Design of a Focussed CNS Screening Collection at Takeda

David Livermore, Takeda Cambridge
UK-QSAR and Cheminformatics Group/Physchem Forum Meeting
GSK Stevenage
March 2016

Takeda's Global Research Facilities

Shonan Research Center

Takeda Boston

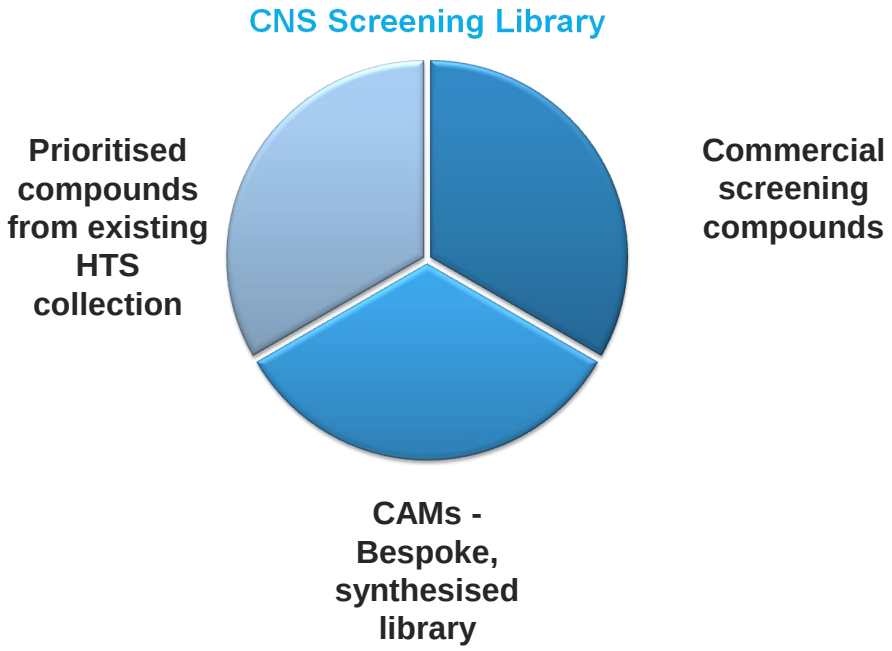
Takeda Cambridge

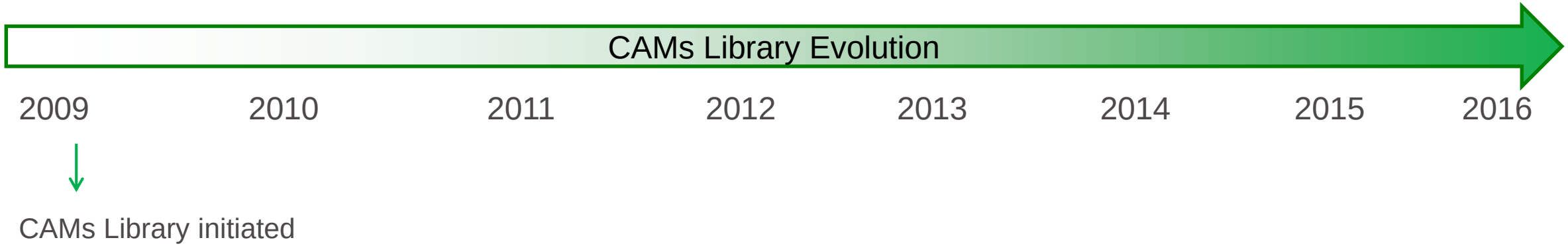
Takeda California

Takeda Central Nervous System (CNS) Disease Focus

- CNS Drug Discovery is a key therapeutic area for Takeda
- Global CNS Drug Discovery Matrix – SRC, TCAL, TCB
- Interest in constructing a cutting-edge CNS HTS collection

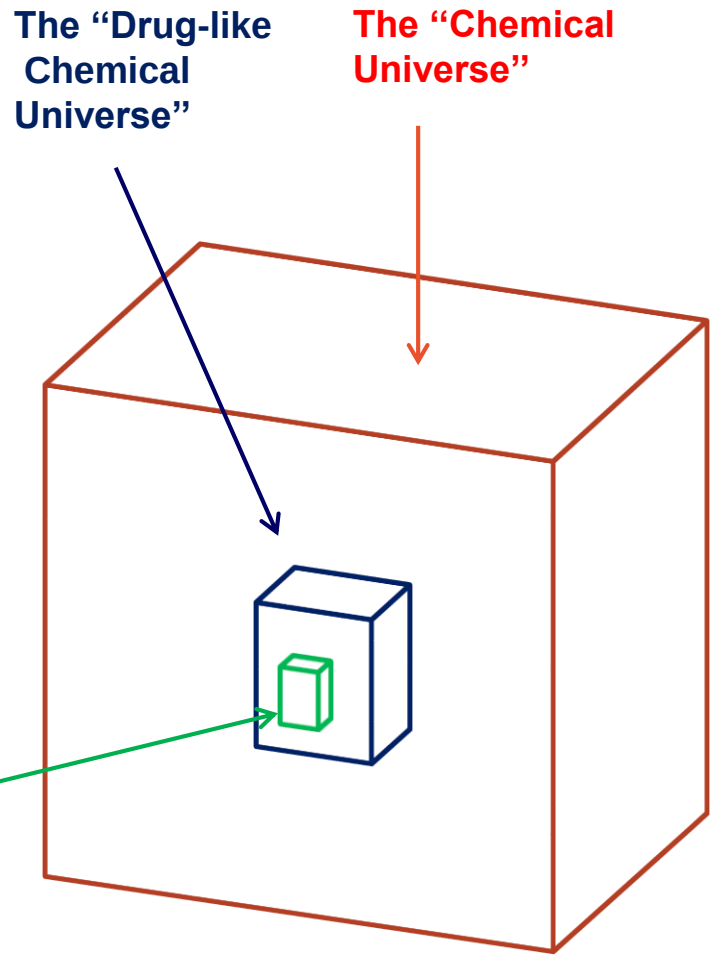
Design of a Focussed CNS Screening Collection at Takeda





CNS versus Standard HTS Screening Libraries

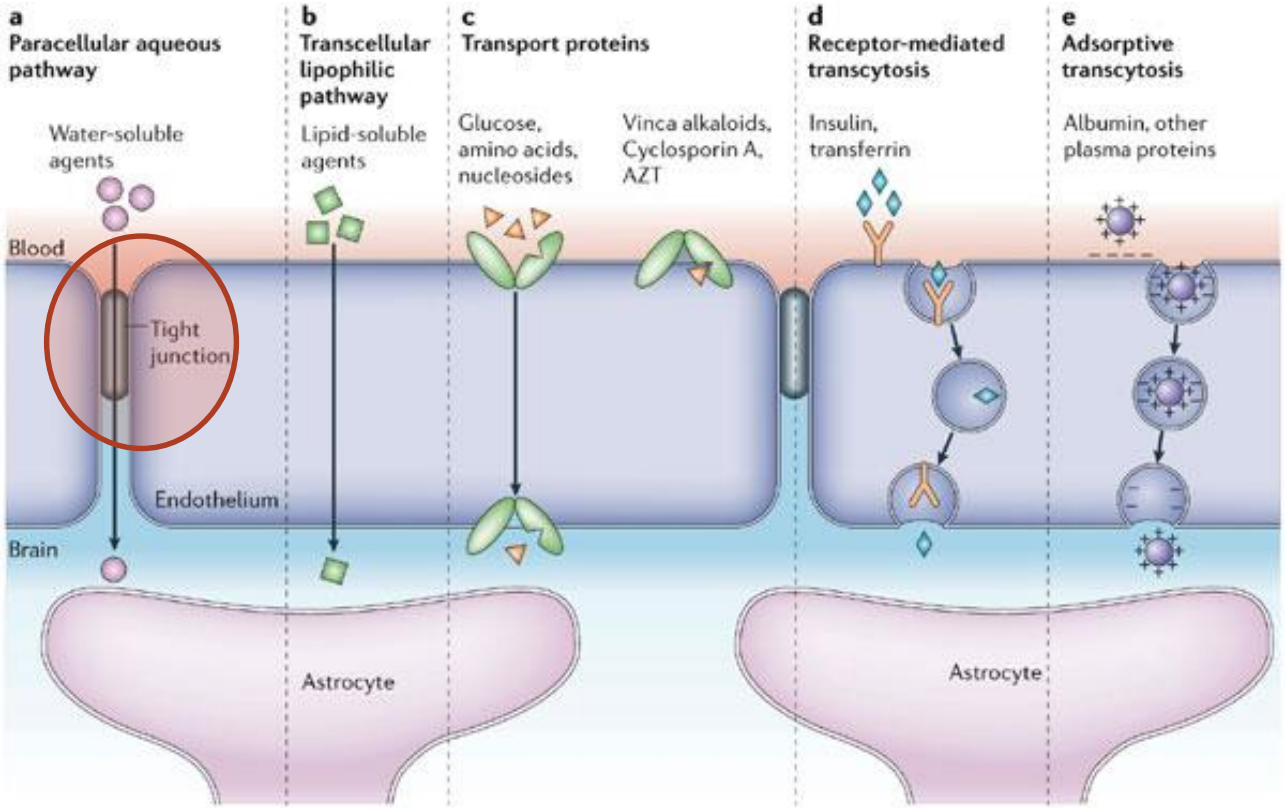
- Access to the CNS is required in order to treat illnesses such as Schizophrenia and Alzheimer's Disease
- HTS screening libraries target the 'Drug-like Chemical Universe'
- HTS hits tend to have a high molecular weight and PSA
- Marketed CNS penetrant drugs have reduced molecular weight and polar surface area compared to marketed non-CNS drugs[1,2] (MW < 400, TPSA < 80)
- Lead Optimisation programmes typically result in increased MW and PSA in order to improve potency or DMPK properties
- Identification of a greater number of high quality small molecule starting points is needed in order to increase the probability of success
- **Therefore Takeda wished to develop a CNS-focussed screening library with desirable physicochemical parameters**



