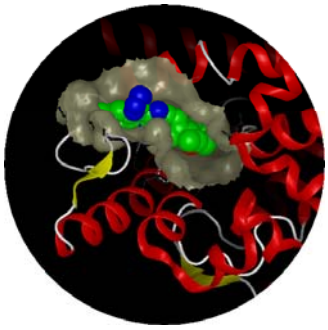


Discovery of new high-affinity PDE10 inhibitors:
Fragment based lead generation and structure-based design

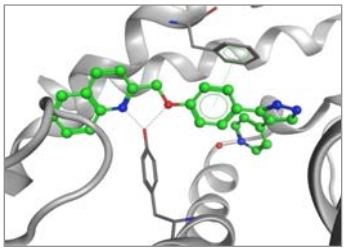
Jeffrey Albert; CNSP, Wilmington

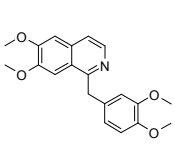
AstraZeneca
RESEARCH & DEVELOPMENT
CNSP RA

PDE10 Hit generation strategy

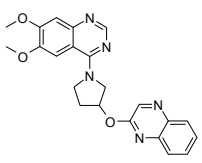
Risks

- Druggability: Many existing have poor physical props.
- Selectivity: High homology with PDE4 and others

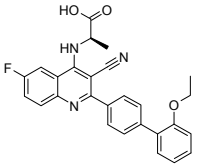




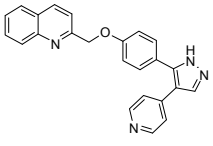
Papavarine



Pfizer



AZ Mölndal



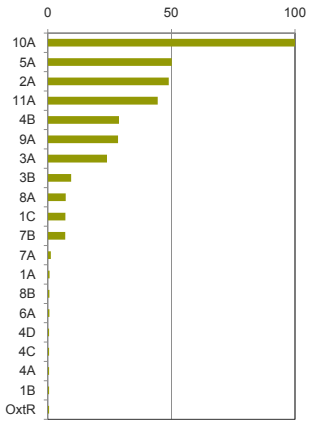
Pfizer

2

Understanding selectivity risks

- What other targets are frequently recognized by PDE10 inhibitors?
- What structural features differentiate PDE10 from isoforms?

Ligand perspective:
"Dual-Actives" from data mining



Target perspective:
Sequence analysis

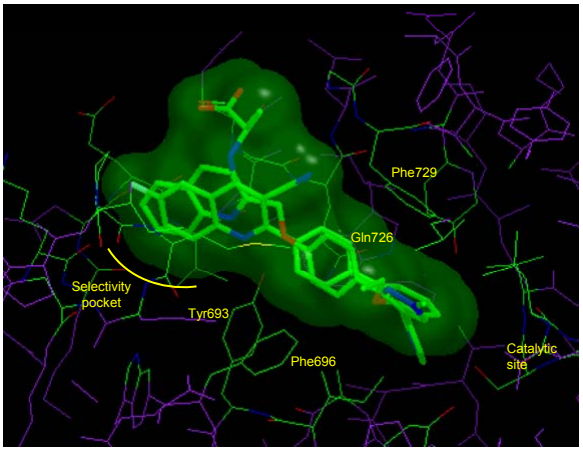
Isoform	% Ident. to PDE10	% Ident. near inhibitor	Key tyrosine?
PDE10	100	100	Y
PDE6A	19	69	N
PDE6B	18	69	N
PDE6C	17	69	N
PDE2A	19	62	Y
PDE5A	22	58	N
PDE11	21	52	N
PDE4A	15	50	N
PDE4B	14	50	N
PDE4C	15	50	N
PDE4D	15	50	N
PDE1B	10	48	N
PDE3A	13	48	N

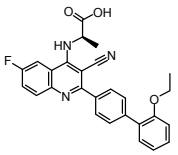
3

Acknowledgments: Ola Engkvist and Andrew Leach

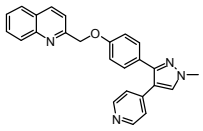
Structural understanding

- Catalytic pocket is largely conserved across all PDEs
- Secondary pocket has differences that can be used to achieve selectivity





