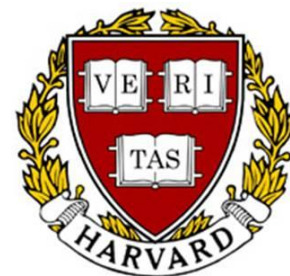


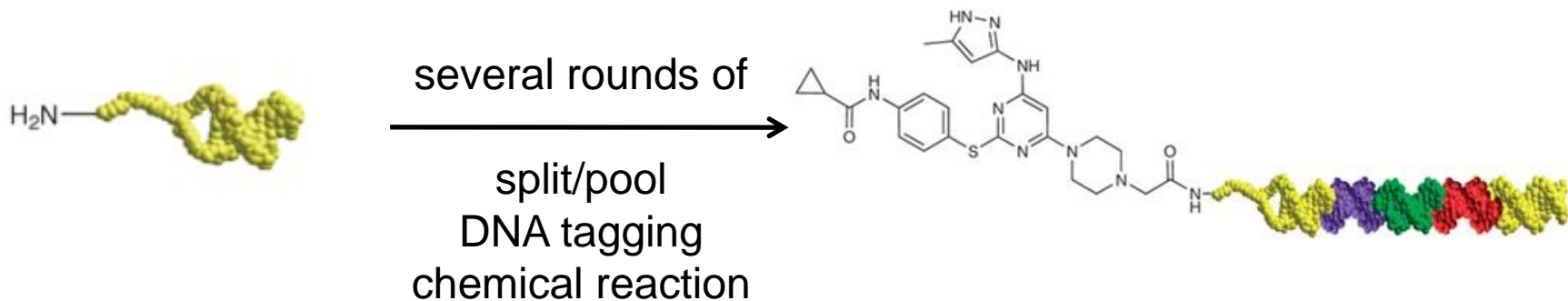
Kinase Inhibitors from a DNA-templated Macrocycle Library

Christoph Dumelin
Symposium on DNA-Encoded Chemical Libraries
Zürich, August 20 2010



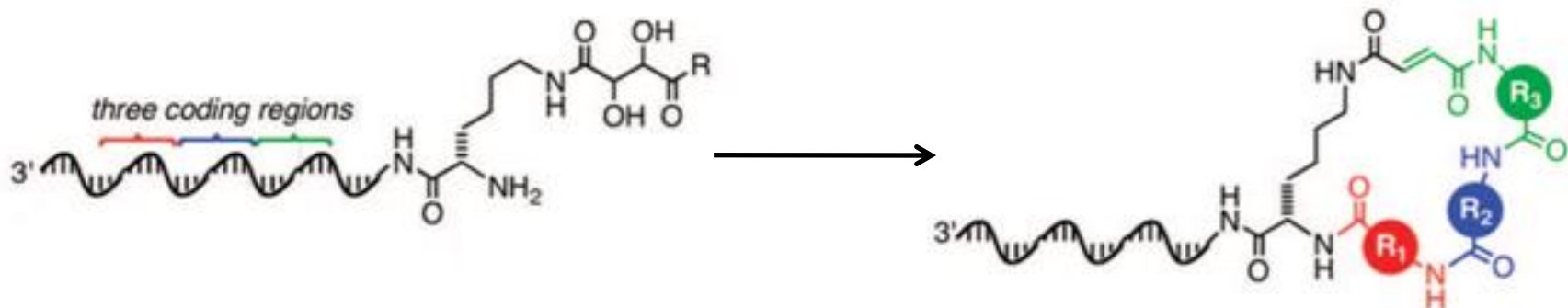
Synthesis of DNA-Encoded Chemical Libraries

