Supporting Information

The conjugates of indolo[2,3-*b*]quinoline as anti-pancreatic cancer agents: design, synthesis, molecular docking and biological evaluations

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In memory of Professor Łukasz S. Kaczmarek

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Figure S19. Stability of 9-[((2-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**2**) dihydrochloride in DMSO solution at ambient temperature : **a)** at starting point "0" **b)** after 120 h

HPLC Metod: the chromatographic analysis was performed using a Waters HPLC system (Waters Assoc., Milford, MA, USA) consisting of two Waters pump 515, Waters autosampler 717-plus, Waters column oven and Photodiode Array Detector 2996. The Stationary phase – Symetry C-18 (250 × 4.6 mm, 5 μm). The mobile phase – A (0.1% TFA in acetonitrile) and B (0.1% TFA in water), elution – linear gradient, flow rate – 1 mL/min, duration time – 25 min.The other parameters: column temp. – 25°C, concentration of conjugates **1** and **2** – 0.05 mg/mL, injection volume – 40 μl, UV detection wavelength ʎ = 330 nm.

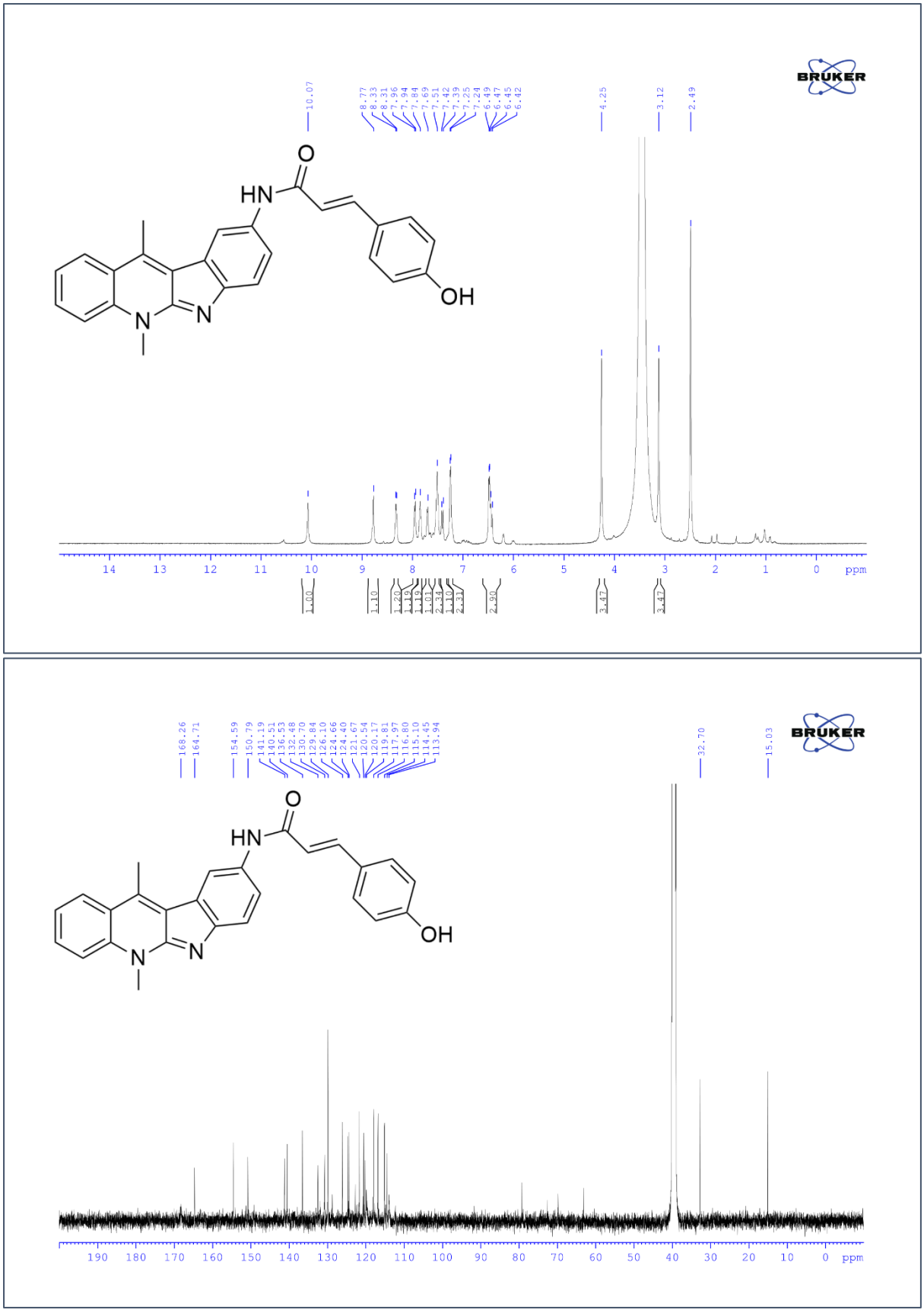


Figure S1. 9-[((4-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**1**)

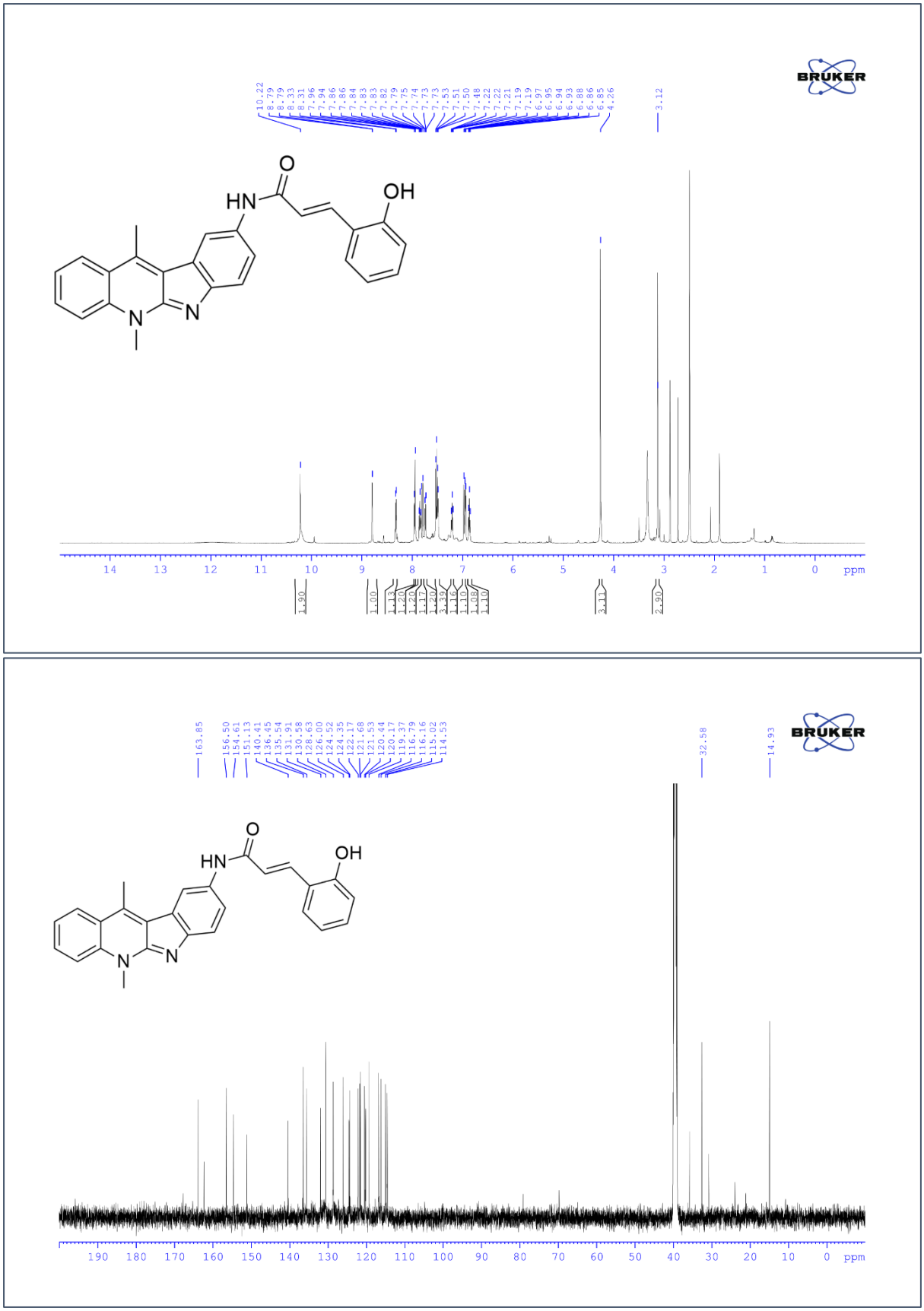


Figure S2. 9-[((2-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**2**)

