

**Table 1 Topotecan mapping to LUDI1 pharmacophore**

Pose	1	2	3	4	5	6
<i>Mapped features</i>	3	3	3	3	4	4
HYD Tyr426	-	-	-	-	-	y
HYD Leu721	-	y	-	-	y	-
HBD Asn722	-	-	y	y	y	-
HBD Asp533	-	y	-	-	-	-
HBA Arg364	y	-	-	y	-	y
HBD Glu356	y	-	y	-	y	y
CYPI	y	y	y	y	y	y
<i>Fit value</i>	0.40	0.36	0.31	0.23	0.12	0.001
<i>RMSD to X-ray pose (Å)</i>	5.00	8.34	9.40	7.22	6.08	8.66

**Table 2 Camptothecin mapping to LUDI1 pharmacophore**

Pose	1	2	3	4	5
<i>Mapped features</i>	2	3	3	3	3
HYD Tyr426	-	y	-	-	-
HYD Leu721	-	y	y	y	-
HBD Asn722	-	y	y	-	-
HBD Asp533	y	-	-	-	-
HBA Arg364	-	-	-	y	y
HBD Glu356	-	-	-	-	y
CYPI	y	-	y	y	y
<i>Fit value</i>	0.39	0.14	0.12	0.001	0.0003
<i>RMSD to X-ray pose (Å)</i>	3.46	7.85	6.11	6.01	9.71

**Table 3 MJ-II-38 mapping to LUDI1 pharmacophore**

Pose	1	2	3
<i>Mapped features</i>	2	2	2
HYD Tyr426	-	y	-
HYD Leu721	y	-	-
HBD Asn722	-	-	-
HBD Asp533	-	-	-
HBA Arg364	-	-	y
HBD Glu356	-	-	-
CYPI	y	y	y
<i>Fit value</i>	0.37	0.34	0.27
<i>RMSD to X-ray pose (Å)</i>	5.79	4.25	6.12

**Table 4 AI-III-52 mapping to LUDI1 pharmacophore**

Pose	1	2	3	4
<i>Mapped features</i>	2	3	3	2
HYD Tyr426	-	y	y	y
HYD Leu721	y	-	y	-
HBD Asn722	-	-	-	-
HBD Asp533	-	-	-	-
HBA Arg364	-	y	-	-
HBD Glu356	-	-	-	-
CYPI	y	y	y	y
<i>Fit value</i>	0.39	0.02	0.01	0.004
<i>RMSD to X-ray pose (Å)</i>	3.12	6.91	8.89	6.67

**Table 5 SA315F mapping to LUDI1 pharmacophore**

Pose	1	2	3	4	5	6	7	8
<i>Mapped features</i>	3	3	4	3	3	4	4	4
HYD Tyr426	-	-	-	-	-	-	-	-
HYD Leu721	-	y	-	-	y	y	-	-
HBD Asn722	y	y	y	-	-	y	y	-
HBD Asp533	y	-	y	-	-	-	-	y
HBA Arg364	-	-	y	y	-	-	y	y
HBD Glu356	-	-	-	y	y	y	y	y
CYPI	y	y	y	y	y	y	y	y
<i>Fit value</i>	0.56	0.41	0.36	0.25	0.22	0.18	0.14	0.04
<i>RMSD to X-ray pose (Å)</i>	8.23	8.13	10.04	6.28	4.93	8.33	7.61	8.73