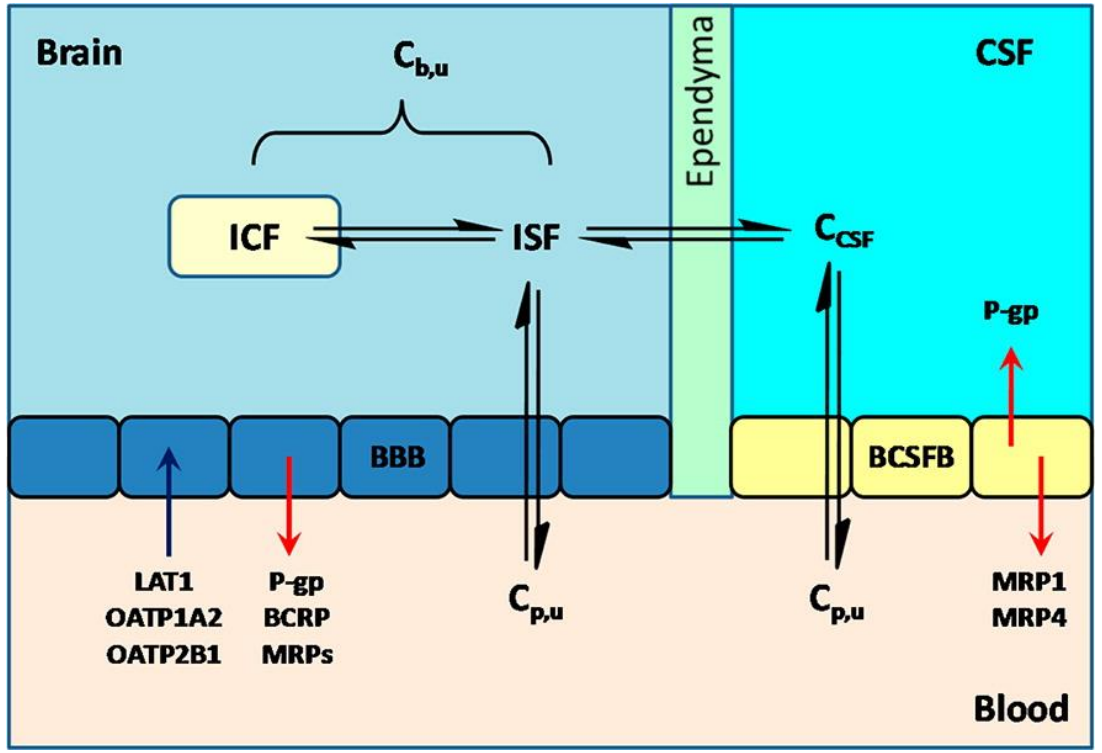
[1] M.S. Alavijeh, M. Chishty, M.Z. Qaiser, A.M. Palmer, *Journal of the American Society for Exptl. Neurotherapeutics, 2005, 2, 554*
[2] Zoran Rankovic; *J. Med. Chem.* 2015, 58, 2584-2608

Why is the ‘CNS Drug-like Chemical Universe’ so small?

The Blood–Brain Barrier



Abbott NJ, Lars Rönnbäck L & Elisabeth Hansson E
Nat. Rev. Neuro. 2006, 7, 41–53



ACS Publications
High quality. High impact.

Li Di; Haojing Rong; Bo Feng
J. Med. Chem. 2013, 56, 2-12
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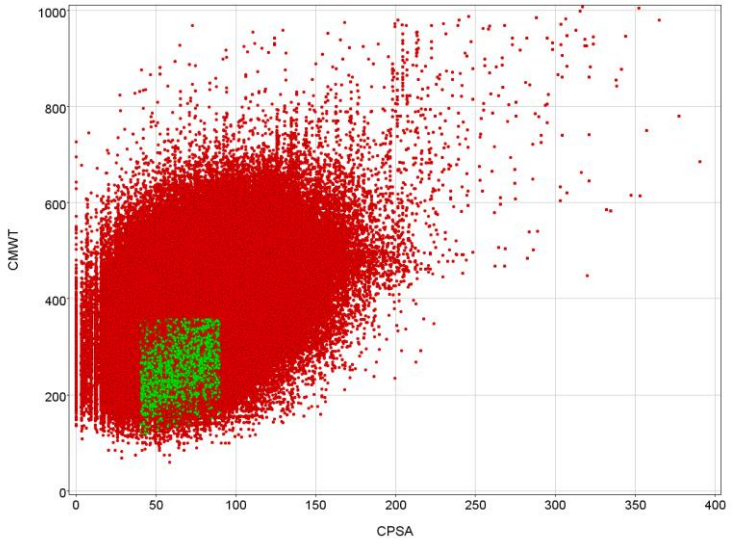
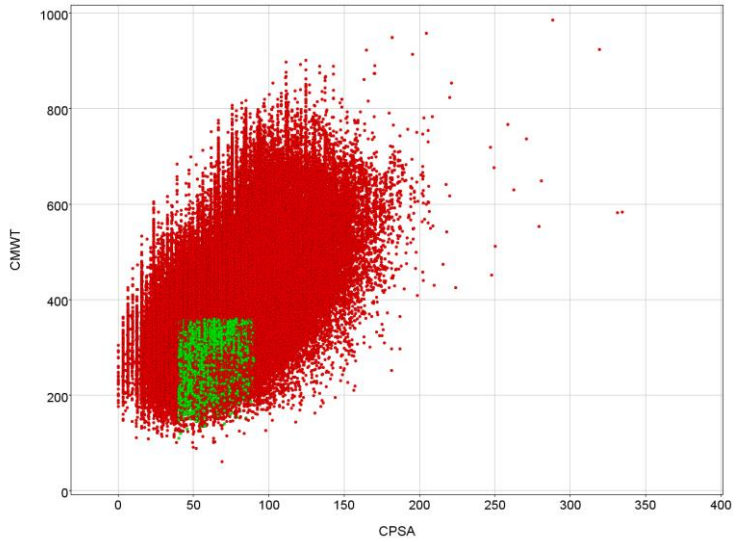
HTS Screening Libraries

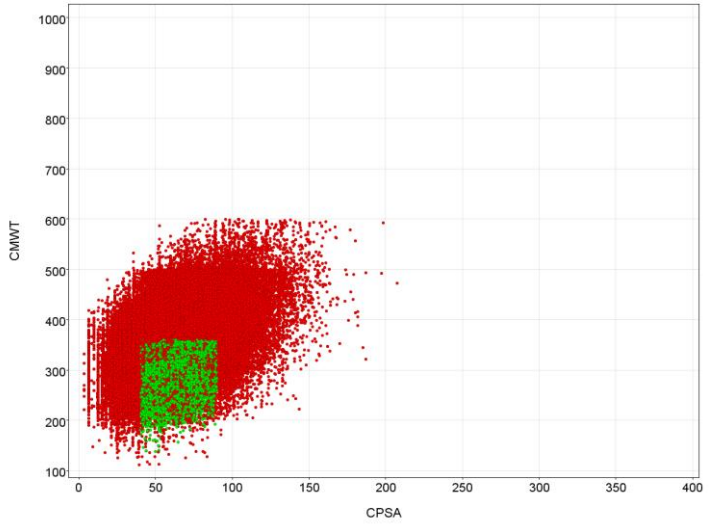
Screening Library 1: MW vs PSA



Screening Library 2: MW vs PSA



Screening Library 3: MW vs PSA



- **Only 12-16% compounds in typical HTS libraries have MW < 400 and TPSA < 80**

- **Waste of time and resource identifying compounds which cannot be progressed for CNS targets**

Commercial Compounds

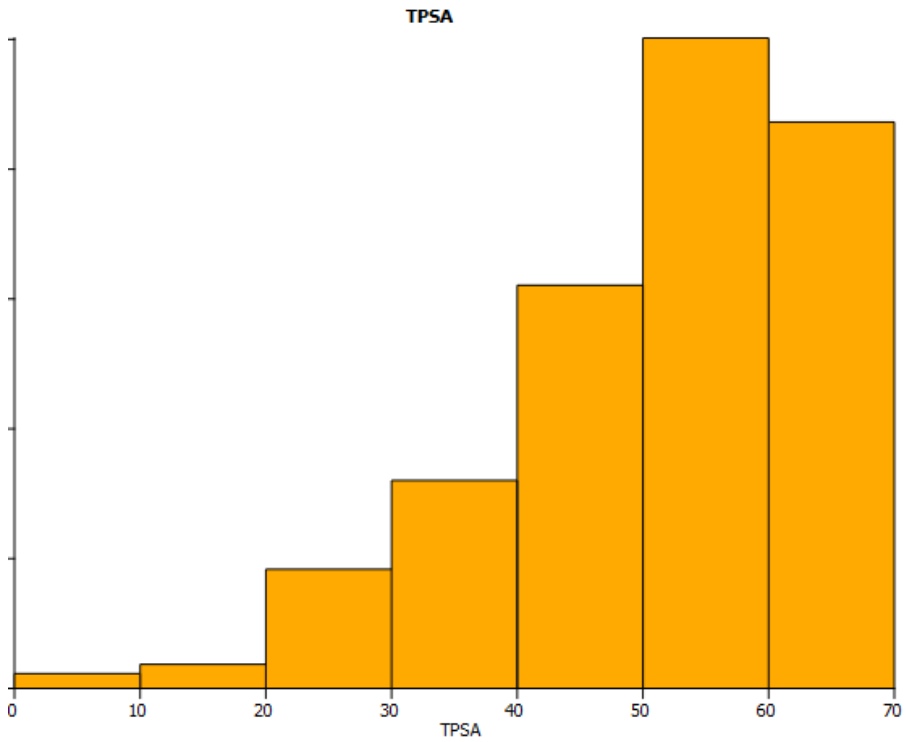
Profiled commercially available compounds from selected screening library suppliers

