Reymond Group

UNIVERSITÄT BERN

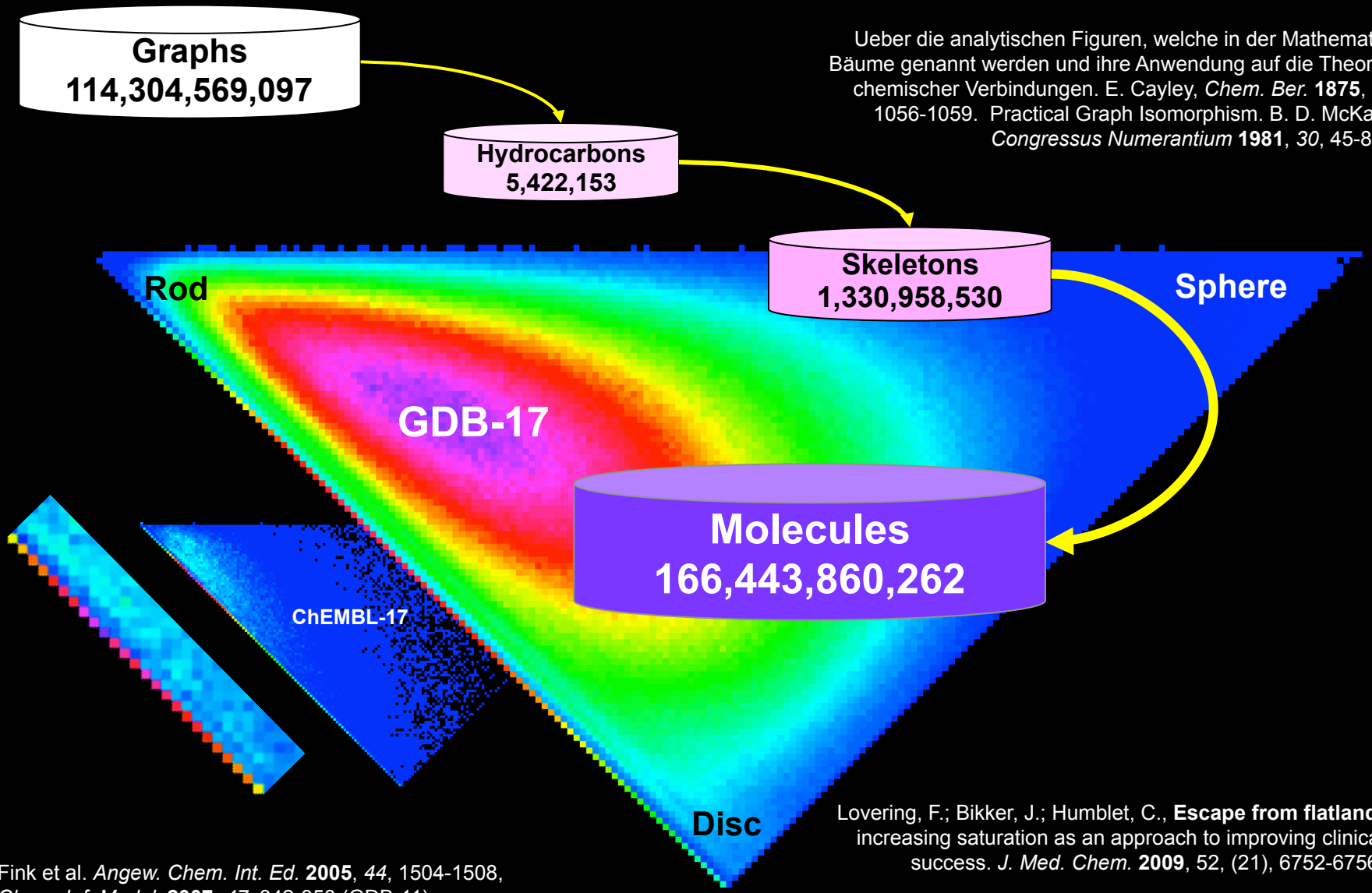
NCCR TransCure
Excellence in Membrane Transport Research

FNSNF
Fonds national suisse
Schweizerischer Nationalfonds
Fondo nazionale svizzero
Swiss National Science Foundation

