NANOCYCLIX: NEXT GENERATION KINASE THERAPEUTICS
A CHEMOCENTRIC APPROACH FOR THE DISCOVERY OF SELECTIVE KINASE INHIBITORS

Petra BLOM, Pascal BENDERITTER, Nicolas GEORGE, Marie-Hélène FOUCHET, Alexis DENIS and Jan HOFLACK

Oncodesign

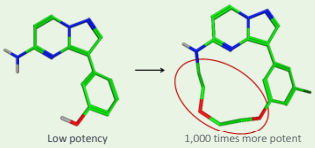
Headquarters: 20, rue Jean Mazen, B.P. 27627, 21076 Dijon Cedex, France
François Hyafil Research Center: 27, avenue du Québec 91140 Villebon-sur-Yvette, France
pblom@oncodesign.com

Our kinase focused library of small macrocycles so called Nanocyclix is designed in a chemocentric approach to identify attractive and selective kinase inhibitors across the kinome. All compounds are in the drug-like properties space and hit compounds display nM potencies and good selectivity against a small number of kinases. Nanocyclix® Oncodesign's proprietary medicinal chemistry technology is used in its drug discovery programs. Conceptually, the Nanocyclix® technology is based on the macrocyclization paradigm of known hinge binder scaffolds resulting in tighter binding site recognition, potency and selectivity towards the ATP site. Exploring different lengths and functionalities of the cyclic linker allows to populate the conformational space of every template and to identify an optimal match between the size and mobility of the binding site and the macrocyclic ligand. Extensive profiling of the full Nanocyclix collection allows selecting and valorizing the most attractive compounds and scaffold-linker combinations at an early stage. Typically, Nanocyclix are profiled against broad panel of kinases in biochemical assays and eADMET parameters.

LIBRARY OF NANOCYCLIX NX

NANOCYCLIX

A key chemical technique: macrocyclization
Intrinsic potency provided by decreasing entropic penalty and specific 3D shape
Selectivity through shape complementarity



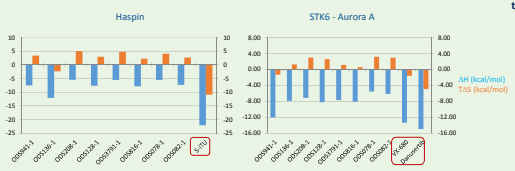
Low potency
No selectivity

1,000 times more potent
and highly selective

Potency and selectivity to create opportunities in new therapeutic areas

Rationalisation of the « Nanocyclix effect » – ITC experiment

with Pr Stefan Knapp - Structural Genomics Consortium, University of Oxford, United Kingdom

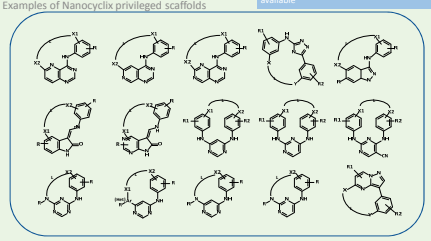


Thermodynamic signatures for proteins in general show favourable enthalpy and a consistently positive contribution of entropy compared to linear and flexible molecules

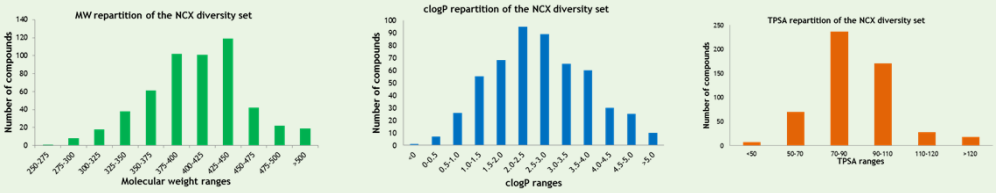
Oncodesign's Nanocyclix library provides a high degree of diversity based on over 50 known and novel "kinase scaffolds" that are combined with a preferred set of over 300 "linkers"

4177 solids > 1 mg, 4643 liquids > 0.1 mL
Diversity set of 453 nanocyclix covering the whole range of scaffolds representative of compound collection.
3969 nanocyclix with no stock but kinase profiling data available

Examples of Nanocyclix privileged scaffolds

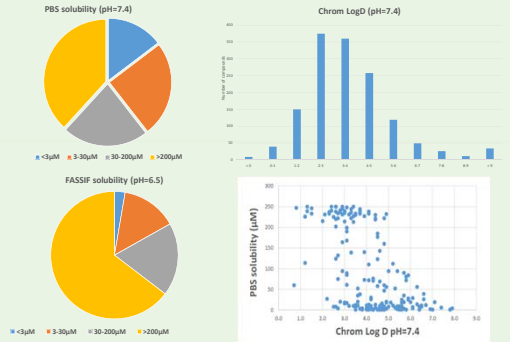


Nanocyclix – In silico descriptors: *Global profiles indicate potential for good drug-like properties*



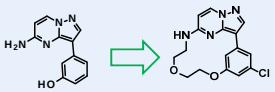
Nanocyclix – Measured parameters:

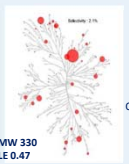
- *Global profiles indicate nice coverage of solubility values correlated with ChromLogD*
- *ChromLogD and Solubilities in good range (> 1200 products measured)*
- *PFI (ChromLogD+ #Aryl): 40 % < 6; 65% < 7*