Physchem filters applied to target CNS druglike properties

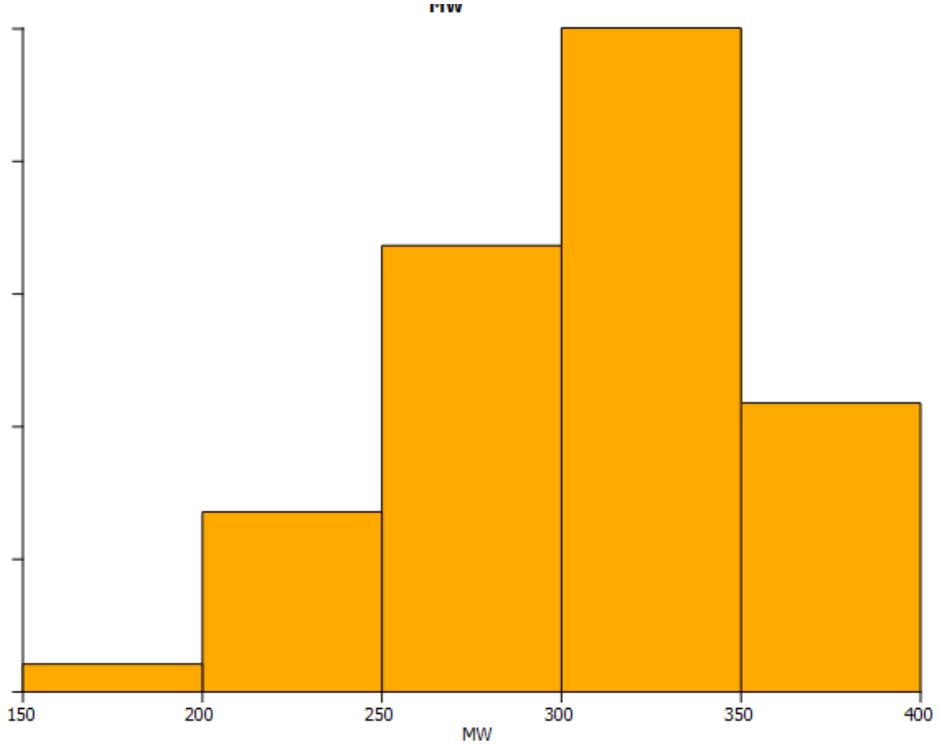
Diversity analysis compared with Takeda screening library

Cherry-picked selection purchased

Commercial Compounds



TPSA Distribution



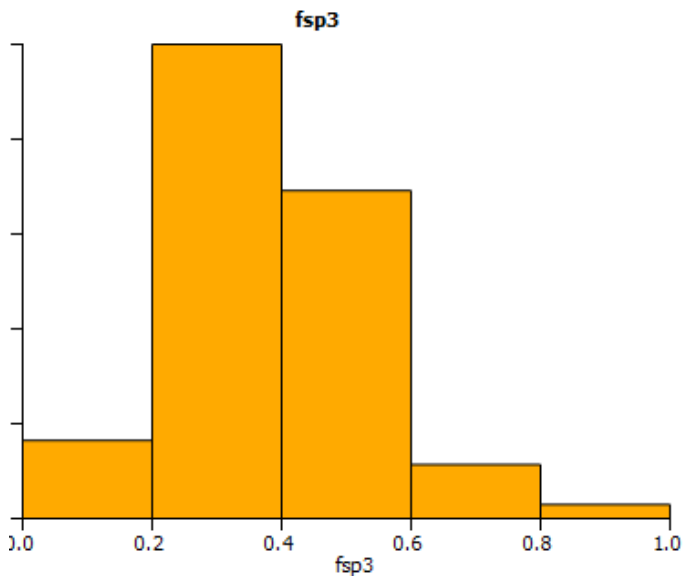
MW Distribution

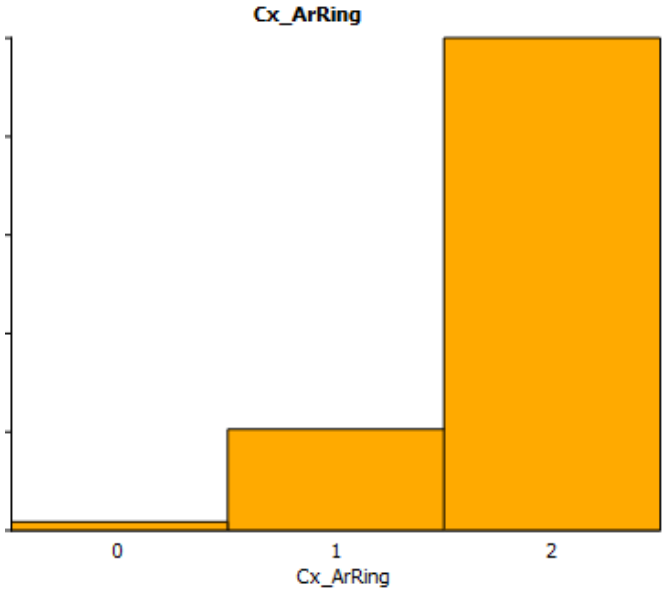
Commercial Compounds

But….
Insufficient numbers

Insufficient diversity

Intellectual Property issues





Many compounds have low fsp3

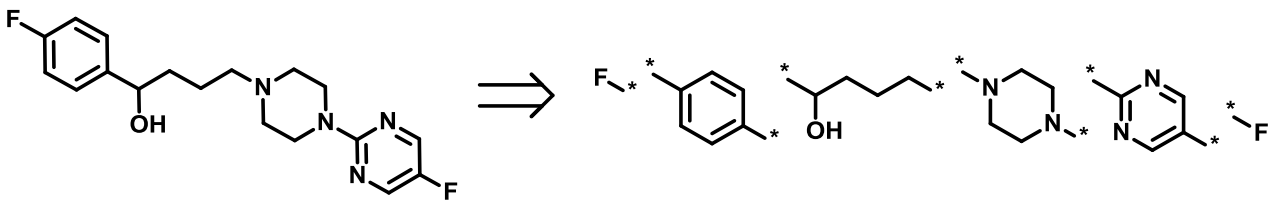
fsp3 is defined as {number of sp3carbons}/{total number of carbons} and is associated with poor solubility and promiscuity

Solution….
Centrally Accessible Molecules (CAMs) Library

CAMS library

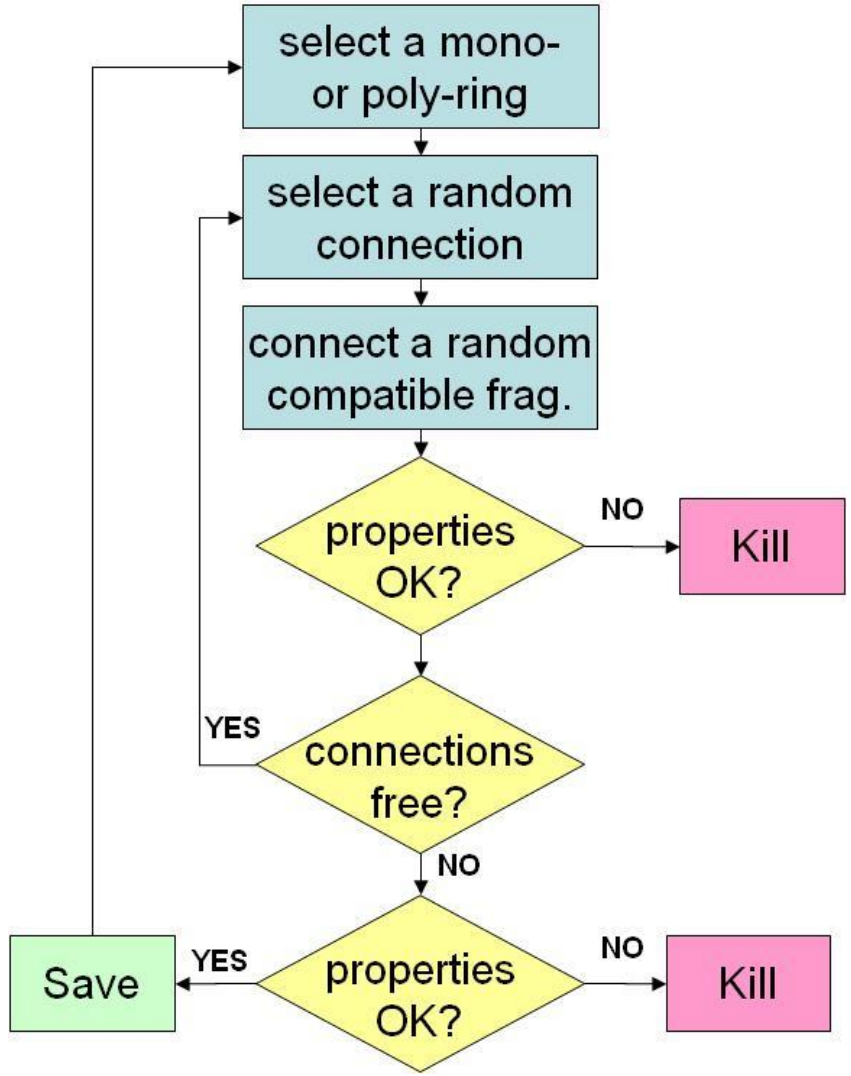
- Library of novel CNS-targeted molecules designed and synthesised at Takeda Cambridge
- Initially analysed the MDL Drug Data Report database (MDDRDB) to classify compounds which have passed into development (excluding cytotoxics, peptides, antibiotics)
- Compounds were binned as CNS (610) or non-CNS (2826) via therapeutic endpoint

  (eg antidepressant, anxiolytic, cognition)
- Simple fragmentation protocol applied to drug molecules – break all acyclic bonds attached to rings
- Count the frequency of occurrence of each fragment in CNS and non-CNS set – Ratio gives a CNS/non-CNS preference
- Selected CNS-preferring fragments



CAMS library

- Rebuild virtual compounds following iterative cycle
- Filtered by CNS Leadlike Properties
- Templates viewed by medicinal chemists and prioritised on basis of chemical tractability and scope for library synthesis
- Focus on increasing fsp3
- Since 2012 scaffold design has been influenced by internal project considerations



CNS Multi-Parameter Optimisation (MPO)