Split and pool synthesis

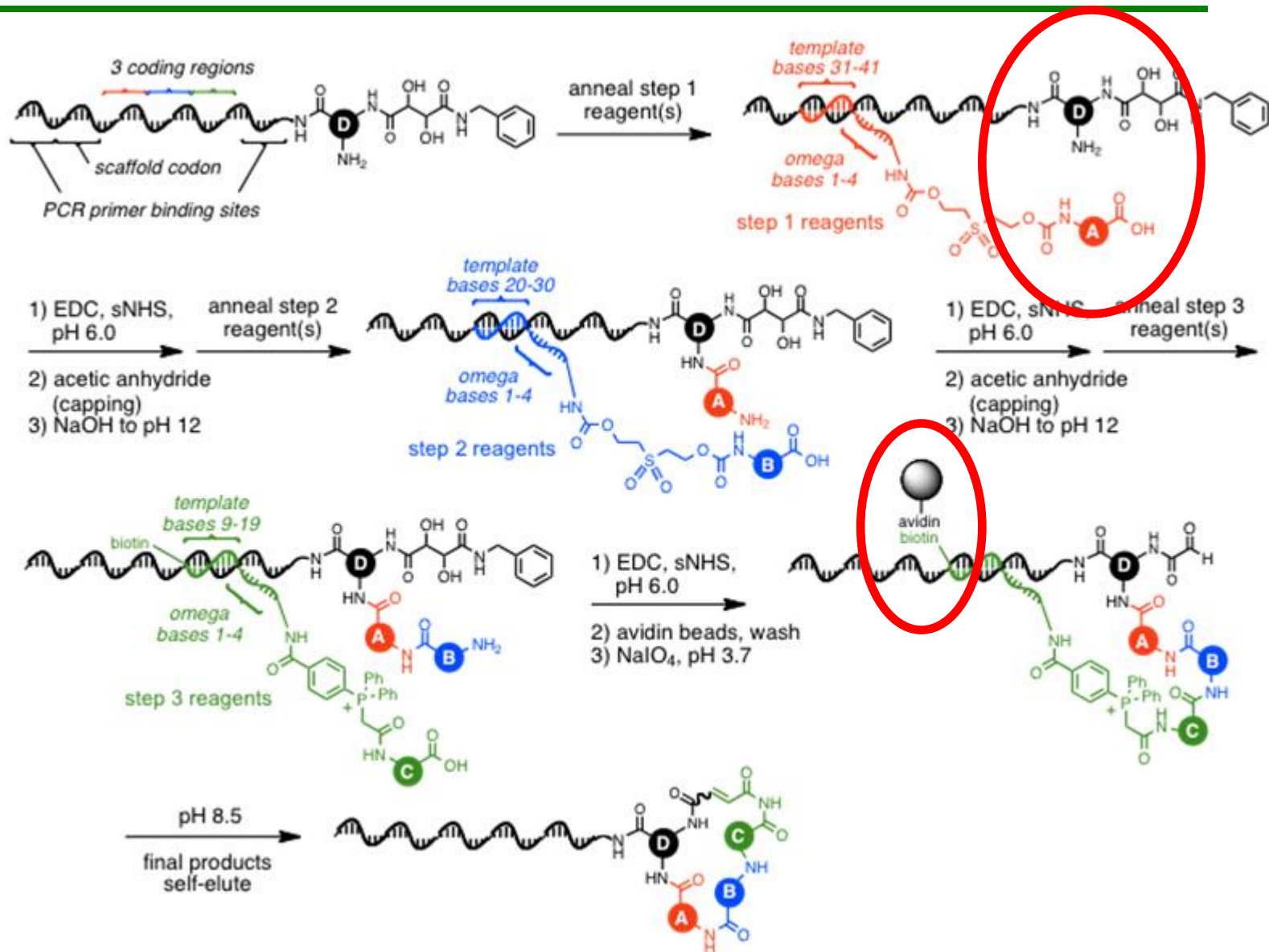


Clark et al. *Nat Chem Biol.* **5**, 647-54 (2009)