Reymond Group

- Cheminformatics (3 students)
  - databases of virtual molecules (GDB)
  - virtual screening methods
  - visualization of chemical space
  - peptide modeling (dendrimers, polycyclic peptides)
- Organic synthesis (9 students)
  - small molecules for drug design
  - reference substrates and inhibitors for structural studies
  - peptide dendrimers and polycyclic peptides
- Biology (2 students)
  - structural biology (lectins, kinases)
  - microbiology (evaluation of antimicrobials and biofilm inhibitors)
  - cell culture (DNA/siRNA transfection reagents, cytotoxicity studies)

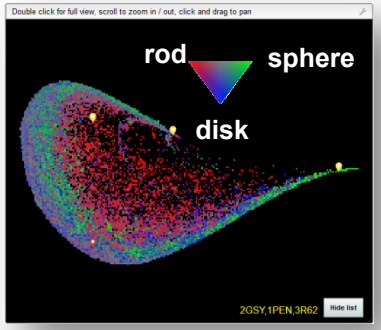
Enumeration



Ueber die analytischen Figuren, welche in der Mathematik Bäume genannt werden und ihre Anwendung auf die Theorie chemischer Verbindungen. E. Cayley, *Chem. Ber.* **1875**, *8*, 1056-1059. Practical Graph Isomorphism. B. D. McKay, *Congressus Numerantium* **1981**, *30*, 45-87.

Lovering, F.; Bikker, J.; Humblet, C., **Escape from flatland:** increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009**, 52, (21), 6752-6756.

T. Fink et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 1504-1508,
J. Chem. Inf. Model. **2007**, *47*, 342-353 (GDB-11)
L. C. Blum, J.-L. Reymond, *J. Am. Chem. Soc.* **2009**, *131*, 8732-3 (GDB-13);
L. Ruddigkeit et al., *J. Chem. Inf. Model.* **2012,** *52*, 2864-2875 (GDB-17)



fp-Design / Visualization

www.cheminfo.org/pdbexplorer

Help Page

Select image: Heavy atom count

Drop your pdb file here

Double click for full view, scroll to zoom in / out, click and drag to pan

2GSY,1PEN,3R62 Hide list

Hovered
Name: 2A18
Position: 79, 195
Avg, stdev: 4760.76, 314.68

2A18 View in jsmol

mode: cartoon

Lookup a list of PDBs

Enter a list of PDBs

1PEN,2GSY,3R62

Sort by similarity

Enter pdb code: 2A18

Max Count: 100

Max Distance: 10000

Search by similarity

List of proteins in clicked cell (2A18)

Download zip

Rank	Code	pdb	pdb....	Jsmol	Distance
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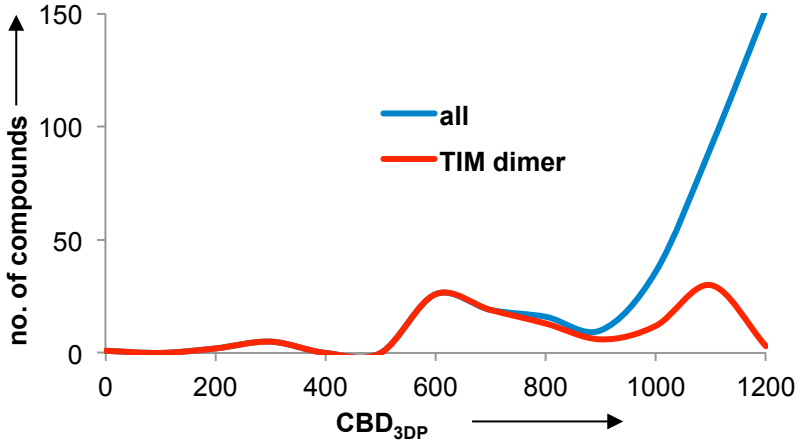
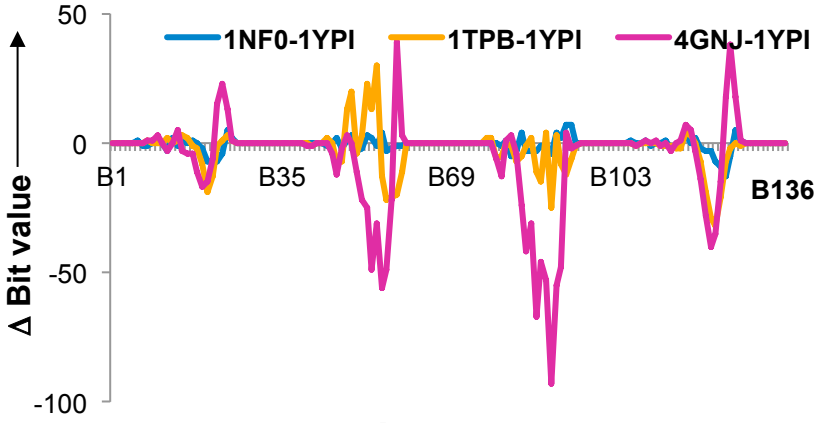
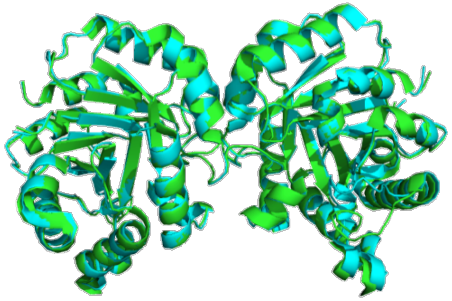
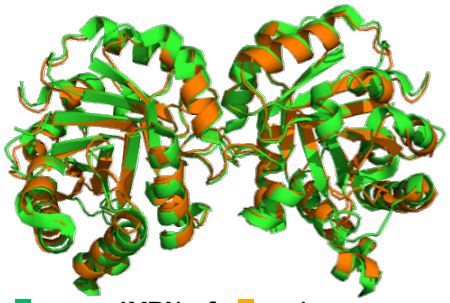
	4A61				
	3BLH				