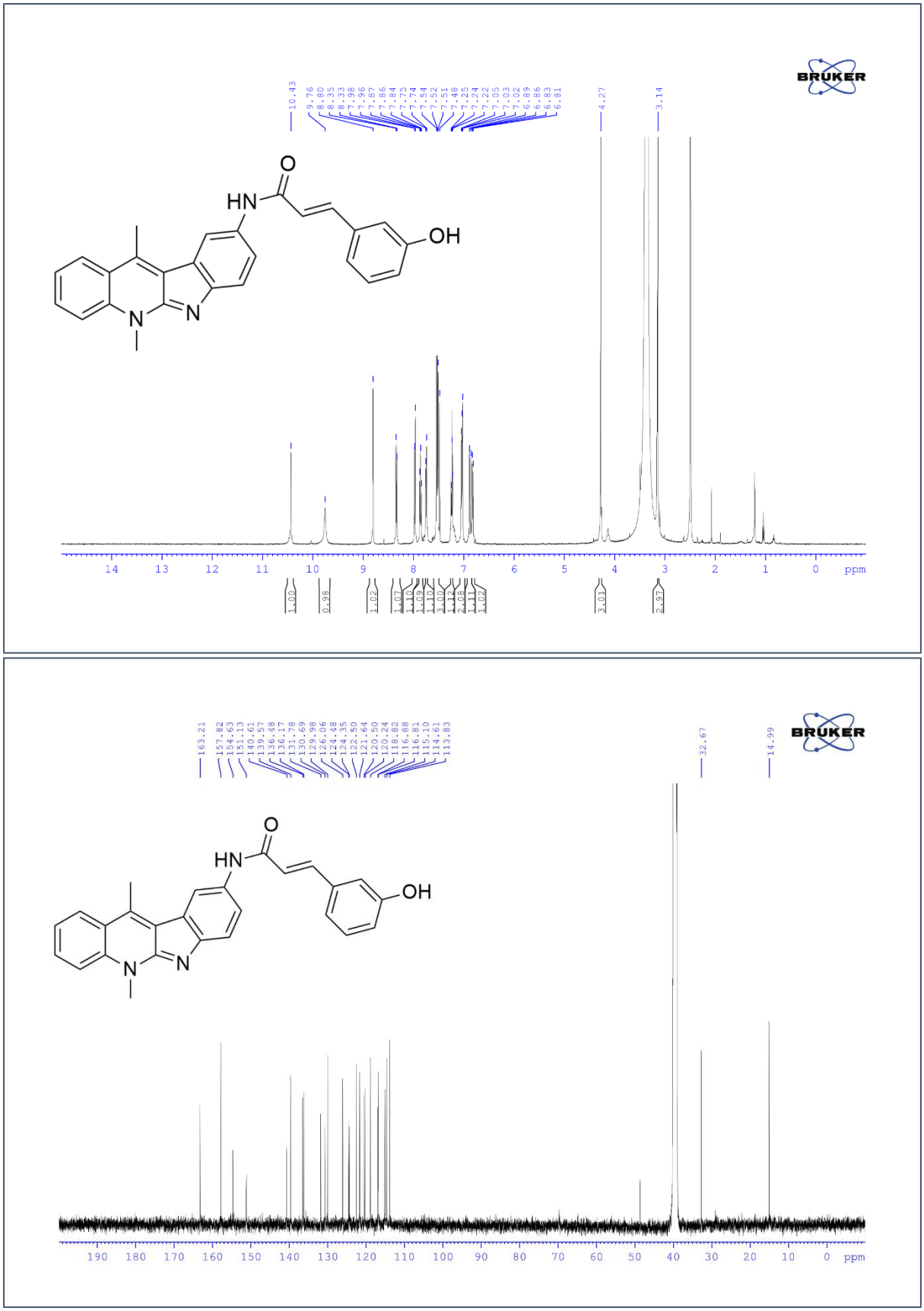


Figure S3. 9-[((3-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5H-indolo[2,3-*b*]quinoline (**3**)

