSO-d_6, δ_H): 12.37 (s, 1H, N11), 10.66 (s, 1H, N5), 8.71 (d, 1H, $^3J(H_{C19})$ = 8.0 Hz, C20), 8.61 (d, 1H, $^3J(H_{C18})$ = 4.9 Hz, C17), 8.21 (s, 1H, C7), 8.10 (d, 1H, $^3J(H_{C2})$ = 8.0 Hz, C1), 7.86 (d, 1H, $^3J(H_{C3})$ = 7.6 Hz, C4), 7.83 (dd, 1H, $^3J(H_{C18})$ = 7.4 Hz, $^3J(H_{C20})$ = 7.4 Hz, C19), 7.50 (d, 1H, $^3J(H_{C9})$ = 8.2 Hz, C10), 7.45 (dd, 1H, $^3J(H_{C2})$ = 7.6 Hz, $^3J(H_{C4})$ = 7.6 Hz, C3), 7.35 (dd, 1H, $^3J(H_{C19})$ = 7.4 Hz, $^3J(H_{C17})$ = 7.4 Hz, C18), 7.25 (dd, 1H, $^3J(H_{C1})$ = 7.4 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2), 7.20 (d, 1H, $^3J(H_{C10})$ = 8.2 Hz, C9), 2.70 (s, 3H, C21), 2.49 (s, 3H, C8a). ^{13}C{^{1}H} NMR (DMSO-d_6, δ_C): 157.28 (C15), 156.43 (C14), 150.67 (C6), 148.86 (C17), 138.72 (C11a), 137.99 (C4a), 136.98 (C10a), 136.24 (C19), 130.00 (C8), 129.40 (C3), 125.85 (C9), 124.46 (C6b), 123.45 (C18), 122.73 (C7), 122.24 (C1), 121.87

(C2), 121.54 (C20), 117.20 (C4), 113.70 (C11b), 111.68 (C10), 105.59 (C6a), 22.03 (C8a), 13.55 (C21). The chemical shift of methyl group protons 8a was determined by a HSQC experiment, as the δ-value coincides with that of DMSO-d_6 solvent residual signal (see Supporting Information, Figure S2). ESI-MS in methanol (positive): 366 $[(HL^{2b})H]^+$. UV−vis (isopropanol), λ_{max} (ε, M^{-1} cm^{-1}): 230 (39700), 267 (31100), 328 (16800), 354 (16550), 408 (19300).

***N*-(8-Chloro-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-methylidene)azine (HL^{3a}). E3** (0.24 g, 0.84 mmol), 2-formylpyridine (88 μL, 0.92 mmol). Yield: 0.28 g, 90%. Anal. Calcd for $C_{21}H_{14}ClN_5$ (M_r = 371.82 g/mol) (%): C, 67.83; H, 3.80; N, 18.84. Found: C, 67.53; H, 3.64; N, 18.44. ^{1}H NMR (DMSO-d_6, δ_H): 12.75 (s, 1H, N11), 10.94 (s, 1H, N5), 8.63 (d, 1H, $^3J(H_{C18})$ = 4.9 Hz, C17), 8.58 (d, 1H, $^3J(H_{C19})$ = 7.9 Hz, C20), 8.52 (s, 1H, C14), 8.39 (s, 1H, C7), 8.14 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 7.90 (d, 1H, $^3J(H_{C3})$ = 8.2 Hz, C4), 7.89 (dd, 1H, $^3J(H_{C18})$ = 7.7 Hz, $^3J(H_{C20})$ = 7.7 Hz, C19), 7.64 (d, 1H, $^3J(H_{C9})$ = 8.7 Hz, C10), 7.53 (dd, 1H, $^3J(H_{C2})$ = 7.9 Hz, $^3J(H_{C4})$ = 7.7 Hz, C3), 7.43−7.35 (m, 2H, C9, C18), 7.28 (dd, 1H, $^3J(H_{C1})$ = 7.6 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 155.35 (C15), 151.96 (C6), 151.49 (C14), 149.79 (C17), 140.19 (C11a), 138.30 (C4a), 137.20 (C10a), 136.60 (C19), 130.15 (C3), 125.82 (C8), 125.19 (C6b), 124.41 (C9), 123.87 (C18), 122.59 (C1), 122.24 (C2), 121.86 (C7), 121.52 (C20), 117.29 (C4), 113.66 (C10), 113.29 (C11b), 104.60 (C6a). ESI-MS in methanol (positive): 372 $[(HL^{3a})H]^+$. UV−vis (isopropanol), λ_{max} (ε, M^{-1} cm^{-1}): 233 (43350), 267 (32400), 304 (16400), 321 (13700), 363 (17400), 408 (19600).

***N*-(8-Chloro-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-ethylidene)azine (HL^{3b}). E3** (0.24 g, 0.85 mmol), 2-acetylpyridine (106 μL, 0.95 mmol). Yield: 0.31 g, 94%. Anal. Calcd for $C_{22}H_{16}ClN_5 \cdot H_2O$ (M_r = 403.86 g/mol) (%): C, 65.43; H, 4.49; N, 17.34. Found: C, 65.46; H, 4.38; N, 17.07. ^{1}H NMR (DMSO-d_6, δ_H): 12.69 (s, 1H, N11), 10.73 (s, 1H, N5), 8.71 (d, 1H, $^3J(H_{C19})$ = 7.9 Hz, C20), 8.62 (d, 1H, $^3J(H_{C18})$ = 4.9 Hz, C17), 8.36 (s, 1H, C7), 8.11 (d, 1H, $^3J(H_{C2})$ = 7.3 Hz, C1), 7.88 (d, 1H, $^3J(H_{C3})$ = 7.9 Hz, C4), 7.89 (dd, 1H, $^3J(H_{C18})$ = 7.6 Hz, $^3J(H_{C20})$ = 7.6 Hz, C19), 7.63 (d, 1H, $^3J(H_{C9})$ = 8.5 Hz, C10), 7.50 (dd, 1H, $^3J(H_{C2})$ = 7.6 Hz, $^3J(H_{C4})$ = 7.9 Hz, C3), 7.41−7.34 (m, 2H, C9, C18), 7.25 (dd, 1H, $^3J(H_{C1})$=7.6 Hz, $^3J(H_{C3})$ = 7.6 Hz, C2), 2.68 (s, 3H, C21). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 157.12 (C6), 156.93 (C15), 150.24 (C14), 148.88 (C17), 139.89 (C11a), 138.37 (C4a), 137.20 (C10a), 136.28 (C19), 130.02 (C3), 125.73 (C8), 125.31 (C6b), 124.25 (C9), 123.60 (C18), 122.51 (C1), 122.05 (C2), 121.81 (C7), 121.62 (C20), 117.36 (C4), 113.64 (C10), 113.32 (C11b), 105.42 (C6a), 13.51 (C21). ESI-MS in methanol (positive): 386 $[(HL^{3b})H]^+$. UV−vis (isopropanol), λ_{max} (ε, M^{-1} cm^{-1}): 231 (44200), 265 (34650), 309 (15900), 321 (15200), 360 (18650), 406 (19450).

