Specs offers a broad kinase targeted library of 2,720 compounds that have been selected in collaboration with Eidogen-Sertanty. A subset of this library was experimentally validated by the Memorial Sloan-Kettering Cancer Center showing an 8-fold hit-rate enhancement.

Selection method

The Kinase Knowledgebase contains more than 160,000 unique kinase inhibitor SAR datapoints and has been used to build 3D-QSAR models for the most therapeutically relevant kinase inhibitors using the method of partial least squares regression. These are based on a three-point pharmacophore model using seven pharmacophore types and six different distance ranges thus making up a 10,549-bit string per structure. For each structure, multiple conformations were calculated up to a maximum of 1,000 conformers.

3-point pharmacophore fingerprint model
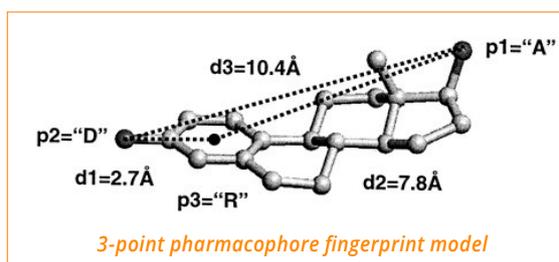
Pharmacophore types	Distance ranges
H-bond acceptor (A)	2 - 4.5 Å
H-bond donor (D)	4.5 - 7 Å
Negative charge (N)	7 - 10 Å
Positive charge (P)	10 - 14 Å
Hydrophobic (H)	14 - 19 Å
Aromatic (R)	19 - 24 Å
Other (X)	

29 of the most predictive eScreen models for therapeutically important kinase targets ($q^2 > 0.8$) were used to score and rank the Specs screening library. The resulting set has been analysed and adjusted for chemical diversity and chemical properties and the selected compounds were grouped into 22 kinase targets.

Validation

A subset of 682 compounds from the Specs kinase targeted library has been screened at the Memorial Sloan-Kettering Cancer Center against in house, cell based targets, all of which involve kinase activity for their signal transduction pathways. A randomly selected set of several thousand compounds from the Specs screening library was used as a control and the kinase targeted library showed an 8-fold hit-rate enhancement.

Chemical properties

For all compounds in the Specs kinase targeted library, the physicochemical properties have been calculated. Due to the nature of the 3D-pharmaco-phore based models, the selected compounds are more drug-like than lead-like but still 90% of the compounds have no or only one violation of the Lipinski and Veber rules.

Plate specification

The Specs kinase targeted library contains 2,720 compounds and is available in 34 plates of 80 compounds, either as a whole set or grouped by kinase target. The plates are available as 100ml 10mM DMSO solution or as dry film. Customized subsets or plate formats can be created to tailor-fit your screening platform specifications. Chemical structures are available under a confidentiality agreement.

Group	Family	eScreen	q2	N
AGC	PKC	PKC	0.887	372
		PRKCA	0.830	163
		PRKCB1	0.898	134
CAMK	PKA	PKA	0.818	127
TKL	RAF	RAF1	0.751	78
CMGC	CDK	CDC2	0.796	119
		CDK1_B	0.873	764
		CDK2	0.759	113
		CDK2_A	0.829	455
		CDK2_E	0.854	623
		CDK4_D1	0.870	656
		CDK5	0.892	474
		CDK5_P25	0.826	417
	MAPK	MAPK14	0.836	485
		MAP2K	0.720	195
	GSK	GSK3A	0.885	77
		GSK3B	0.860	243
TK-NR	CSK	CSK	0.841	439
	SRC	SRC	0.955	210
		LCK	0.845	199
	ABL	ABL	0.853	190
TK-R	EGFR	EGFR	0.876	932
		ERBB2	0.930	189
	FGFR	FGFR	0.850	368
	PDGFR	PDGFRB	0.741	390
	VEGFR	FLT1	0.757	103
		KDR	0.817	281
Other	ADK	ADK	0.846	255
	PDHK	PDK	0.799	59

Models used in kinase targeted library design

Target	# plates	# cmpds
PKC	3	240
PKA	1	80
RAF1	1	80
CDK1	3	240
CDK2	3	240
CDK4	2	160
CDK5	2	160
MAPK14	2	160
MAP2K	1	80
GSK3	2	160
ABL	1	80
CSK	1	80
LCK	1	80
SRC	1	80
EGFR	3	240
ERBB2	1	80
FGFR	1	80
FLT1	1	80
KDR	1	80
PDGFRB	1	80
ADK	1	80
PDK	1	80
PKC/PKA/RAF	5	400
CDKs	10	800
MAPK/GSK	5	400
TK-NR	4	360
TK-R	8	640
ADK/PDK	2	160

Compounds per plate and target