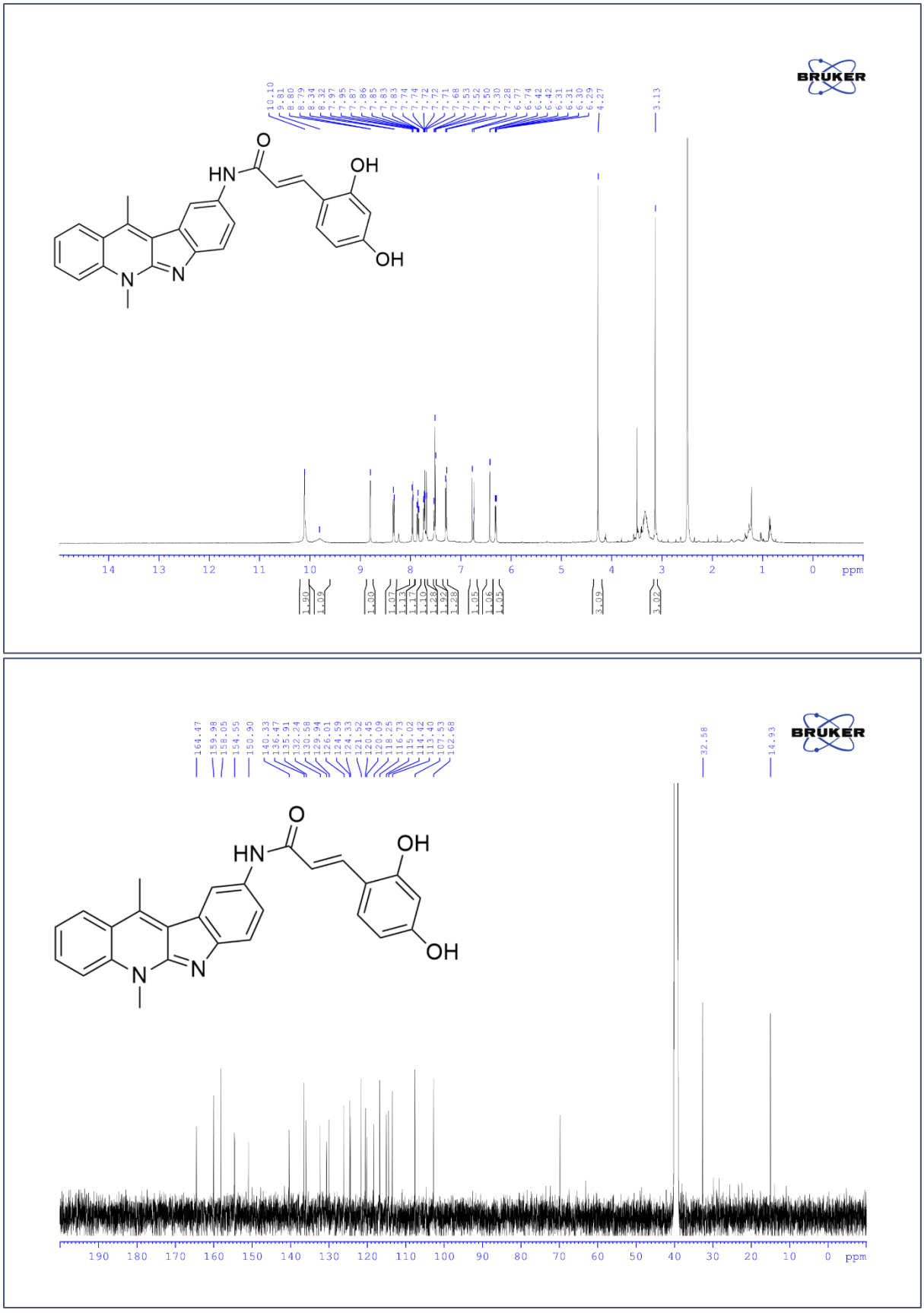


Figure S4. 9-[(2,4-dihydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**4**)

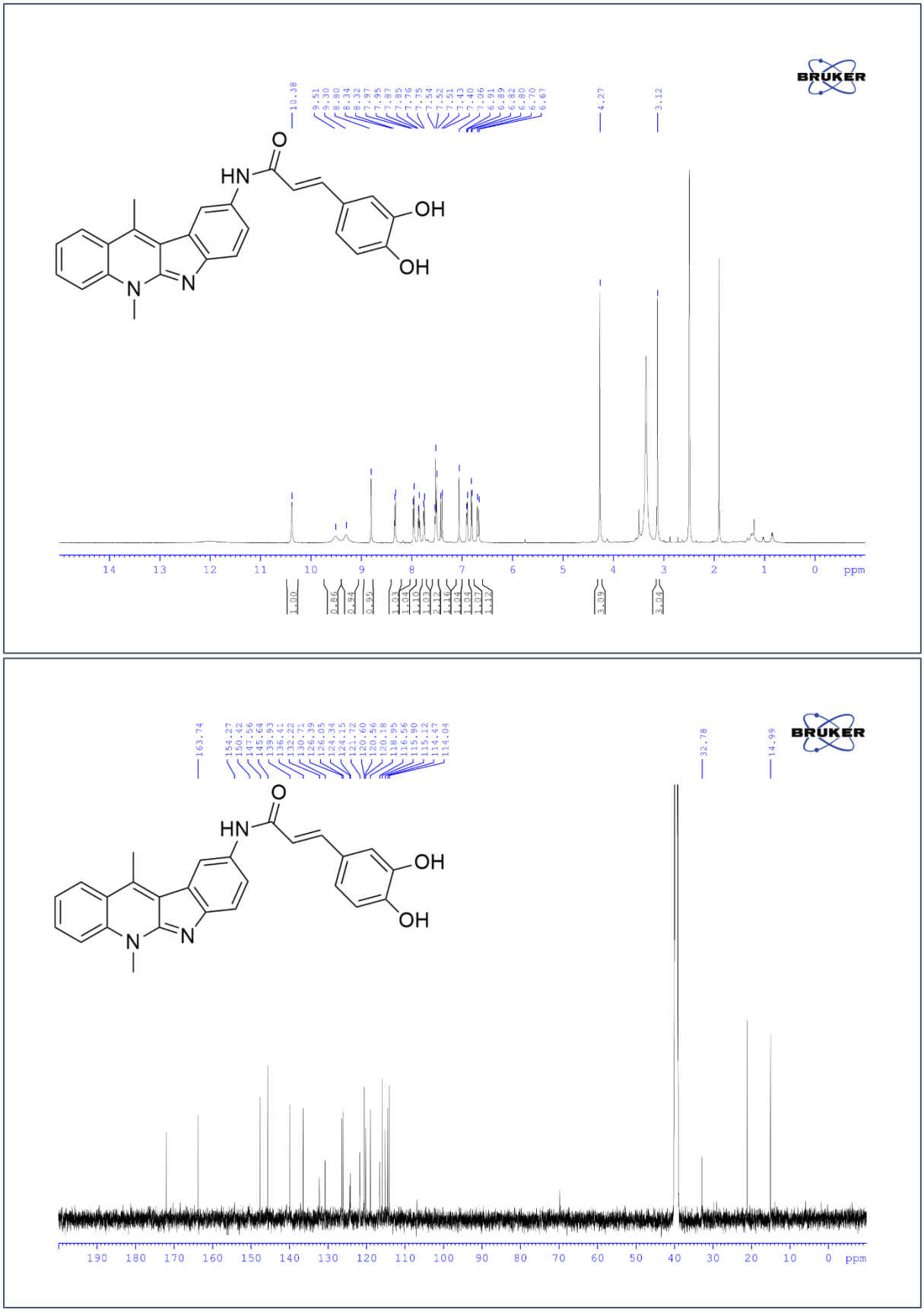


Figure S5. 9-[(3,4-dihydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**5**)

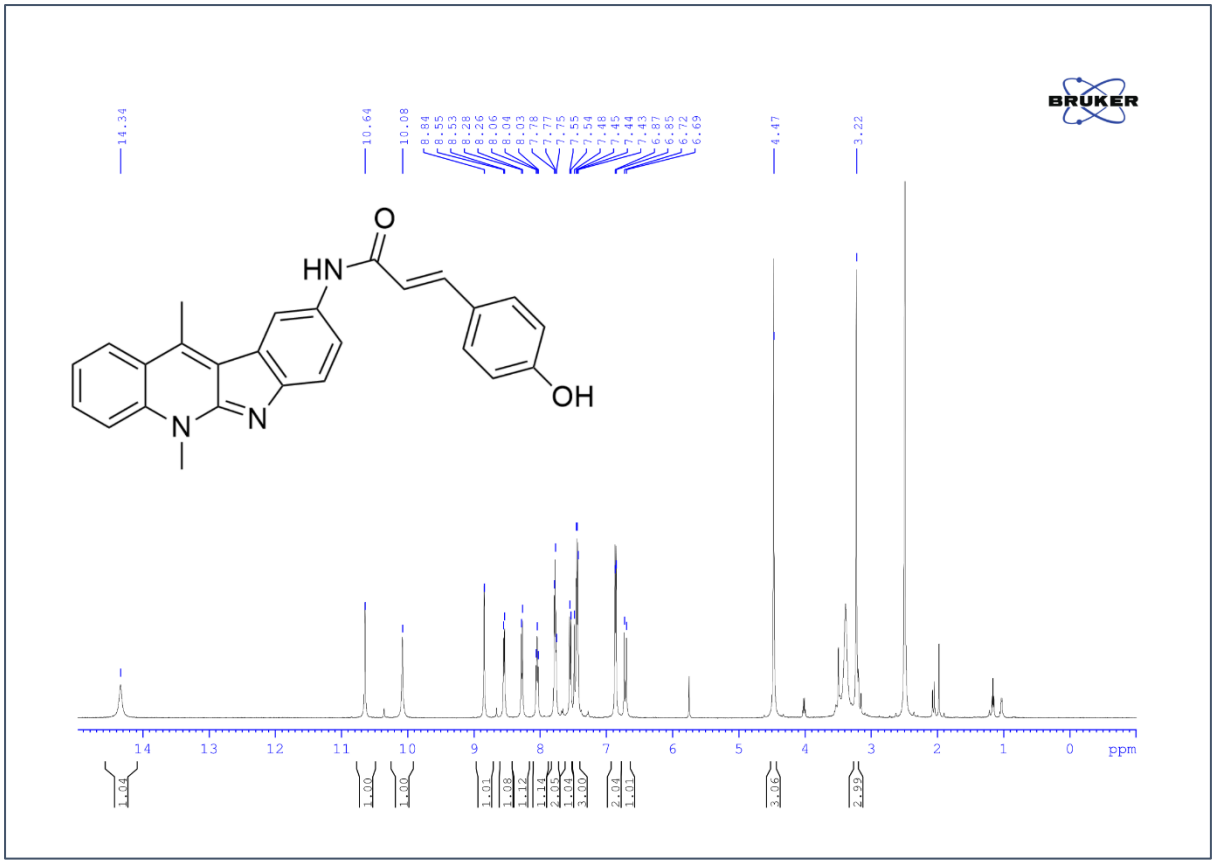


Figure S6. 9-[((4-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**1**) dihydrochloride

