Mansouramycins A - D, Cytotoxic Isoquinolinequinones from a Marine Streptomycete

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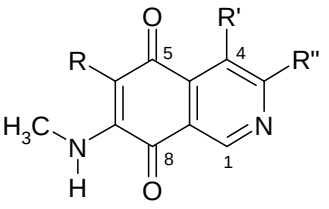
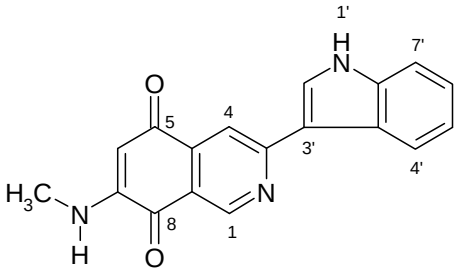
Supporting Information

High-resolution SEM image of *Streptomyces* sp. Mei37, ^{1}H NMR spectra of isoquinolinequinones **1**-**5**, ^{13}C and 2D NMR spectra of mansouramycin D (**4**) and data of their cytotoxicity





5

	R	R'	R"
1	H	Me	Me
2	H	H	Me
3	Cl	H	Me
4	H	H	COOMe

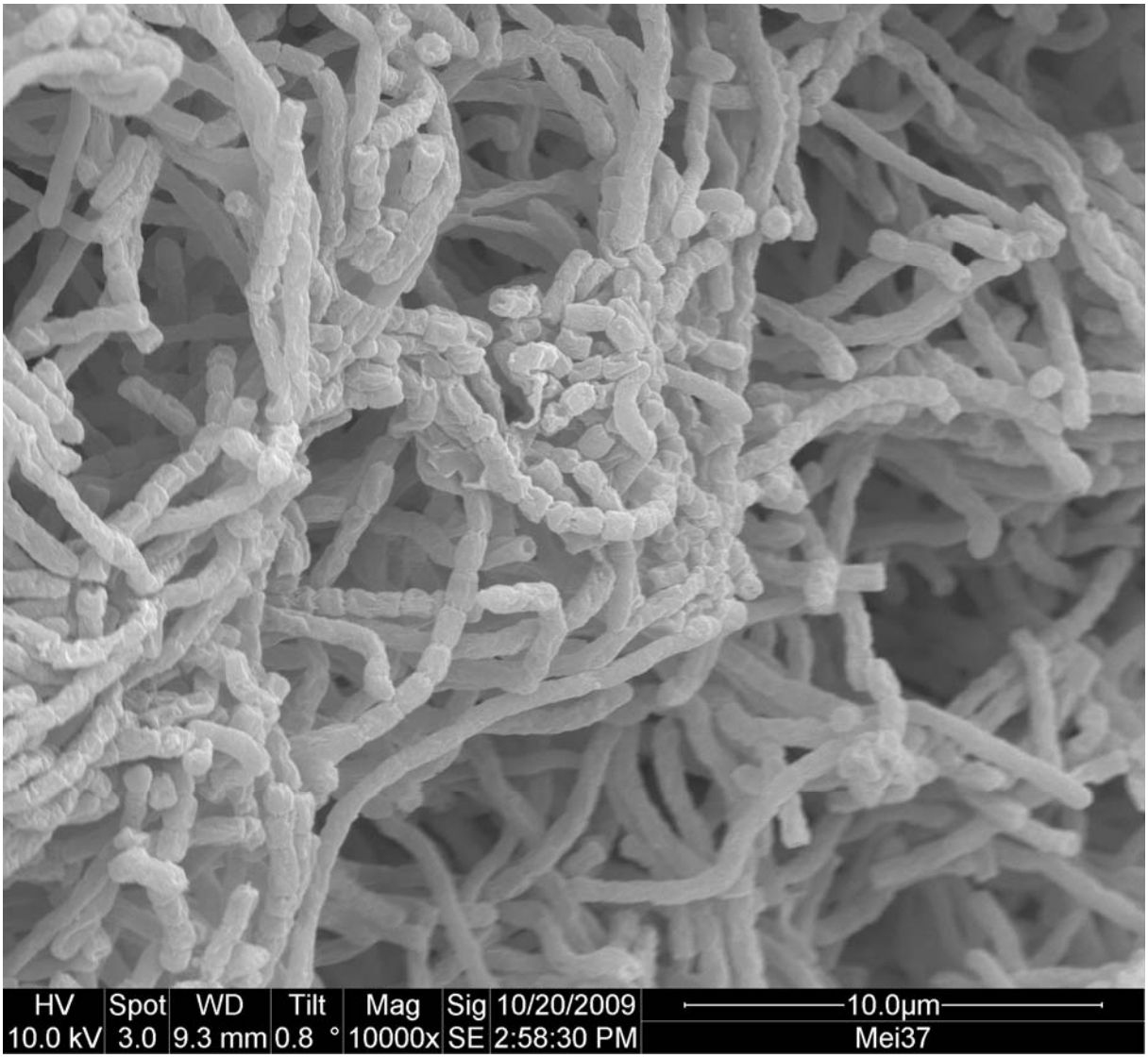


Figure S1: High-resolution SEM image of *Streptomyces* sp. Mei37

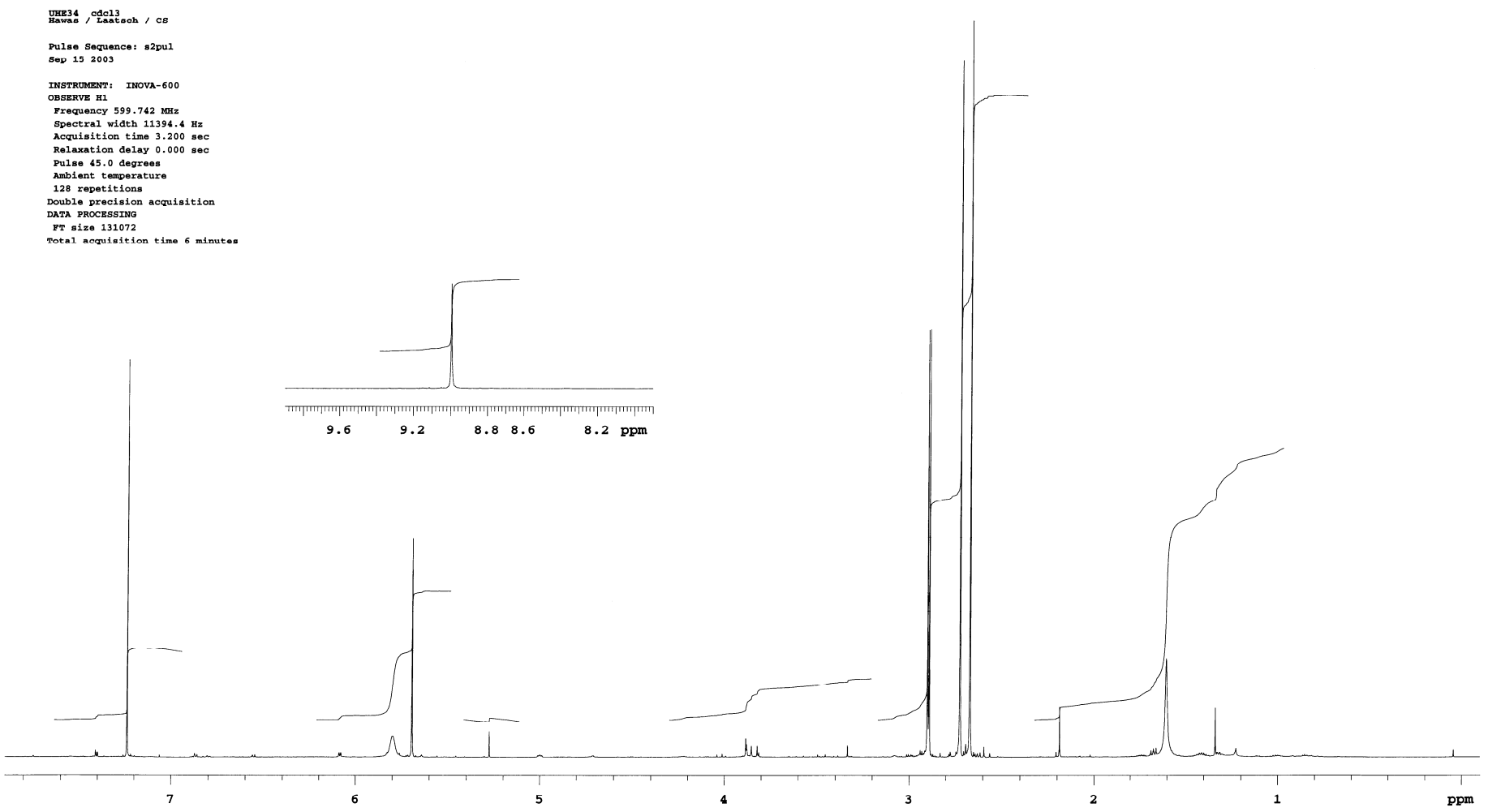


Figure S2: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Mansouramycin A (**1**).