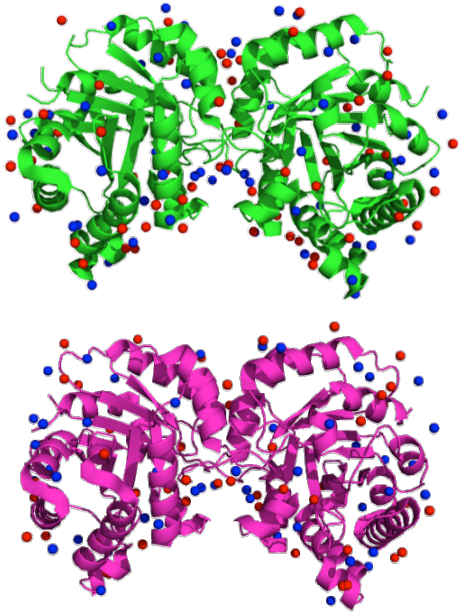




1YPI(reference) 1NF0(rank2)
(CBD_{3DP}=189)



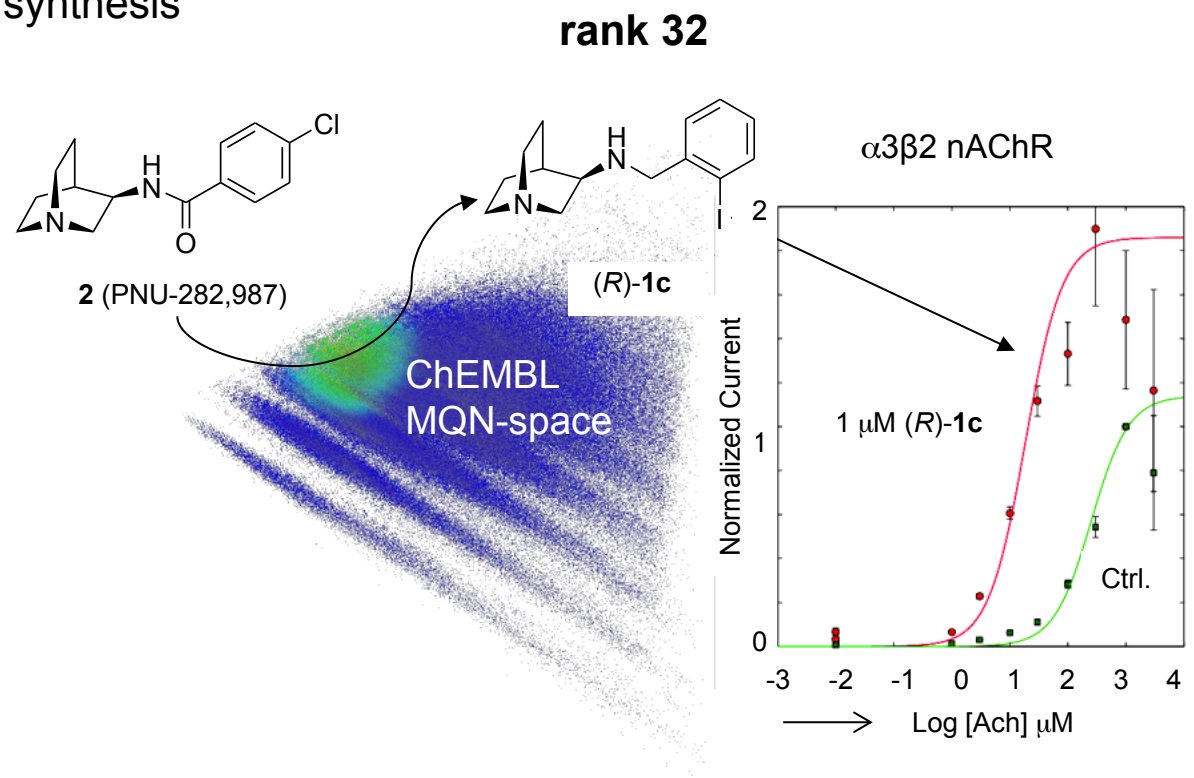
1YPI(reference) 1TPB(rank10)
(CBD_{3DP}=517)