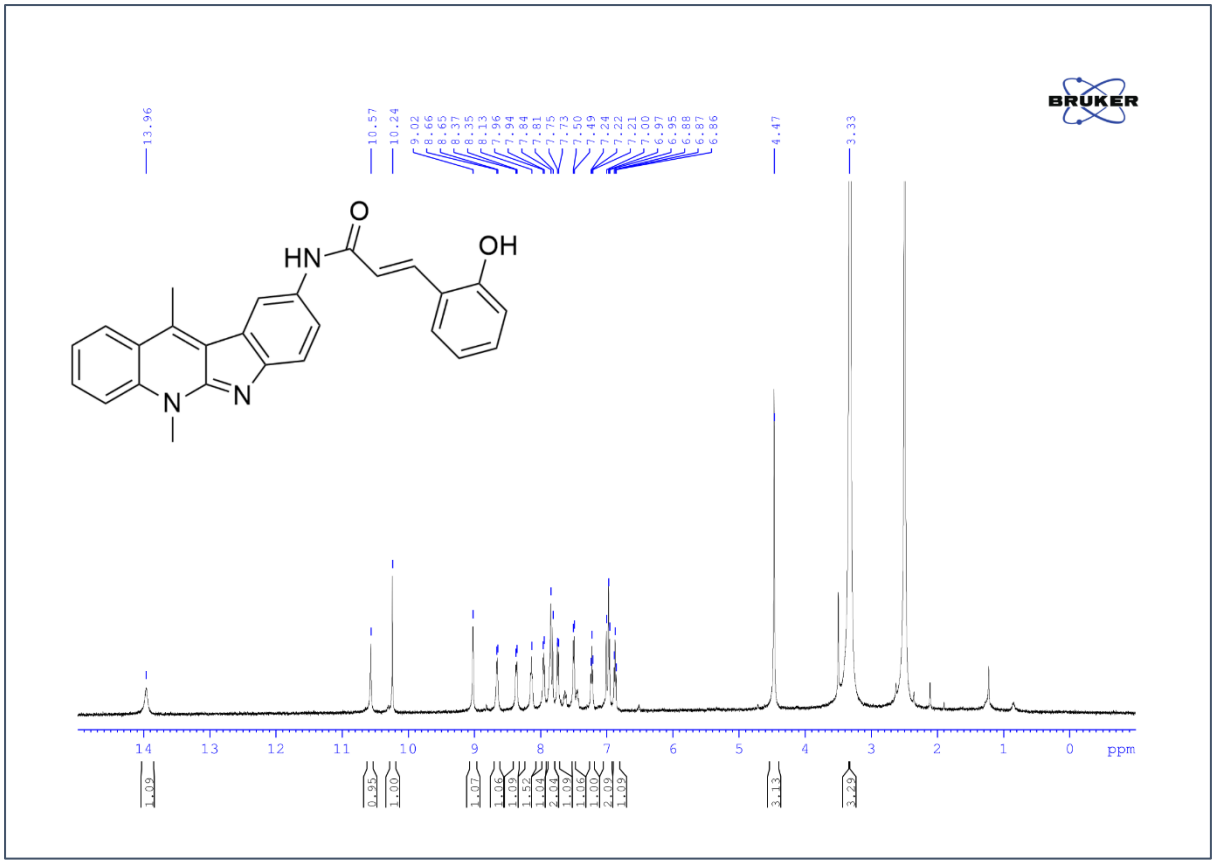


Figure S7. 9-[((2-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**2**) dihydrochloride

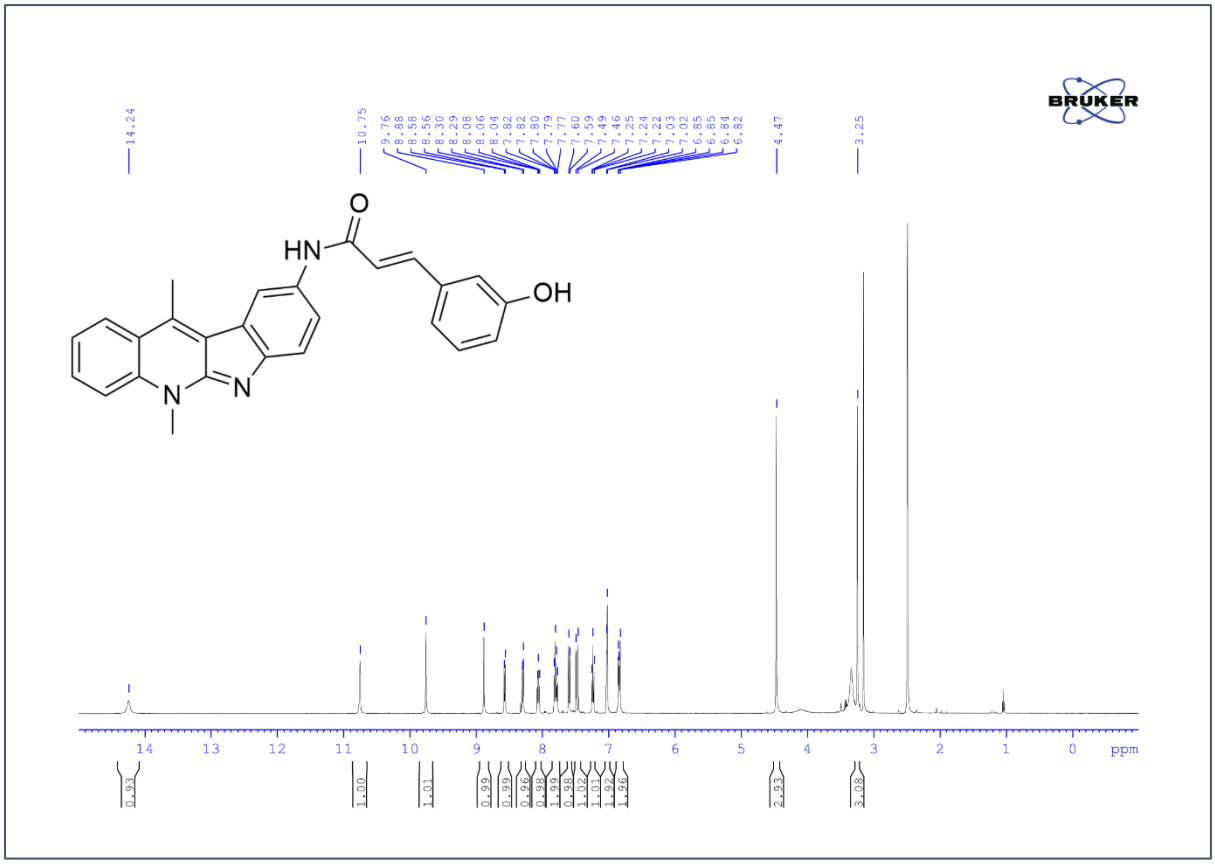


Figure S8. 9-[((3-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**3**) dihydrochloride

