

# SBDD FROM A DIVERSIFIED NP-INSPIRED CHEMICAL SPACE



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Hugues Lemoine

# EDELIRIS

- - > Edelris is a private CRO company founded in 2005
  - > Located in Lyon (France)
  - > Currently 50+ employees (60% with Ph.D.)
  - > State of the art facility dedicated to chemistry



# EXPLORING THE CHEMICAL SPACE



Registered molecules

GDB-17

Nuevolution DEL library

Possible drugs

$10^8$

$10^{11}$

$10^{13}$

$>10^{20}$



Volume:  $10^{-12} \text{ m}^3$



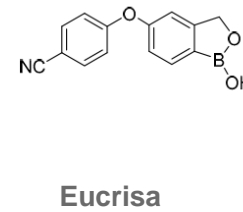
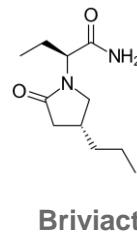
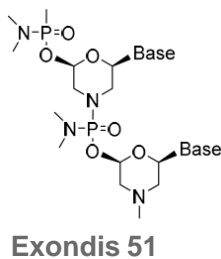
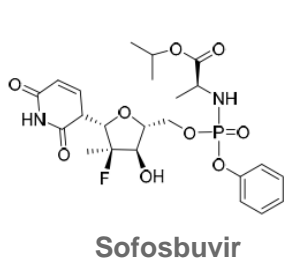
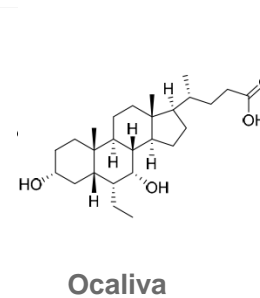
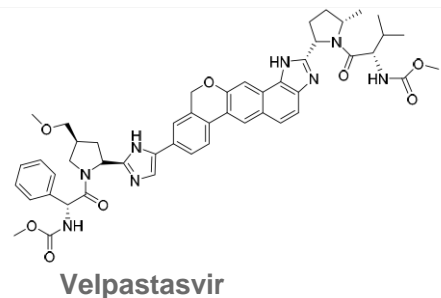
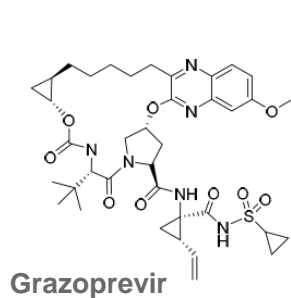
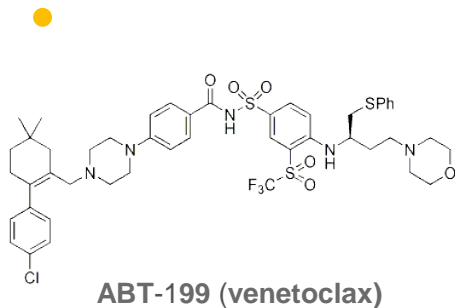
Copacabana beach  
Volume:  $10^8 \text{ m}^3$

Consider a grain of sand as a molecule, the drug space would be the size of Copacabana beach

Enumeration of 166 Billion Organic Small Molecules in the Chemical Universe Database GDB-17. J. L. Reymond et al. *J. Chem. Inf. Model.*, 2012, 52, 2864–2875

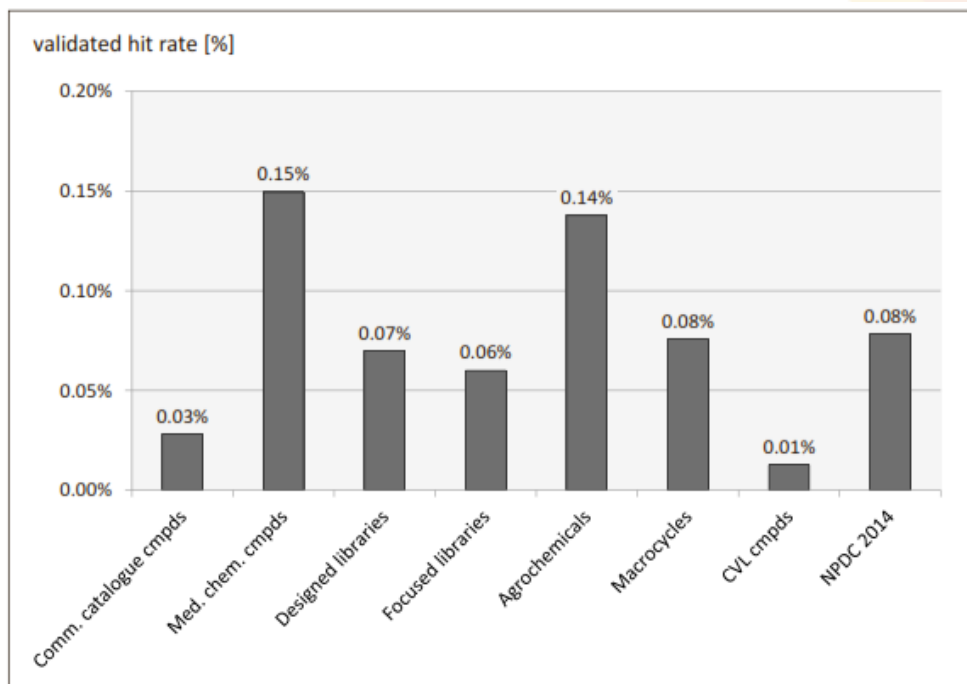
How DNA-encoded libraries are revolutionizing drug discovery. B. Halford *C&EN* 2017, 95, 28-33