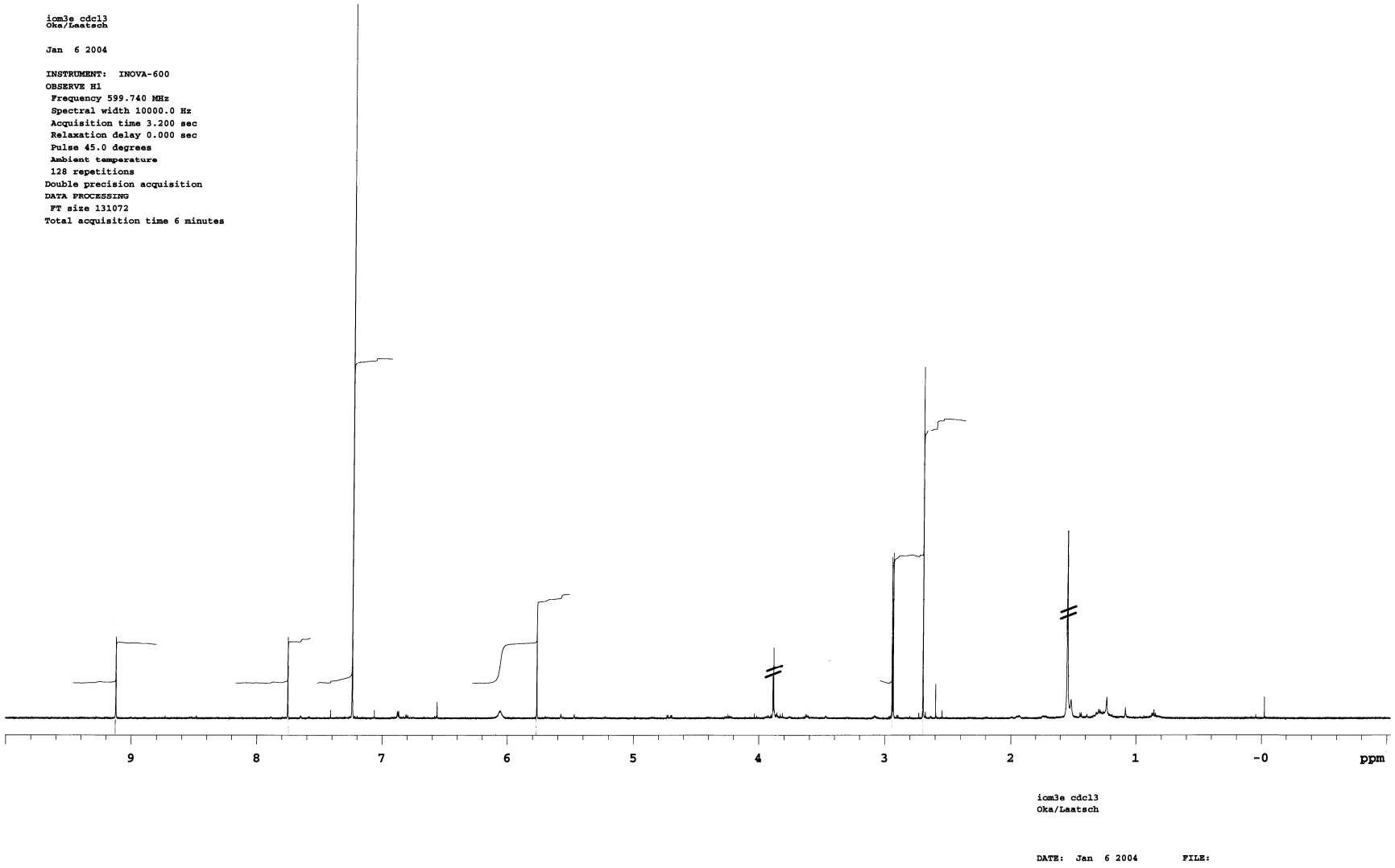


Figure S3: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of 3-methyl-7-(methylamino)-5,8-isoquinolinedione (**2**).