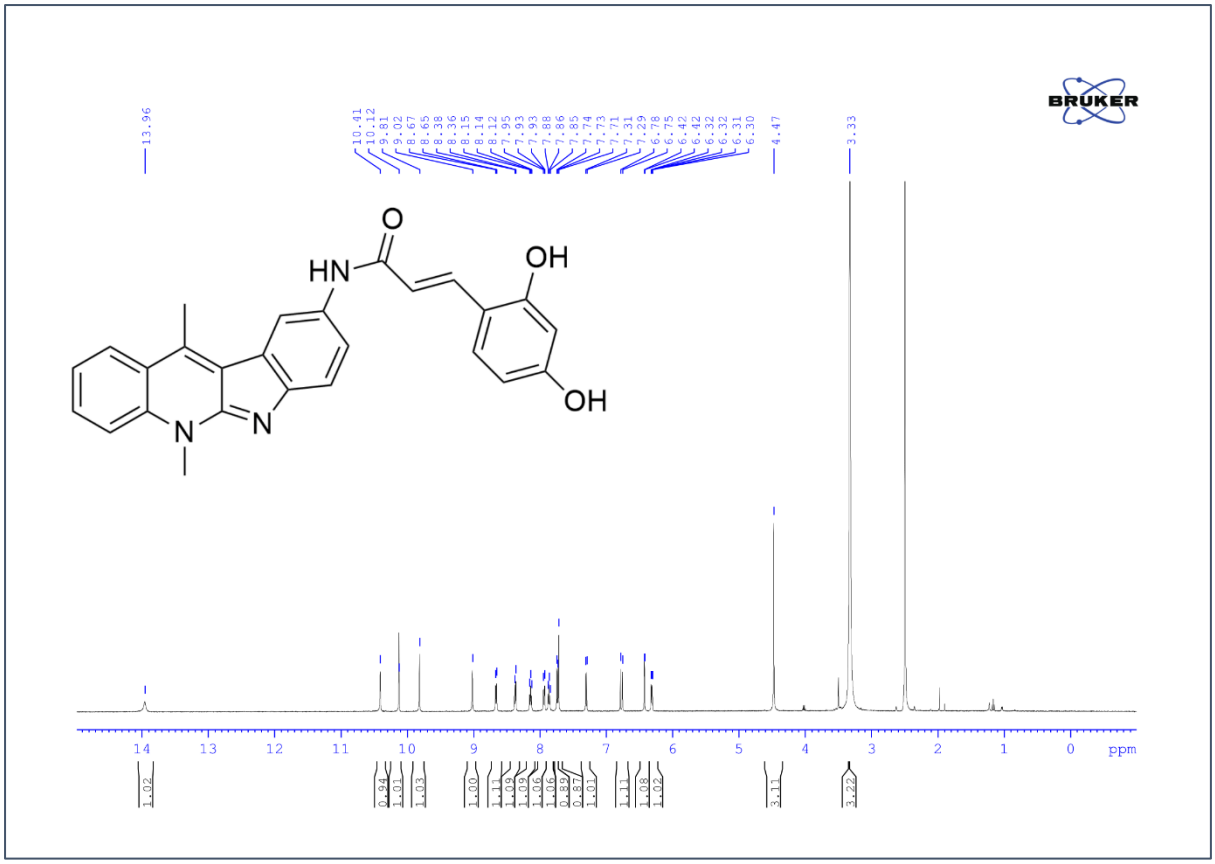


Figure S9. 9-[(2,4-dihydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**4**) dihydrochloride

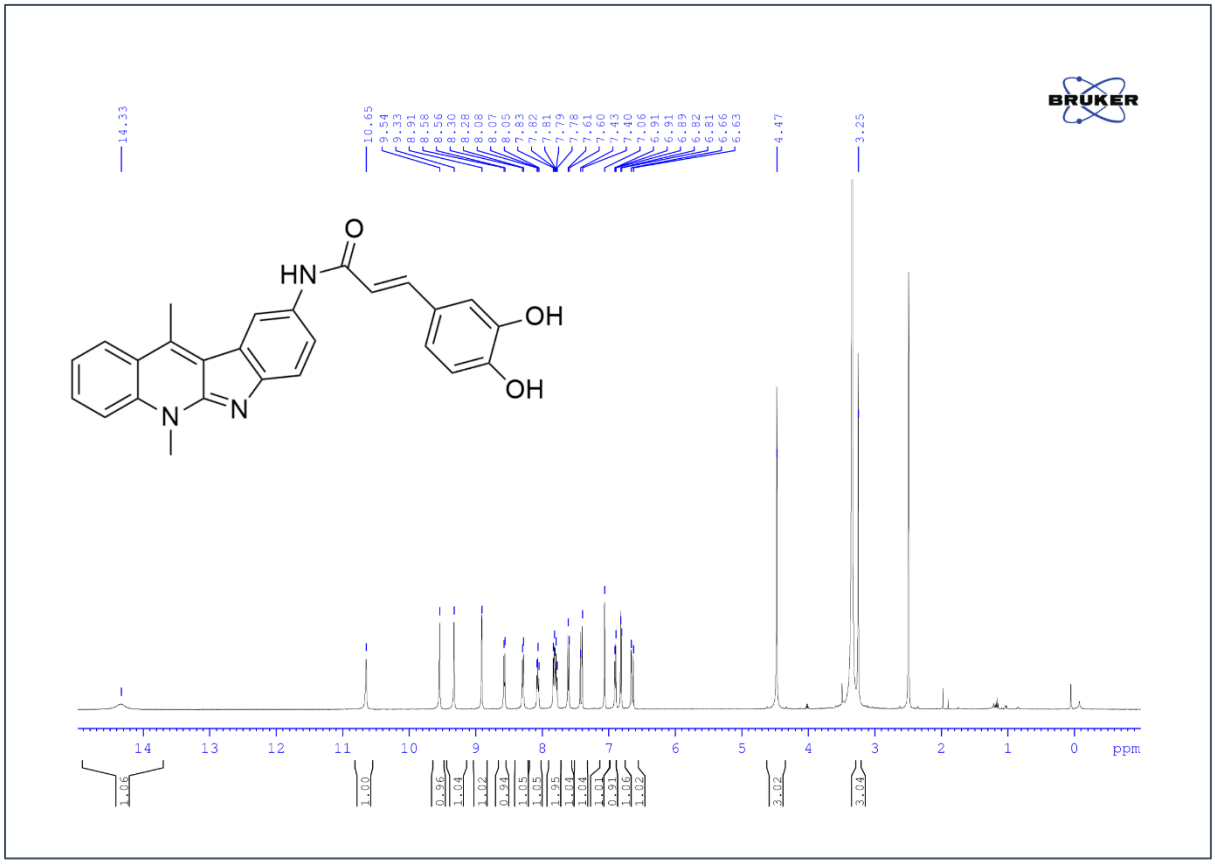


Figure S10. 9-[(3,4-dihydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**5**) dihydrochloride

Table S1. Selected, predicted ADMET properties of compounds investigated in this work.

compound	MW[a]	dipole[b]	vol[c]	SASA[d]	dHB[e]	aHB[f]	logP[g]	logS[h]	metab[i]	P[j]	Ro3[k]	Ro5[l]
1	407.5	12.7	1271.7	711.1	2	5.25	4.40	-6.37	3	435	1	0
2	407.5	13.2	1267.6	707.8	2	5.25	4.46	-6.31	3	534	1	0
3	407.5	12.0	1271.7	711.1	2	5.25	4.40	-6.37	3	435	1	0
4	423.5	8.7	1290.6	720.2	3	6	3.69	-5.99	4	163	1	0
5	423.5	10.5	1292.7	721.9	3	6	3.69	-6.01	4	158	1	0
DiMIQ (6)	246.3	8.4	815.1	474.1	0	2	3.89	-4.15	2	6597	0	0

[a]MW – molecular weight (Da); [b]dipole – dipole moment (D); [c]vol – total molecular volume (Å^3); [d]SASA – solvent accessible surface (Å^2); [e]dHB – estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution; [f]aHB – estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution; [g]logP – octanol/water partition coefficient; [g]logS – predicted aqueous solubility (mol/dm^3); [i]metab – number of likely metabolic reactions; [j]P – apparent Caco-2 permeability (nm/sec); [k]Ro3 – number of violations of Jorgensen's rule of three; [l]Ro5 – number of violations of Lipinski's rule of five.

