

Supporting information for

A multi-disciplinary team-based classroom exercise for small molecule drug discovery

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Dear Team,

You have won the contract to develop an inhibitor against the serine / threonine kinase Chk1 to use in a synthetic lethal strategy for the treatment of breast cancer.

Our screening team has screened a fragment library against Chk1 and provided you with the structures of the top hits. Other physical parameters and properties have been provided where available. Using the available information you must choose one or more of these hits as leads for further development.

Over the development period, your team will carry out at least four rounds of compound optimisation. Each week, you will be able to submit a maximum of four potential drug structures which will be synthesised and will undergo biological testing. We have the capacity to carry out four experiments a week – this may be one experiment on each of four compounds, four experiments on one compound, or any other combination. Each compound will also be submitted for crystallography. The results of each assay, together with the physical properties of each compound, will help in the next round of compound design.

You have free choice in your assay selection, however the results of your assay will only help in the next round of compound design if your assays are chosen to answer a scientific question.

At the end of the programme, you will need to identify your team's lead compound and to provide an individual written report on the programme to support your choice of lead. In order to be taken further by investors, your lead compound should be supported by a range of assay data. It should be orally available and have the following characteristics:

- an *in vitro* IC₅₀ for Chk1 of < 0.5 µM
- cLogP > 3
- LogD_{7.4} > ~3
- LogS < ~-3
- tPSA > 90

You will also need to provide a synthesis for your lead compound, starting from commercially available, cheap reagents. The process of reagent selection will be considered in greater detail in Workshop 4.

You may find the following points helpful in your development programme:

- Good compound design involves optimising biological activity, organic synthesis and physical compound properties (*eg* solubility; stability in an aqueous biological environment) and ultimately biological safety. Structural biology (compound binding mode) is a helpful tool.
- Drug discovery is an iterative process and compound affinity is likely to increase throughout the design process.

Structures and requested assays for Round 1 must be made by **[Date and time]** using the form on **[the VLE]**.

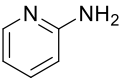
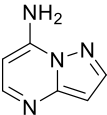
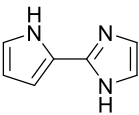
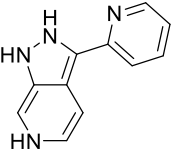
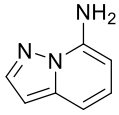
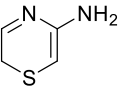

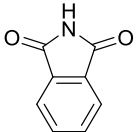
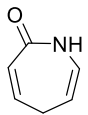
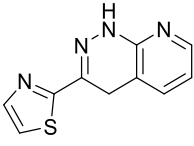
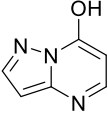
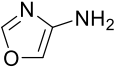
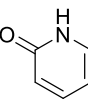
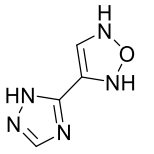
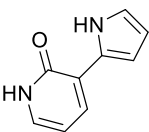
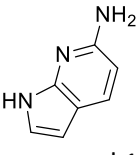
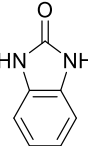
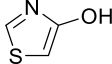
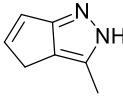
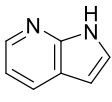
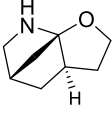
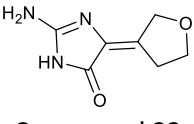
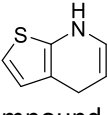
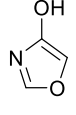
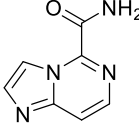
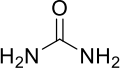
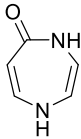
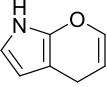
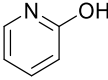
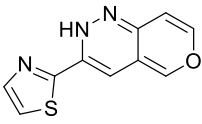
Good luck!

Yours faithfully,

Maud Menten, MD PhD

CEO Minerva Pharmaceuticals

Technical information: fragment hits

 <p>Compound 1</p>	 <p>Compound 2</p>	 <p>Compound 3</p>	 <p>Compound 4</p>
 <p>Compound 5</p>	 <p>Compound 6</p>	 <p>Compound 7</p>	 <p>Compound 8</p>
 <p>Compound 9</p>	 <p>Compound 10</p>	 <p>Compound 11</p>	 <p>Compound 12</p>
 <p>Compound 13</p>	 <p>Compound 14</p>	 <p>Compound 15</p>	 <p>Compound 16</p>
 <p>Compound 17</p>	 <p>Compound 18</p>	 <p>Compound 19</p>	 <p>Compound 20</p>
 <p>Compound 21</p>	 <p>Compound 22</p>	 <p>Compound 23</p>	 <p>Compound 24</p>
 <p>Compound 25</p>	 <p>Compound 26</p>	 <p>Compound 27</p>	 <p>Compound 28</p>
 <p>Compound 29</p>	 <p>Compound 30</p>		

Physical properties of fragment hits and thermal shifts measured in screen

Compound	MW	tPSA /Å	cLogP	LogS	clogD _{7.4}	ΔT _m /°C
1	94.12	38.38	0.32	-0.97	0.48	2.7
2	134.14	53.98	0.18	-1.16	-2.29	3.4
3	133.15	36.42	1.03	-1.71	0.95	3.3
4	198.23	48.45	-0.12	-3.55	-0.18	4.2
5	133.15	41.62	0.69	-1.09	-2.58	3.7
6	114.17	38.38	-1.16	-1.06	-2.27	2.5
7	100.14	38.38	0.23	-0.39	0.55	2.5
8	147.13	46.17	1.15	-1.652	1.1	3.4
9	109.13	29.1	-0.12	-1.01	-0.07	2.7
10	216.26	49.11	1.04	-2.719	2.18	3.9
11	135.13	48.19	0.8	-1.08	0.64	3.5
12	84.08	47.61	-0.51	0.06	-0.26	2.3
13	95.1	29.1	-0.57	-0.602	-0.52	2.6
14	139.12	70.04	-1.2	-1.89	-2.55	2.7
15	160.18	41.13	0.42	-1.89	1.02	3.8
16	133.15	50.41	0.85	-2.22	1.07	3.4
17	134.14	41.13	1.13	-1.46	1.11	3.2
18	101.12	32.59	0.85	-0.67	0.51	2.5
19	120.16	24.39	0.99	-1.55	1.57	2.9
20	118.14	24.39	1.18	-1.9	1.61	3.3
21	139.2	21.26	0.29	-1.03	-1.51	2.6
22	167.17	76.71	-2.18	-0.3	-0.34	3.3
23	137.2	12.03	2.69	-1.84	2.11	3.4
24	85.06	41.82	0.11	0.1	-0.19	2.3
25	162.15	71.05	-0.14	0.23	-0.56	3.7
26	60.06	69.11	-1.66	0.62	-1.92	1.5
27	110.12	41.13	-0.84	-0.94	-2.8	2.6
28	121.14	21.26	1.63	-1.8	1.64	3.3
29	95.1	32.59	0.93	-0.91	0.33	2.7
30	217.25	48.98	0.49	-2.87	1.38	3.9