**Table 6 Topotecan mapping to LUDI2 pharmacophore, top 10 poses**

Pose	1	2	3	4	5	6	7	8	9	10
<i>Mapped features</i>	4	5	6	4	4	4	4	4	4	4
HYD Tyr426	y	y	y	-	-	y	-	y	y	-
HBD Asn722	-	-	-	-	-	y	-	-	-	-
HBD Thr718	y	y	-	-	-	-	y	-	-	-
HBD Asp533	-	-	-	-	-	-	-	-	-	-
HBA Arg364	-	-	y	-	-	-	y	y	y	y
HBD Glu356	-	-	-	-	-	-	-	-	-	-
HBD Lys354	-	-	-	-	-	-	-	-	-	y
HBA Asn352	-	y	y	y	y	-	y	-	-	-
HBD Asn352 bb	-	-	y	-	y	-	-	y	-	-
HBD DNA sugar1	-	-	-	-	-	-	-	-	-	-
HBD DNA sugar2	-	y	y	y	y	-	-	-	-	y
HBD DNA sugar3	y	-	-	y	-	y	-	-	y	-
CYPI	y	y	y	y	y	y	y	y	y	y
<i>Fit value</i>	0.33	0.33	0.11	0.08	0.05	0.02	0.02	0.005	0.002	0.001
<i>RMSD to X-ray pose (Å)</i>	9.00	9.00	10.00	3.47	3.83	9.27	3.72	5.41	6.34	4.21

**Table 7 Camptothecin mapping to LUDI2 pharmacophore**

Pose	1	2
<i>Mapped features</i>	4	4
HYD Tyr426	y	y
HBD Asn722	-	-
HBD Thr718	-	-
HBD Asp533	-	-
HBA Arg364	y	-
HBD Glu356	-	y
HBD Lys354	-	-
HBA Asn352	-	y
HBD Asn352 bb	-	-
HBD DNA sugar1	-	-
HBD DNA sugar2	-	-
HBD DNA sugar3	y	-
CYPI	y	y
<i>Fit value</i>	0.0003	0.0002
<i>RMSD to X-ray pose (Å)</i>	6.05	9.89

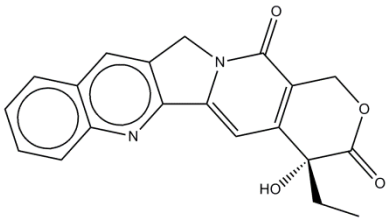
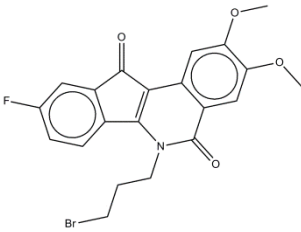
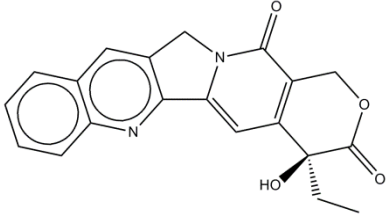
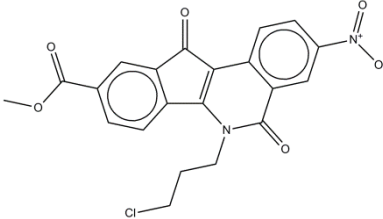
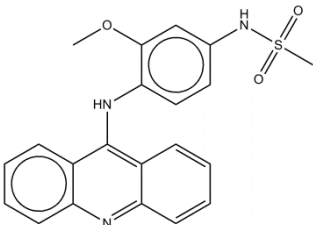
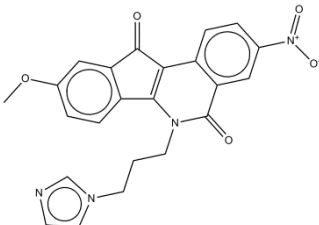
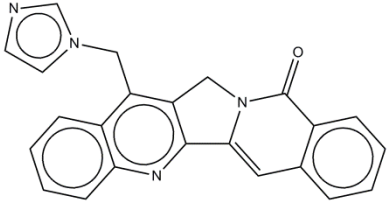
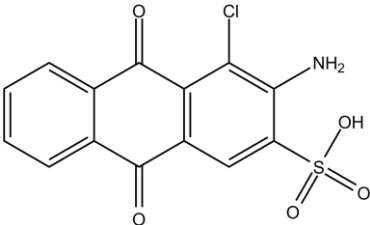
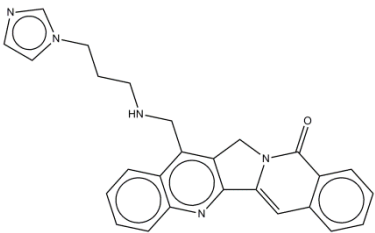
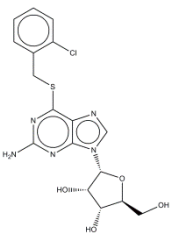
**Table 8 MJ-II-38 and AI-III-52 mapping to LUDI2 pharmacophore**