# DRUG DIVERSITY CAN HARDLY BE MATCHED BY COMPOUND COLLECTIONS



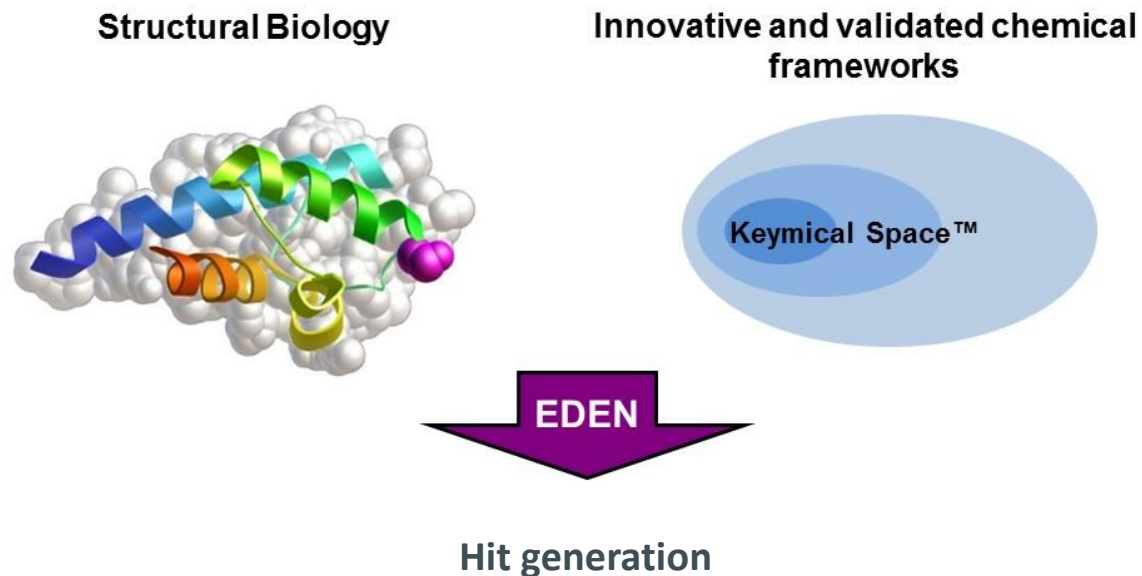
The Pharmaceutical Industry in 2016. An Analysis of FDA Drug Approvals from a Perspective of the Molecule Type. BG Torre, F. Albericio, *Molecules*. 2017, 27, E368

# PLAYING AGAINST THE ODDS

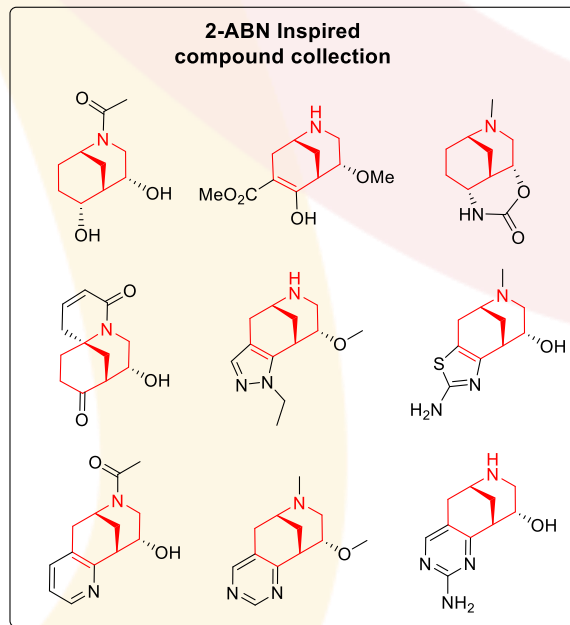
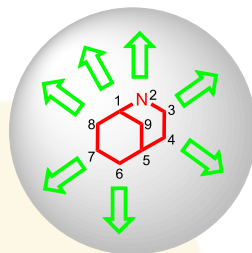
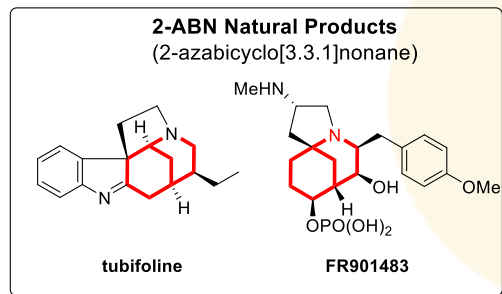