1YPI(reference) 4GNJ(rank321)
(CBD_{3DP}=1178)

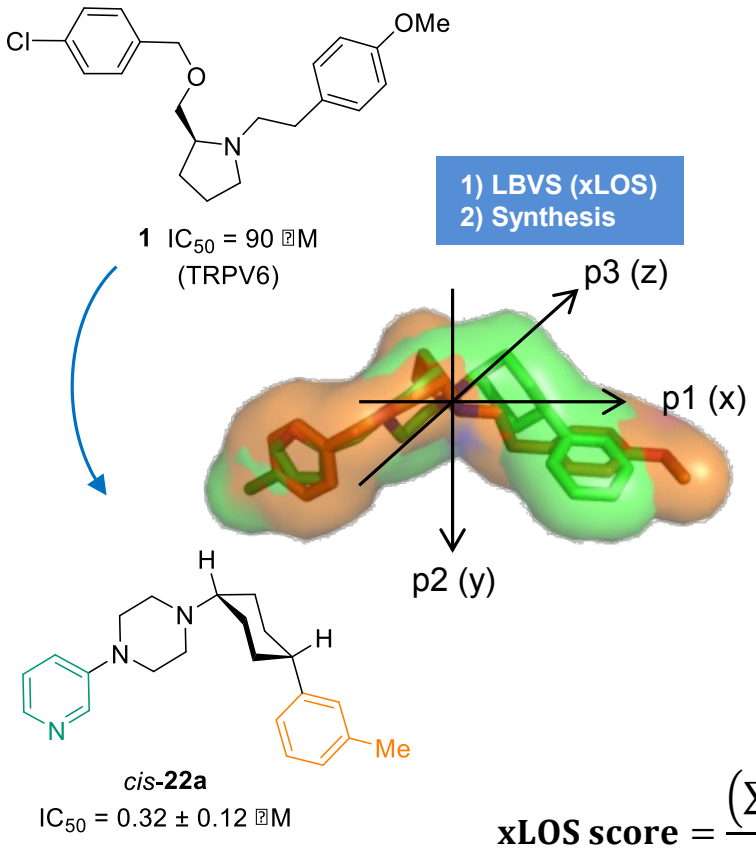
Applications of Virtual Screening: MQN

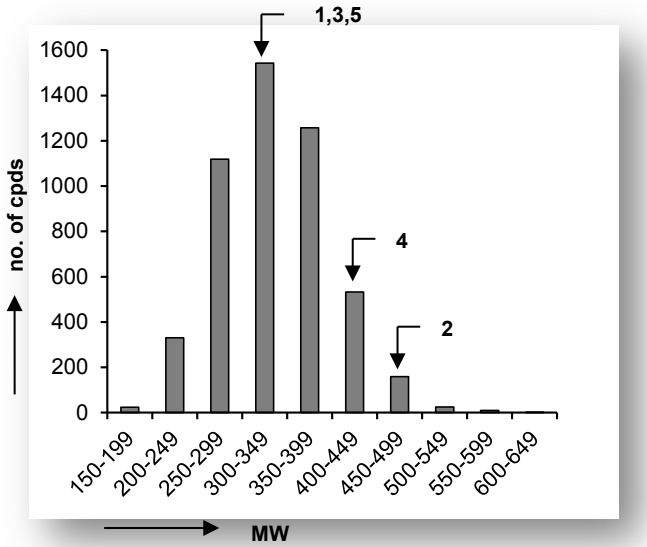
- survey MQN-space neighbours
- buy and test
- optimize by chemical synthesis
- in vivo effects