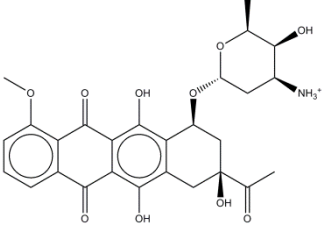
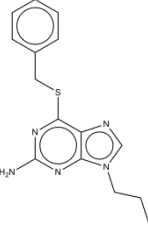
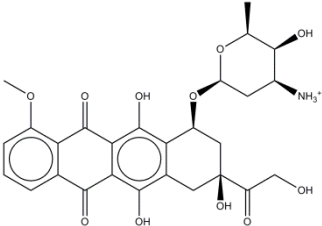
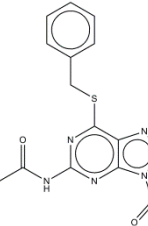
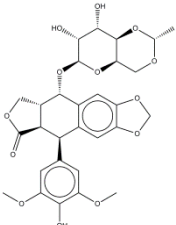
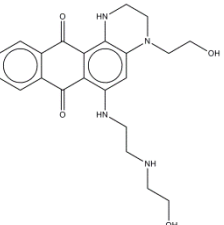
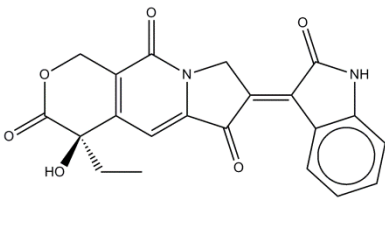
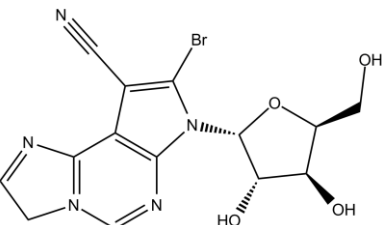
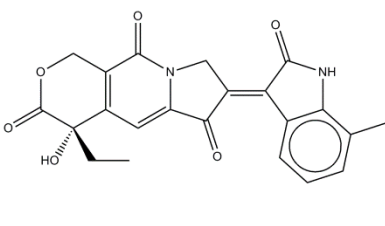
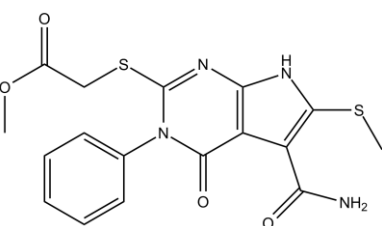
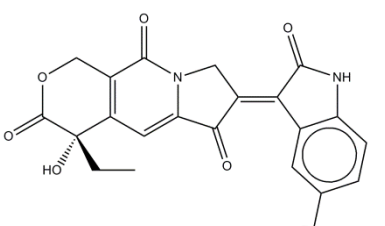
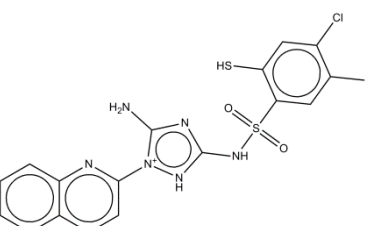
Pose	MJ-II-38	AI-III-52
<i>Mapped features</i>	4	4
HYD Tyr426	y	y
HBD Asn722	-	-
HBD Thr718	-	-
HBD Asp533	-	-
HBA Arg364	y	y
HBD Glu356	-	-
HBD Lys354	-	-
HBA Asn352	y	y
HBD Asn352 bb	-	-
HBD DNA sugar1	-	-
HBD DNA sugar2	-	-
HBD DNA sugar3	-	-
CYPI	y	y
<i>Fit value</i>	0.00004	0.008
<i>RMSD to X-ray pose (Å)</i>	6.14	7.09