ALK1/2 – A LEAD OPTIMIZATION STAGE PROGRAM

Impact of macrocyclization on compound profile





MW 330
LE 0.47
LipE 5.2

Optimisation enabled separation of the signature kinase affinities

ODS ID	Project	iC50 (nM) ALK2	LRRK2	RIP2	TGFβR2	S50 @0.1µM	S50 @1µM
ODS2003818	Multi	3	152	5	87	4.5%	18%
ODS2004641	TGFβR2	>1000	>100	985	10	1.1%	4.3%
ODS2005212	RIP2	113	3001	19	321	1.1%	8.3%
ODS2005204	ALK2	9	1252	79	3001	2.1%	8.3%

→ Identification of distinct sub-series
→ Exquisite selectivity in kinase subfamilies from the start
→ Increase in selectivity while retaining strong potency
→ Inherent cellular potency for this series

ALK2	LRRK2	RIP2	SIK2	TGFBR2
2465	3001	710	1846	2817

IC_{50} (nM)

ALK2	LRRK2	RIP2	SIK2	TGFBR2
3	152	5	6	87

"Signature" of first generation compound ODS2003818 (386 kinases panel) shows high potency with selectivity for small subset of kinases

Initial probe (ODS2003818) displayed high affinities for ALK1 kinase but medium selectivity. A first round of rapid analoging gave compounds with exquisite selectivity but limited developability and DMPK

ODS LOT ID	MW	CLOGP	TPSA	ALK1 IC50 in nM	ALK2 IC50 in nM	S50 @ 0.1uM	S50 @ 1uM
ODS2003818-1	330.8	2.7	60.7	17	3	4.5%	18.2%
ODS2005401-1	416.42	0.86	94.79	10	7	3.1%	10.4%
ODS2005204-1	364.44	1.78	75.76	13	9	2.1%	8.3%
ODS2005873-1	443.5	2.77	80.99	15	6	1.0%	12.5%
ODS2005730-1	350.42	1.55	74.56	16	26	1.0%	9.4%
ODS2003016-1	371.48	4.89	44.3	17	30	4.2%	33.3%
ODS2003800-1	380.44	2.02	71.6	30	18	4.2%	16.7%
ODS2005780-1	377.44	2.58	71.76	39	7	4.2%	12.5%
ODS2004538-1	393.44	1.91	80.99	44	8	2.1%	9.4%
ODS2005771-1	323.39	2.57	54.69	44	16	4.2%	16.7%
ODS2005713-1	309.37	2.19	68.06	56	14	4.2%	20.8%
ODS2005764-1	338.36	2.15	88.75	59	44	6.3%	22.9%

Progression to LO

IC_{50}(Alk1)= 7 nM/Kd= 9 nM
EC_{50} (Mouse 2H11 BMP9)= 68 nM
LE= 0.38 / LLE= 4.4 / PFI= 6.7

Rat IV and PO (1 and 3mpk)
DNAUC (0-inf): 1166 (ng.h/mL)/mpk
$T_{1/2}$= 1.9h - MRT= 2.5h - Vss= 2.1 L/kg
Cl_b= 14 mL/min/kg (15% LBF)
DNAUC (0-inf): 967 (ng.h/mL)/mpk; F 87%

Lead Compound

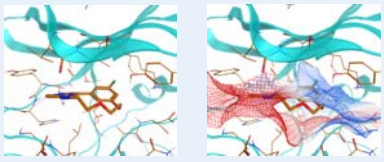
Good selectivity/potency (biochi; cell)
Excellent developability profile (sol~100 µg/mL)

Good DMPK parameters (rat, mouse)
No toxicological alerts
Pharmacological evaluation ongoing
Scale-up

X-ray structure of Nanocyclix (ALK2 – 5OY6) and modeling

With Dr Alex Bullock and Dr Eleanor Williams - SGC, University of Oxford, United Kingdom

> 15 structures available with several kinases.
Strong and consistant support of modeling to current LO.

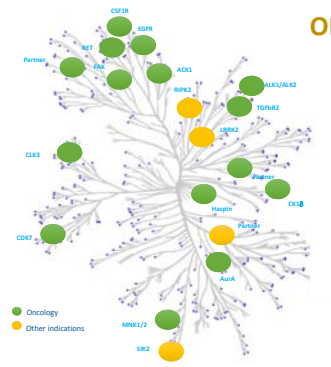


The shape of NCX nicely complements the cavity of the pocket.
Further elaboration of the linker provides increased potency and selectivity.

CONCLUSION

- Exploring the Nanocyclix diversity in combination with broad profiling across the kinome is a unique approach developed by Oncodesign.
- Available results show that this approach can provide high value leads for most relevant kinases in the human kinome.
- The application of the technology in a diversity based chemocentric platform approach has allowed Oncodesign to identify potent and selective lead compounds against therapeutic kinases in many indications such as oncology, immuno-inflammation and CNS such as ALK1, RIPK2 and LRRK2. A PET tracer targeting activated EGFR is currently in phase I in oncology.
- Nanocyclix is also proposed for partnering as illustrated by the ongoing programs with pharmaceutical and biotech companies.

PROGRAMS & PARTNERING OPPORTUNITIES



Kinome coverage by selective Nanocyclix

Oncodesign Pipeline