Discovery of Potent Positive Allosteric Modulators of the α3β2 Nicotinic Acetylcholine Receptor by a Chemical Space Walk in ChEMBL. J. Bürgi, M. Awale, S. Boss, T. Schaer, F. Marger, J. Viveros-Paredes, S. Bertrand, J. Gertsch, D. Bertrand, J.-L. Reymond, *ACS Chem. Neurosci.* **2014**, *5*, 346-359.

xLOS Analogs in ZINC

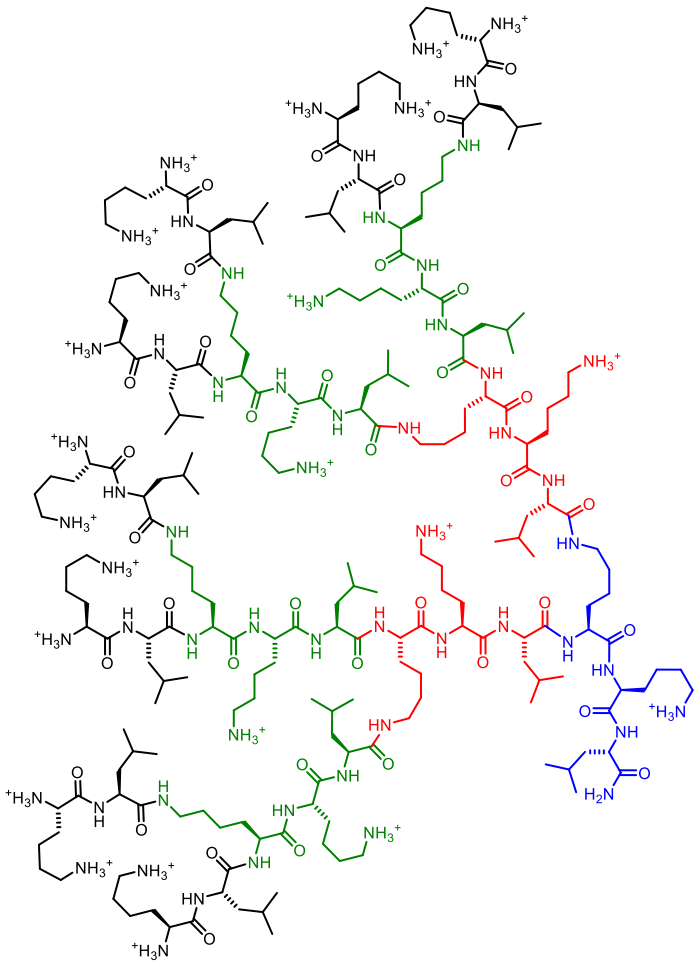




$$\textbf{xLOS score} = \frac{\left(\sum_{j=1}^{m_d}\sum_{i=1}^{n_d} e^{-d_{ij}^2}\right)}{m_d + n_d} + \frac{\left(\sum_{j=1}^{m_a}\sum_{i=1}^{n_a} e^{-d_{ij}^2}\right)}{m_a + n_a} + \frac{2 \times \left(\sum_{j=1}^{m_h}\sum_{i=1}^{n_h} e^{-d_{ij}^2}\right)}{m_h + n_h}$$

Optimization of TRPV6 Calcium Channel Inhibitors Using a 3D Ligand-Based Virtual Screening Method. C Simonin, M Awale, Michael Brand, R van Deursen, J Schwartz, M Fine, G Kovacs, P Häfliger, G Gyimesi, A Sithampari, RP Charles, MA Hediger, JL Reymond, *Angew. Chem. Int. Ed. Engl.* **2015**, DOI: 10.1002/anie.201507320., in press.

