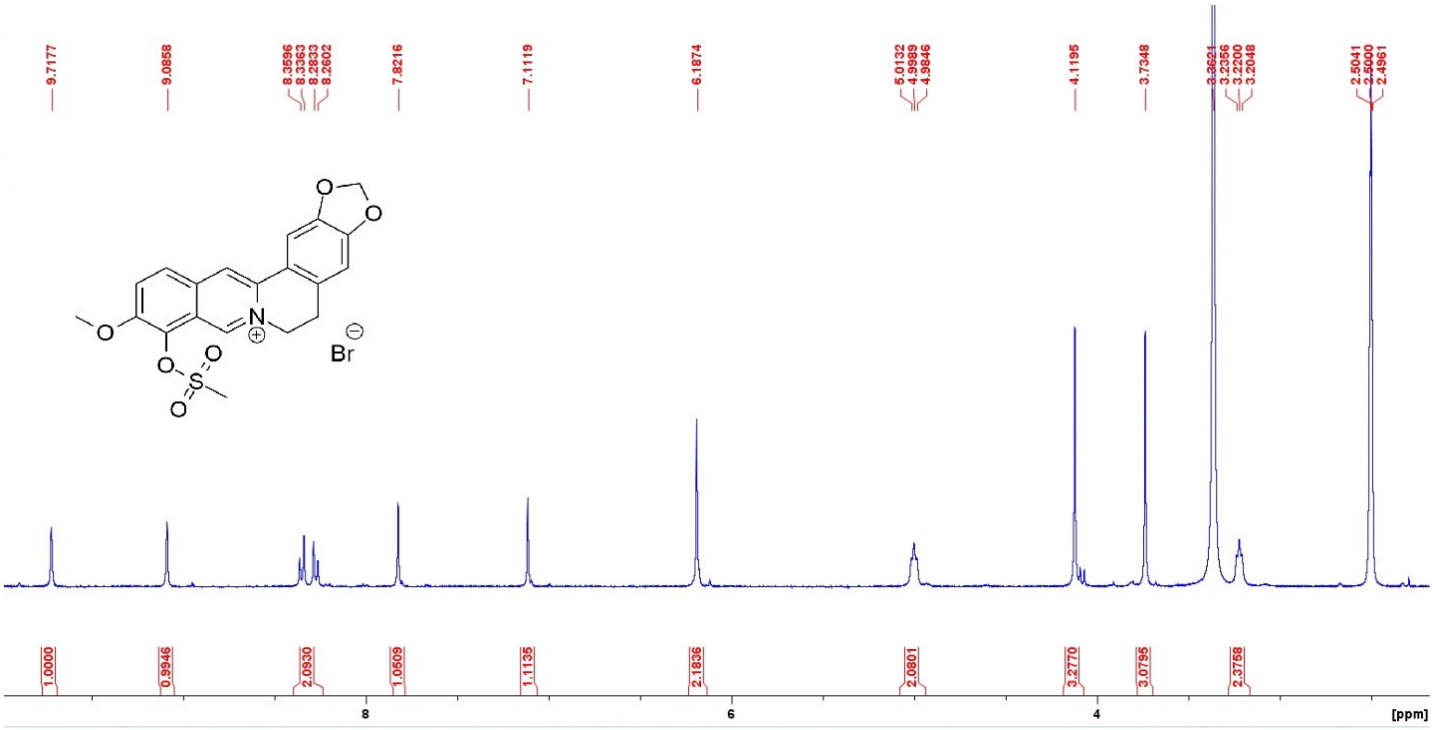
SUPPLEMENTARY MATERIALS

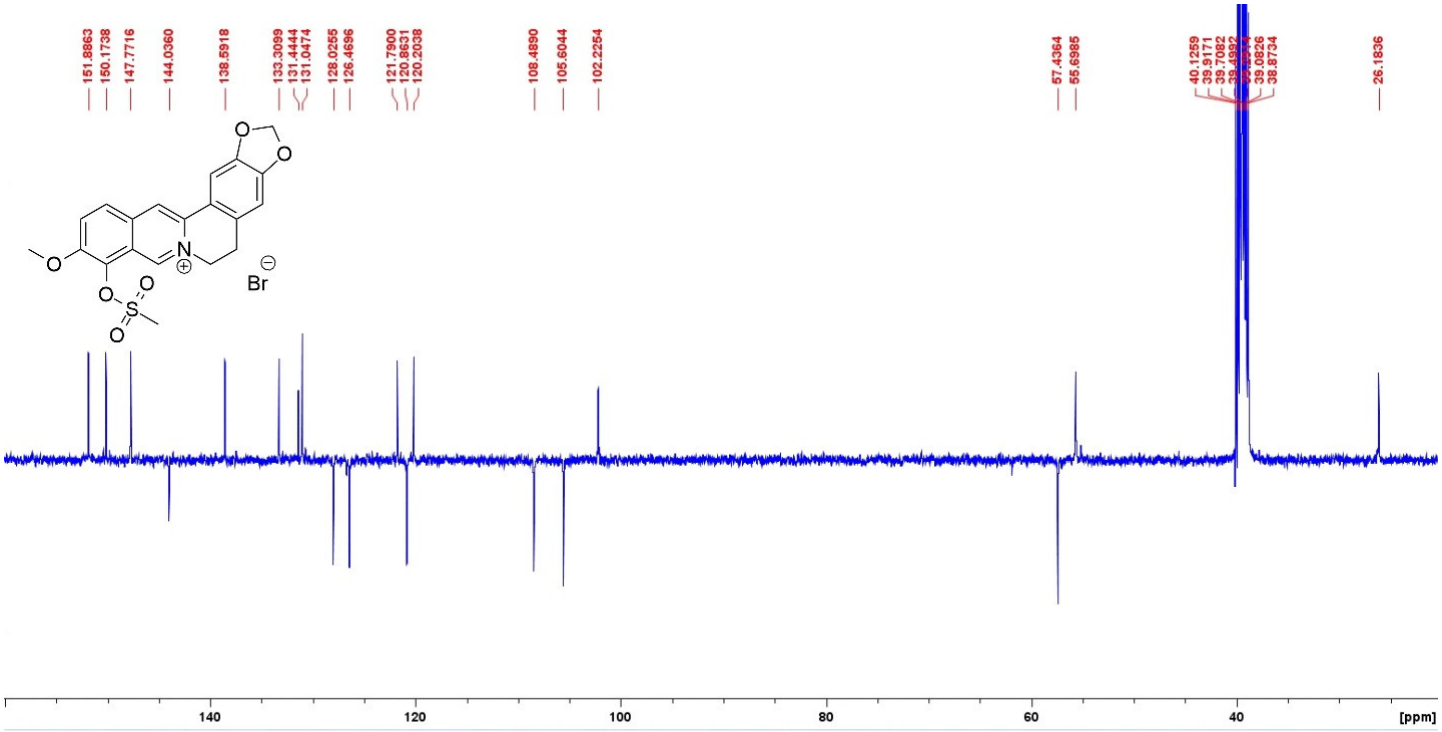
The first berberine-based inhibitors of tyrosyl-DNA phosphodiesterase 1 (Tdp1), an important DNA repair enzyme

Elizaveta D. Gladkova, Ivan V. Nechepurenko, Roman A. Bredikhin, Arina A. Chepanova, Alexandra L. Zakharenko, Olga A. Luzina, Ekaterina S. Ilina, Nadezhda S. Dyrkheeva, Evgeniya M. Mamontova, Rashid O. Anarbaev, Jóhannes Reynisson, Konstantin P. Volcho, Nariman F. Salakhutdinov and Olga I. Lavrik