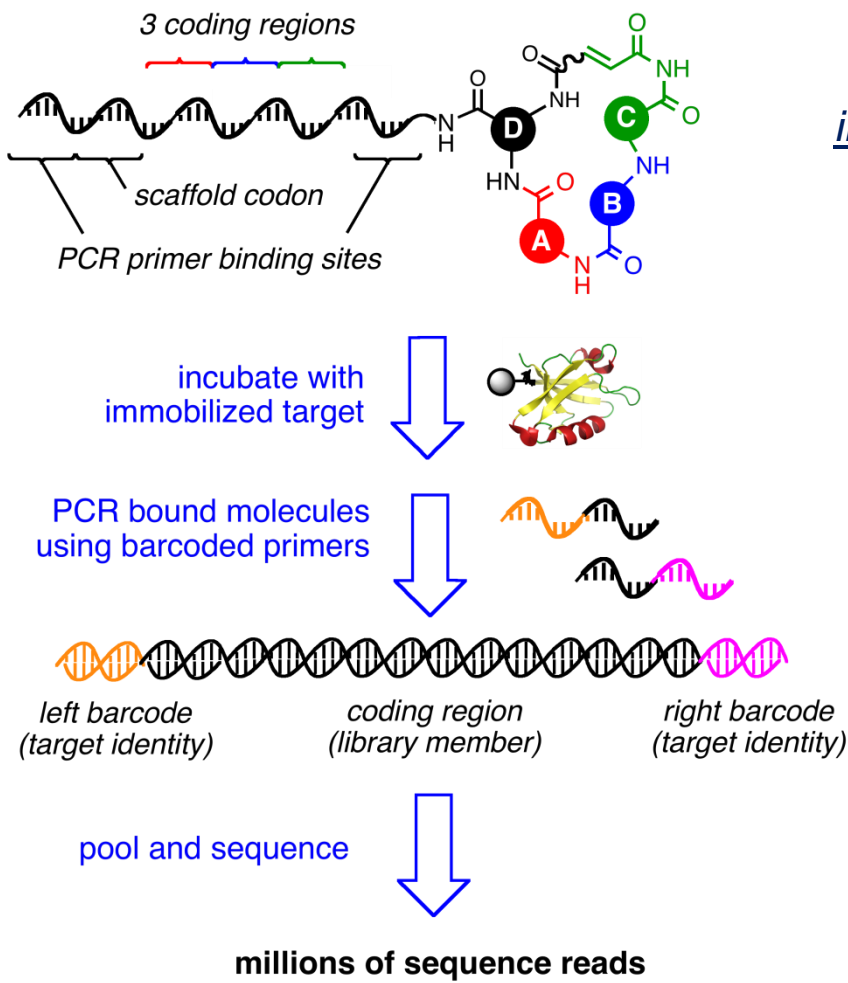
DNA-templated synthesis (DTS)