***N*-(8-Bromo-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-methylidene)azine (HL^{4a}). E4** (0.26 g, 0.77 mmol), 2-formylpyridine (82 μL, 0.85 mmol). Yield: 0.25 g, 78%. Anal. Calcd for $C_{21}H_{14}BrN_5 \cdot 0.25H_2O$ (M_r = 420.78 g/mol) (%): C, 59.94; H, 3.47; N, 16.64. Found: C, 59.98; H, 3.32; N, 16.44. ^{1}H NMR (DMSO-d_6, δ_H): 12.77 (s, 1H, N11), 10.94 (s, 1H, N5), 8.64 (d, 1H, $^3J(H_{C18})$ = 4.7 Hz, C17), 8.58 (d, 1H, $^3J(H_{C19})$ = 7.7 Hz, C20), 8.54 (s, 1H, C7), 8.51 (s, 1H, C14), 8.14 (d, 1H, $^3J(H_{C2})$ = 7.4 Hz, C1), 7.94−7.85 (m, 2H, C4, C19), 7.59 (d, 1H, $^3J(H_{C9})$ = 8.5 Hz, C10), 7.53 (dd, 1H, $^3J(H_{C2})$ = 7.7 Hz, $^3J(H_{C4})$ = 7.7 Hz, C3), 7.50 (d, 1H, $^3J(H_{C10})$ = 8.5 Hz, C9), 7.37 (dd, 1H, $^3J(H_{C17})$ = 6.9 Hz, $^3J(H_{C19})$ = 7.1 Hz, C18), 7.28 (dd, 1H, $^3J(H_{C1})$ = 7.3 Hz, $^3J(H_{C3})$ = 7.3 Hz, C2). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 155.31 (C15), 151.95 (C6), 151.47 (C14), 149.80 (C17), 140.02 (C11a), 138.29 (C4a), 137.48 (C10a), 136.63 (C19), 130.15 (C3), 126.99 (C9), 125.77 (C6b), 124.87 (C7), 123.87 (C18), 122.60 (C1), 122.27 (C2), 121.53 (C20), 117.29 (C4), 114.09 (C10), 113.75 (C8), 113.24 (C11b), 104.43 (C6a). ESI-MS in methanol (positive): 416 $[(HL^{4a})H]^+$, 438 $[(HL^{4a})Na]^+$. UV−vis (isopropanol), λ_{max} (ε, M^{-1} cm^{-1}): 233 (38700), 267 (29000), 303 (13350), 321 (12100), 361 (15150), 410 (18500).

***N*-(8-Bromo-5,11-dihydroindolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-ethylidene)azine (HL^{4b}). E4** (0.22 g, 0.52 mmol), 2-acetylpyridine (85 μL, 0.76 mmol). Yield: 0.19 g, 84%. Anal. Calcd for $C_{22}H_{16}BrN_5 \cdot H_2O$ (M_r = 448.32 g/mol) (%): C, 58.94; H, 4.05; N, 15.62. Found: C, 58.81; H, 4.05; N, 15.38. ^{1}H NMR (DMSO-d_6, δ_H): 12.70 (s, 1H, N11), 10.74 (s, 1H, N5), 8.72 (d, 1H, $^3J(H_{C19})$ = 8.0 Hz, C20), 8.63 (d, 1H, $^3J(H_{C18})$ = 4.7 Hz, C17), 8.52 (s, 1H, C7), 8.12 (d, 1H, $^3J(H_{C2})$ = 8.0 Hz, C1), 7.89 (d, 1H, $^3J(H_{C3})$ = 8.0 Hz, C4), 7.85 (dd, 1H, $^3J(H_{C18})$ = 7.7 Hz, $^3J(H_{C20})$ = 7.7 Hz, C19), 7.59 (d, 1H, $^3J(H_{C9})$ = 8.5 Hz, C10), 7.54−7.49 (m, 2H, C3, C9), 7.37 (dd, 1H, $^3J(H_{C17})$ = 7.3 Hz, $^3J(H_{C19})$ = 7.3 Hz, C18), 7.26 (dd, 1H, $^3J(H_{C1})$ = 7.5 Hz, $^3J(H_{C3})$ = 7.5 Hz, C2), 2.68 (s, 3H, C21). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 157.13 (C14), 157.00 (C15), 150.24 (C6), 148.89 (C17), 139.72 (C11a), 138.38 (C4a), 137.47 (C10a), 136.29 (C19), 130.05 (C3), 126.82 (C9), 125.94 (C6b), 124.91 (C7), 123.62 (C18), 122.54 (C1), 122.07 (C2), 121.64 (C20), 117.38 (C4), 114.10 (C10), 113.70 (C8), 113.29 (C11b), 105.30 (C6a), 13.48 (C21). ESI-MS in methanol (positive): 430 $[(HL^{4a})H]^+$, 452 $[(HL^{4a})Na]^+$. UV−vis (isopropanol), λ_{max} (ε, M^{-1} cm^{-1}): 231 (40400), 265 (32500), 310 (14500), 322 (13950), 360 (17450), 407 (18000).

Synthesis of Indolotriazoloquinoline L^7. HL^{2a} (19 mg, 0.05 mmol) was dissolved in hot ethanol (96%, 15 mL). The solution was filtered, concentrated to two-thirds of the initial volume and left to stand at −20 °C for 96 h. The yellow precipitate formed was filtered off and dried in vacuo. Yield: 15 mg, 80%. $C_{22}H_{15}N_5$, M_r = 349.39 g/mol. ^{1}H NMR (DMSO-d_6, δ_H): 12.67 (s, 1H, N11), 8.85 (d, 1H, $^3J(H_{C18})$ = 4.7 Hz, C17), 8.49 (d, 1H, $^3J(H_{C2})$ = 7.9 Hz, C1), 8.20−8.14 (m, 2H, C8, C19), 8.03 (d, 1H, $^3J(H_{C19})$ = 7.7 Hz, C20), 7.71 (dd, 1H, $^3J(H_{C17})$ = 7.9 Hz, $^3J(H_{C19})$ = 7.9 Hz, C18), 7.65 (dd, 1H, $^3J(H_{C1})$ = 7.7 Hz, $^3J(H_{C3})$ = 7.7 Hz, C2), 7.62 (d, 1H, $^3J(H_{C9})$ = 8.4 Hz, C10), 7.53 (d, 1H, $^3J(H_{C3})$ = 8.4 Hz, C4), 7.46 (dd, 1H, $^3J(H_{C2})$ = 7.9 Hz, $^3J(H_{C4})$ = 7.9 Hz, C3), 7.31 (d, 1H, $^3J(H_{C10})$ = 8.4 Hz, C9), 2.57 (s, 3H, C8a). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ_C): 150.29 (C17), 149.59 (C15), 148.03 (C14), 147.61 (C6), 138.49 (C19), 137.09 (C10a), 134.55 (C11a), 130.64 (C8), 130.56 (C4a), 128.27 (C3), 126.88 (C9), 126.77 (C2), 126.44 (C20), 125.74 (C18), 123.69 (C1), 122.82 (C6b), 121.22 (C7), 118.92 (C4), 117.07 (C11b), 112.36 (C10), 101.57 (C6a), 21.73 (C8a).

General Procedure for the Synthesis of Complexes 1a−4b. To a solution of the corresponding ligand in isopropanol, a solution of $CuCl_2 \cdot 2H_2O$ in methanol (1 mL) was added at 60 °C. The reaction mixture, which turned dark-red, was heated at reflux for further 15 min. The reaction mixture was cooled to room temperature and the dark-red solid filtered off, washed with isopropanol, and dried in vacuo.

***N*-(11*H*-Indolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-methylidene)azine-dichlorido-copper(II) (1a). HL^{1a}** (0.10 g, 0.30 mmol), $CuCl_2 \cdot 2H_2O$ (0.06 g, 0.35 mmol), isopropanol (70 mL). Yield: 0.115 g, 82%. Anal. Calcd for $C_{21}H_{15}Cl_2CuN_5 \cdot 0.5CH_3OH$ (M_r = 487.85 g/mol) (%): C, 52.93; H, 3.51; N, 14.36. Found: C, 52.98; H, 3.25; N, 14.33. ESI-MS in methanol (positive): 399 $[CuL^{1a}]^+$, 435 $[Cu(HL^{1a})Cl]^+$, 736 $[CuL^{1a}(HL^{1a})]^+$. ATR-IR, selected bands, cm^{-1}: 3090, 1581, 1527, 1224, 912, 741. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 238 (38100), 249 (34600), 257 (33400), 298 (18900), 319 (17500), 333 (15100), 461 (15000).