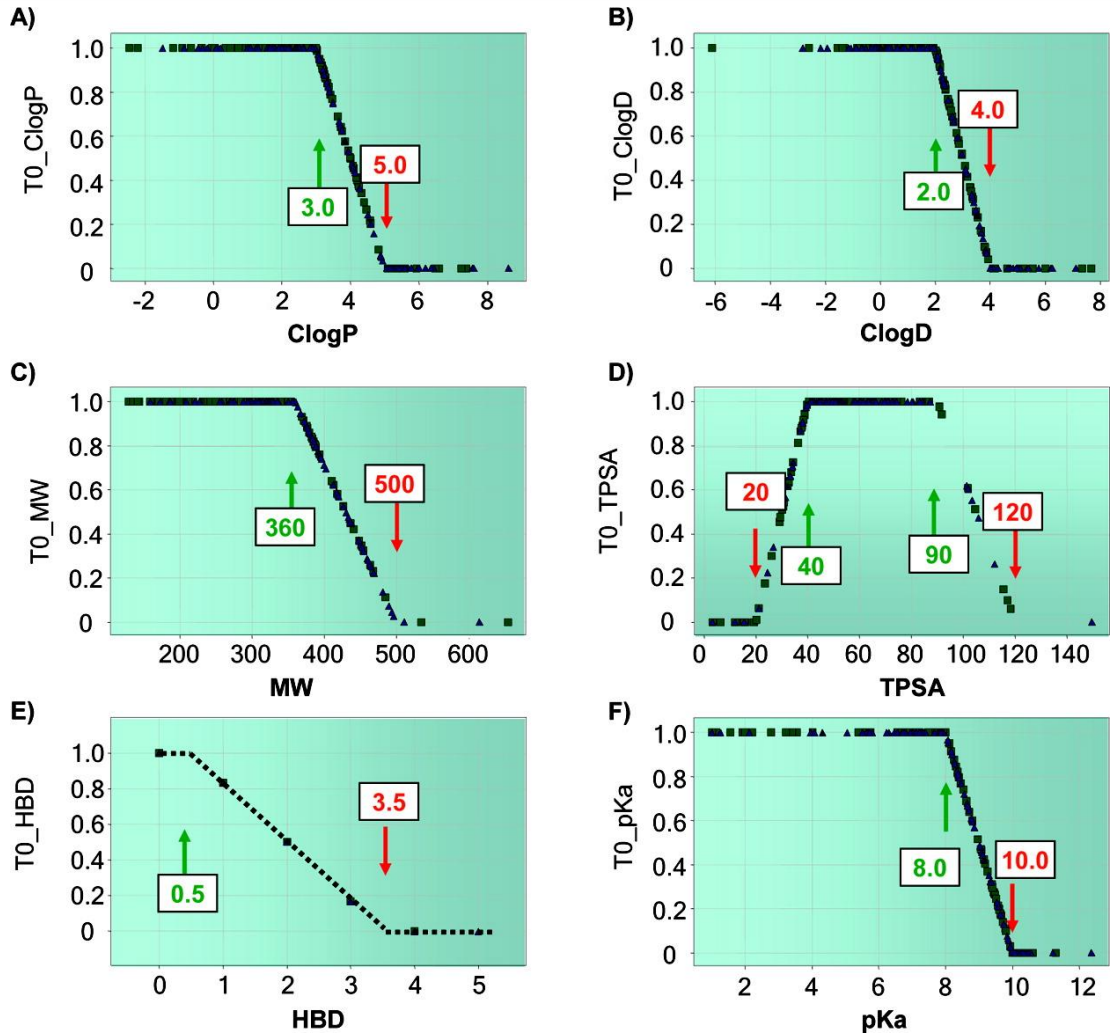
Analysis of CNS drugs carried out by Pfizer[1,2]

More desirable range	Less desirable range
clogP ≤ 3	clogP > 5
$clogD_{7.4}$ ≤ 2	$clogD_{7.4}$ > 4
MW ≤ 360	MW > 500
40 ≤ TPSA ≤ 90	TPSA ≤ 20; TPSA > 120
HBD ≤ 0.5	HBD > 3.5
pK_a ≤ 8	pK_a > 10

[1]Travis T. Wager; Ramalakshmi Y. Chandrasekaran; Xinjun Hou; Matthew D. Troutman; Patrick R. Verhoest; Anabella Villalobos; Yvonne Will *ACS Chem. Neurosci.* 2010, 1, 420-434

[2]Travis T. Wager; Xinjun Hou; Patrick R. Verhoest; Anabella Villalobos *ACS Chem. Neurosci.* 2010, 1, 435-449.

Desirability Scores



Travis T. Wager; Xinjun Hou; Patrick R. Verhoest; Anabella Villalobos
ACS Chem. Neurosci. 2010, 1, 435-449.
DOI: 10.1021/cn100008c

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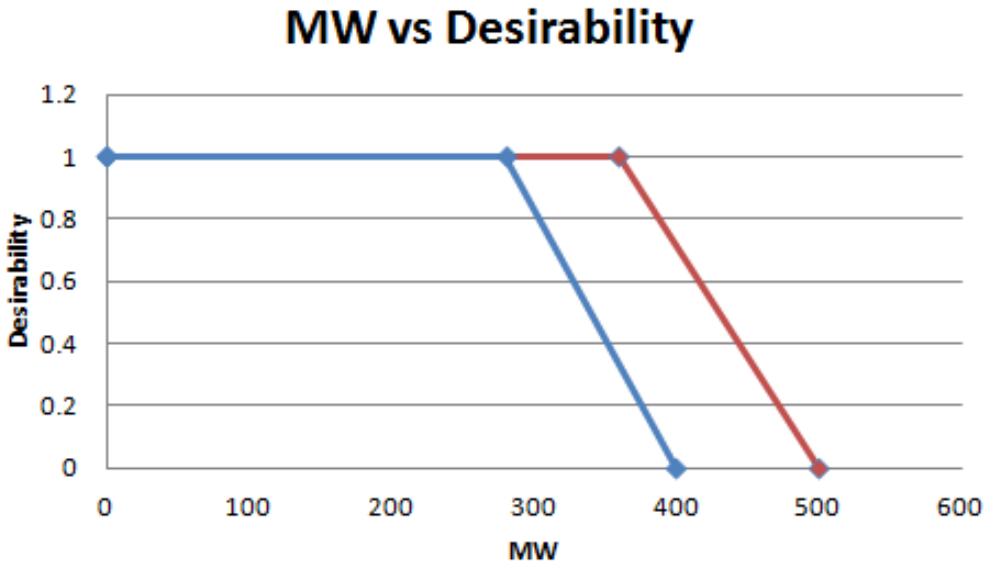
ACS Publications
High quality. High impact.

MPO score obtained by adding individual desirability scores for each property

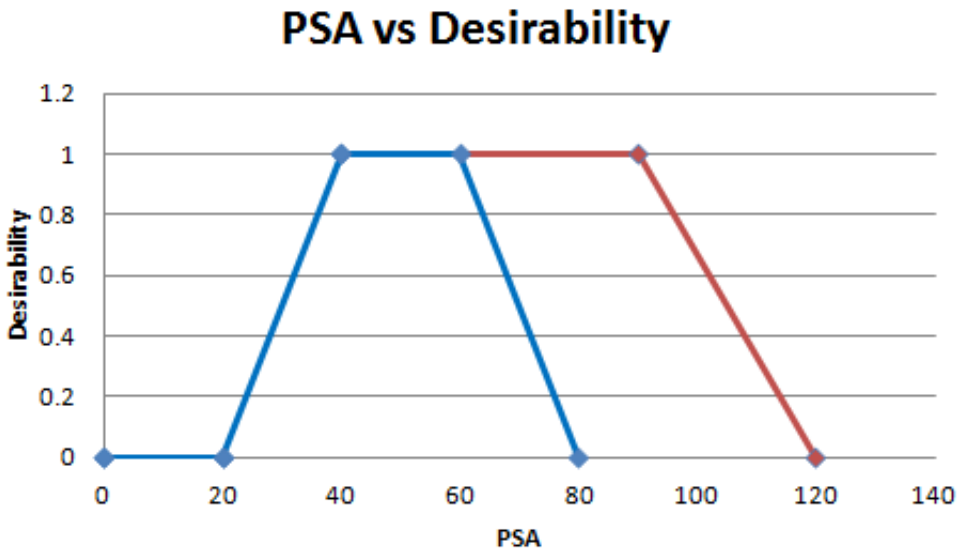
MPO score 4-6 recommended for CNS drugs

CAMs Library design

- Focus on lead-like molecules rather than drug-like molecules
- Use of ‘Hard cut offs’ was too restrictive so moved to modified MPO system
- desirability thresholds for clogP, clog$D_{7.4}$, HBD and pKa unchanged
- Lowered desirability thresholds for MW to 280-400 (was 360-500)
- Lowered desirability thresholds for PSA to 60-80 (was 90-120)
- Provides scope for increasing size and polarity during lead optimisation stage

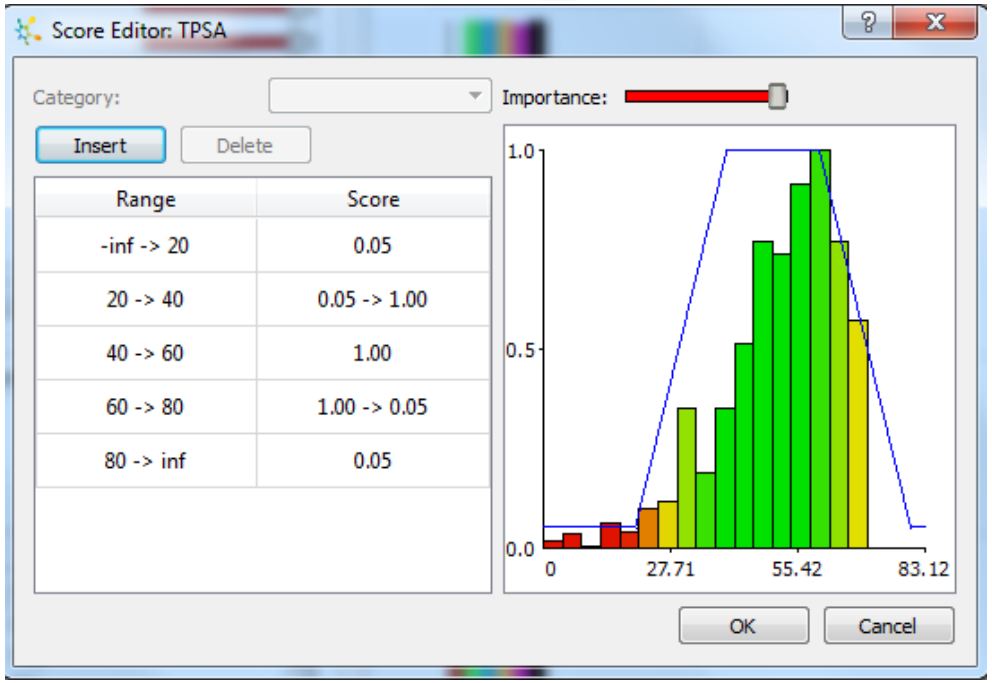


Red = Pfizer score
Blue = CAMs score



CAMs MPO scoring profile in StarDrop ®

Property	Desired Value	Importance
TPSA	40 -> 60	
MW	-inf -> 280	
HBD	-inf -> 0.5	
Pfizer basic pKa category u...	OK	
Cx_logD7.4	-inf -> 2	
Cx_logP	-inf -> 3	