Synthesis of a DNA-Templated Macrocyclic Library



Interrogation of 497,000 Small Molecule–Target Interactions

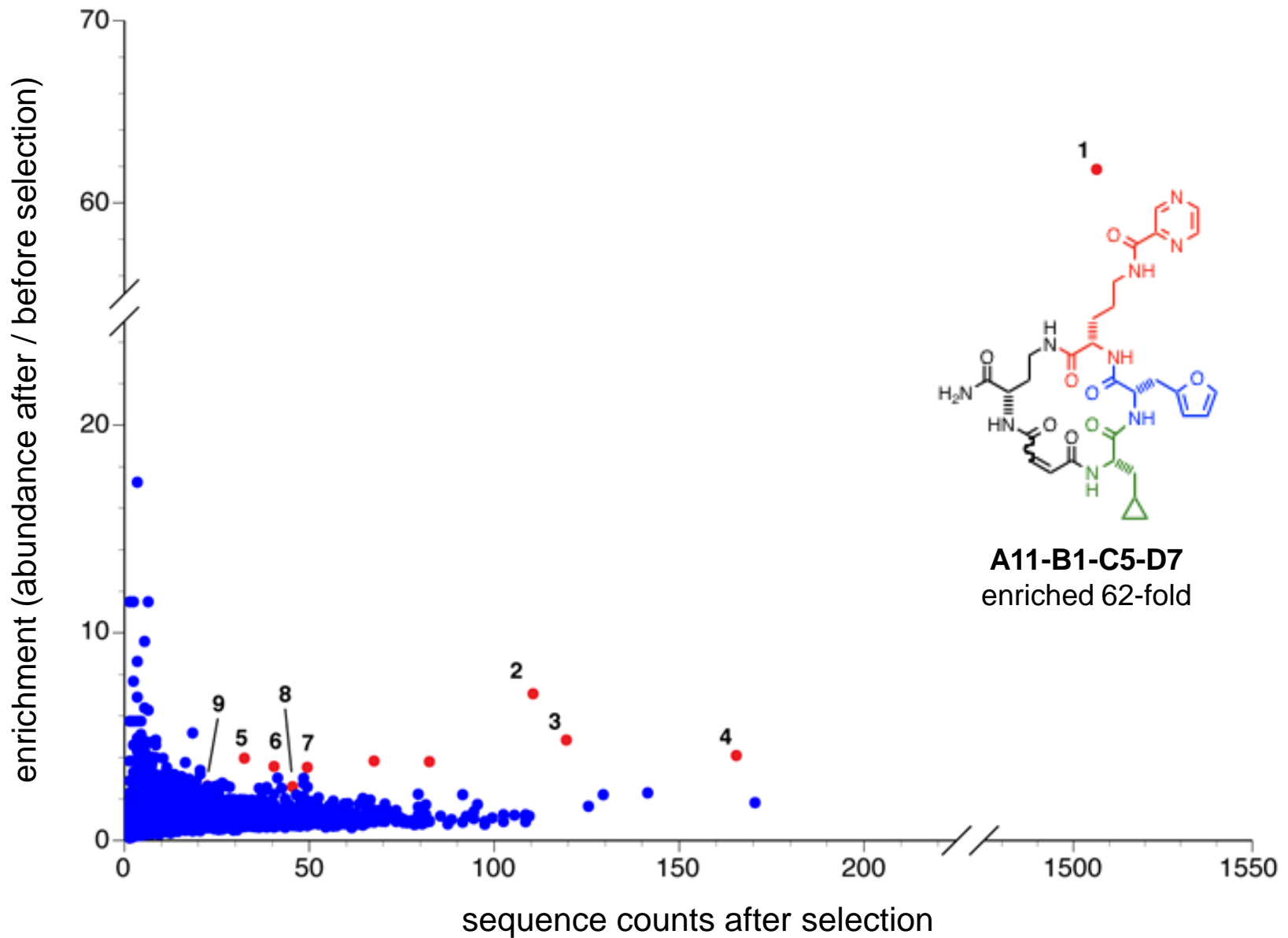


in vitro selections completed against 36 protein targets

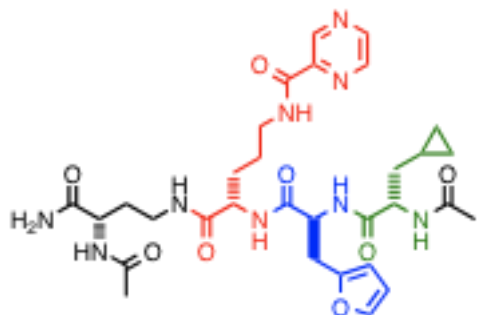
kinases	phosphatases	PDZ domains	SH2 domains
Akt3	DEP1	Dvl1-3	Abl1
AMPK	MEG2	Erbin	Abl2
ERBB4	PRL2	γ 1-syntrophin	P85 α N
MK2		Magi1	P85 α C
p38 α	GTPases	MUPP1	P55 γ C
MKK6	Cdc42	PAR6B	other proteins
Pim1	H-Ras-V12	PSD95	
Src	RhoA	RGS3	Bcl-xL
VEGFR2		SAP97	BIR3 (XIAP)
		Semcap3	PPAR δ
		Shank3	