Table S2. Selected, predicted ADMET properties of compounds investigated in this work.

compound	FOSA[a]	FISA[b]	PISA[c]	glob[d]	HERG[e]	BB[f]	MDCK[g]	Kp[h]	HSA[i]	Jm[j]	LD_{50}[k]
1	146.1	143.1	421.9	0.80	-6.81	-1.24	201.4	-2.19	0.78	0.001	680
2	141.8	133.7	432.3	0.80	-6.82	-1.13	251.4	-1.98	0.77	0.002	680
3	146.1	143.2	421.9	0.80	-6.81	-1.24	201.0	-2.19	0.78	0.001	680
4	141.8	188.1	390.4	0.80	-6.70	-1.78	69.7	-3.03	0.58	0.000	680
5	146.1	189.6	386.2	0.79	-6.69	-1.80	67.2	-3.08	0.58	0.000	10000
DiMIQ (6)	132.7	18.6	322.8	0.89	-4.85	0.41	3801.3	-0.73	0.45	3.252	330

[a]FOSA – hydrophobic component of the SASA; [b]FISA – hydrophilic component of the SASA; [c]PISA – π (carbon and attached hydrogen) component of the SASA; [d]glob – globularity descriptor; [e]HERG – predicted IC_{50} value for blockage of HERG K^+ channels; [f]BB – predicted brain/blood partition coefficient; [g]MDCK – predicted apparent MDCK cell permeability (nm/sec); [g]K_p – predicted skin permeability; [i]HSA – prediction of binding to human serum albumin; [j]J_m – Predicted maximum transdermal transport rate (μg cm^{-2} hr^{-1}); [k]LD_{50} – predicted value of median lethal dose (mg/kg).

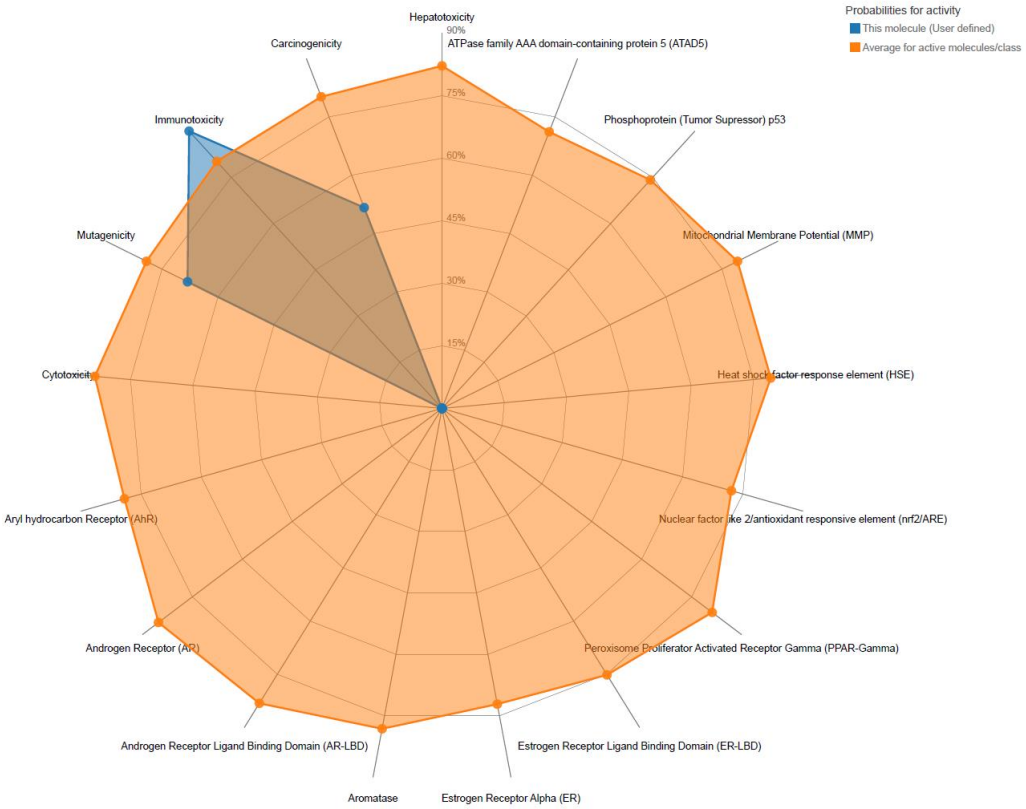


Figure S11. Chart of probabilities for activities related to potential toxocity for compound **1**.

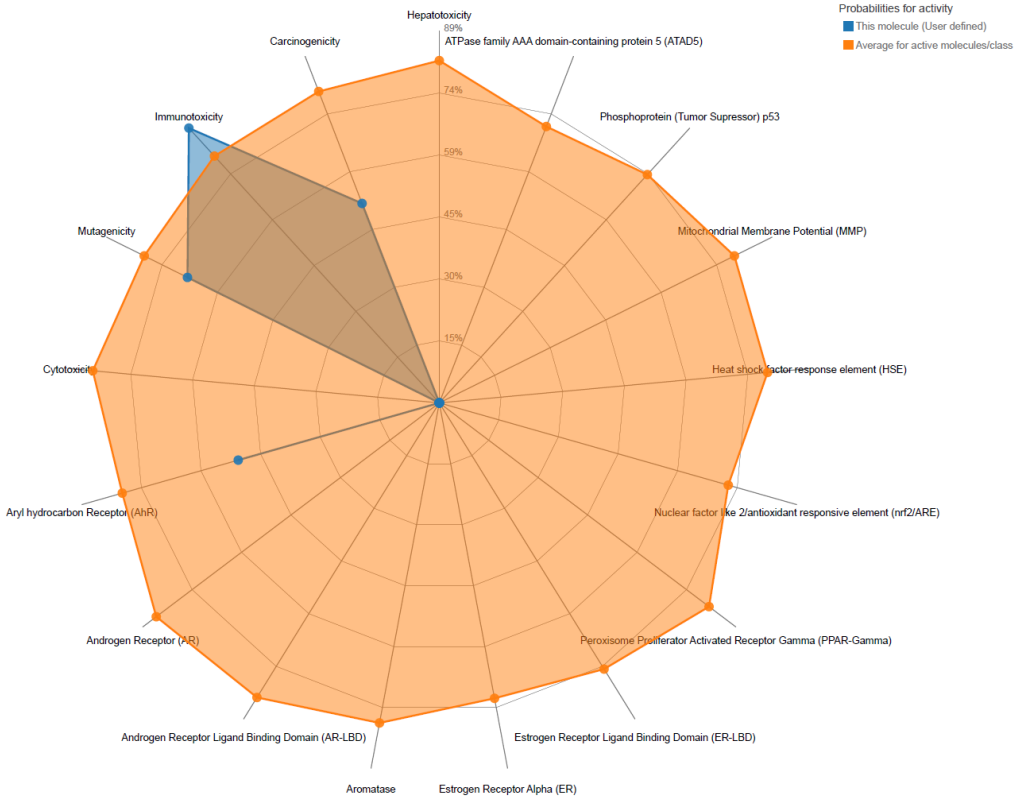


Figure S12. Chart of probabilities for activities related to potential toxocity for compound **2**.