***N*-(11*H*-Indolo[3,2-*c*]quinolin-6-ylidene)-*N'*-(1-pyridin-2-yl-ethylidene)azine-dichlorido-copper(II) (1b). HL^{1b}** (0.10 g, 0.28 mmol), $CuCl_2 \cdot 2H_2O$ (0.06 g, 0.35 mmol), isopropanol (70 mL). Yield: 0.125 g, 90%. Anal. Calcd for $C_{22}H_{17}Cl_2CuN_5$ (M_r = 485.86 g/mol) (%): C, 54.39; H, 3.53; N, 14.41. Found: C, 54.16; H, 3.42; N, 14.17. ESI-MS in methanol (positive): 413 $[CuL^{1b}]^+$, 449 $[Cu(HL^{1b})Cl]^+$. ATR-IR, selected bands, cm^{-1}: 3029, 1584, 1533, 1205, 750. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 237 (41450), 256 (33850), 299 (19850), 318 (19300), 333 (16900), 453 (17200).

***N*-(8-Methyl-11*H*-indolo[3,2-*c*]quinolin-6-ylidene)-*N*′-(1-pyridin-2-yl-methylidene)azine-dichlorido-copper(II) (2a). HL^{2a}** (0.02 g, 0.06 mmol), $CuCl_2 \cdot 2H_2O$ (0.01 g, 0.07 mmol), isopropanol (20 mL). Yield: 0.026 g, 86%. Anal. Calcd for $C_{22}H_{17}Cl_2CuN_5 \cdot 0.5H_2O$ (M_r = 494.86 g/mol) (%): C, 53.40; H, 3.67; N, 14.15. Found: C, 53.79; H, 3.53; N, 13.90. ESI-MS in methanol (positive): 413 $[CuL^{2a}]^+$, 449 $[Cu(HL^{2a})Cl]^+$. ATR-IR, selected bands, cm^{-1}: 3214, 1585, 1536, 1230, 756. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 237 (39000), 253 (35300), 302 (18300), 323 (17900), 336 (16100), 462 (15250).

***N*-(8-Methyl-11*H*-indolo[3,2-*c*]quinolin-6-ylidene)-*N*′-(1-pyridin-2-yl-ethylidene)azine-dichlorido-copper(II) (2b). HL^{2b}** (0.06 g, 0.15 mmol), $CuCl_2 \cdot 2H_2O$ (0.03 g, 0.18 mmol), isopropanol (70 mL). Yield: 0.052 g, 94%. Anal. Calcd for $C_{23}H_{19}Cl_2CuN_5 \cdot 0.5H_2O$ (M_r = 508.89 g/mol) (%): C, 54.28; H, 3.96; N, 13.76. Found: C, 54.23; H, 3.75; N, 13.43. ESI-MS in methanol (positive): 427 $[CuL^{2b}]^+$, 463 $[Cu(HL^{2b})Cl]^+$. ATR-IR, selected bands, cm^{-1}: 3141, 1585, 1523, 1188, 768. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 237 (42000), 255 (35500), 300 (19700), 320 (19600), 334 (17500), 454 (16300).

***N*-(8-Chloro-11*H*-indolo[3,2-*c*]quinolin-6-ylidene)-*N*′-(1-pyridin-2-yl-methylidene)azine-dichlorido-copper(II) (3a). HL^{3a}** (0.07 g, 0.19 mmol), $CuCl_2 \cdot 2H_2O$ (0.04 g, 0.22 mmol), isopropanol (70 mL). Yield: 0.077 g, 83%. Anal. Calcd for $C_{21}H_{14}Cl_3CuN_5 \cdot 0.2C_3H_8O$ (M_r = 518.29 g/mol) (%): C, 50.05; H, 3.03; N, 13.51. Found: C, 49.71; H, 2.76; N, 13.16. ESI-MS in methanol (positive): 372 $[(HL^{3a})H]^+$, 433 $[CuL^{3a}]^+$, 469 $[Cu(HL^{3a})Cl]^+$, 804 $[CuL^{3a}(HL^{3a})]^+$. ATR-IR, selected bands, cm^{-1}: 3271, 3203, 3045, 1583, 1230, 755. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 232 (52300), 260 (31200), 299 (17150), 320 (15200), 336 (13900), 465 (9700).

***N*-(8-Chloro-11*H*-indolo[3,2-*c*]quinolin-6-ylidene)-*N*′-(1-pyridin-2-yl-ethylidene)azine-dichlorido-copper(II) (3b). HL^{3b}** (0.07 g, 0.18 mmol), $CuCl_2 \cdot 2H_2O$ (0.04 g, 0.21 mmol), isopropanol (70 mL). Yield: 0.078 g, 86%. Anal. Calcd for $C_{22}H_{16}Cl_3CuN_5 \cdot 0.2C_3H_8O$ (M_r = 532.32 g/mol) (%): C, 50.99; H, 3.33; N, 13.16. Found: C, 50.65; H, 3.08; N, 12.93. ESI-MS in methanol (positive): 447 $[CuL^{3b}]^+$, 483 $[Cu(HL^{3b})Cl]^+$, 832 $[CuL^{3b}(HL^{3b})]^+$. ATR-IR, selected bands, cm^{-1}: 3144, 2659, 1579, 1527, 1210, 933, 763. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 235 (54800), 260 (33000), 303 (20000), 318 (19400), 333 (17700), 453 (15800). Single crystals of the composition **3b**·3DMF, suitable for an X-ray diffraction study, were obtained by slow diffusion of diethyl ether into a solution of the complex in DMF.

***N*-(8-Bromo-11*H*-indolo[3,2-*c*]quinolin-6-ylidene)-*N*′-(1-pyridin-2-yl-methylidene)azine-dichlorido-copper(II) (4a). HL^{4a}** (0.09 g, 0.22 mmol), $CuCl_2 \cdot 2H_2O$ (0.04 g, 0.26 mmol), isopropanol (80 mL). Yield: 0.078 g, 85%. Anal. Calcd for $C_{21}H_{14}BrCl_2CuN_5 \cdot 0.25H_2O$ (M_r = 555.23 g/mol) (%): C, 45.42; H, 2.63; N, 12.61. Found: C, 45.66; H, 2.52; N, 12.21. ESI-MS in methanol (positive): 477 $[CuL^{4a}]^+$, 513 $[Cu(HL^{4a})Cl]^+$, 892 $[CuL^{4a}(HL^{4a})]^+$. ATR-IR, selected bands, cm^{-1}: 3129, 1580, 1528, 1368, 1220, 761. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 238 (47300), 303 (17500), 320 (16800), 336 (15600), 461 (14100).

***N*-(8-Bromo-11*H*-indolo[3,2-*c*]quinolin-6-ylidene)-*N*′-(1-pyridin-2-yl-ethylidene)azine-dichlorido-copper(II) (4b). HL^{4b}** (0.09 g, 0.21 mmol), $CuCl_2 \cdot 2H_2O$ (0.05 g, 0.28 mmol), isopropanol (80 mL). Yield: 0.082 g, 91%. Anal. Calcd for $C_{22}H_{16}BrCl_2CuN_5$ (M_r = 564.75 g/mol) (%): C, 46.79; H, 2.86; N, 12.40. Found: C, 46.96; H, 2.81; N, 12.11. ESI-MS in methanol (positive): 491 $[CuL^{4b}]^+$, 527 $[Cu(HL^{4b})Cl]^+$. ATR-IR, selected bands, cm^{-1}: 3140, 2831, 1575, 1526, 1212, 757. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 237 (47700), 304 (17650), 319 (16850), 333 (15600), 456 (13800). Single crystals of X-ray diffraction quality of the composition **4b**·2.4DMF were obtained by slow diffusion of diethyl ether into a solution of the complex in DMF.