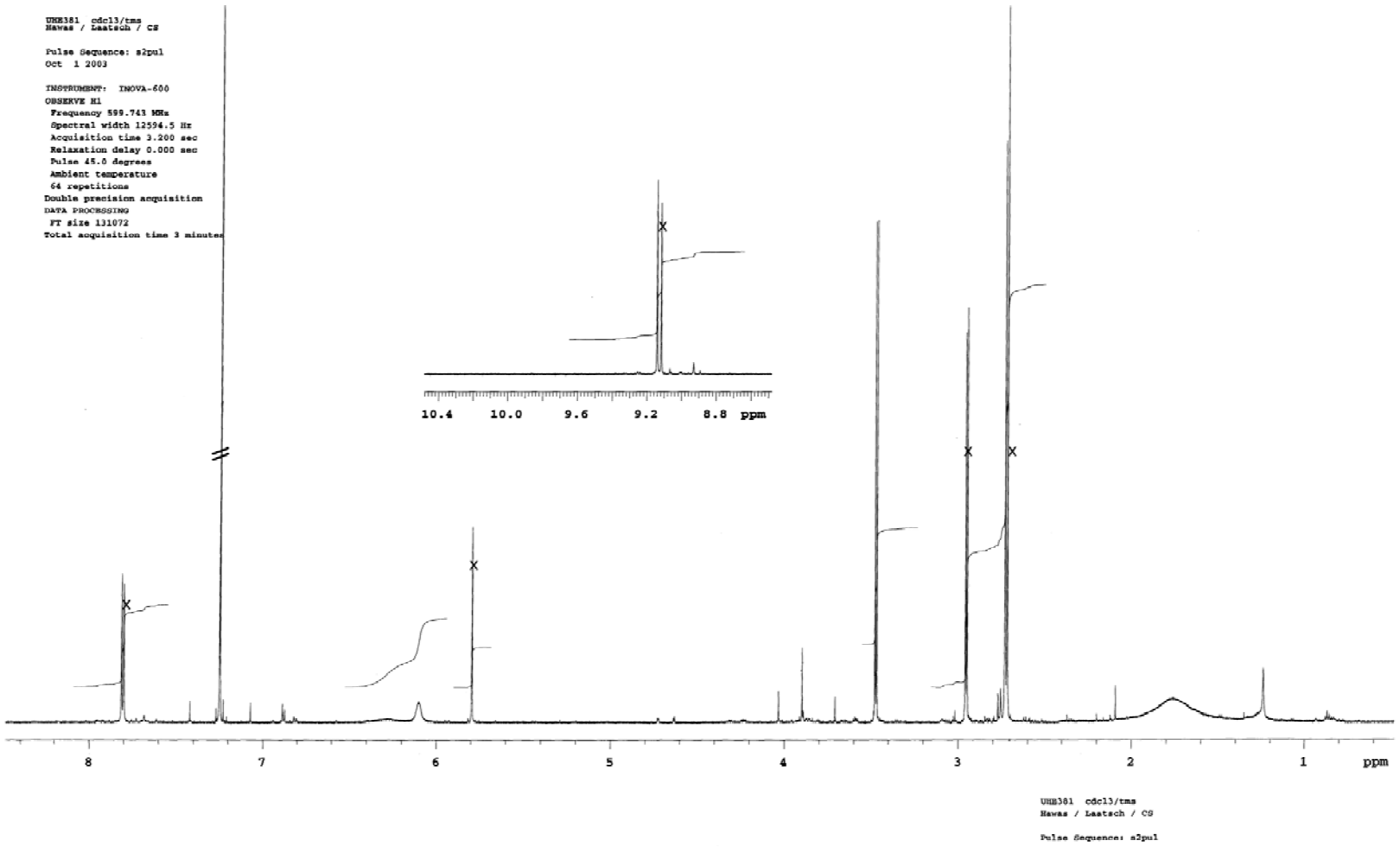


Figure S4: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Mansouramycin B (**3**), containing some **1** (x).