Figure S13. Chart of probabilities for activities related to potential toxocity for compound **3**.

Figure S14. Chart of probabilities for activities related to potential toxocity for compound **4**.

Figure S15. Chart of probabilities for activities related to potential toxocity for compound **5**.

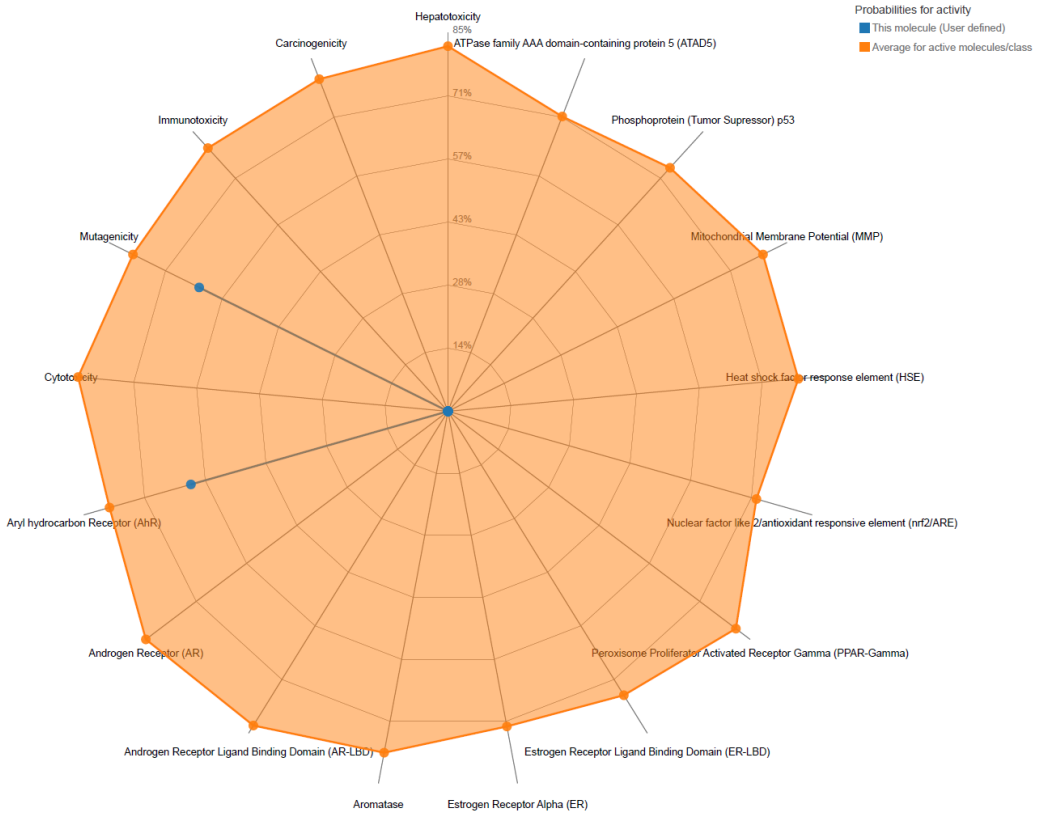


Figure S16. Chart of probabilities for activities related to potential toxocity for DiMIQ.

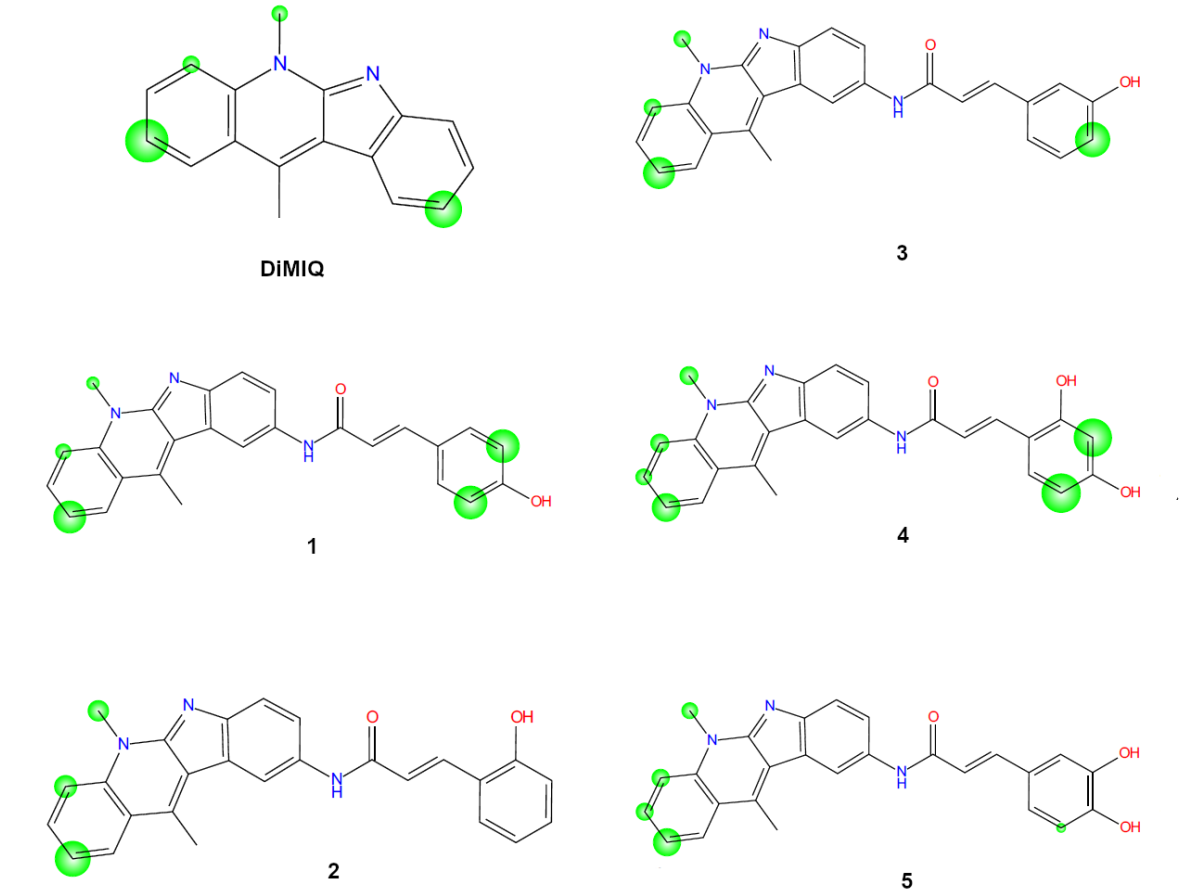
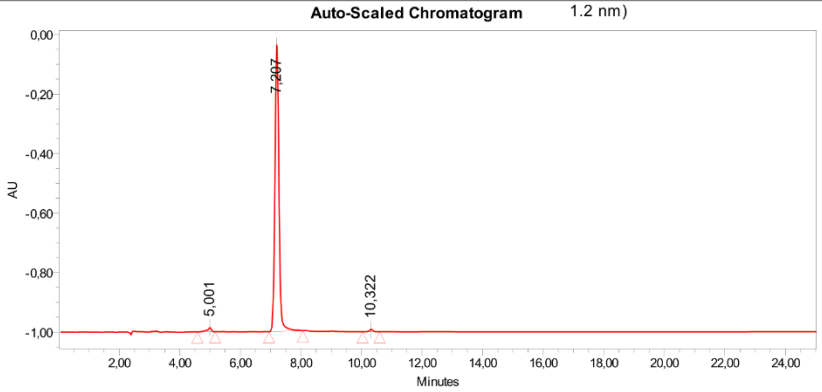


Figure S17. Predicted sites of CYP450 metabolism for compounds **1**-**5** and DiMIQ.