***N*-(7,12-Dihydroindolo[3,2-*d*][1]benzazepin-6-yliden)-*N*′-(1-pyridin-2-yl-ethylidene)azine-dichlorido-copper(II) (5b).** A mixture of 7,12-dihydroindolo[3,2-*d*][1]benzazepine-6(5*H*)-thione (0.31 g, 1.2 mmol) and 2-acetylpyridine hydrazone (0.20 g, 1.5 mmol) in dry ethanol (25 mL) was refluxed for 96 h. The yellow precipitate formed was filtered off, washed with ethanol, and dried in vacuo. The ^{1}H NMR spectrum confirmed the formation of the ligand and the presence of minor amounts of side products. The mother liquor allowed to stand at −20 °C for 2 days generated X-ray diffraction quality single crystals of **HL^{5b}**. To a refluxed solution of the crude ligand (0.11 g) in methanol (14 mL) was added copper(II) chloride dihydrate (0.052 g) in methanol (1 mL). The resulting brown solution was filtered hot and allowed to stand at room temperature for 48 h. The crystals formed were filtered off, washed with cold methanol, and dried in vacuo. Yield: 0.07 g. Anal. Calcd for $C_{23}H_{19}Cl_2CuN_5 \cdot 0.5CH_3OH$ (M_r = 515.90 g/mol) (%): C, 54.71; H, 4.10; N, 13.57. Found: C, 54.46; H, 3.90; N, 13.33. ESI-MS in methanol (positive): 427 $[CuL^{5b}]^+$. UV−vis (1% v/v DMSO/H_2O), λ_{max} (ε, M^{-1} cm^{-1}): 239 (31400), 299 (20400), 422 (8800). Single crystals of the composition **5b**·0.5CH_3OH suitable for an X-ray diffraction study were picked directly from the reaction vessel.

Physical Measurements. ^{1}H and ^{13}C, NOE difference and two-dimensional ^{1}H-^{1}H COSY, ^{1}H-^{1}H TOCSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC NMR spectra were recorded on a Bruker Avance III spectrometer (Ultrashield Magnet) in DMSO-d_6 or $CDCl_3$ at 25 °C using standard pulse programs at 500.10 (^{1}H) and 125.76 (^{13}C) MHz. ^{1}H and ^{13}C chemical shifts are quoted relative to the residual solvent signals. Elemental analyses were carried out at the Microanalytical Service of the Faculty of Chemistry of the University of Vienna. Electrospray ionization mass spectrometry was carried out using a Bruker Esquire 3000 instrument (Bruker Daltonic, Bremen, Germany) on samples dissolved in methanol. UV−vis spectra were recorded on a Perkin-Elmer Lambda 650 spectrophotometer, using samples dissolved in isopropanol for **HL^{1a-4b}** and 1% (v/v) DMSO-water mixture for **1a**−**5b**. The aqueous solution behavior of complexes **1a**, **1b**, **4a**, **4b**, and **5b** was monitored on a Perkin-Elmer 12 UV−vis spectrophotometer in a 1% (v/v) DMSO/water mixture at room temperature over 24 h. IR spectra were measured with a Bruker Vertex 70 Fourier transform IR spectrometer by means of the attenuated total reflection (ATR) technique. Magnetic susceptibility measurements were conducted in solution on a Bruker Avance III spectrometer (Ultrashield Magnet) in DMSO-d_6 at 298 K using the Evans method.[41−43] The μ_{eff} calculated for a 0.018 M $Cu(acac)_2$ solution in DMSO-d_6 was 1.75 μ_B.

Crystallographic Structure Determination. X-ray diffraction measurements were performed on a Bruker X8 APEXII CCD diffractometer. Single crystals were positioned at 35 mm from the detector, and 1241, 2557, 1226, and 2619 frames were measured, each for 60, 80, 90, and 20 s over 1° scan width for **3b**·3DMF, **4b**·2.4DMF, **HL^{5b}**, and **5b**·0.5CH_3OH, correspondingly. The data were processed using the SAINT software.[36] Crystal data, data collection parameters, and structure refinement details are given in Table 1. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-H atoms

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Table 1. Crystal Data and Details of Data Collection for **3b**·3DMF, **4b**·2.4DMF, $\mathbf{HL^{5b}}$, and **5b**·0.5CH_3OH

	3b·3DMF	**4b**·2.4DMF	$\mathbf{HL^{5b}}$	**5b**·0.5CH_3OH
empirical formula	$C_{31}H_{37}Cl_3CuN_8O_3$	$C_{29.2}H_{32.8}BrCl_2CuN_{7.4}O_{2.4}$	$C_{23}H_{19}N_5$	$C_{23.5}H_{21}Cl_2CuN_5O_{0.5}$
Fw	739.58	740.18	365.43	515.89
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a [Å]	17.5197(16)	17.439(2)	10.6889(7)	12.6541(4)
b [Å]	14.2545(12)	14.3150(17)	13.6296(11)	13.9929(5)
c [Å]	14.4463(11)	14.5007(18)	12.8100(9)	13.3138(4)
α [deg]				
β [deg]	113.551(4)	113.292(5)	107.747(4)	107.041(2)
γ [deg]				
V [Å^3]	3307.2(5)	3324.9(7)	1777.4(2)	2253.94(13)
Z	4	4	4	4
λ [Å]	0.71073	0.71073	0.71073	0.71073
ρ_{calcd} [g cm^{-3}]	1.485	1.479	1.366	1.520
crystal size [mm^3]	0.25 × 0.25 × 0.01	0.40 × 0.15 × 0.01	0.14 × 0.09 × 0.02	0.20 × 0.12 × 0.07
T [K]	100(2)	100(2)	100(2)	100(2)
μ [mm^{-1}]	0.949	2.059	0.084	1.230
R_1[a]	0.0758	0.0865	0.0572	0.0327
wR_2[b]	0.2069	0.2404	0.1308	0.0990
GOF[c]	1.017	1.092	0.931	1.024

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = \{\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2\}^{1/2}$. [c] GOF = $\{\sum[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined.

were refined with anisotropic displacement parameters with exception of those of co-crystallized solvent molecules in **3b**·3DMF, **4b**·2.4DMF, and **5**·0.5CH_3OH. H atoms were inserted in calculated positions and refined with a riding model. The disorder of solvent molecules in **3b**·3DMF was resolved with constrained isotropic displacement parameters and restrained bond distances using SADI instructions of SHELX97. The following software programs were used: structure solution, SHELXS-97;[37] refinement, SHELXL-97;[38] molecular diagrams, ORTEP;[39] computer, Pentium IV.

Cell Lines and Cell Culture Conditions. For cytotoxicity determination, three different human cancer cell lines were used: A549 (non-small cell lung cancer) and SW480 (colon carcinoma) (both kindly provided by Brigitte Marian, Institute of Cancer Research, Department of Medicine I, Medical University Vienna, Austria) as well as CH1 (ovarian carcinoma) (kindly provided by Lloyd R. Kelland, CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, U.K.). Cells were grown as adherent monolayer cultures in 75 cm^2 culture flasks (Iwaki/Asahi Technoglass) in Minimal Essential Medium supplemented with 10% heat-inactivated fetal bovine serum, 1 mM sodium pyruvate, 1% non essential amino acids (100×) and 2 mM L-glutamine but without antibiotics at 37 °C under a moist atmosphere containing 5% CO_2 and 95% air. All cell culture media and reagents were purchased from Sigma-Aldrich Austria.

Cytotoxicity Assay. Cytotoxicity was determined by the colorimetric MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide). For this assay, cells were harvested by trypsinization and seeded into 96-well plates in volumes of 100 μL/well. Depending on the cell line, different cell densities were used to ensure exponential growth of the untreated controls during the experiment: 1.5×10^3 cells/well (CH1), 2.5×10^3 cells/well (SW480), 4.0×10^3 cells/well (A549). In the first 24 h the cells were allowed to settle and resume exponential growth. Then the test compounds were dissolved in DMSO, mixed with medium to a maximum DMSO concentration of 0.5% v/v, serially diluted and added to the plates in volumes of 100 μL/well. After continuous exposure for 96 h (in the incubator at 37 °C and under 5% CO_2), the medium was replaced by 100 μL/well RPMI 1640 medium (supplemented with 10% heat-inactivated fetal bovine serum and 2 mM L-glutamine) and 20 μL/well MTT solution (MTT reagent in phosphate-buffered saline, 5 mg/mL), and plates were incubated for further 4 h. Then the medium/MTT mixture was removed and the formed formazan product was dissolved in DMSO (150 μL/well). Optical densities at 550 nm (and at a reference wavelength of 690 nm) were measured with a microplate reader (Tecan Spectra Classic). The quantity of vital cells was expressed as a percentage of untreated controls, and 50% inhibitory concentrations (IC_{50}) were calculated from the concentration−effect curves by interpolation. Every test was repeated in at least three independent experiments, each consisting of three replicates per concentration level.