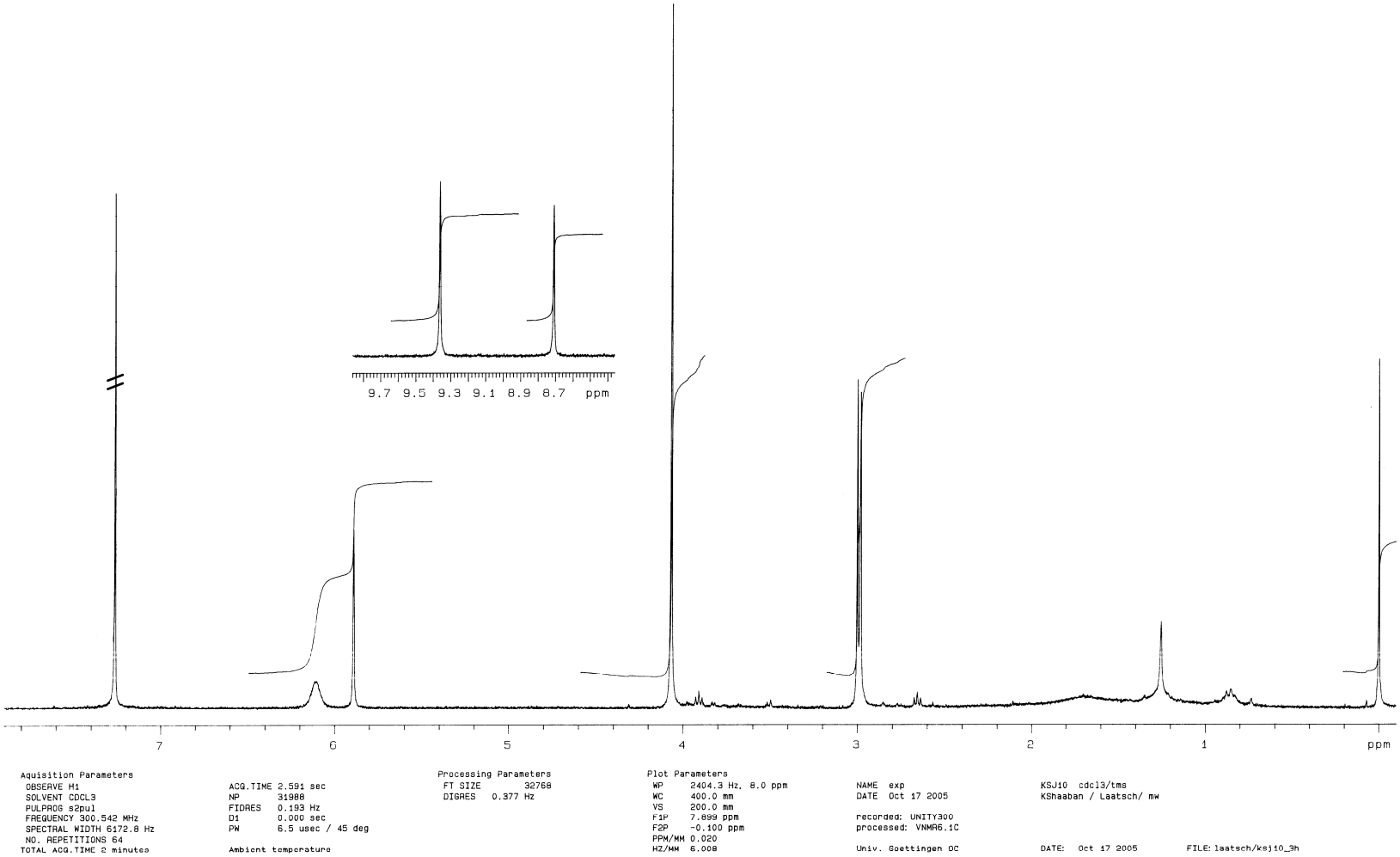


Figure S5: ^{1}H NMR Spectrum ($CDCl_3$, 300 MHz) of Mansouramycin C (**4**).