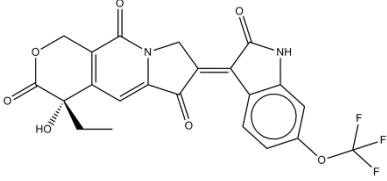
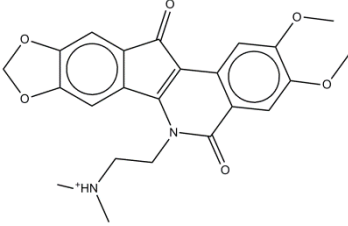
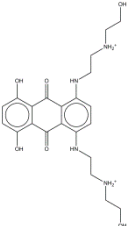
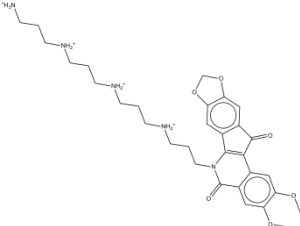
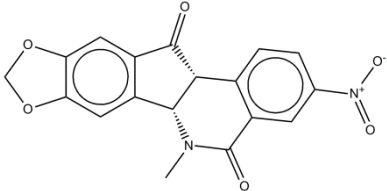
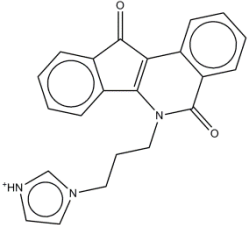
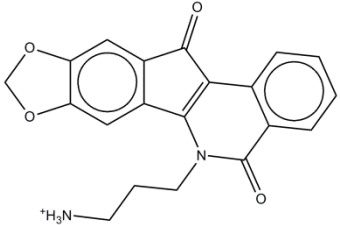
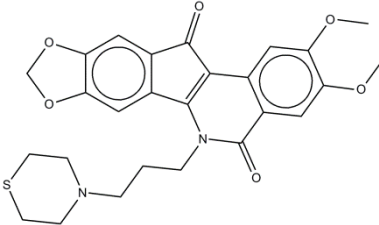
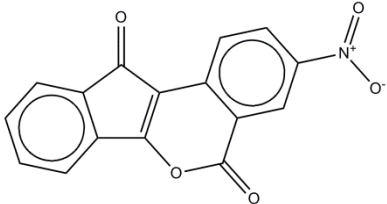
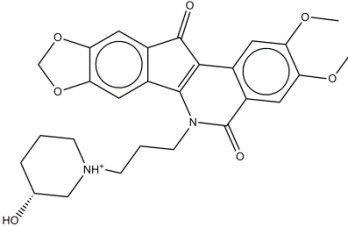
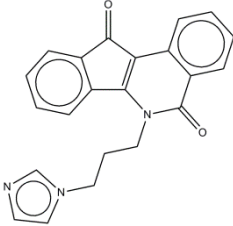
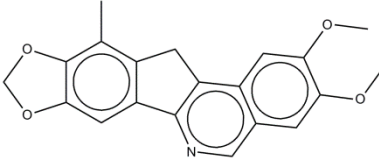
**Table 9 SA315F mapping to LUDI2 pharmacophore, top 6 poses**

<b>Pose</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>
<i>Mapped features</i>	5	6	5	8	6	7	5	5	5	5
HYD Tyr426	-	y	y	y	-	-	y	y	y	-
HBD Asn722	-	-	y	-	y	y	-	-	-	y
HBD Thr718	y	-	-	-	y	y	-	-	-	y
HBD Asp533	y	-	-	-	y	y	-	-	-	y
HBA Arg364	y	-	-	y	y	y	-	y	-	-
HBD Glu356	-	y	y	y	-	-	y	y	y	-
HBD Lys354	-	y	-	y	-	-	-	-	-	-
HBA Asn352	-	y	-	y	-	y	y	-	-	-
HBD Asn352 bb	-	y	y	y	-	-	y	y	y	-
HBD DNA sugar1	y	-	-	-	y	-	-	-	-	y
HBD DNA sugar2	-	-	-	y	-	y	-	-	-	-
HBD DNA sugar3	-	-	-	-	-	-	-	-	y	-
CYPI	y	y	y	y	y	y	y	y	y	y
<i>Fit value</i>	0.49	0.46	0.42	0.42	0.41	0.40	0.40	0.39	0.38	0.38
<i>RMSD to X-ray pose (Å)</i>	9.36	5.76	6.05	6.62	9.15	6.09	6.48	6.47	6.62	9.07