Results and Discussion

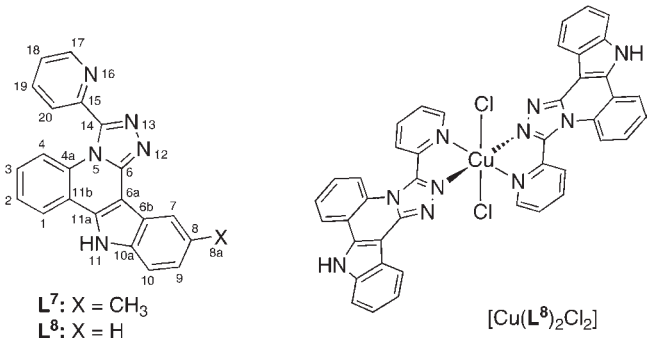
Syntheses of Ligands and Copper(II) Complexes. The syntheses of modified indoloquinoline ligands and their copper(II) complexes were performed as shown in Scheme 1. Efforts by us were focused on the synthesis of potentially tridentate ligands, taking into account our recent experience with bi- and tridentate paullone ligands and their copper(II) complexes. The copper(II) complexes with bidentate paullones were found to dissociate easily in an aqueous DMSO solution, while those of tridentate paullones remained intact over 20 h.[18]

The 8-substituted 5,11-dihydroindolo[3,2-*c*]quinolin-6-ones (**C1**−**C4**) were synthesized from isatin and the corresponding benzylamines **B1**−**B4** via the mechanism described by Bergman et al.[32] in moderate to good yields (56−80%). It should be noted that the use of dihydrochlorides of **B2**−**B4** as starting materials leads in each case to the formation of an unidentified side product, which can not be separated from the desired indoloquinoline. Reaction of **C1**−**C4** with $POCl_3$ provided the 8-substituted 6-chloro-11*H*-indolo[3,2-*c*]quinolines (**D1**[35]−**D4**) in good to excellent yields (72−97%). Treatment of these compounds with hydrazine hydrate yielded the hydrazine derivatives **E1**−**E4** in very good yields (86−92%).

The potentially tridentate Schiff bases $\mathbf{HL^{1a}}$−$\mathbf{HL^{4b}}$ were obtained by condensation reaction of the hydrazines (**E1**−**E4**) with 2-formylpyridine ($\mathbf{HL^{1a}}$, $\mathbf{HL^{2a}}$, $\mathbf{HL^{3a}}$, and $\mathbf{HL^{4a}}$) and 2-acetylpyridine ($\mathbf{HL^{1b}}$, $\mathbf{HL^{2b}}$, $\mathbf{HL^{3b}}$, $\mathbf{HL^{4b}}$), respectively, in good to excellent yields.

Attempts to recrystallize $\mathbf{HL^{2a}}$ from ethanol (96%) in the presence of air oxygen resulted in formation of

Chart 2. Structures of the Ligand $\mathbf{L}^7$ and Copper(II) Complex $[Cu(\mathbf{L}^8)_2Cl_2]$ with a Relevant Atom Numbering Scheme



indolotriazoloquinoline $\mathbf{L}^7$ (Chart 2). A similar transformation was discovered for $\mathbf{HL}^{1a}$ coordinated to copper(II). Crystallization of $[Cu(\mathbf{HL}^{1a})Cl_2]$ (**1a**) from DMSO at room temperature over 3 weeks afforded a new complex of the composition $[Cu(\mathbf{L}^8)_2Cl_2]$ (Chart 2). The structure of this compound was established by X-ray diffraction (Supporting Information, Figure S4), although the collected data set was generally rather poor.

Cyclization to a triazole ring with formation of chelating ligands $\mathbf{L}^7$ and $\mathbf{L}^8$ presumably occurs via nucleophilic attack by a secondary amino group $=N^5H$ at the imino carbon atom C^{14} of the neighboring Schiff base forming C=N bond in $\mathbf{HL}^{2a}$ and $\mathbf{HL}^{1a}$, respectively, accompanied by 2 electron oxidation coupled with a loss of two protons. It should be also noted that the synthesis of some indolotriazolobenzazepines, which, however, are not suitable for chelating metal ions, is well-documented in the literature.[40] In contrast, we did not observe cyclization with triazole ring formation in the case of $\mathbf{HL}^{6a}$ (Chart 2), indicating its lower reactivity compared to related indoloquinolines.

Complexes **1a**−**4b** were obtained in good to excellent yields (82−94%), as shown in Scheme 1, by reacting the corresponding ligands $\mathbf{HL}^{1a-4b}$ in hot isopropanol with copper(II) chloride dihydrate in methanol. The new complex **5b** and previously reported complexes **6a** and **6b** were prepared analogously starting from $\mathbf{HL}^{5b}$, $\mathbf{HL}^{6a}$, and $\mathbf{HL}^{6b}$, and copper(II) chloride dihydrate in methanol.[18] The modified paullone $\mathbf{HL}^{5b}$ resulted from reaction of 7,12-dihydroindolo[3,2-*d*][1]benzazepine-6(5*H*)-thione with 2-acetylpyrdine hydrazone in dry boiling ethanol. The synthesis of $\mathbf{HL}^{6a}$ and $\mathbf{HL}^{6b}$ was realized in two steps. First, 9-bromo-7,12-dihydroindolo[3,2-*d*][1]benzazepine-6(5*H*)-thione was reacted with hydrazine hydrate in dry ethanol, yielding 9-bromo-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6-ylhydrazine. This species was further condensed with 2-formylpyridine or 2-acetylpyridine, affording $\mathbf{HL}^{6a}$ and $\mathbf{HL}^{6b}$, correspondingly.

Characterization of Ligands and Copper(II) Complexes. Analytical data of the ligands and complexes are in agreement with their formulations. The ^1H and ^{13}C NMR spectral data of the ligands along with their assignments are given in the Experimental Section. All ligands adopt a configuration with an exocyclic $C^6=N^{12}$ double bond, which could be confirmed by the presence of a proton at N^5 in the ^1H NMR spectra and the chemical shifts of C^6 in the ^{13}C NMR spectra.

Formation of copper(II) complexes was confirmed by ESI mass spectrometry and magnetic susceptibility measurements in solution. The spectra of complexes in methanol showed peaks with *m*/*z* 399 (**1a**), 413 (**1b**), 413 (**2a**), 427 (**2b**), 433 (**3a**), 447 (**3b**), 477 (**4a**), 491 (**4b**) and 427 (**5**), which were attributed to $[CuL]^+$. In addition peaks with *m*/*z* 435 (**1a**), 449 (**1b**), 449 (**2a**), 463 (**2b**), 469 (**3a**), 483 (**3b**), 513 (**4a**), and 527 (**4b**) were assigned to $[Cu(HL)Cl]^+$. In some cases, peaks with high *m*/*z* values of 736 (**1a**), 804 (**3a**), 832 (**3b**), and 892 (**4a**) were attributed to the formation of $[CuL(HL)]^+$ ions in the mass spectrometer.

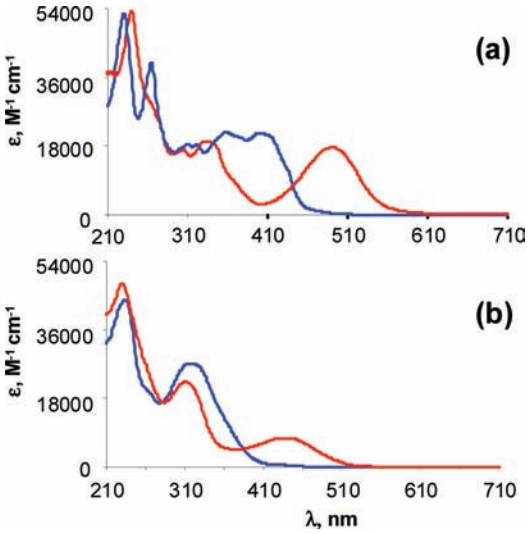


Figure 1. UV−vis spectra of (a) $\mathbf{HL}^{4b}$ (blue) and **4b** (red), compared with (b) $\mathbf{HL}^{6b}$ (blue) and **6b** in methanol.