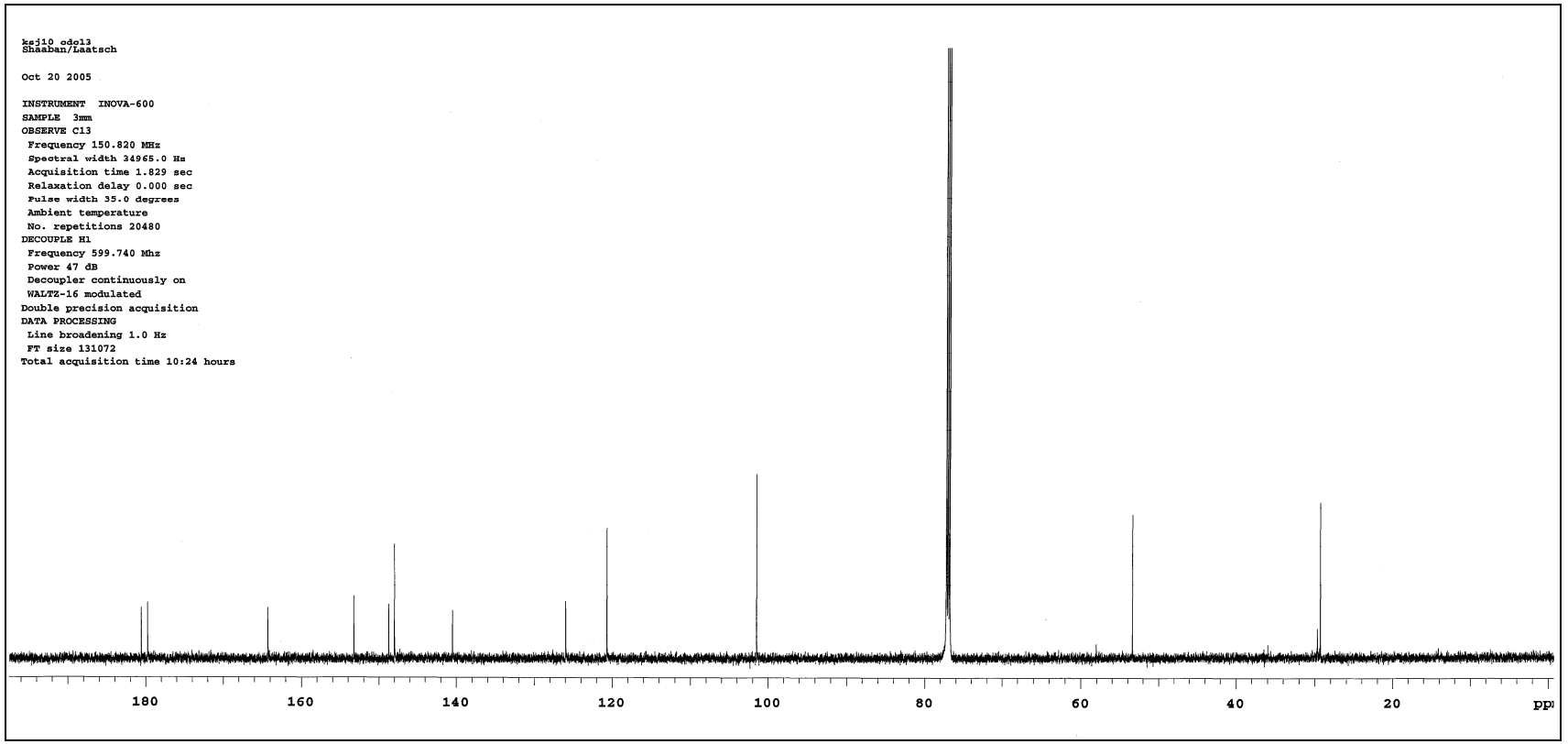


Figure S6: ^{13}C NMR Spectrum ($CDCl_3$, 150 MHz) of Mansouramycin C (**4**).

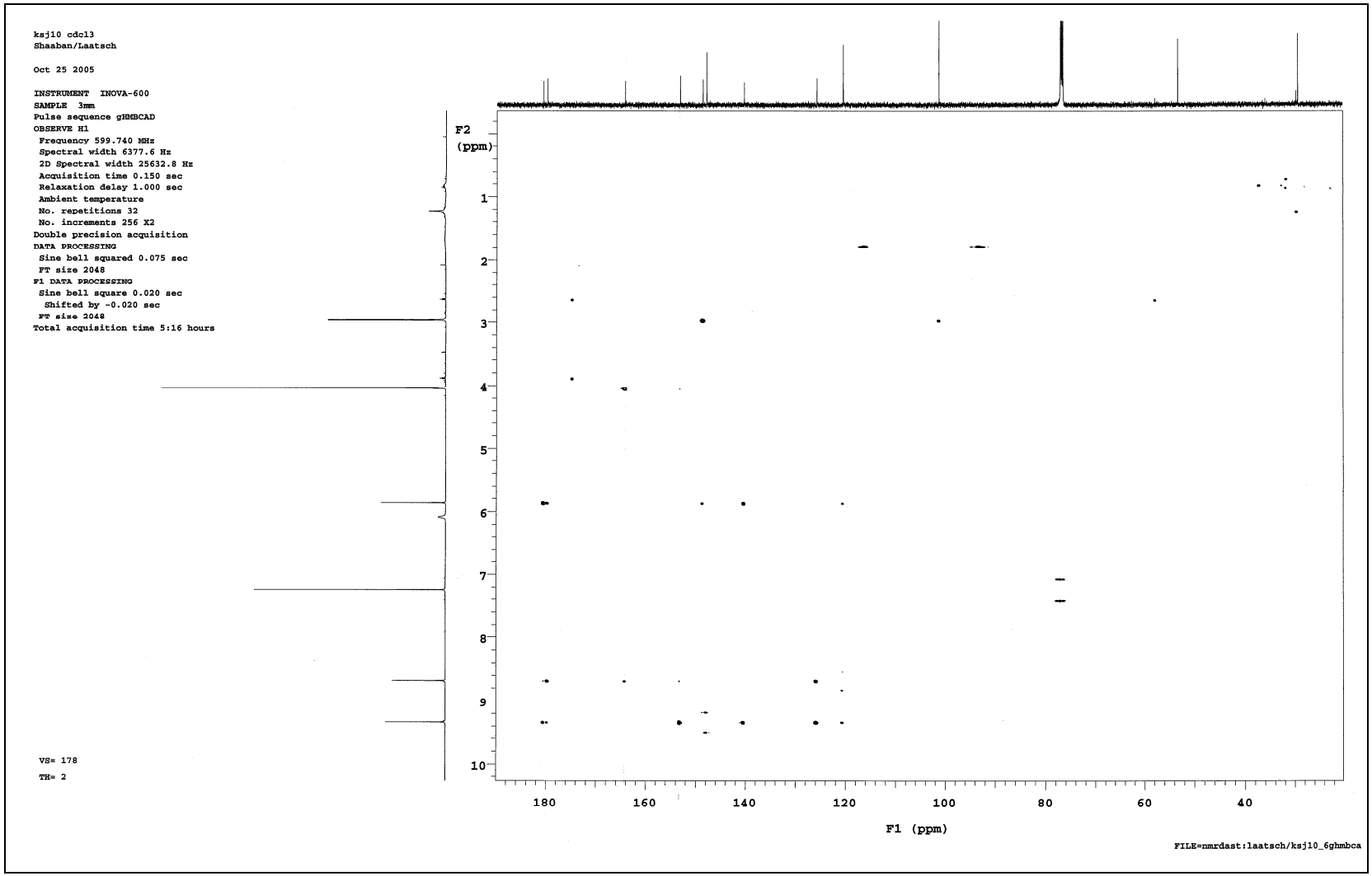


Figure S7: HMBC Spectrum ($CDCl_3$, 600 MHz) of Mansouramycin C (**4**).