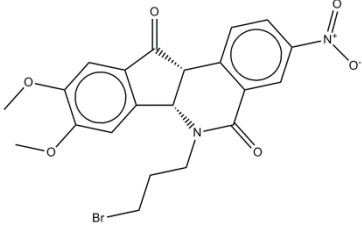
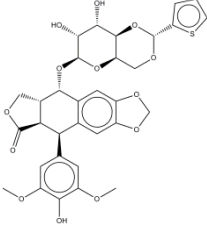
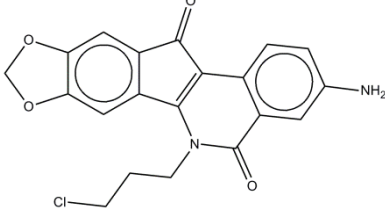
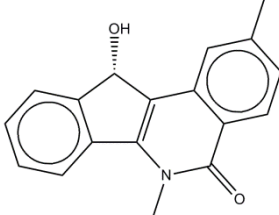
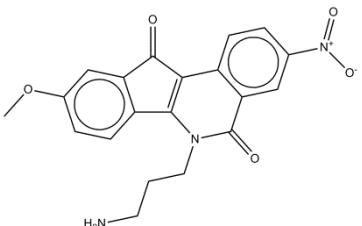
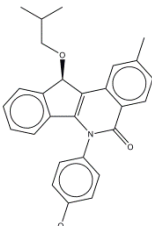
**Table 10 Validation set for Top1 docking**

Compound	Activity <sup>a</sup>	Compound	Activity <sup>a</sup>
20R-Camptothecin 	0 [1]	Morrell2007(2)_mol145 	3 [2]
20S-Camptothecin 	4 [1]	Morrell2007(2)_mol190 	1 [2]
Amsacrine 	0 [3]	Morrell2007_Mml38 	4 [4]
Cinelli2009_mol27d 	3 [5]	NSC 39875 	1.5 [6]
Cinelli2009_mol27j 	2 [5]	NSC 40666 	0 [6]

Compound	Activity <sup>a</sup>	Compound	Activity <sup>a</sup>
Daunorubicin 	0 [7]	NSC 42379 	1 [6]
Doxorubicin 	0 [8]	NSC 53340 	1 [6]
Etoposide 	0 <sup>b</sup>	NSC 270924 	0 [6]
Lackey1995_mol10 	0 [9]	NSC 318814 	1 [6]
Lackey1995_mol25 	0 [9]	NSC 661172 	1 [6]
Lackey1995_mol26 	0 [9]	NSC 674004 	1.5 [6]

Compound	Activity <sup>a</sup>	Compound	Activity <sup>a</sup>
Lackey1995_mol27	0 [9]	Nagarajan2003_mol23	0 [10]
			
Mitoxantrone	0 [11]	Nagarajan2003_mol7b	5 [10]
			
Morrell2004_mol14	3 [12]	Nagarajan2004_mol17	5 [13]
			
Morrell2004_mol31	1 [12]	Nagarajan2006_mol12	2 [14]
			
Morrell2006(2)_mol20	0 [15]	Nagarajan2006_mol13	3 [14]
			
Morrell2006(2)_mol30	5 [15]	Song2010_mol15	2 [16]
			



Compound	Activity <sup>a</sup>	Compound	Activity <sup>a</sup>
Morrell2006_mol37 	5 [17]	Teniposide 	0 <sup>b</sup>
Morrell2006_mol40 	0 [17]	Van2007_mol12b 	0 [18]
Morrell2006_mol6 	0 [17]	Van2007_mol15l 	5 [18]

<sup>a</sup> measured semi-quantitatively in DNA cleavage assay as described in the Methods section (for values higher than 0); <sup>b</sup> unpublished data, measured in DNA cleavage assay; [reference number], reference list at the end of this document.