Magnetic susceptibility measurements were carried out in DMSO-d_6 at 298 K exemplarily for complexes **1a** and **4b** using the Evans method.[41,42] The calculated effective magnetic moments of 1.76 and 1.75 μ_B, respectively, are in accord with the d^9 electronic configuration of copper(II) with $S = 1/2$.

UV−vis spectra of complexes **4b**, **6b** and their corresponding ligands $\mathbf{HL}^{4b}$ and $\mathbf{HL}^{6b}$ in methanol are shown in Figure 1. The spectrum of the heteroaromatic indoloquinoline-based ligand $\mathbf{HL}^{4b}$ differs strongly from that of the paullone ligand $\mathbf{HL}^{6b}$, in which the extended π system is disrupted by methylene group carbon atom C7, and as a result the ligand as a whole is non-planar. The light absorption by $\mathbf{HL}^{4b}$ is extended to the visible region, with strong bands between 360 and 430 nm.

Coordination of ligands $\mathbf{HL}^{4b}$ and $\mathbf{HL}^{6b}$ to copper(II) via the pyridine nitrogen atom, the hydrazine nitrogen and the pyridine ring nitrogen atom or azepine nitrogen atom, correspondingly, alters significantly the conjugated π systems in both ligands, resulting in significantly different electronic absorption spectra. The orange solution of **4b** and the yellow solution of **6b** show significant absorption in the visible region, namely, a broad charge-transfer band with a maximum at 490 and 420 nm, respectively.

Crystal Structures. The molecular structures of copper(II) complexes **3b** and **4b** are shown in Figure 2. Selected bond distances (Å) and bond angles (deg) are given in the legend to the figure. Both complexes (**3b** and **4b**) crystallized in the monoclinic space group $P2_1/c$ with 3 and 2.4 molecules of dimethylformamide, correspondingly, in

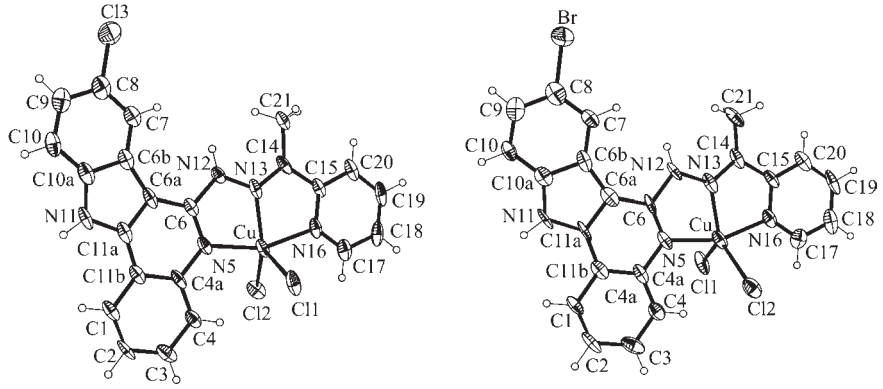


Figure 2. ORTEP plot of the molecules of **3b** (left) and **4b** (right) with thermal ellipsoids drawn at the 50% probability level. Selected bond distances (Å) and bond angles (deg) in **3b**: Cu−Cl1 2.4304(18), Cu−Cl2 2.3045(19), Cu−N5 2.027(5), Cu−N13 1.974(6), Cu−N16 2.023(5) Å, N5−Cu−N16 157.7(2), N13−Cu−Cl2 133.86(16)°; in **4b**: Cu−Cl1 2.439(3), Cu−Cl2 2.309(3), Cu−N5 2.021(8), Cu−N13 1.988(9), Cu−N16 2.019(8) Å, N5−Cu−N16 158.5(4), N13−Cu−Cl2 134.2(2)°.

the asymmetric unit. The molecules **3b** partake in intermolecular hydrogen bonding interactions of the type N11−H···Cl1^{i} [N11···Cl1^{i} 3.180 Å], where i denotes a symmetry code $-x$, $y + 0.5$, $-z + 0.5$ for generating equivalent atom positions. In addition, a hydrogen bond between the molecule of **3b** and one of the neighboring dimethylformamide molecules N12−H···O1^{i} [N12···O1^{i} 2.760 Å] is evident in the crystal structure (Supporting Information, Figure S3). The pattern of hydrogen bonding interactions in the crystal structure of **4b**·2.4DMF is similar.

HL^{3b} and **HL^{4b}** act as neutral tridentate ligands in **3b** and **4b**, respectively, coordinating to copper(II) via the quinoline nitrogen atom N5 [Cu−N5 = 2.027(5) (**3b**) and 2.021(8) Å (**4b**)], the hydrazine group nitrogen atom N13 [Cu−N13 = 1.974(6) (**3b**) and 1.988(9) Å (**4b**)], and the pyridine ring nitrogen atom N16 [Cu−N16 = 2.023(5) (**3b**) and 2.019(8) Å (**4b**)]. In contrast to paullone ligands, which have a folded conformation both in the metal-free and in the coordinated forms, the indoloquinolines **HL^{3b}** and **HL^{4b}** in **3b** and **4b** are essentially planar. The copper(II) center is five-coordinate, the remaining two coordinating sites being occupied by two chlorido ligands. The τ descriptor for **3b** and **4b**, expressed as the difference between the angles N5−Cu−N16 and N13−Cu−Cl2 [157.7(2) and 133.86(16)° (**3b**), and 158.5(4) and 134.2(2)° (**4b**)] divided by 60°, gives the same value for both complexes (0.40), which is between that for a trigonal bipyramid (1) and that for a square pyramid (0), and close to 0.52 found in [Ga(**L^{6b}**)Cl$_2$].[43] Furthermore, the interatomic bond distance Cu−Cl2 is significantly longer in complexes **3b** [Cu−Cl2 = 2.3045(19) Å] and **4b** [Cu−Cl2 = 2.309(3) Å] with indoloquinoline ligands than in complexes **5b** [Cu−Cl2 = 2.2461(5) Å] and [Cu(**HL^{6a}**)Cl$_2$][18] [Cu−Cl2 = 2.2411(8) Å] with paullone ligands.

The results of X-ray diffraction studies of the ligand **HL^{5b}** and complex **5b**·0.5CH$_3$OH are shown in Figure 3, and selected bond lengths and bond angles are given in the caption. Both the ligand and the complex crystallized in the monoclinic space group $P2_1/c$.

Formation of a centrosymmetric dimer is due to a bifurcated hydrogen bonding interaction between N12 as a proton donor and atoms N17^{i} and N14^{i} as proton acceptors [N12−H 0.880, H···N17^{i} 2.079, N12···N17^{i} 2.881 Å, N12−H···N17^{i} 151.1°; H···N14^{i} 2.633, N12···N14^{i} 3.356 Å, N12−H···N14^{i} 151.1°]; i denotes a symmetry code $-x + 1$, $-y$, $-z + 2$ for generating equivalent atom positions (Supporting Information, Figure S5). In addition, a hydrogen bond between N5 and N12^{i} [N5−H 0.880, H···N12^{i} 2.528, N5···N12^{i} 3.335 Å, N5−H···N12^{i} 152.78°] is evident in the crystal structure of **HL^{5b}**.

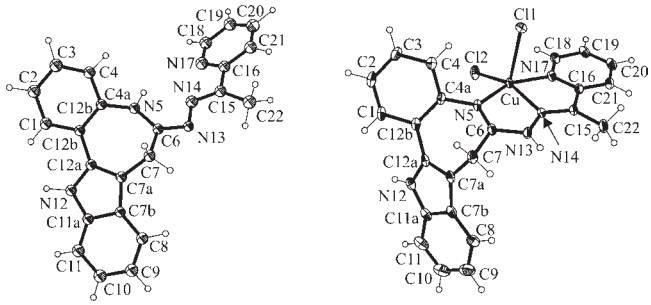


Figure 3. ORTEP plots of metal-free ligand molecule **HL^{5b}** and its copper(II) complex in **5**·0.5CH$_3$OH. Selected bond distances (Å) and bond angles (deg) in **HL^{5b}**: C4a−N5 1.417(3), N5−C6 1.359(3), C6−N13 1.329(3), N13−N14 1.382(3), N14−C15 1.297(3); in **5b**: Cu−Cl1 2.4681(5), Cu−Cl2 2.2461(5), Cu−N5 2.0220(15), Cu−N14 1.9787(15), Cu−N17 2.0466(15), N5−Cu−N14 78.94(6), N14−Cu−N17 78.18(6), N5−Cu−N17 156.85(6), N14−Cu−Cl2 153.96(5), N14−Cu−Cl1 98.79(4).