Minimal infrastructure required

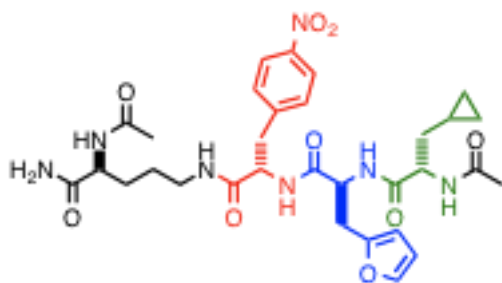
Src Kinase Selection Fingerprint



SAR of Src-Inhibiting Macrocycles



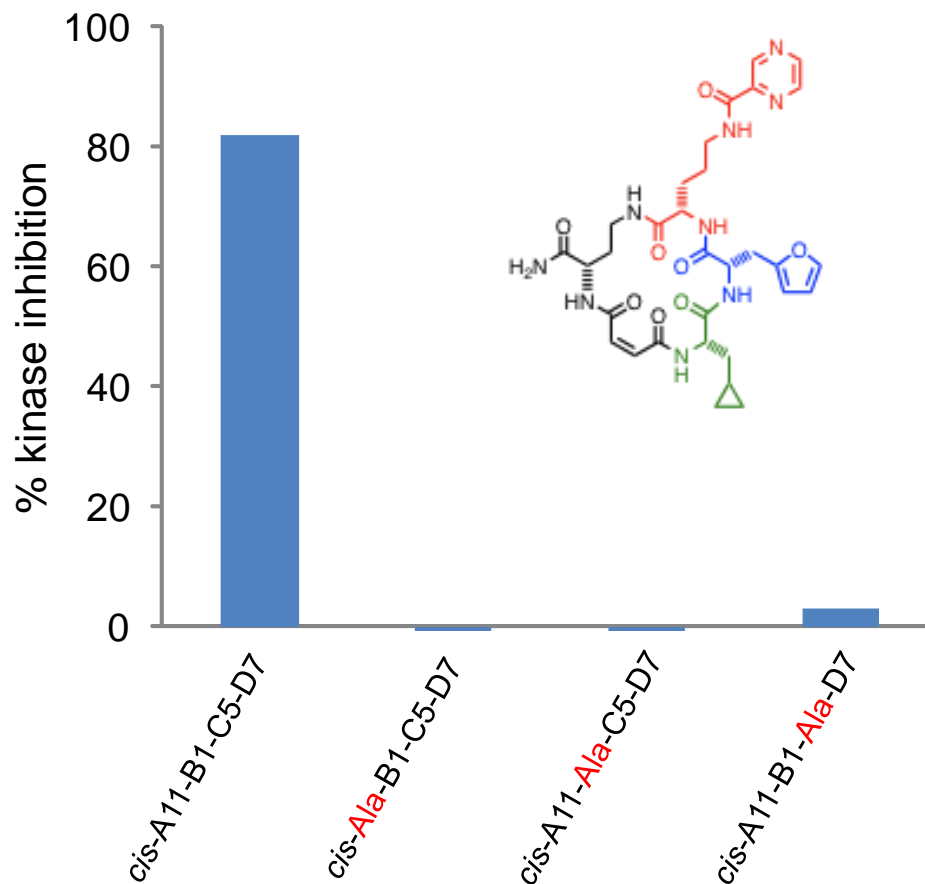
linear **Macrocycle 1**
 $IC_{50} > 100 \mu M$