Quinoline series

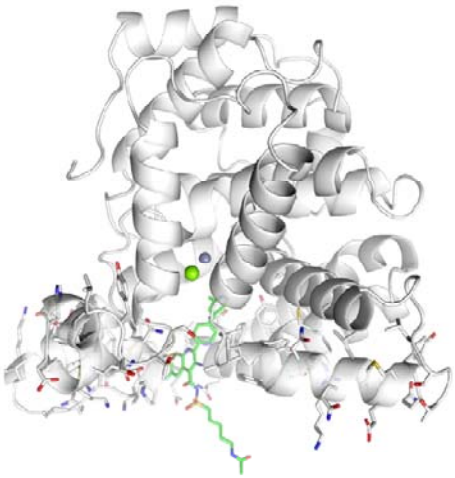


Pfizer Phase-2

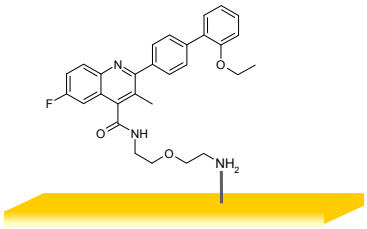
4

Acknowledgments: Udo Bauer and AZ Mölndal project team

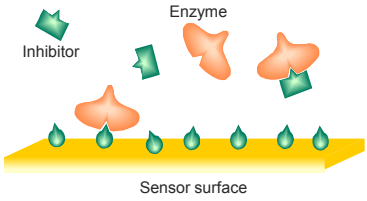
Biacore-based screening assay



Computational model



Biacore assay

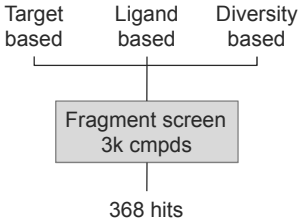


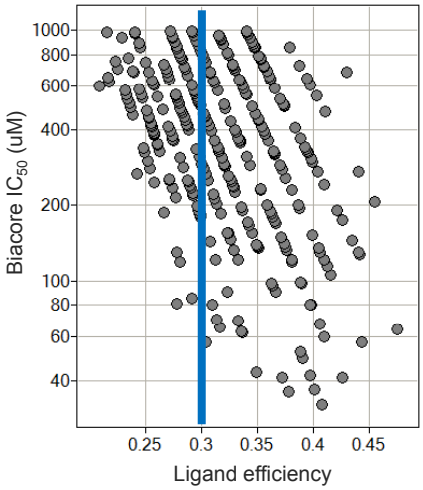
Sensor surface

5

Acknowledgments: Stefan Geschwindner

Fragment screening design and results



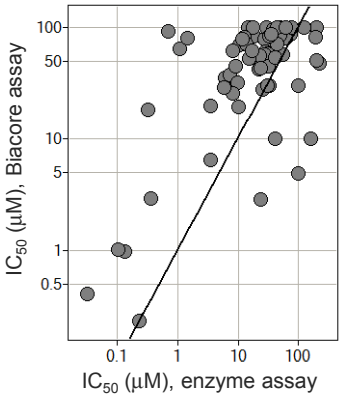


6

Acknowledgments: Loredana Spadola

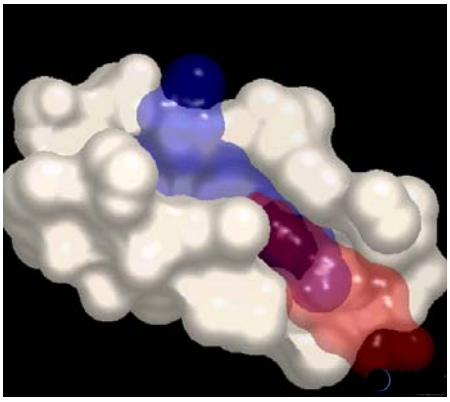
Fragment validation

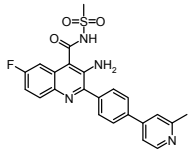
Enzyme inhibition assay



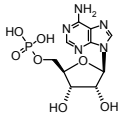
(and inactive at PDE2A)

