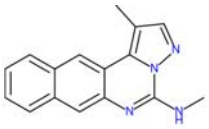
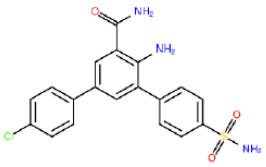
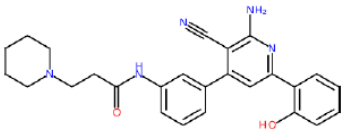
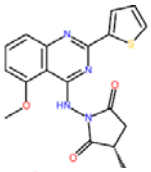
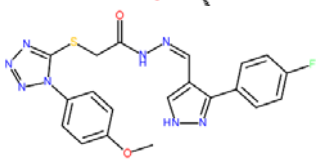
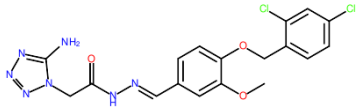
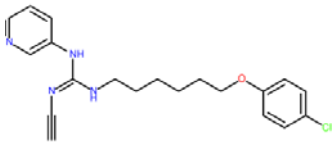
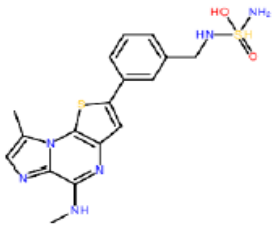
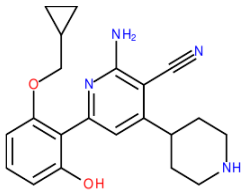
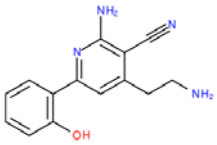
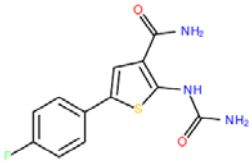
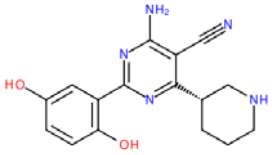
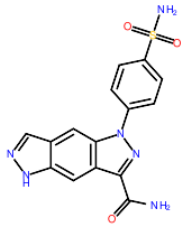
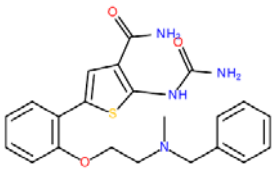
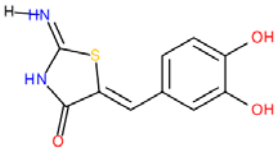
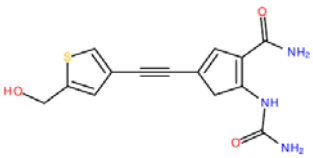
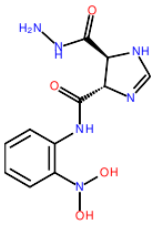
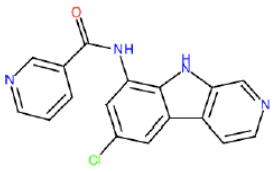
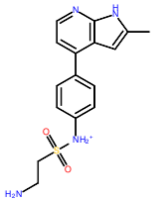
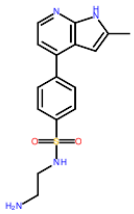
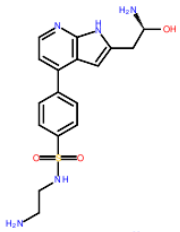
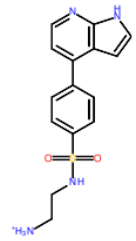
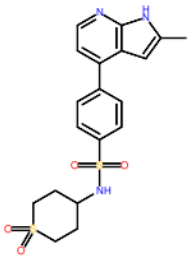
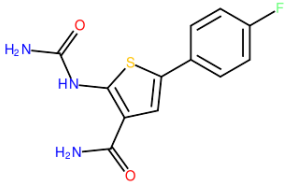
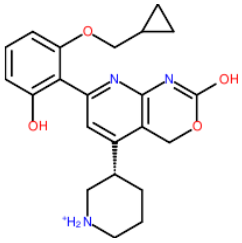
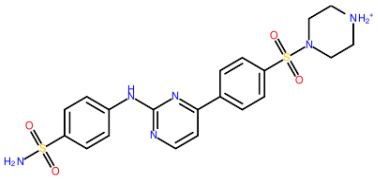
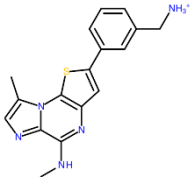
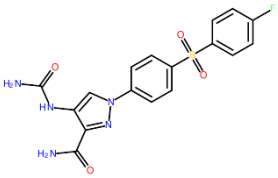
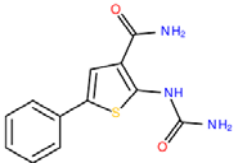
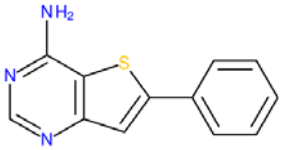
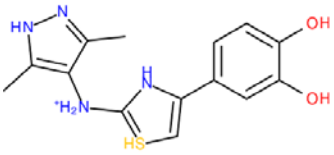
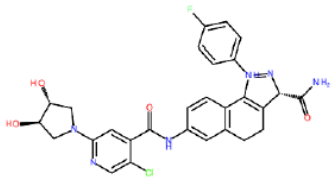
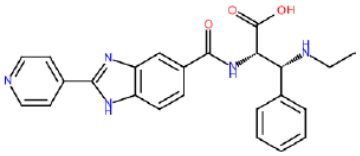
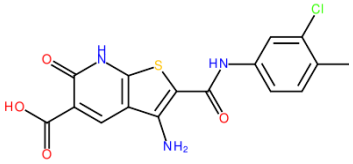
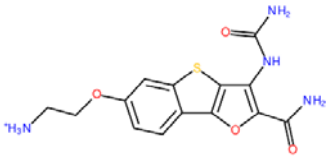
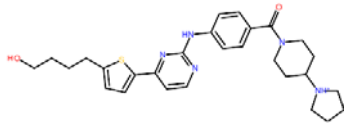
Table S1. hIKK-2 inhibitors from different chemical families docked with the hIKK-2 homology model.