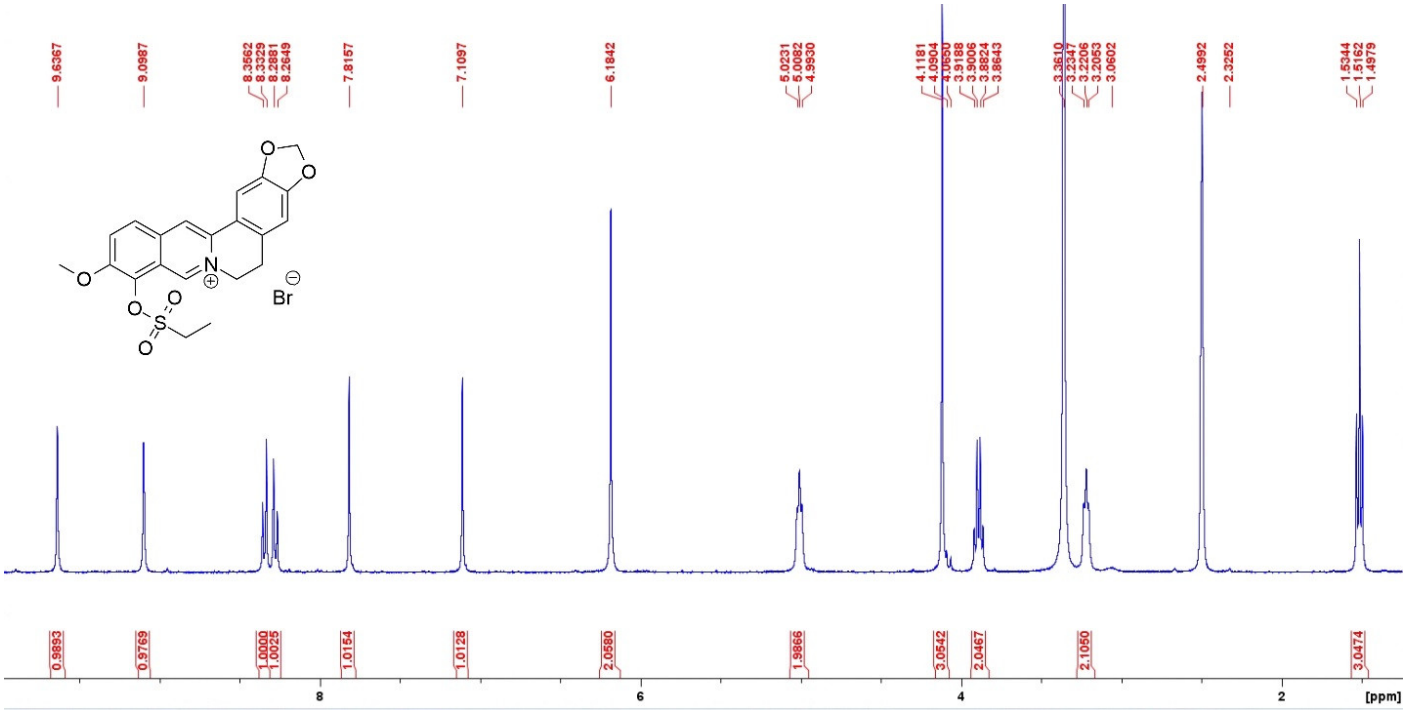
Compound **10a (^{1}H NMR)**



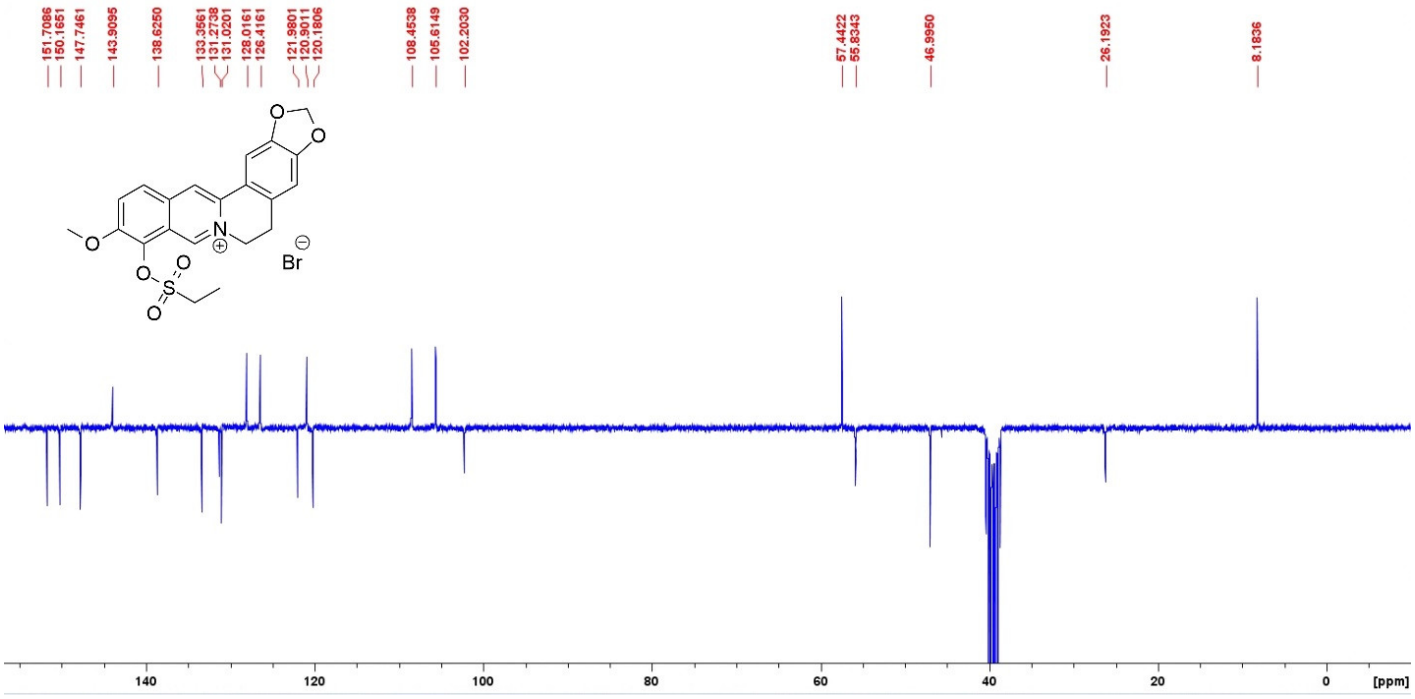