The distribution of electron density over the fragment N5−C6−N13 [N5−C6 1.359(3), C6−N13 1.329(3) Å] indicates the presence of an exocyclic amidine double bond. As expected, the conformation of the metal-free ligand **HL^{5b}** is very similar to that of the 9-bromo-derivative.[44] The indolobenzazepine backbone in both **HL^{5b}** and **5b** mainly consists of sp^2-hybridized carbon and nitrogen atoms. The only exception is the methylene group carbon atom in the seven-membered azepine ring, which is sp^3-hybridized. This atom disrupts the conjugation of the π system, and as a result the ligand as a whole is non-planar.

Intermolecular hydrogen bonding interaction between molecules of **5b**, namely, N12−H···Cl2^{i} [N12−H 0.880, H···Cl2^{i} 2.612, N12···Cl2^{i} 3.338 Å, N12−H···Cl2^{i} 140.56°], are responsible for their association in a dimer (i denotes the symmetry code $-x + 1$, $-y + 2$, $-z + 1$) (Supporting Information, Figure S6). An interdimeric hydrogen bond N13−H···Cl1^{ii} (ii $-x + 2$, $y - 0.5$, $-z + 1.5$)

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[N13−H 0.880, H···Cl1^{ii} 2.383, N13···Cl1^{ii} 3.149 Å, N13−H···Cl1^{ii} 145.67°] is evident in the crystal structure as well.

In the complex **HL^{5b}** acts as a neutral tridentate ligand coordinating to copper(II) through the azepine ring nitrogen atom N5 [Cu−N5 = 2.022(15) Å], hydrazine nitrogen atom N14 [Cu−N14 = 1.9787(15) Å], and pyridine nitrogen atom N17 [Cu−N17 = 2.0466(15) Å]. The copper(II) atom is five-coordinate, the remaining binding sites being occupied by two chlorido ligands [Cu−Cl1 = 2.4681(5) Å; Cu−Cl2 = 2.2461(5) Å]. The τ descriptor for five-coordinate complexes, expressed as the difference between the angles N5−Cu−N17, 156.85(6)°, and Cl2−Cu−N14, 153.96(5)°, divided by 60, gives a value of 0.05, which is very close to the ideal one for a square pyramid (0).[44] A similar value (0.10) was reported for a closely related complex [Cu(**HL^{6a}**)Cl$_2$].[18] It is noteworthy that the interatomic bond distances Cu−N5 and Cu−N17 in **5b** are significantly shorter than in [Cu(**HL^{6a}**)Cl$_2$],[18] whereas both Cu−Cl bonds in **5b** are longer.

The conformation of the coordinated ligand **HL^{5b}** in **5b** differs slightly from that adopted by the metal-free ligand (Figure 3). The angle of 74.34(4)° between the mean plane of the indole moiety and the pyridine ring in **5** is very close to that reported for [Cu(**HL^{6a}**)Cl$_2$] (78.6°).[18] The bond distances N5−C6 = 1.359(3), C6−N13 = 1.329(3) and N13−N14 = 1.382(3) Å in **HL^{5b}** are altered by the coordination to copper(II). Whereas the N5−C6 and N13−N14 bonds are shorter in **5b** [1.298(2) Å and 1.358(2) Å, correspondingly], the bond C6−N13 = 1.362(2) Å is longer, indicating the configurational change from an exocyclic C^6=N^{13} double bond in **HL^{5b}** to an endocyclic N^5=C^6 double bond in complex **5b**.

Stability Studies. The kinetic stability of complexes **1a**, **1b**, **4a**, **4b**, and **5b** in aqueous solution with a dimethylsulfoxide content of 1% v/v was studied by UV−vis spectroscopy over 24 h. Coordination of the corresponding ligands to copper(II) via the pyridine nitrogen atom, the hydrazine nitrogen, and the pyridine ring or azepine ring nitrogen atom alters significantly the conjugated π systems of the yellow-colored ligands **HL^{1a}**, **HL^{1b}**, **HL^{4a}**, **HL^{4b}**, and **HL^{5b}**, resulting in significantly different electronic absorption spectra. As a result, solutions of **1a**, **1b**, **4a**, **4b**, and **5b** show significant absorption in the visible region, namely, a broad charge-transfer band with a maximum at 461, 453, 461, 456, and 422 nm, respectively (Supporting Information, Figures S7−S9). A small decrease in absorption (ca. 5%) was observed for **1a**, **1b**, and **5b** over the first 4 h, with no further changes over the next 20 h, indicating that the coordination sphere of copper(II) remained intact. These results are in accord with those reported previously for complexes [Cu(**HL^{6a}**)Cl$_2$] and [Cu(**HL^{6b}**)Cl$_2$].[18] For complexes **4a** and **4b** the decrease in absorption over the first 4 h is slightly higher (ca. 7%), with no further changes over the next 20 h.

Cytotoxicity in Cancer Cells. The cytotoxicity of the copper(II) complexes was determined by means of a colorimetric microculture assay (MTT) in three human cancer cell lines (A549, CH1, SW480), yielding IC$_{50}$ values in the 10^{-8} to 10^{-6} M range (Table 2). Note that the IC$_{50}$ values for cisplatin, carboplatin, and oxaliplatin in SW480 cells are at 4.5 ± 1.7, 61 ± 10, and 0.30 ± 0.08 μM.[45] A549, a generally more chemoresistant cell line, is the least sensitive to all the tested compounds, whereas IC$_{50}$ values in CH1 and SW480 cells are up to ten and seven times lower, respectively. The corresponding uncomplexed ligands could not be tested because of insufficient solubility in biocompatible media.

Table 2. Cytotoxicity of Copper(II) Complexes with Indoloquinoline- (**1a**−**4b**) or Paullone-Based (**5b**, **6a**, **6b**) Ligands in Three Human Cancer Cell Lines

	IC$_{50}$ (μM), 96 h[a]		
compound	A549	SW480	CH1
1a	1.72 ± 0.03	1.3 ± 0.1	0.40 ± 0.07
1b	0.18 ± 0.04	0.024 ± 0.001	0.030 ± 0.005
2a	1.7 ± 0.1	0.75 ± 0.04	0.33 ± 0.07
2b	0.14 ± 0.01	0.024 ± 0.002	0.026 ± 0.006
3a	1.4 ± 0.3	0.64 ± 0.11	0.41 ± 0.05
3b	0.23 ± 0.01	0.049 ± 0.003	0.065 ± 0.012
4a	1.6 ± 0.1	0.47 ± 0.03	0.36 ± 0.03
4b	0.20 ± 0.03	0.032 ± 0.004	0.052 ± 0.008
5b	0.67 ± 0.15	0.21 ± 0.04	0.064 ± 0.015
6a	1.28 ± 0.03	0.40 ± 0.04	0.28 ± 0.03
6b	0.43 ± 0.03	0.18 ± 0.02	0.080 ± 0.005

[a] 50% inhibitory concentrations (means ± standard deviation from at least three independent experiments), as obtained by the MTT assay using exposure times of 96 h.

Comparison of the copper(II) complexes reveals the following structure−activity relationships: methyl (**2a**), chloro (**3a**), or bromo (**4a**) substitution at position 8 has nearly no impact on cytotoxicity compared to **1a** lacking a substituent in this position. In contrast, a methyl group in position 14 results in a dramatic enhancement of cytotoxicity, with about 10 times lower IC$_{50}$ values in A549 and CH1 and about 50 times lower IC$_{50}$ values in SW480 cells in the case of compound **1b** (Figure 4A−C). Likewise, IC$_{50}$ values of **2b**, **3b**, and **4b** are 1 order of magnitude lower than those of the analogues **2a**, **3a**, and **4a**, confirming the impact of this methyl substitution as well as the irrelevance of electron-releasing or electron-withdrawing substituents at position 8.