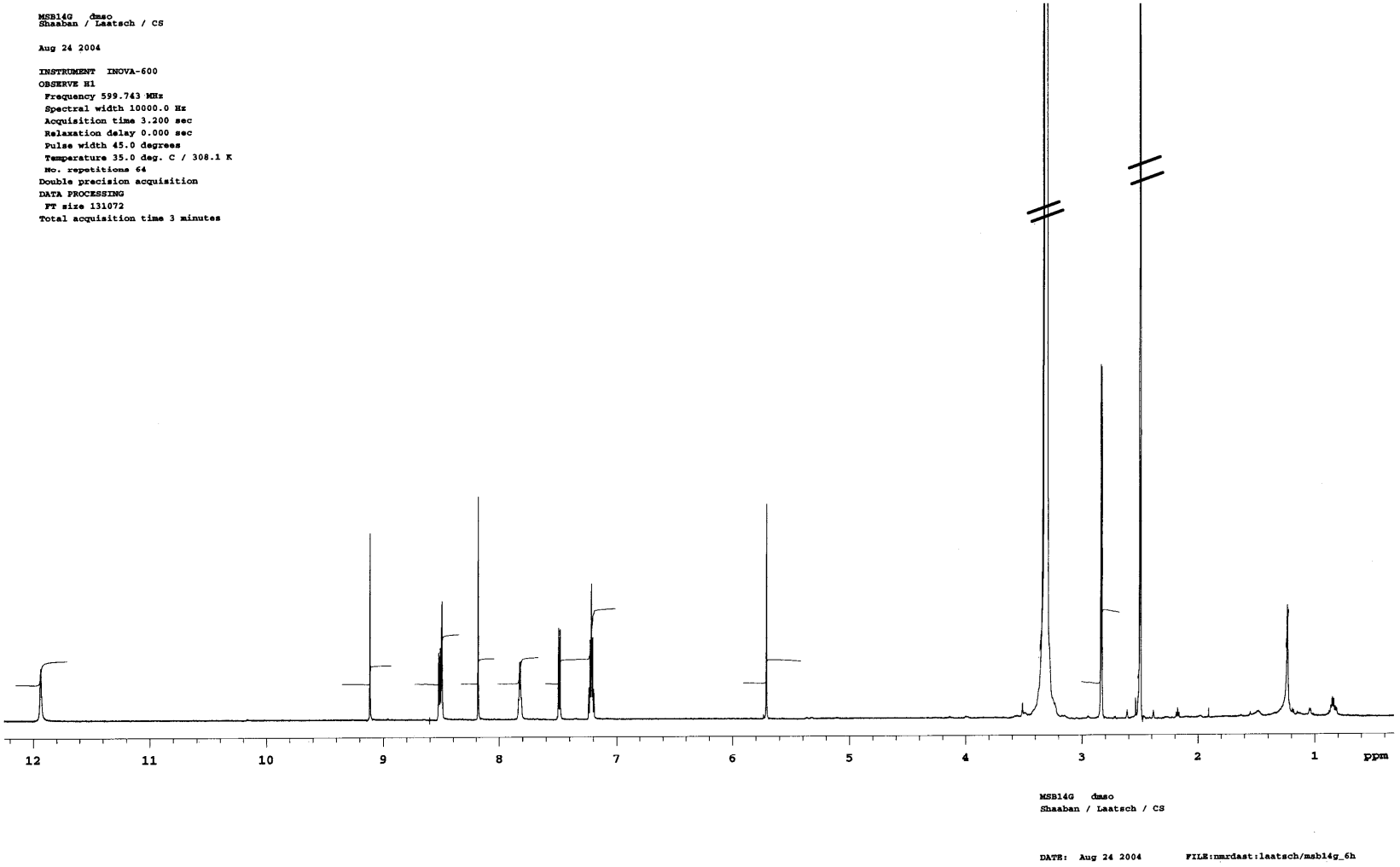


Figure S8: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Mansouramycin D (**5**).

Table S1. Cytotoxic activity of isoquinolinequinones **1** - **4** against tumor cell lines in a monolayer proliferation assay.