Compound **10a (^{13}C NMR)**



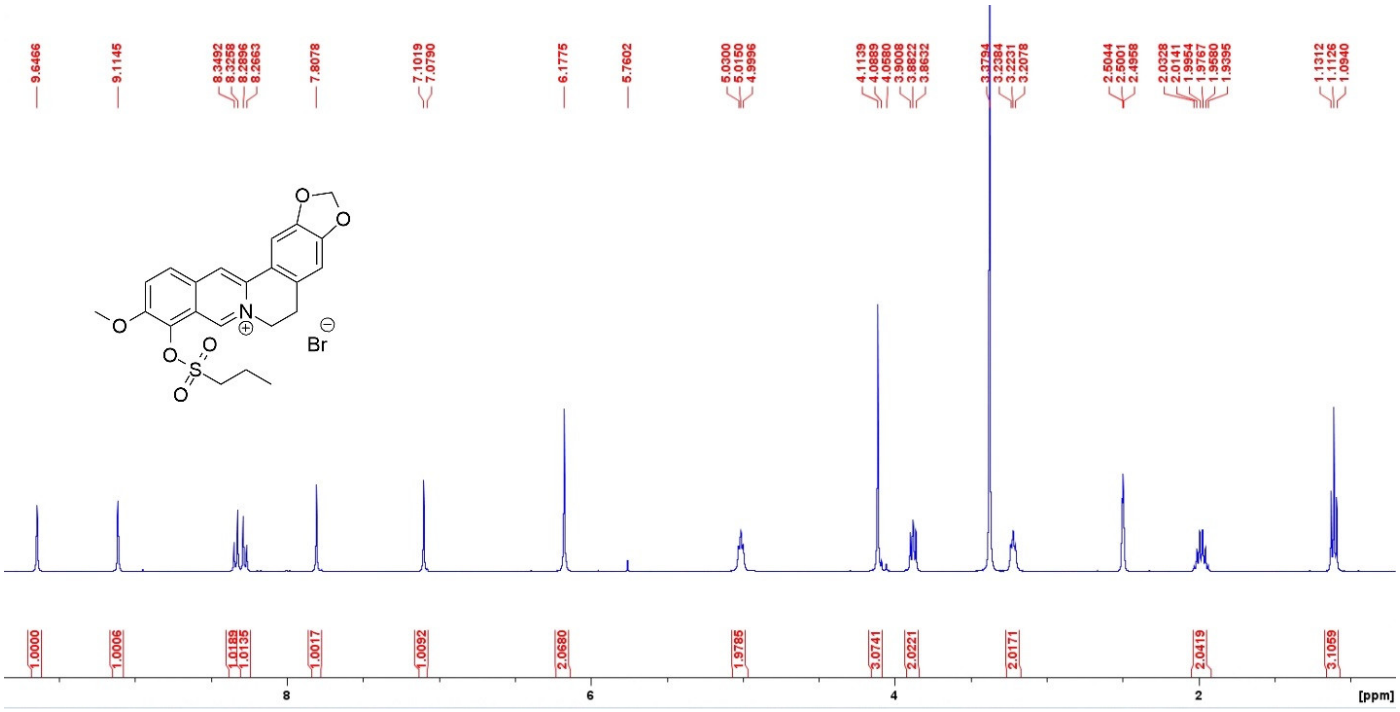
Compound **10b (^{1}H NMR)**