2D structure	Molecule name	pIC_{50}	cluster	Knowledge-based coherent docking poses
	**13**a [1]	7,96	6	3
	**8h** [2]	7.0	6	0
	**26** [3]	6,22	6	0
	**SCP-839** [4]	8,10	6	0
	**M8012-3312** [4]	ND	6	0
	**M8008-5430** [4]	ND	6	0
	**CHS-828** [4]	8,10	6	0
	**22d** [5]	8,52	6	1

	**4j** [6]	8,07	6	1
	**4a** [7]	7,15	6	4
	**SKB-TPCA1** [4]	7,74	6	3
	**Pharmacia** [4]	6,50	6	2
	**Pharmacia_02** [4]	6,17	6	4
	**Astra Zeneca** [4]	7,40	6	1
	**M4891-3155** [4]	5,75	5	2
	**1b** [8]	6,71	9	2
	**M2295-0236** [4]	ND	6	0

	**PS-1145** [9]	6,82	6	0
	**14** [10]	7,8	6	3
	**13** [10]	7,7	6	2
	**12** [10]	7,7	6	4
	**1** [10]	7,4	6	1
	**17** [10]	7,7	6	0
	**Ureido** [9]	7,74	6	1

	**Compound A** [11]	8,4	6	0
	**8u** [12]	7,96	8	0
	**22a** [5]	8,07	7	1
	**204** [13]	7,88	8	0
	**13** [14]	7,88	8	2
	**12** [15]	6,01	8	2
	**M7790-1103** [4]	ND	8	0

	**PF-184** [16]	7,43	6	0
	**Aventis** [4]	7,15	6	0
	**M4296-0831** [4]	ND	10	1
	**16k** [17]	7,96	8	2
	**24** [18]	7,60	9	1

These 36 hIKK-2 inhibitors were docked with our hIKK-2 homology model without imposing constraints that forced poses to make specific intermolecular interactions with the target. Next, the resulting hIKK-2 complexes were analyzed with the help of LigandScout to determine which complexes exhibited target-inhibitor intermolecular interactions equivalent to those described in prior studies. This knowledge-based analysis enabled us to identify at least one knowledge-based coherent pose (43 in total) for 21 out of the 36 hIKK-2 inhibitors assayed (regardless of their scoring by eHiTS; see their values in the *Knowledge-based coherent docking poses* column). By analyzing the chemical features used by each pose in its intermolecular interaction with hIKK-2, a common pharmacophore was derived that describes the mechanism of the ligand-target interaction. The *Cluster* column shows the cluster in which each molecule was classified after running a Schrödinger script that clusters molecules based on Tanimoto similarities between MOLPRINT 2D fingerprints (using the Knime v.2.0.3 module in the Schrödinger software package). The molecules distributed in these clusters are the natural

products obtained as hits in our virtual-screening protocol and all known hIKK-2 inhibitors used in the present work [either for validation (see Table S2) or for pharmacophore-generation purposes]. The pIC_{50} values were obtained from the literature.

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