For comparison, complexes with paullone ligands (**5b**, **6a**, **6b**) closely related to the indoloquinoline complexes **1b**, **4a**, and **4b**, but containing a folded seven-membered azepine ring instead of a flat six-membered pyridine ring were also tested. In contrast to a previously reported comparison of indoloquinoline versus paullone complexes of ruthenium(II) and osmium(II) that yielded differences of mostly 1 order of magnitude,[19] differences in cytotoxicity are much less pronounced for the copper(II) complexes reported here. Only in SW480 cells, comparison of **4b** with **6b** and **1b** with **5b** (all bearing a methyl group in position 14 (**1b**, **4b**) or 15 (**5b**, **6b**)) reveals 6 and 9 times higher cytotoxicity of the indoloquinoline complex, respectively (Figure 4D−F), whereas **4a** and **6a** (lacking a substituent in position 14 and 15, correspondingly) are comparably cytotoxic in all three cell lines. A possible reason can be the increased reactivity of the azomethine carbon atom C^{14} in **4a** and the conversion of this complex into other species, similar to [Cu(**L^8**)$_2$Cl$_2$], which may behave similar to **6a**. The reason for the

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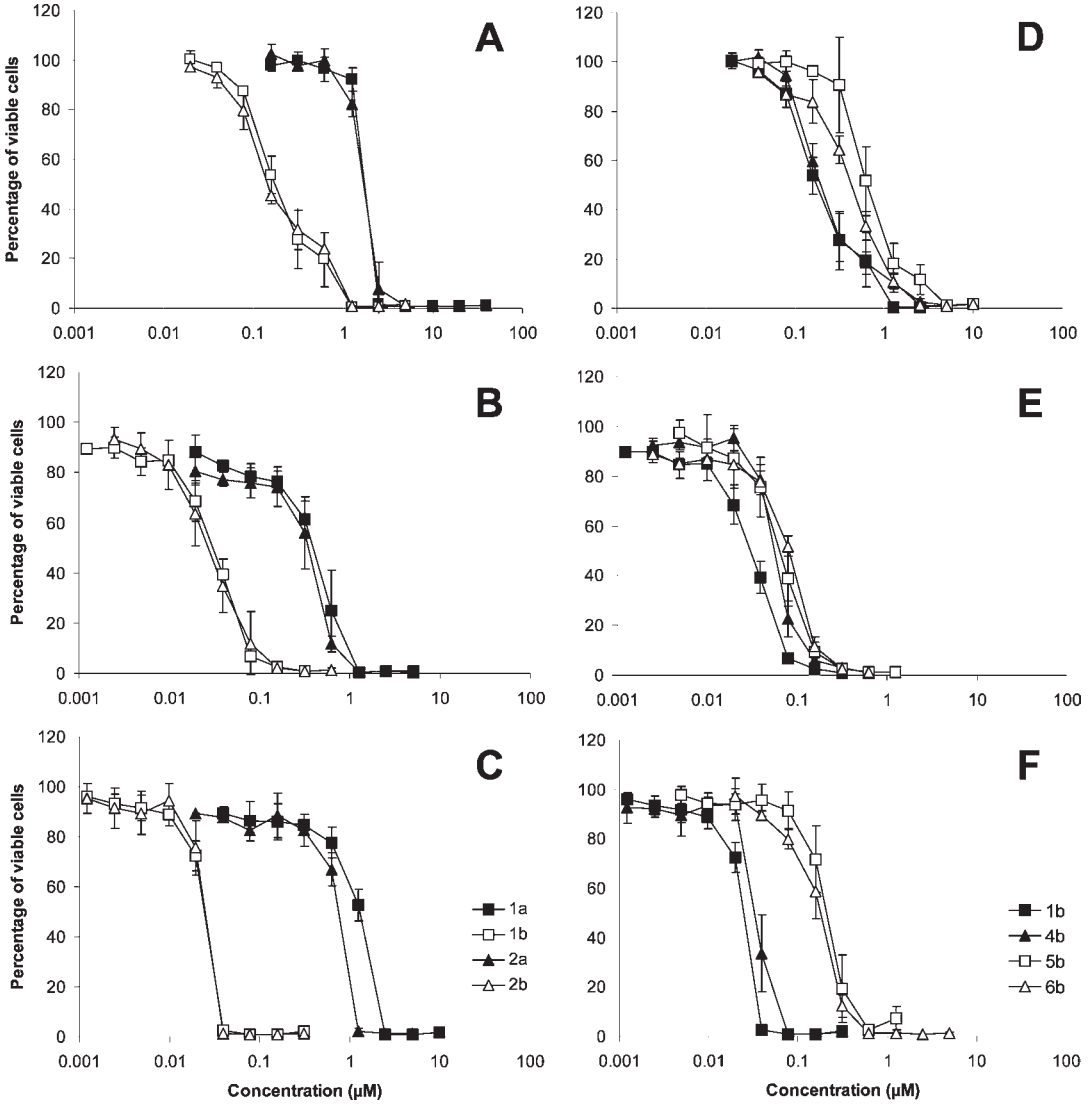

Figure 4. Concentration-effect curves of complexes **1a**, **1b**, **2a**, and **2b** in the human cancer cell lines A549 (A), CH1 (B), SW480 (C), indicating the different impact of methyl substitution depending on the position; and concentration-effect curves of complexes **1b** and **4b** in comparison with the corresponding paullone ligands **5b** and **6b** in the human cancer cell lines A549 (D), CH1 (E), SW480 (F), all determined by the MTT assay using continuous exposure for 96 h.

generally smaller differences as well as the generally higher cytotoxicity of the copper(II) complexes may either be related to the different central metal or to the different metal-binding sites in the ligands and the consequences of coordination to the metal or a combination of both. Comparisons with the uncomplexed ligands were not possible for lack of solubility, but even if the role of the metal for biological activity remains yet unclear, it should be emphasized that metal complexation renders these compounds applicable for biological testing in solution.

Final Remarks

The reported results establish synthetic access to a new class of highly cytotoxic copper(II) complexes. Complexation of copper(II) chloride with potentially tridentate indolo [3,2-*c*]quinolines and indolo[3,2-*d*]benzazepines modified at the lactam function resulted in five-coordinate copper(II) complexes, which practically remain intact in aqueous solution containing 1% DMSO over 24 h. The complexes show remarkably high antiproliferative activities in human cancer cell lines with IC_{50} values in the 10^{-8} to 10^{-6} M concentration range. The effect of copper(II) on cytotoxicity could not be elucidated because of the very low solubility of the metal-free ligands in biocompatible media. Binding to copper(II) improved the solubility of the resulted complexes, enabling them to be tested as potential antitumor agents. The use of 2-acetylpyridine instead of 2-formylpyridine for the synthesis of tridentate indoloquinoline Schiff-bases results in a huge enhancement of cytotoxicity by a factor of 10 to 50. The presence of an electron-releasing group (methyl), or electron-withdrawing substituents (Cl, Br) compared to H in position 8 of the indoloquinoline backbone does not have any effect on cytotoxicity of the corresponding copper(II) complexes. The effect of substitution of the seven-membered azepine ring in copper(II) complexes with modified paullones by a flat six-membered pyridine ring is clearly seen upon comparing the antiproliferative activities of complexes **5b** and **6b** with those of compounds **1b** and **4b**, correspondingly, in SW480 cells, revealing a six- to nine-fold decrease of

IC_{50} values. Further experiments are in progress to shed light onto the mechanism of action of these compounds, including their DNA-intercalating and DNA-breaking potencies. The ability of copper(II) complexes to cut DNA is well-documented in the literature.[46−50]

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Supporting Information Available: Further details are given in Figures S1−S10 and Table S1, and crystallographic data is given in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.