SAMPLE INFORMATION

Sample Name:	Conjugate 1 HCl DMSO "0" (3)	Acquired By:	tobiaszj
Sample Type:	Unknown		
Vial:	8	Acq. Method Set:	Indolochinoliny
Injection #:	1		
Injection Volume:	40,00 ul	Processing Method:	Indolochinoliny Con 1
Run Time:	25,0 Minutes	Channel Name:	330 nm
		Proc. Chnl. Descr.:	[PDA 330,0 nm] - Labeled: Blank.[330] (PDA 190.0 to 800.0 nm at 1.2 nm)



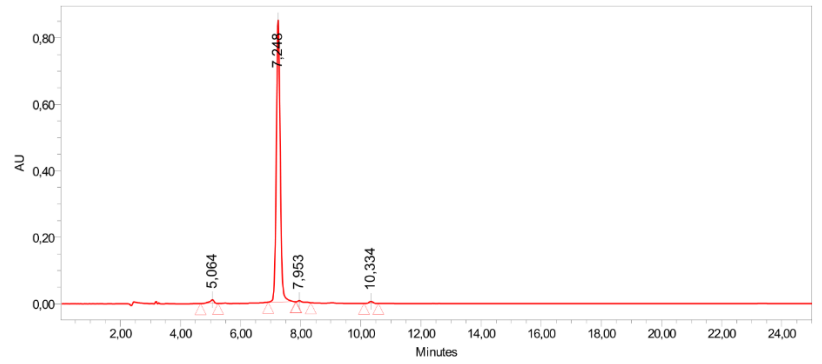
Peak Results

	Name	RT	Area	% Area	Symmetry Factor	Baseline Start (min)	Baseline End (min)	Selectivity	Resolution
1		5,001	139651	1,52	0,682992	4,583	5,167		
2		7,207	8966050	97,78	1,069331	6,950	8,067	1,551	9,734574
3		10,322	64042	0,70	0,918081	10,033	10,600	1,502	13,876856

a)

SAMPLE INFORMATION

Sample Name:	Conjugate 1 HCl DMSO 120h RT (3)	Acquired By:	tobiaszj
Sample Type:	Unknown		
Vial:	4	Acq. Method Set:	Indolochinoliny
Injection #:	1		
Injection Volume:	40,00 ul	Processing Method:	Indolochinoliny Con 1
Run Time:	25,0 Minutes	Channel Name:	330 nm
		Proc. Chnl. Descr.:	PDA 330,0 nm (PDA 190.0 to 800.0 nm at 1.2 nm)



Peak Results

	Name	RT	Area	% Area	Symmetry Factor	Baseline Start (min)	Baseline End (min)	Selectivity	Resolution
1		5,064	122377	1,55	0,701518	4,667	5,250		
2		7,248	7670360	97,36	1,077603	6,917	7,833	1,537	9,148555
3		7,953	31429	0,40	2,347202	7,850	8,333	1,113	3,040656
4		10,334	54244	0,69	0,995788	10,100	10,583	1,343	10,271641

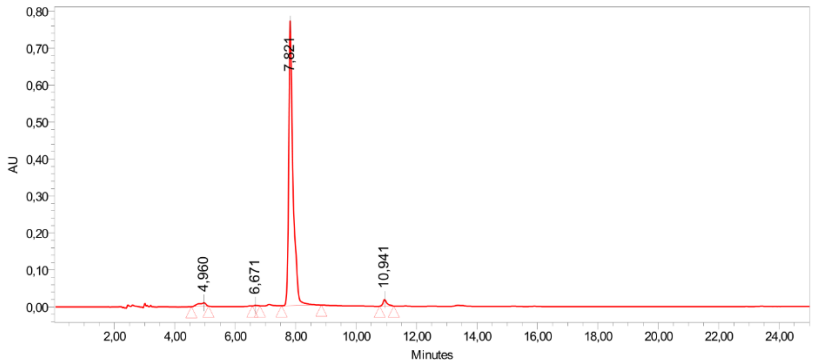
b)

Figure S18. Stability of 9-[((4-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**1**) dihydrochloride in DMSO solution at ambient temperature : **a)** at starting point "0" **b)** after 120 h

SAMPLE INFORMATION

Sample Name:	Conjugate 2 HCl DMSO "0" (2)	Acquired By:	tobiaszj
Sample Type:	Unknown		
Vial:	13	Acq. Method Set:	Indolochinoliny
Injection #:	1		
Injection Volume:	40,00 ul	Processing Method:	Indolochinoliny Con 2
Run Time:	25,0 Minutes	Channel Name:	330 nm
		Proc. Chnl. Descr.:	PDA 330,0 nm (PDA 190.0 to 800.0 nm at 1.2 nm)

Auto-Scaled Chromatogram



Peak Results

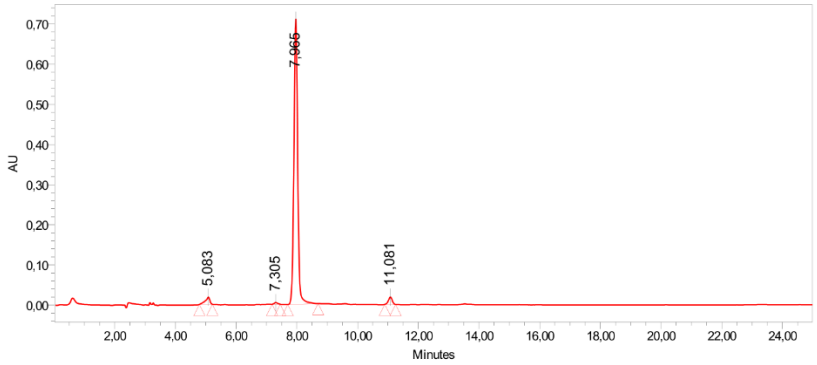
	Name	RT	Area	% Area	Symmetry Factor	Baseline Start (min)	Baseline End (min)	Selectivity	Resolution
1		4,960	174032	2,20	0,685754	4,550	5,117		
2		6,671	9794	0,12	1,278447	6,567	6,817	1,432	4,553160
3		7,821	7568744	95,59	1,592467	7,533	8,850	1,203	5,772222
4		10,941	165354	2,09	1,536011	10,783	11,250	1,457	14,560164

a)

SAMPLE INFORMATION

Sample Name:	Conjugate 2 HCl DMSO 120h RT (2)	Acquired By:	tobiaszj
Sample Type:	Unknown		
Vial:	5	Acq. Method Set:	Indolochinoliny
Injection #:	1		
Injection Volume:	40,00 ul	Processing Method:	Indolochinoliny Con 2
Run Time:	25,0 Minutes	Channel Name:	330 nm
		Proc. Chnl. Descr.:	PDA 330,0 nm (PDA 190.0 to 800.0 nm at 1.2 nm)

Auto-Scaled Chromatogram



Peak Results

	Name	RT	Area	% Area	Symmetry Factor	Baseline Start (min)	Baseline End (min)	Selectivity	Resolution
1		5,083	183802	2,81	0,708198	4,783	5,217		
2		7,305	35293	0,54	1,118553	7,183	7,450	1,544	9,322693
3		7,965	6165959	94,22	1,016905	7,700	8,700	1,105	3,014682
4		11,081	159193	2,43	0,940313	10,900	11,250	1,447	13,877319

b)

Figure S19. Stability of 9-[((2-hydroxy)cinnamoyl)amino]-5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (**2**) dihydrochloride in DMSO solution at ambient temperature : **a)** at starting point "0" **b)** after 120 h