NMR competition assay





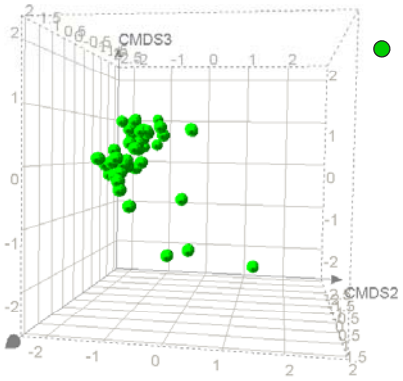
IC_{50} 266 nM



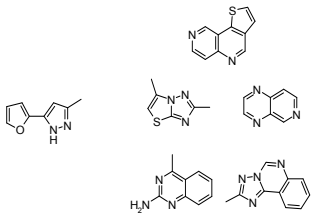
K_D 2.6 uM

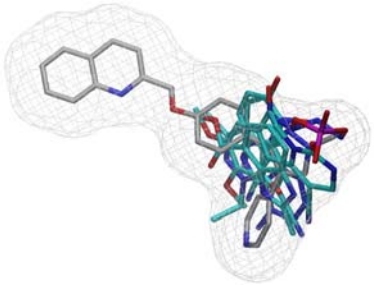
7 Acknowledgments: Tomas Åkerud

Building fragment understanding



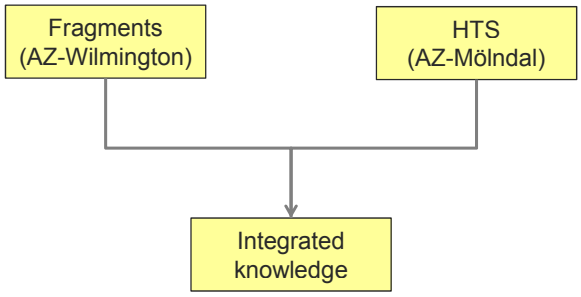
LE
>0.4





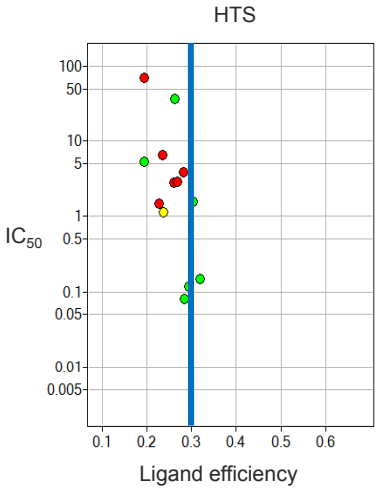
8

Integration of lead generation approaches

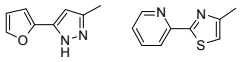


9

Fragment assisted lead generation



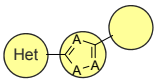
Fragment knowledge



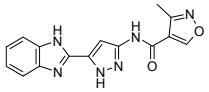
IC_{50} 851 mM
LE 0.38

IC_{50} 324 uM
LE 0.40

HTS data mining, triage and validation



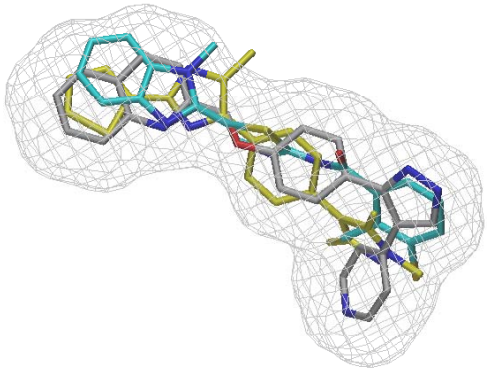
Chemotype

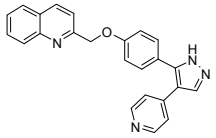


IC_{50} 3.8 µM
LE 0.32

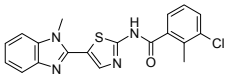
10

Developing understanding of mechanism of binding

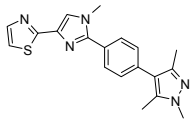




Pfizer (X-ray)



IC_{50} 16 nM (model)



IC_{50} 250 nM (model)

11

Additional acknowledgements

- David Aharony: Project leader
- Mike Wood: Target team leader
- Patrick Johansson: PDE10 structural support
- Clay Scott: PDE10 pre-project co-leader
- Rob Horsefeld: Structural support
- Niek Dekker: Enabling Capabilities and Sciences

12