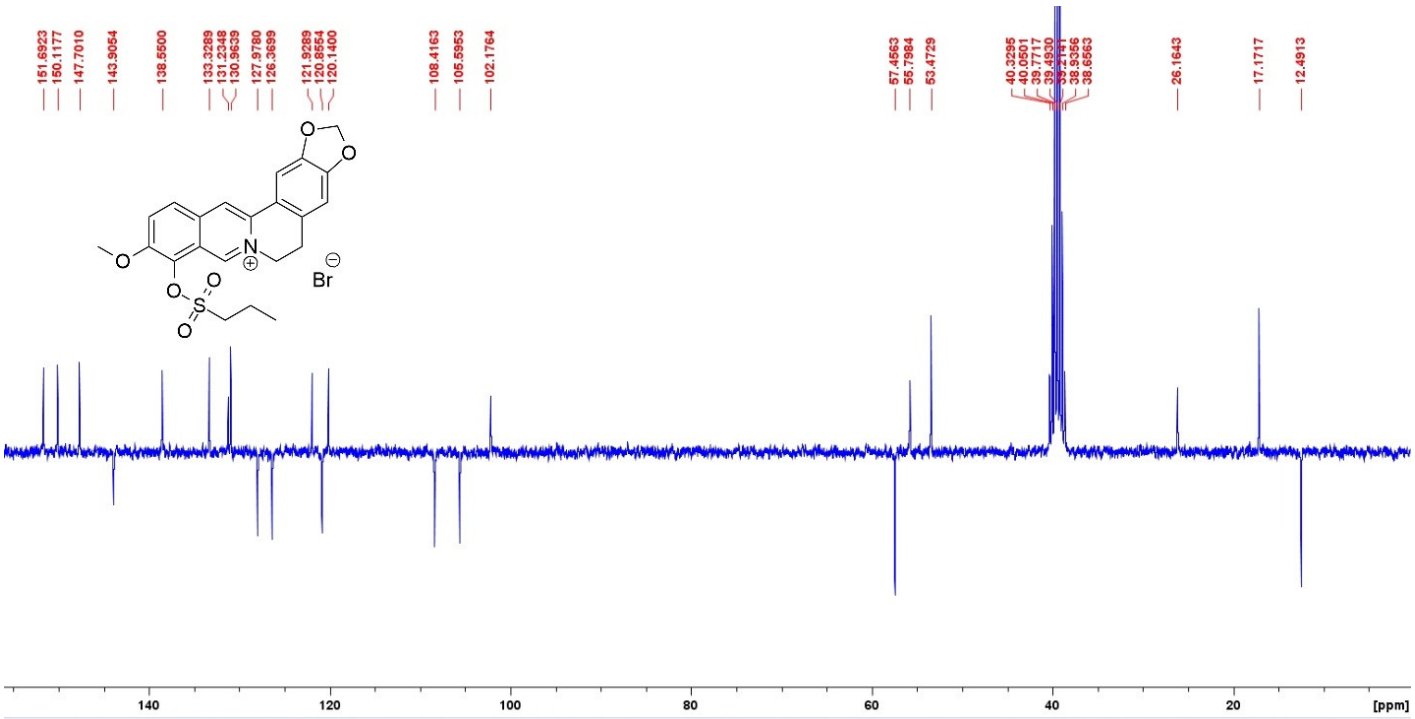
Compound **10b (^{13}C NMR)**



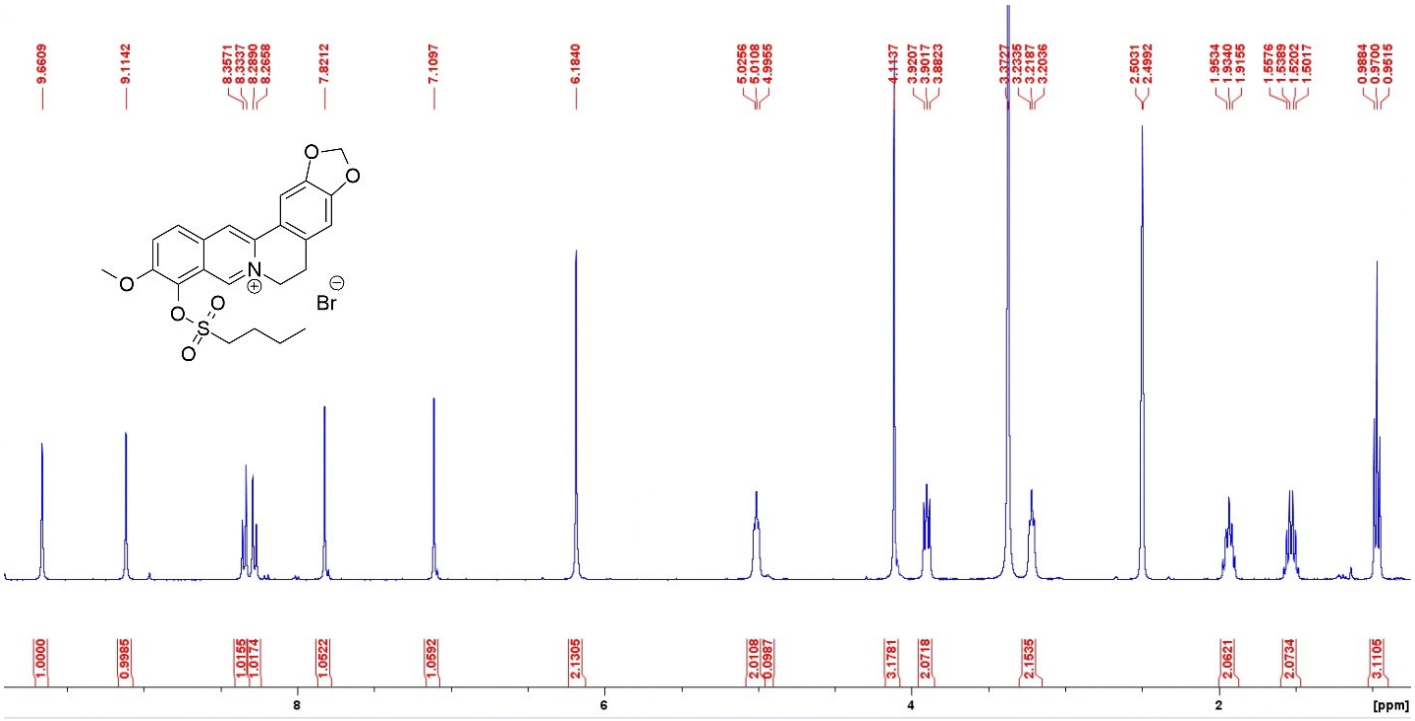