Peptide Dendrimers



$(KL)_8(KKL)_4(KKL)_2KKL$

Table 2: MIC values of AMPDs for multidrug-resistant isolates and LPS mutant strains of *P. aeruginosa*.[a]

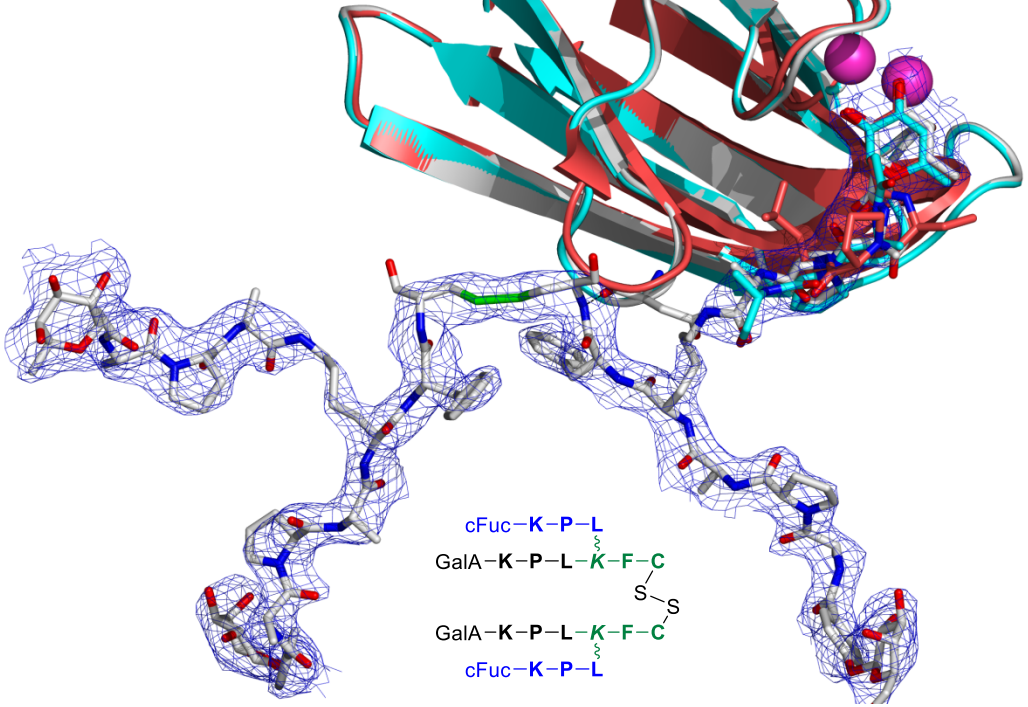
Strain	G3KL	DG3kl	G3RL	bH1	Polymyxin
ZEM1.A	4	4	8	> 64	0.25
ZEM9.A	32	32	32	> 64	8
PEJ2.6	8	4	8	> 64	1
PEJ9.1	32	32	8	> 64	2
A. baumannii	8	16	8	16	1
E. coli	4	2	4	8	0.5
E. aerogenes	64	32	16	64	0.5
PAO1	4	4	8	> 64	1
PAO1*rmd* (A-)	4	4	8	> 64	1
PAO1*rmlC* (A-B-)	4	4	4	64	0.5
AK1012 (*algC*)	2	2	4	16	1

[a] MIC values were determined by serial two-fold dilutions in Mueller–Hinton (MH) broth in 96 well plates after incubation for 18–22 hours at 37 °C. Experiments were performed in triplicates with at least two independent experiments giving the same value. For the resistance profiles, see Table S1. bH1 was active against PAO1 in LB broth (Table 1), but inactive in MH broth (this table).

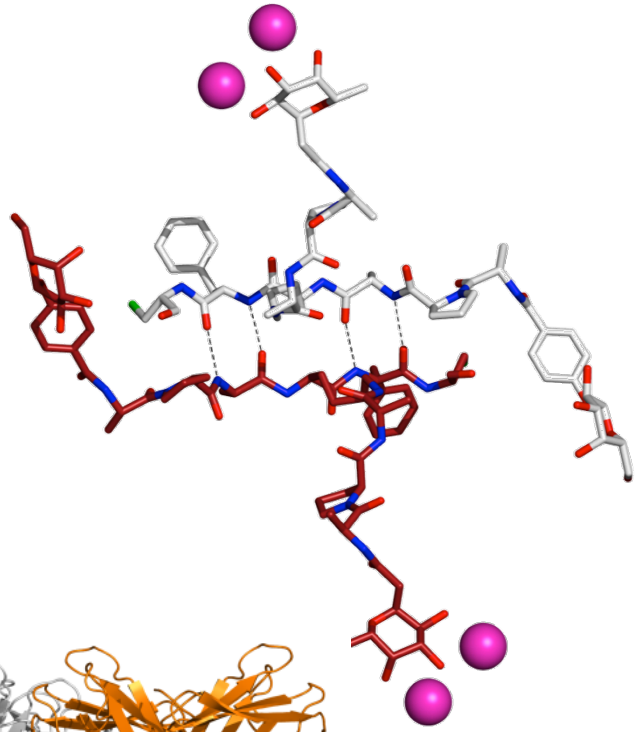
Table S2: Minimal Inhibitorial concentration (MIC) determined in presence of 30% human serum. The results represent two independent experiments done in triplicate .