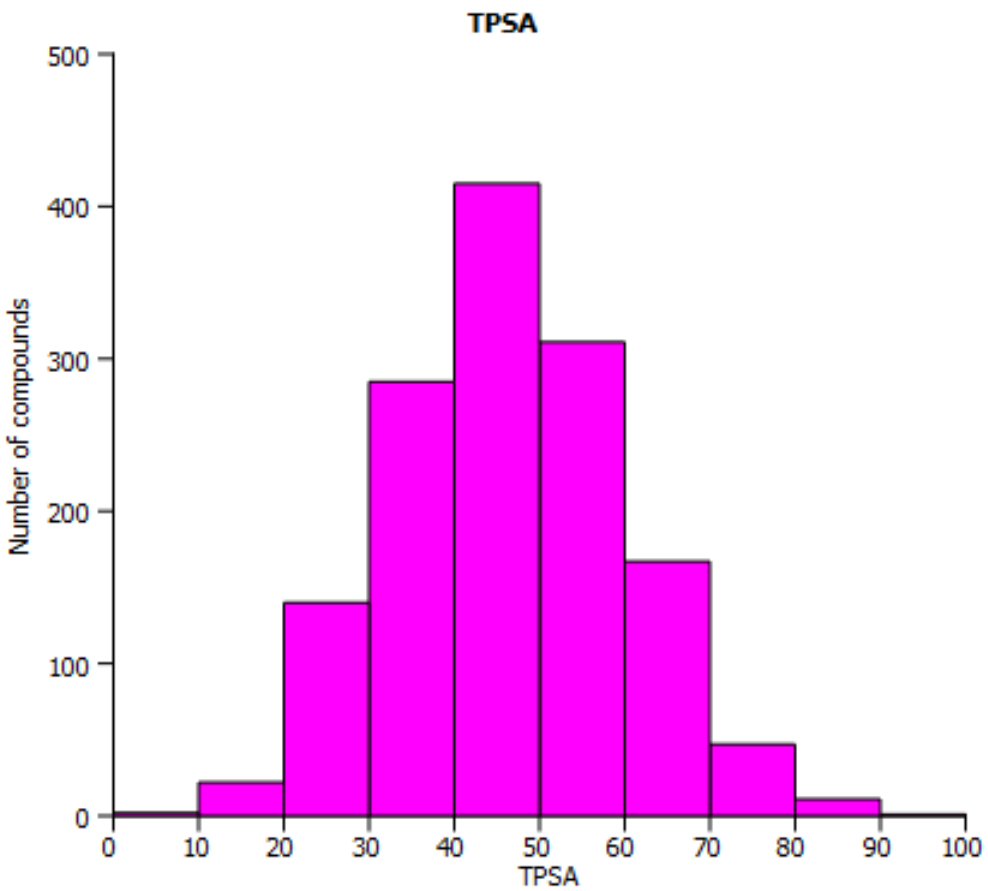
MPO score calculated through Perl/Python scripts and ChemAxon webservices

	CAMS_MPO	CAMs MPO model (	TPSA	MW	HBD	Pfizer basic pKa category	Cx_logD7.4	Cx_logP
1	0.8556	5.863	56.05	259.4	0	OK	2.274	2.278
2	0.9854	6	49.33	262.4	0	OK	1.733	1.738
3	0.4584	5.43	58.56	348.4	0	OK	0.805	0.808
4	0.5551	5.512	49.33	290.4	0	OK	2.802	2.808
5	0.1402	4.699	71.45	367.4	0	OK	1.387	1.39
6	0.01381	4.238	84.59	371.4	0	OK	0.635	0.638
7	0.7643	5.788	52.57	305.4	0	OK	1.937	1.973

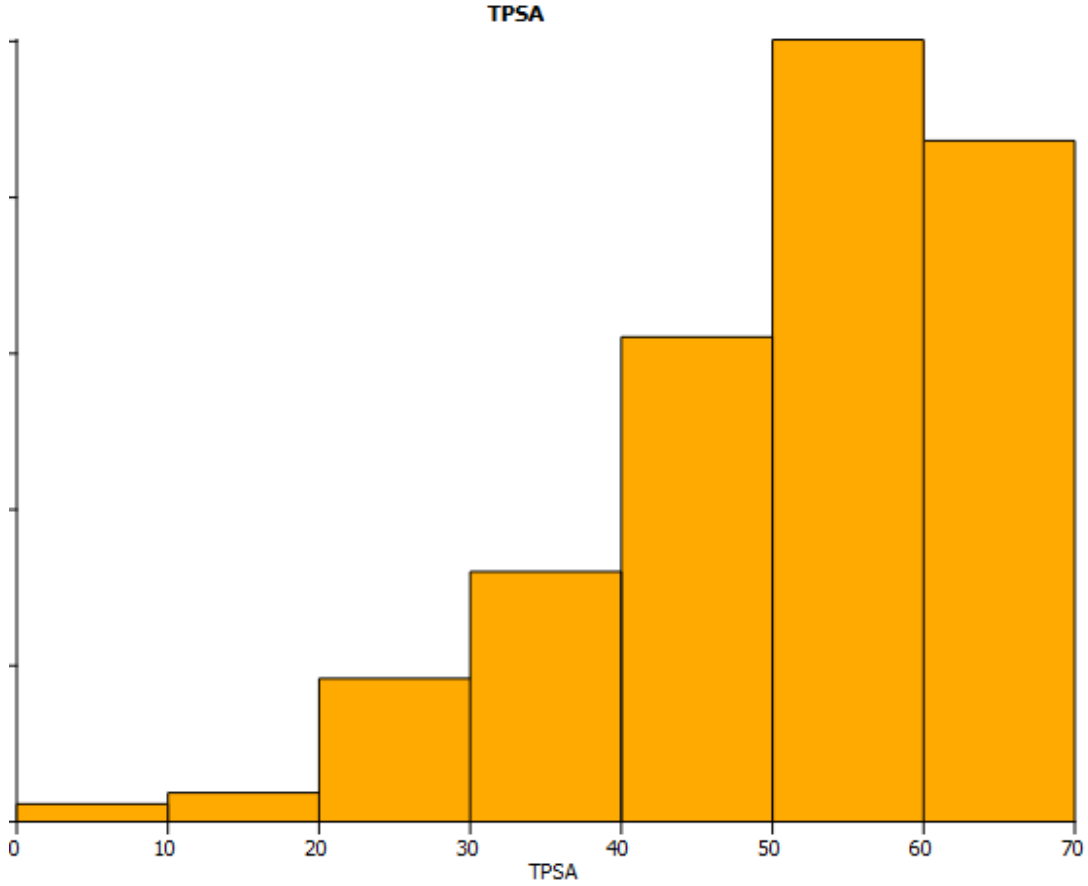
Structural Criteria for CAMs compounds

- Compounds should contain no more than one hydrogen bond donor.
- Compounds should contain no more than one basic amine.
- No carboxylic acid functionality in final compounds.
- No undesirable chemical functionality:
    - Electrophilic groups
    - Acid labile groups
    - Toxicophores
- Stereochemistry – compounds should not be a mixture of more than two stereoisomers
- Markush novelty search of final compounds