Compound **10c (^{1}H NMR)**



Compound **10c (^{13}C NMR)**



Compound **10d (^{1}H NMR)**



Compound **10d (^{13}C NMR)**

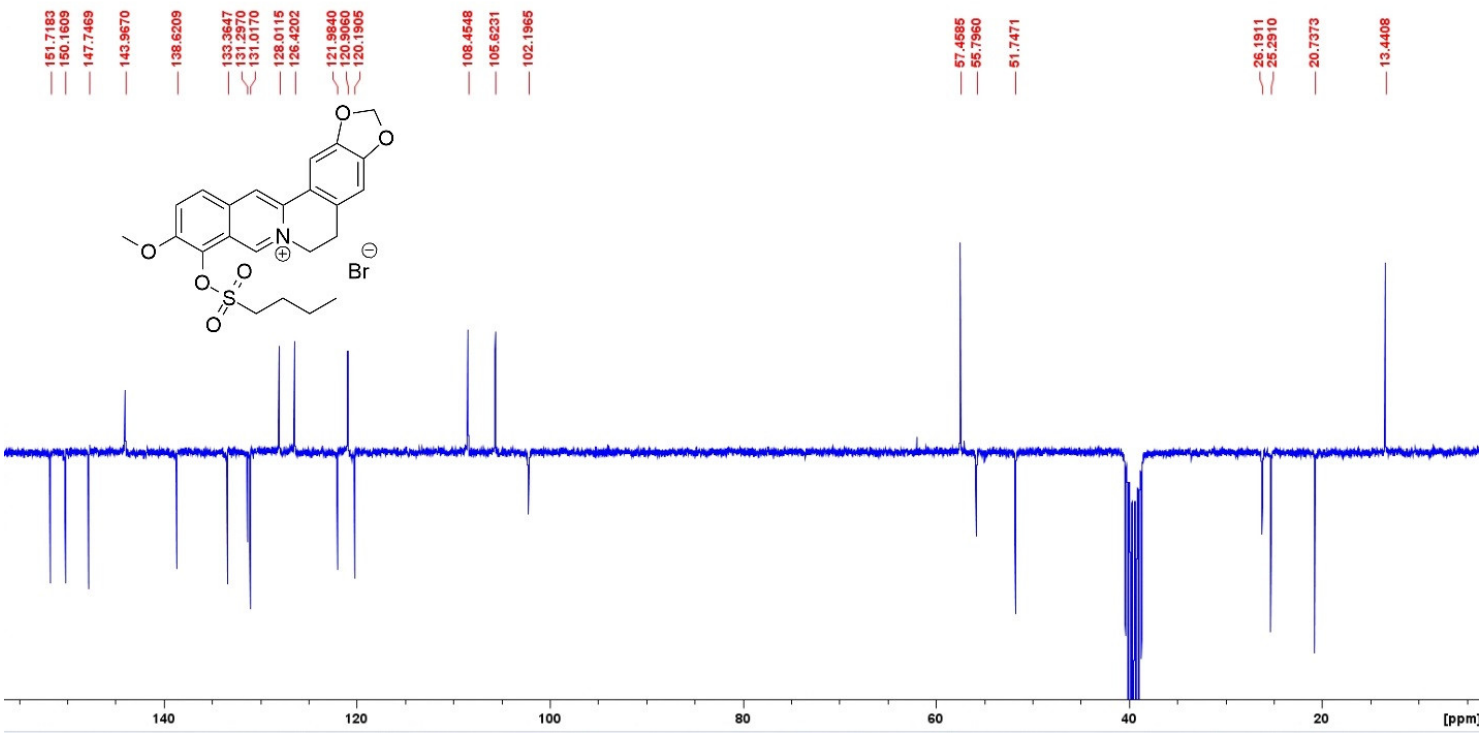


Table S1. The binding scores for the scoring functions used.