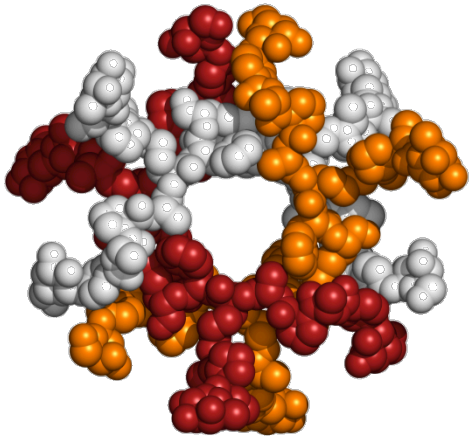
Cpd.	Sequence	PA01 (µg/ml)1	PA01 (µg/ml)2
bH1	$(L)_8(BL)_4(BF)_2BK$	> 128	> 128
G3KL	$(KL)_8(KKL)_4(KKL)_2KKL$	2	2
G3RL	$(RL)_8(KRL)_4(KRL)_2KRL$	> 128	> 128
DG3kl	$(kl)_8(kkl)_4(kkl)_2kkl$	0.5	0.5
LinKYL13	KYKKALKKLAKLL	32	32
Polymyxin B	Cyclic peptide	4	2

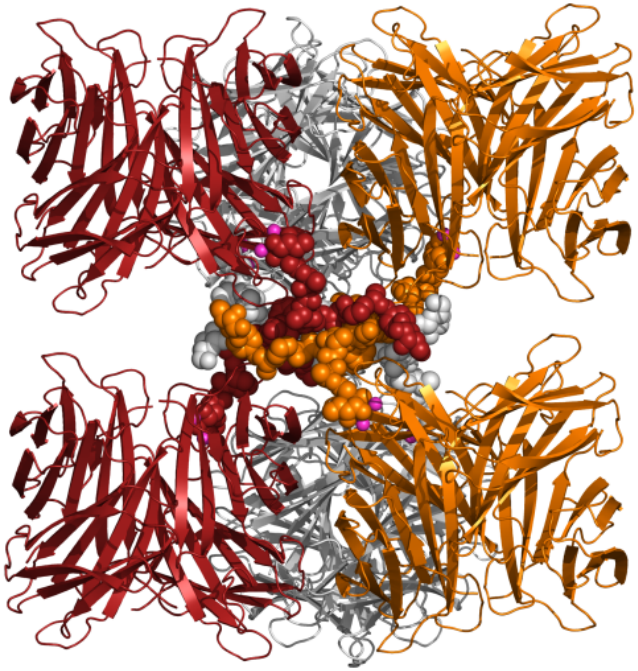
Combining Topology and Sequence Design for the Discovery of Potent Antimicrobial Peptide Dendrimers against Multidrug-Resistant Pseudomonas aeruginosa. Stach M, Siriwardena TN, Köhler T, van Delden C, Darbre T, Reymond JL, *Angew. Chem., Int. Ed.* **2014**, *53*, 12827-12831