CAMs TPSA Profile

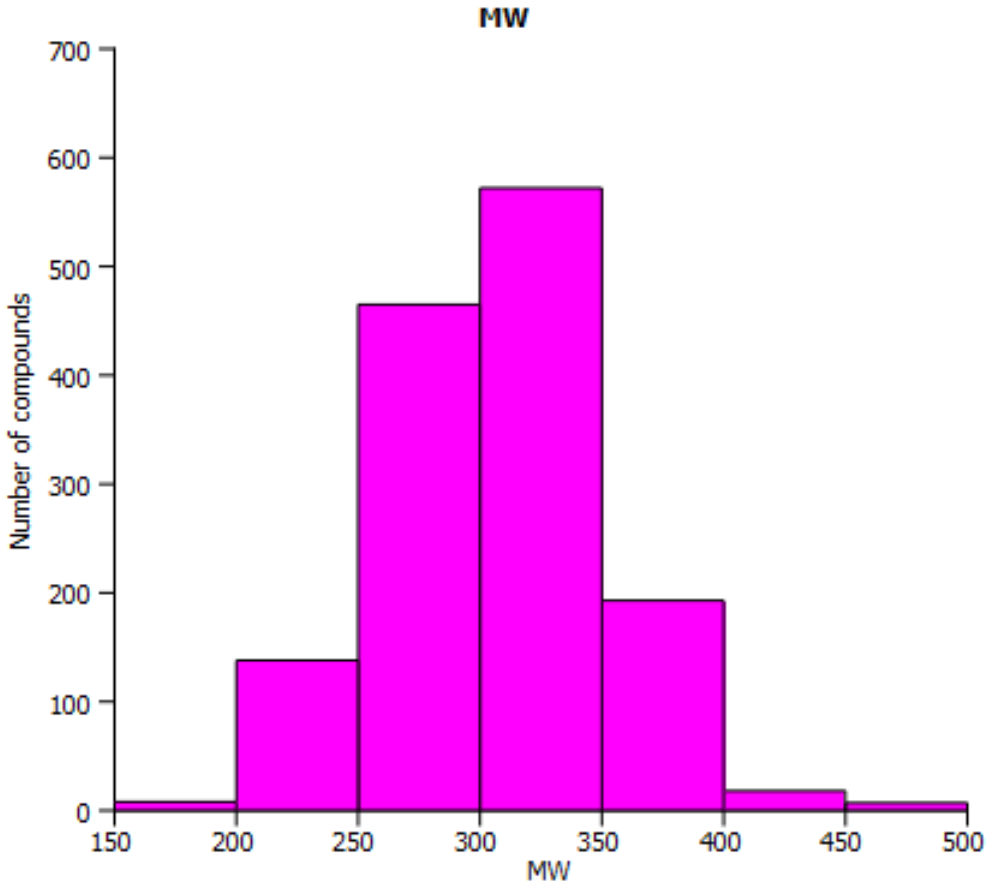


CAMS Library

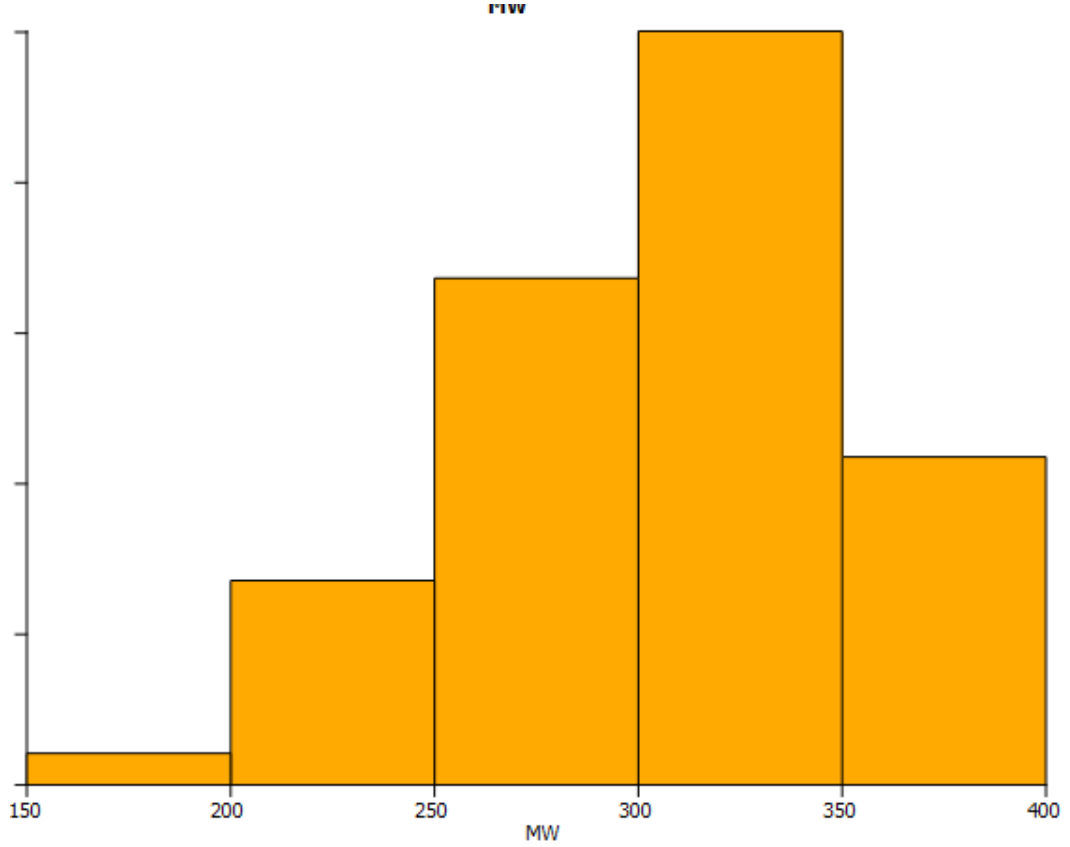


Commercial CNS selection

CAMs MW Profile

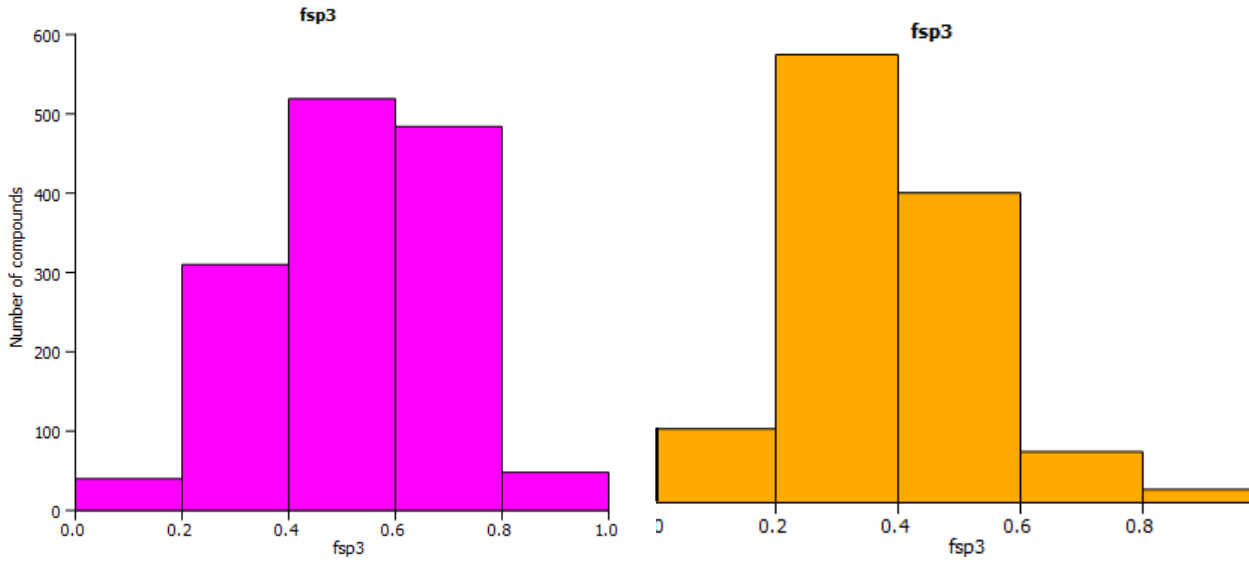


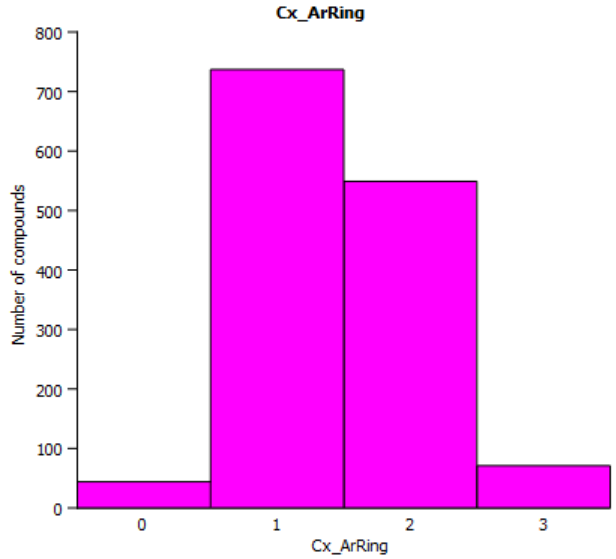
CAMS Library

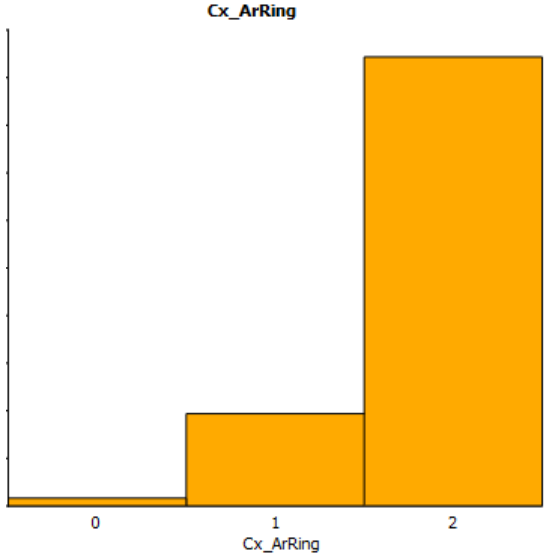


Commercial CNS selection

CAMs fsp3 properties







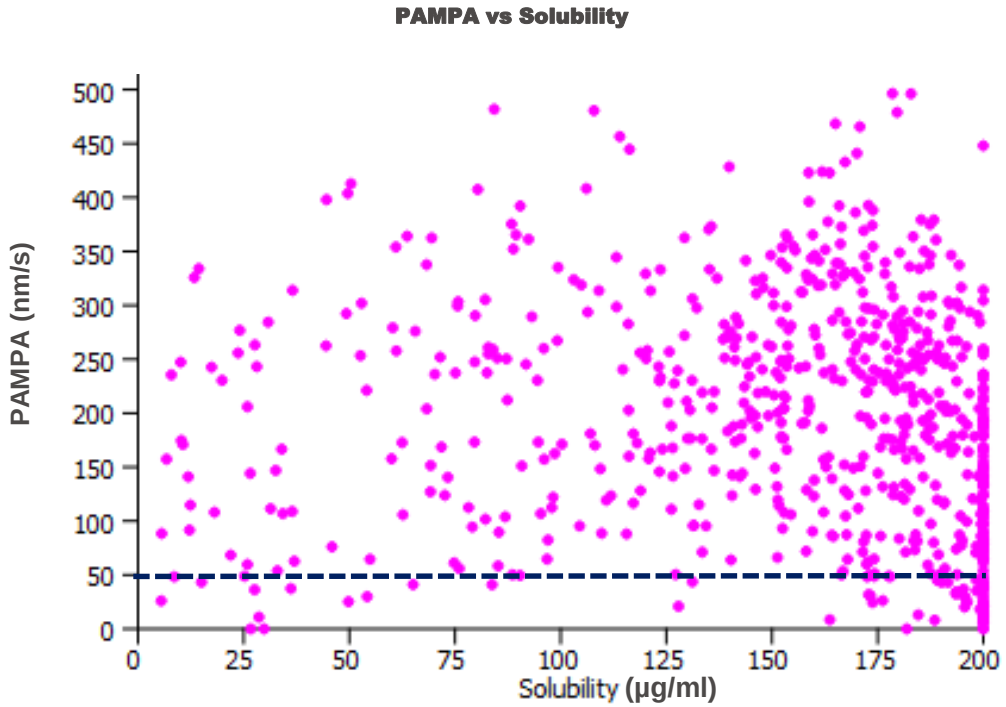
CAMS
75% fsp3 > 0.4

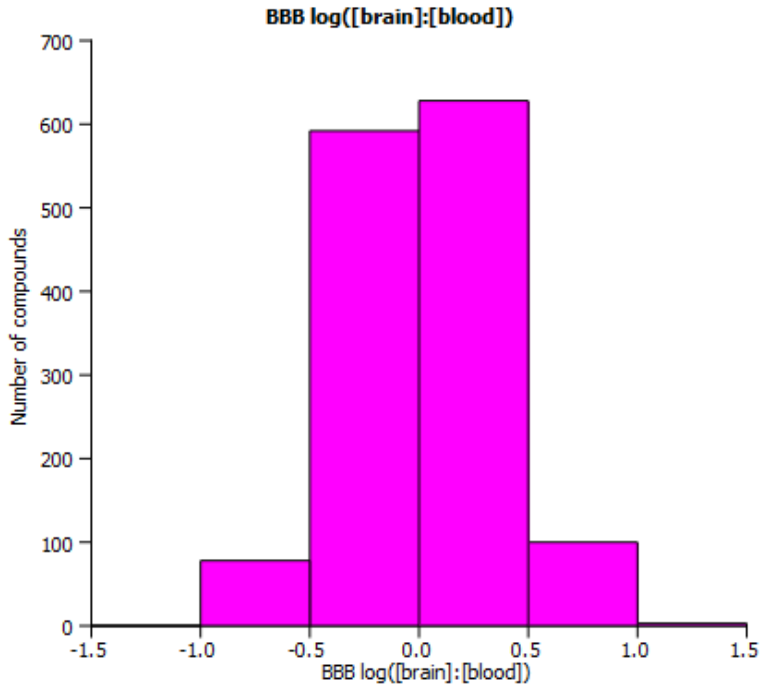
CNS Commercial
40% fsp3 > 0.4

CAMS
56% Cx_ArRing < 2

CNS Commercial
18% Cx_ArRing < 2

Analysis of CAMs compounds





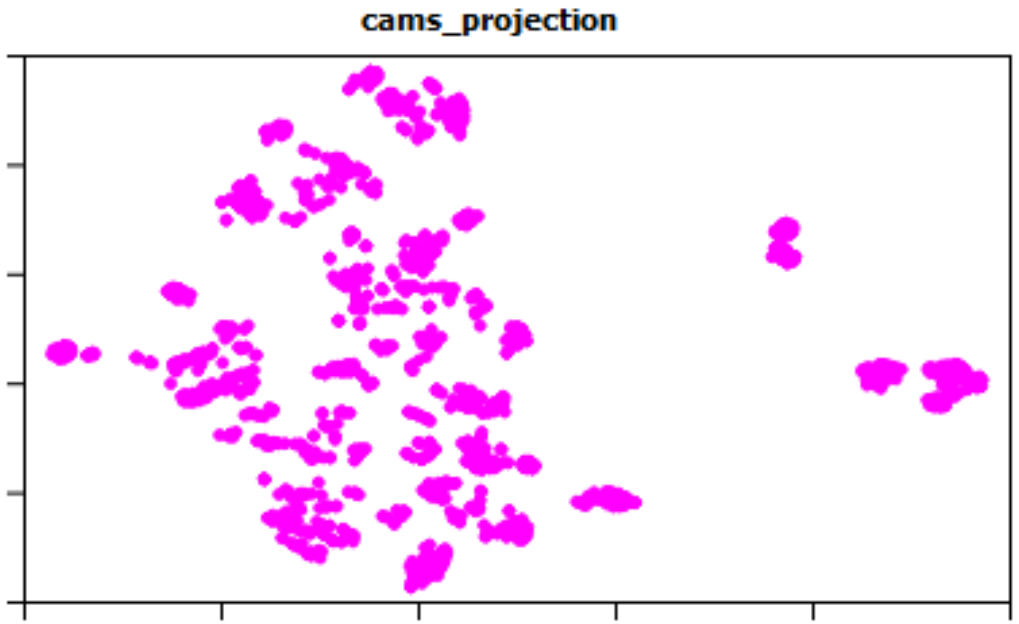