Ligand	ASP	ChemScore	GoldScore	ChemPLP	IC_{50} (μM)
9	31.0	23.4	48.8	55.9	>15
10a	33.4	27.6	59.6	62.0	>15
10b	34.9	28.1	60.9	63.3	>15
10c	33.8	27.9	66.2	62.8	>15
10d	34.4	29.0	59.6	72.6	>15
11a	34.3	26.5	52.0	55.0	>15
11b	31.4	27.9	58.8	59.6	>15
11c	32.6	24.9	55.4	59.7	>15
11d	33.1	27.0	57.4	63.9	>15
11e	38.1	31.6	67.9	63.1	>15
11f	39.2	24.1	58.8	65.7	0.98±0.20
11g	38.2	25.3	62.7	64.8	1.045±0.05
11h	42.5	26.5	67.4	70.2	0.93±0.22
12a	34.0	25.0	56.6	61.0	>15
12b	34.8	28.4	60.4	63.1	>15
12c	33.3	28.0	61.3	60.8	2.86±1.25
12d	34.6	27.1	58.2	59.8	4.06±1.05
12e	39.0	31.6	67.9	64.3	>15
12f	38.4	26.3	59.4	60.9	0.53±0.01
12g	38.3	27.4	59.0	62.3	1.33±0.28
12h	39.1	25.9	58.5	69.1	1.38±0.30

Table S2. The molecular descriptors and their corresponding Known Drug Indexes 2a and 2b (KDI2a/2b).

Name	MW	Log P	HA	HD	PSA	Rot.Bond.	KDI2a	KDI2b
9[a]	336.4	2.3	4	0	x	x	x	x
10a[a]	400.4	1.6	6	0	x	x	x	x
10b[a]	414.5	1.9	6	0	x	x	x	x
10c[a]	428.5	2.4	6	0	x	x	x	x
10d[a]	442.5	2.8	6	0	x	x	x	x
11a	403.4	1.7	8.75	0	67.1	3	5.36	0.48
11b	417.5	2.0	8.75	0	67.4	4	5.40	0.51

11c	431.5	2.1	8.75	0	72.9	5	5.39	0.50
11d	445.5	2.8	8.75	0	71.8	6	5.34	0.47
11e	479.5	3.4	8.75	0	77.0	4	5.27	0.43
11f	555.5	4.2	8.75	0	71.1	4	4.91	0.26
11g	537.5	3.9	8.75	0	71.1	4	5.00	0.30
11h	605.5	4.9	8.75	0	69.1	4	4.62	0.15
12a	482.3	2.3	8.75	0	66.1	3	5.21	0.41
12b	496.4	2.5	8.75	0	73.4	4	5.22	0.41
12c	510.4	2.6	8.75	0	72.6	5	5.16	0.38
12d	524.4	3.3	8.75	0	71.4	6	5.06	0.33
12e	558.4	3.9	8.75	0	75.0	4	4.93	0.26
12f	634.4	4.6	8.75	0	71.6	4	4.58	0.12
12g	616.4	4.4	8.75	0	72.1	4	4.67	0.15
12h	684.4	5.4	8.75	0	70.9	4	4.35	0.06

[a] Values generated using Scigress, x – no values

Table S3. Definition of lead-like, drug-like and Known drug space (KDS) in terms of molecular descriptors. The values given are the maxima for each descriptor for the volumes of chemical space used.

	Lead-like Space	**Drug-like Space**	**Known Drug Space**
Molecular weight (g mol^{-1})	300	500	800
Lipophilicity (Log P)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area ($Å^2$) (PSA)	60	140	180
Rotatable bonds (RB)	3	10	17