**Table 11 Docking scores and performance in different docking settings**

<b>Compound</b>	<b>Flexible docking<sup>a</sup>, GOLD score<sup>b</sup></b>	<b>Flexible docking<sup>a</sup>, ChemPLP score<sup>b</sup></b>	<b>Flexible docking<sup>a</sup> with waters<sup>c</sup>, GOLD score<sup>b</sup></b>	<b>Flexible docking<sup>a</sup> with waters<sup>c</sup>, mean GOLD score<sup>d</sup></b>
20R-Camptothecin	76.22	88.96	83.77	77.14
20S-Camptothecin	81.07	102.40	89.63	79.69
Amsacrine	68.20	85.93	75.99	72.36
Cinelli2009_27d	94.75	110.38	98.32	95.31
Cinelli2009_27j	106.04	119.14	106.38	101.56
Daunorubicin	83.41	97.19	85.02	74.70
Doxorubicin	86.58	89.47	74.90	66.20
Etoposide	72.43	58.01	53.55	48.62
Lackey1995_10	50.69	95.66	57.15	52.06
Lackey1995_25	84.74	100.76	83.23	77.42
Lackey1995_26	82.78	96.85	88.65	77.58
Lackey1995_27	87.61	107.33	90.76	82.33
Mitoxantrone	81.31	115.24	67.08	57.49
Morrell2004_14	68.21	74.43	72.30	64.63
Morrell2004_31	85.39	99.40	90.55	76.00
Morrell2006(2)_20	79.50	90.79	81.83	78.33
Morrell2006(2)_30	84.31	106.45	85.14	84.42
Morrell2006_37	81.77	64.21	89.57	76.79
Morrell2006_40	79.94	97.63	81.40	78.64
Morrell2006_6	92.98	113.31	95.42	90.43
Morrell2007(2)_45	91.23	101.93	95.45	90.59
Morrell2007(2)_90	98.75	107.49	94.87	90.20
Morrell2007_38	95.88	111.05	91.92	88.93
NSC 0039875	81.60	100.96	90.61	77.86
NSC 0040666	77.76	70.19	65.62	72.63
NSC 0042379	81.18	101.53	97.18	74.98
NSC 0053340	75.78	109.94	101.20	77.02
NSC 0270924	71.33	113.92	96.32	65.16
NSC 0318814	74.44	79.94	85.24	68.79
NSC 0661172	75.22	75.98	78.80	70.17
NSC 0674004	92.98	82.18	80.74	78.12
Nagarajan2003_23	86.91	84.95	80.57	84.45
Nagarajan2003_7b	60.16	105.65	71.20	62.94
Nagarajan2004_17	88.18	79.63	71.83	91.00
Nagarajan2006_12	98.49	77.83	75.79	92.66
Nagarajan2006_13	90.31	65.83	80.92	88.26
Song2010_15	83.61	94.03	88.17	84.16
Teniposide	24.52	61.17	30.07	-0.06
Van2007_12b	76.79	96.23	80.45	77.33
Van2007_15l	99.61	100.19	108.60	96.95
<b>Area under the curve ROC evaluation</b>	<b>0.729 fair</b>	<b>0.561 fail</b>	<b>0.764 fair</b>	<b>0.722 fair</b>

<sup>a</sup> Flexible side chains defined as described in Methods section; <sup>b</sup>Score of the best pose of the largest cluster; <sup>c</sup> waters handled as described in Methods section; <sup>d</sup> mean score of largest cluster of poses.

**Table 12 Evaluation of different score thresholds on the retrieval of true positives and true negatives in flexible docking with waters, using GOLD scoring function**

Score threshold	True positives	True negatives
GOLD score $\geq$ 80	77 %	39 %
GOLD score $\geq$ 85	68 %	72 %
GOLD score $\geq$ 90	45 %	83 %
mean GOLD score $\geq$ 75	77 %	50 %
mean GOLD score $\geq$ 80	50 %	83 %

The score represents the best score of the largest cluster of poses at a 2.0 Å clustering distance. The mean score represents the mean score of the largest cluster.

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