All compounds synthesized are highly soluble and 94% have >50 nm/s permeability

96% of all compounds synthesized are predicted to be highly brain penetrant

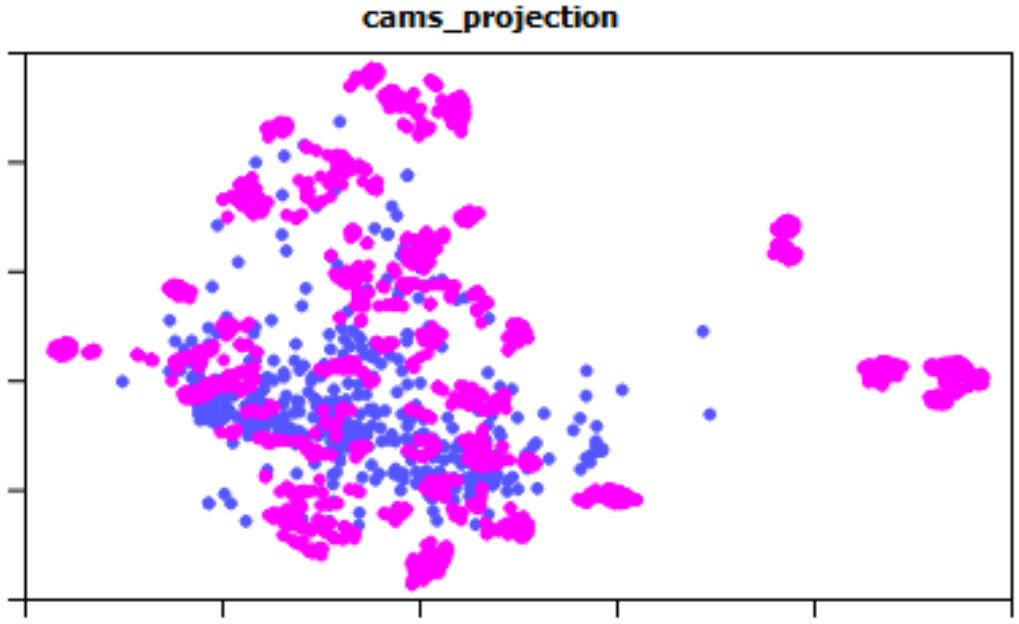
StarDrop® (log([brain]:[blood] > -0.5

Confirmed with MDCK assay for representative compounds

CNS Drug Space



CAMS CNS Set

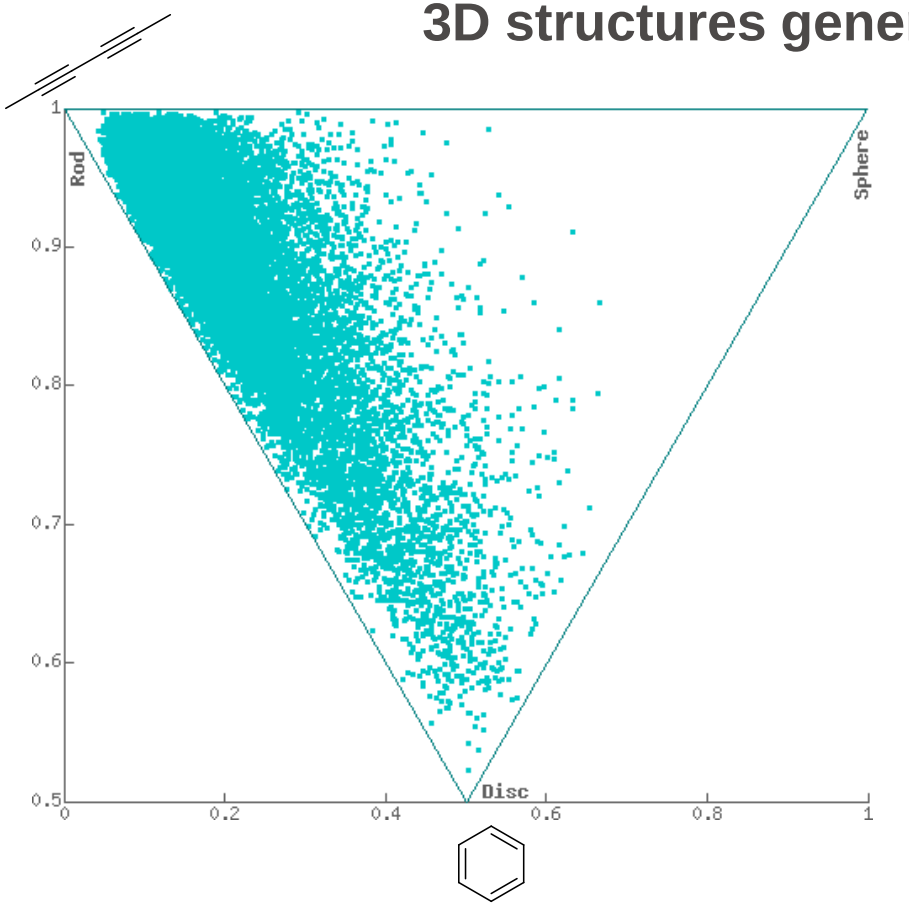


CNS Component of MDDR Database

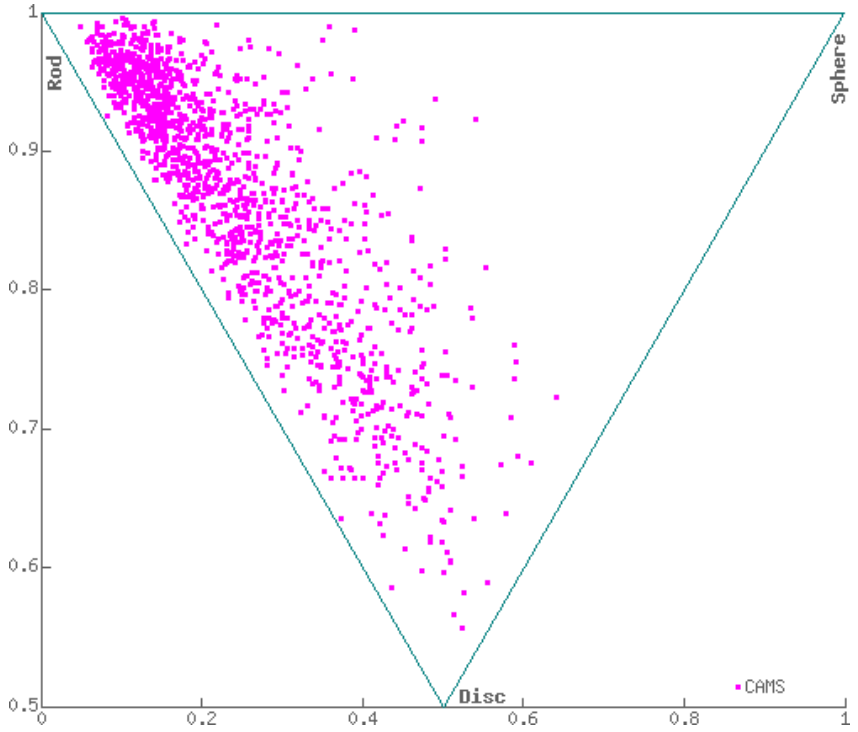
- Each compound is represented by a point
- The similarity between two compounds is represented by their proximity
- Defined using path-based fingerprints and Tanimoto similarity
- CAMS library is more structurally diverse than MDDR CNS drug set