linear **Macrocycle 4**
 $IC_{50} > 100 \mu M$

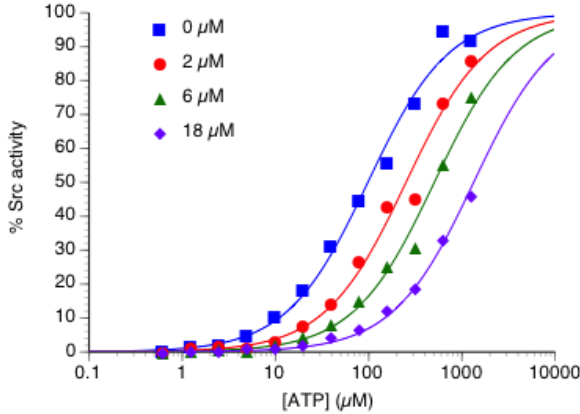
Linear peptide analogs are inactive

Every building block
essential for inhibition

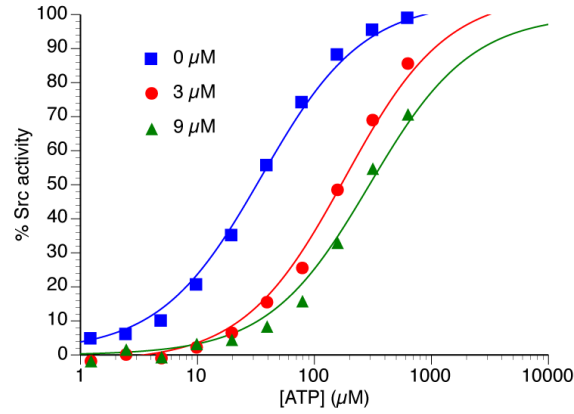


Src Inhibitors are ATP Competitive and Highly Selective

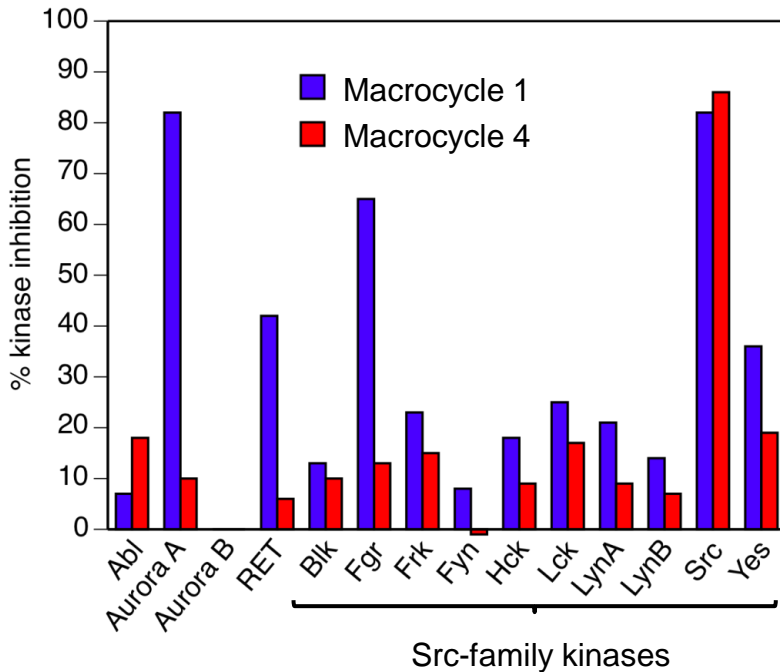
Macrocycle 1



Macrocycle 4



Macrocycles bind ATP competitively



Inhibition of human kinases at 5 μM:

Macrocycle 1 inhibits 5% of 58 kinases

Macrocycle 4 inhibits only Src

→ Highly selective Src inhibitors

Macrocycles enriched in selections inhibit their target kinases

Discovery of two novel classes of highly selective inhibitors

All building blocks and cyclic nature contribute substantially to binding affinity

→ Demonstrate applicability of DTS and potential use of macrocycles in drug discovery

Acknowledgements

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