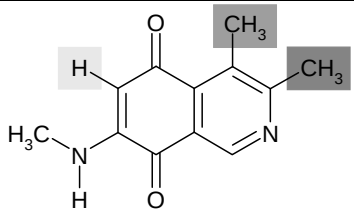
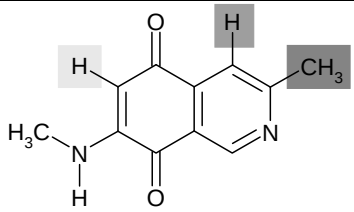
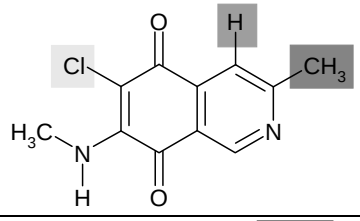
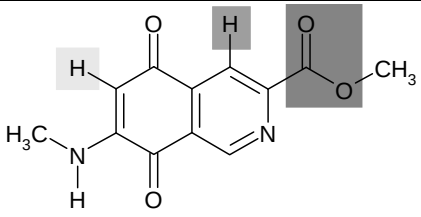
Tumor type	Cell line	IC_{50} [μM]			
		1	**2**	**3**	**4**
Bladder	BXF 1218L	28.19	10.26	1.38	0.134
	BXF T24	12.58	0.61	n.d.[a]	0.008
Glioblastoma	CNXF 498NL	14.39	5.21	1.34	0.130
	CNXF SF268	14.41	1.8	n.d.	0.008
Colon	CXF HCT116	9.11	3.62	n.d.	0.114
	CXF HT29	4.63	1.98	n.d.	0.146
Stomach	GXF 251L	31.9	3.6	1.75	0.167
Head & neck	HNXF 536L	0.71	0.38	n.d.	0.146
Lung	LXF 1121L	27.14	6.56	n.d.	0.150
	LXF 289L	19.05	3.04	5.96	0.130
	LXF 526L	18.99	10.62	n.d.	0.110
	LXF 529L	12.42	4.88	1.54	0.089
	LXF 629L	4.1	1.18	1.23	0.016
	LXF H460	7.11	3.92	n.d.	0.134
Breast	MAXF 401NL	47.76	17.31	3.55	0.195
	MAXF MCF7	2.34	1.11	n.d.	0.012
Melanoma	MEXF 276L	2.44	0.35	0.36	0.008
	MEXF 394NL	15.57	5.72	n.d.	0.106
	MEXF 462NL	49.93	18.97	5.64	0.179
	MEXF 514L	2.6	2.02	n.d.	0.012
	MEXF 520L	5.45	0.24	n.d.	0.012
Ovary	OVXF 1619L	13.15	4.01	n.d.	0.045
	OVXF 899L	34.89	6.6	13.91	0.134
	OVXF OVCAR3	32.31	7.64	2.0	0.012
Pancreas	PAXF 1657L	26.03	4.93	1.81	0.061
	PAXF PANC1	26.75	3.83	n.d.	0.549
Prostate	PRXF 22RV1	21.74	4.69	5.67	0.671
	PRXF DU145	1.25	0.34	n.d.	0.992
	PRXF LNCAP	21.67	6.36	n.d.	1.431
	PRXF PC3M	32.56	6.04	3.23	0.215
Mesothelioma	PXF 1752L	46.3	6.02	5.19	0.130
Kidney	RXF 1781L	16.36	9.89	n.d.	0.114
	RXF 393NL	18.65	4.16	1.57	0.122
	RXF 486L	59.14	50.62	17.89	1.646
	RXF 944L	18.1	5.43	n.d.	0.020
Uterus	UXF 1138L	18.02	2.23	1.68	0.012
Mean		13.44	3.49	2.7	0.089
Selectivity[b]		6/36	6/36	1/18	10/36

[a] n.d.: not determined, [b] IC_{50} < 1/2 mean IC_{50} value / total

Table S2. Cytotoxic activity of 3-methyl-7-(methylamino)-5,8-isoquinolinedione (**2**) against cell suspensions derived from tumor xenografts in a clonogenic assay.

Tumor type	Tumor model	IC_{50} [µM]
Blood stem cells	AHS NSB005	4.58
	AHS NSB008	4.53
Bladder	BXF 1218	4.34
Colon	CXF 243	10.32
Liver	LIXF 575	8.35
Lung	LXFA 526	4.31
	LXFA 629	1.63
Breast	MAXF 1322	8.35
	MAXF 401	3.89
Melanoma	MEXF 276	0.33
	MEXF 514	0.05
Ovary	OVXF 899	5.35
Kidney	RXF 631	7.81
Mean		2.94

Table S3. Structure-activity relationship of isoquinolinequinones **1 - 4**.

Compound	Structure	FA potency (mean IC_{50}, µM)	FA selectivity (n, %)
Mansouramycin A (**1**)		13.44	6/36 17
3-methyl-7-(methyl-amino)-5,8-isoquinoline-dione (**2**)		3.49	6/36 17
Mansouramycin B (**3**)		2.7	1/18 6
Mansouramycin C (**4**)		0.089	10/36 28