PMI Plot

Shape-based analysis of CNS libraries based on Principal Moments of Inertia 3D structures generated using Corina (Molecular Networks GMBH)

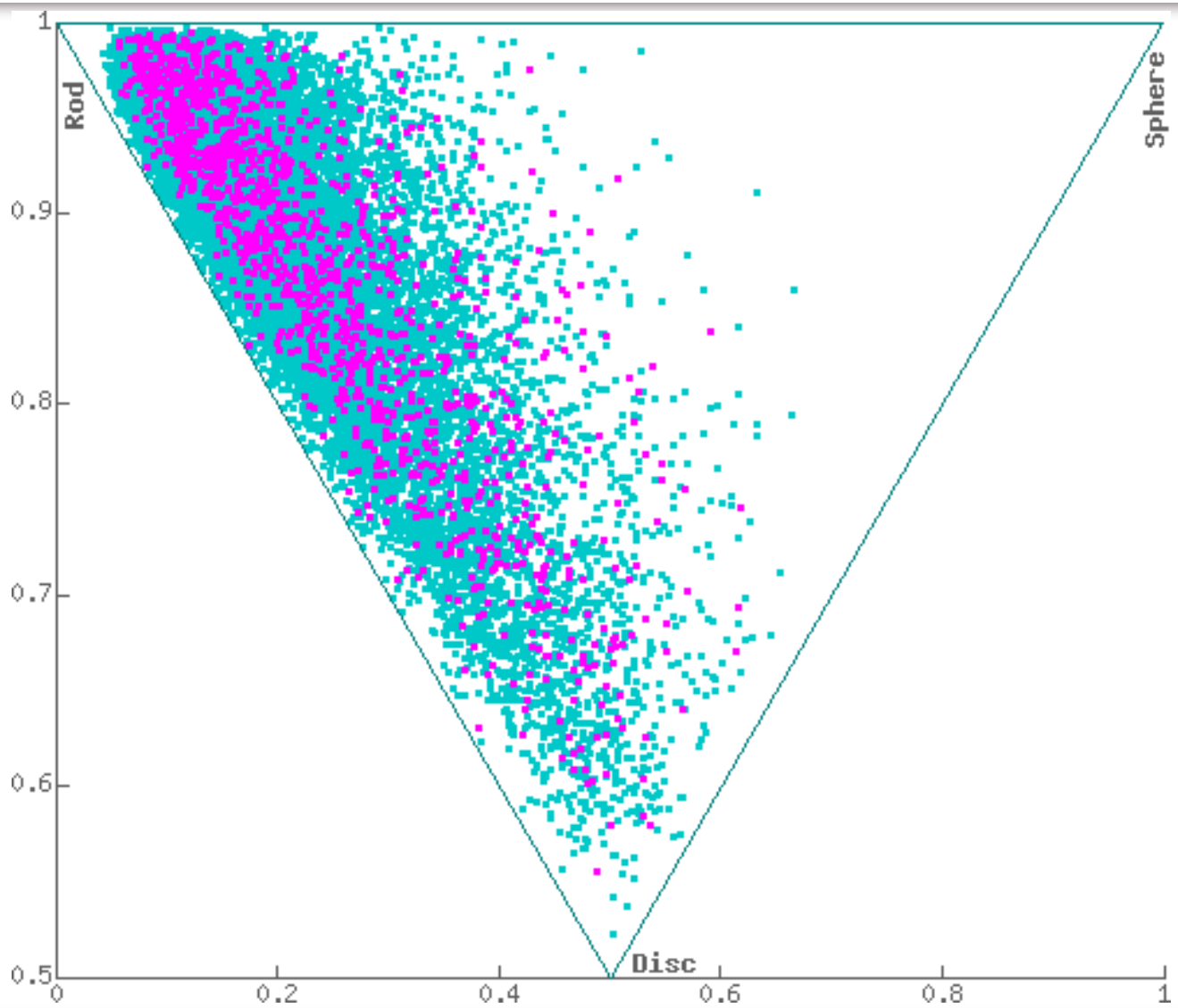


Commercial CNS library



CAMS

PMI Plot



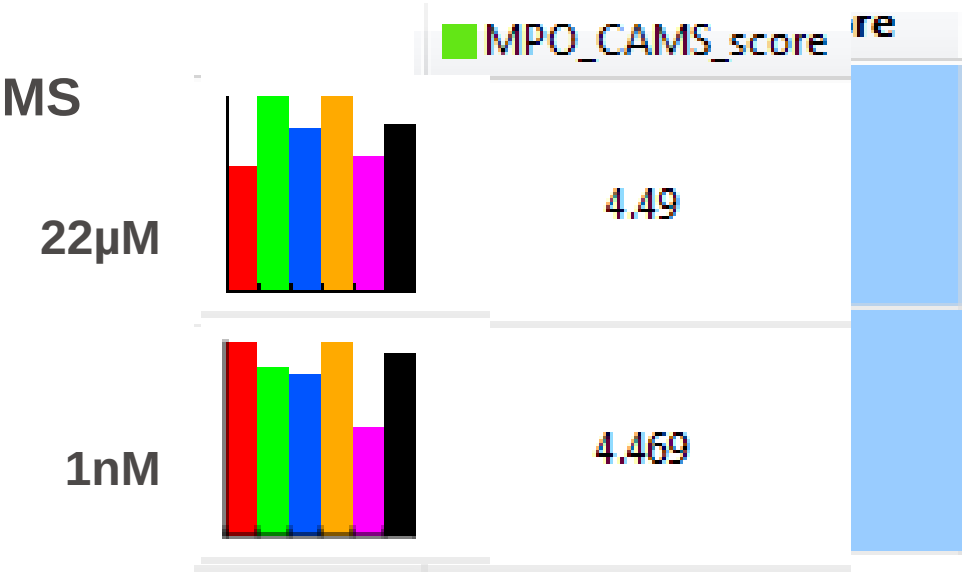
CAMs Library Screening Hits

- CAMs Library aimed to provide robust leads with excellent physicochemical properties (soluble, permeable, CNS-penetrant) suitable for optimisation
- 40% of recently completed CNS Project screens contained novel hits from CAMS component
- Now incorporated routinely into CNS Project HTS campaign

Property	Desired Value
TPSA	40 -> 60
MW	-inf -> 280
HBD	-inf -> 0.5
Pfizer basic pKa category ...	OK
Cx_logD7.4	-inf -> 2
Cx_logP	-inf -> 3

Examples of Lead generation and progress from earlier CAMS screens

Project 1	**5µM ⇨ 40nM**
Project 2	**500nM**
Project 3	**22µM ⇨ 1nM**



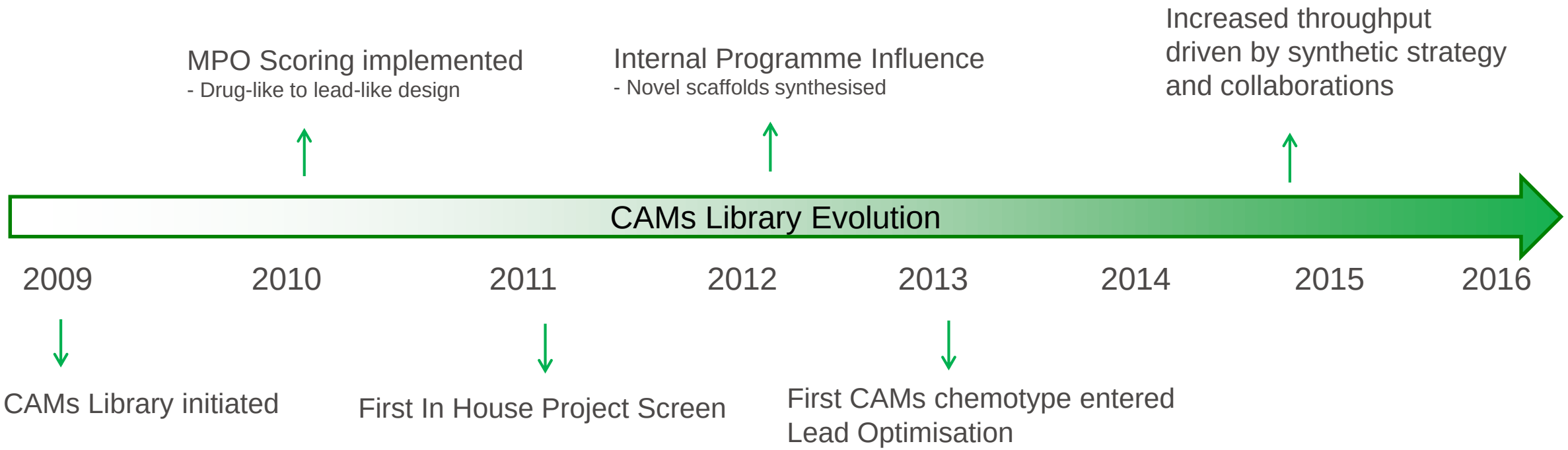
CAMs Library Current Status

- Small library with proven value in hit identification for CNS projects
- Synthesis carried out by industrial placement students at Takeda Cambridge

Current activities include

- access high throughput chemistry technologies at Shonan to rapidly develop novel cores
- leverage global Takeda knowledge in synthetic chemistry
- novel cores proposed by Takeda chemistry teams and incorporated into design strategy
- collaborate with academic groups developing synthetic strategies to efficiently access novel chemical space

Development of CAMS library since 2009



Acknowledgements

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Katy White
Susanne Wright

Will Farnaby

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