(**Het2G1**-Cys)$_2$

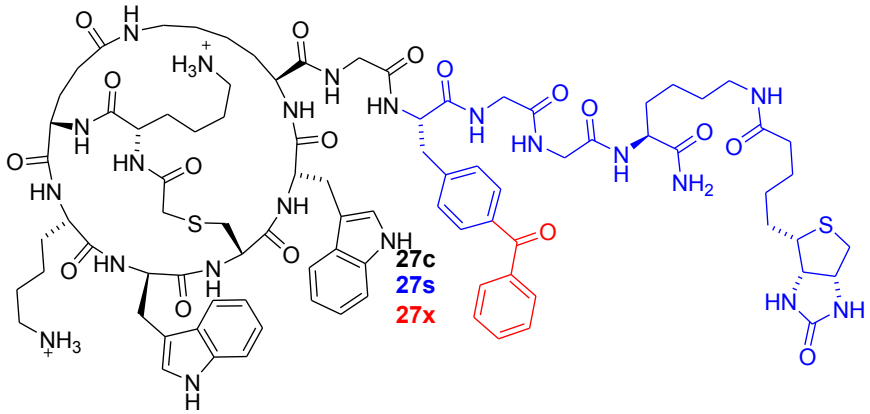


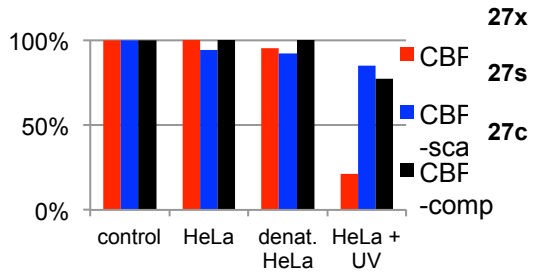




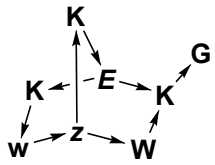
G. Michaud, R. Visini et al., Chem. Sci. **2016**

Bicyclic Peptides

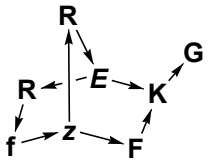




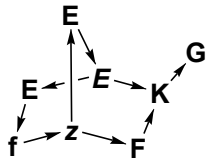
BBP	Target identified by CCMS
27x	CALM1 (calmodulin), NPEPPS (puromycin-sensitive aminopeptidase),USP9X (deubiquitinating enzyme FAF-X)
28x	EIF4A3 (eukaryotic initiation factor 4A-III), NPEPPS,USP9X
29x	ARL6IP5 (PRA1 family protein 3), NDNL2 (MAGE-G1, melanoma-associated antigen G1), ITGB1 (integrin β1, CD29)



27c



28c



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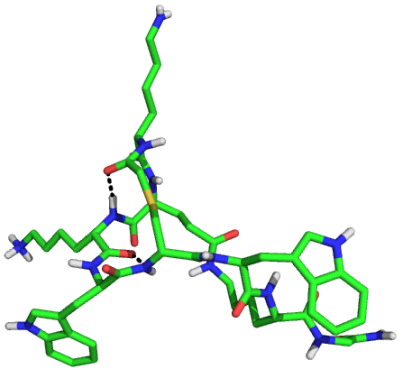
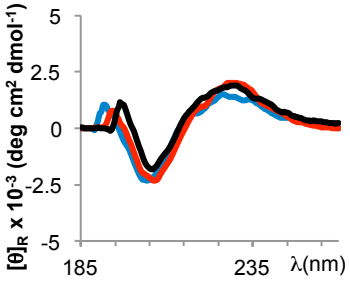
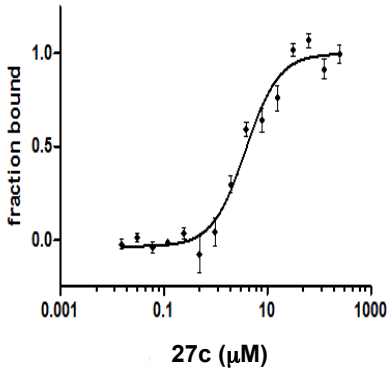
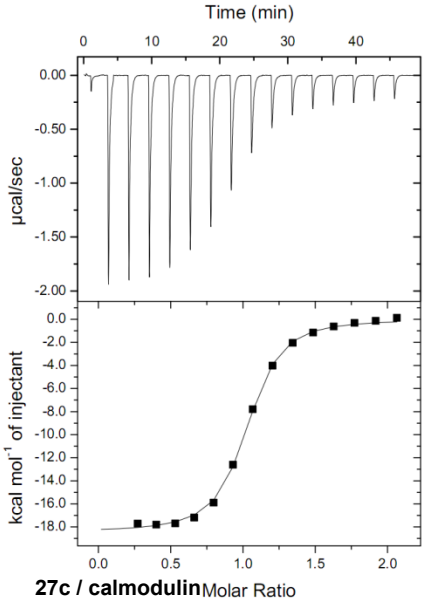


27c (NMR structure)







M. Bartoloni et al., *Chem. Sci.* **2015,** *6*, 5473

Projects for BigChem

- GDB-17 fragments
  - selection
  - property predictions
  - virtual screening