**The Screening Compound Collection: A Key Asset for Drug Discovery.** C. Boss et al. *CHIMIA*, 2017, 71, 667-677

# ENHANCING HIT RATE WITHOUT COMPROMISING THE EXPLORATION OF NEW MOLECULAR SPACES



# KEYMICAL SPACE™: NATURAL BY DESIGN

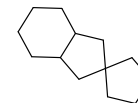
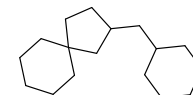
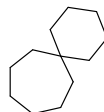
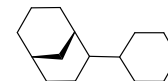
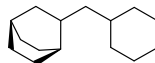
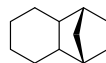
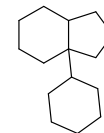
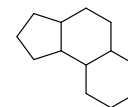
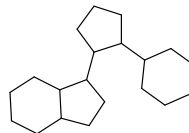
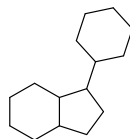
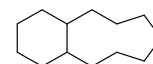
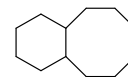
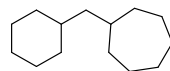
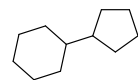
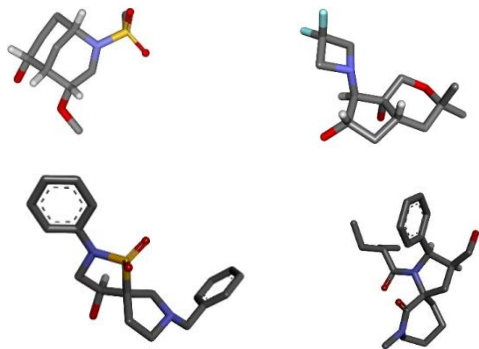


# REPRESENTATIVE FRAMEWORKS



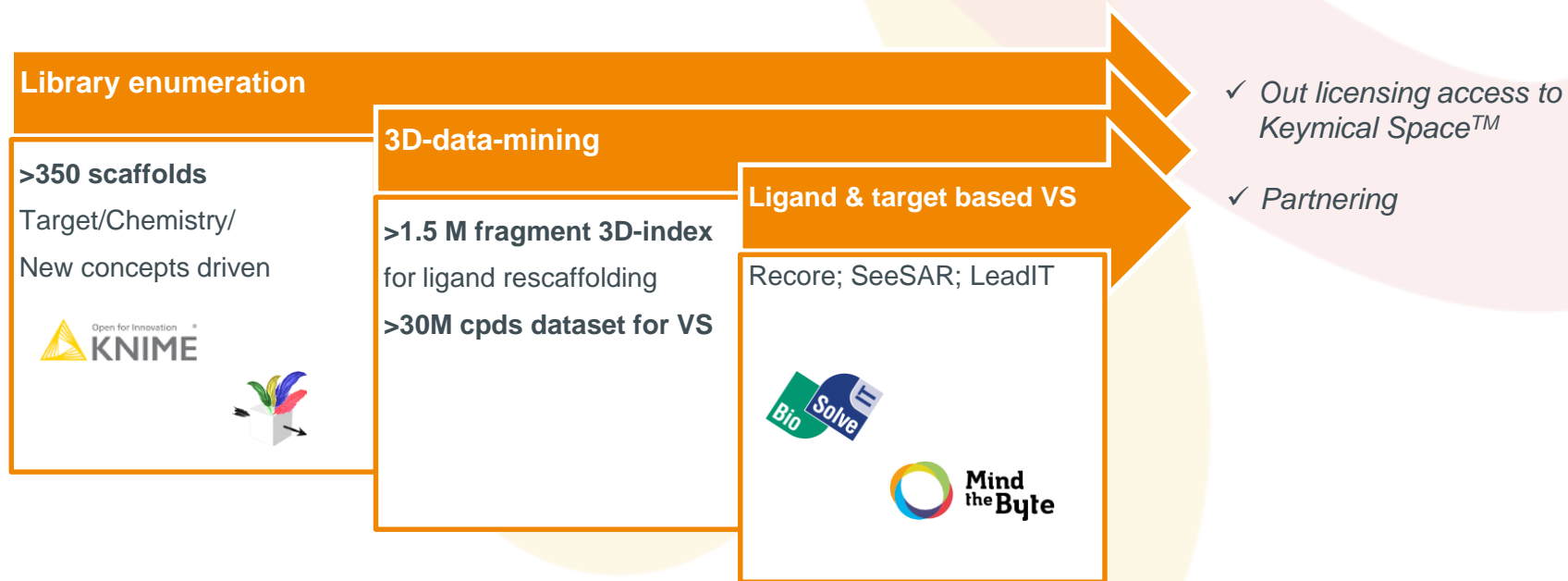
> Strong diversity of frameworks

> High  $sp^3$  fraction

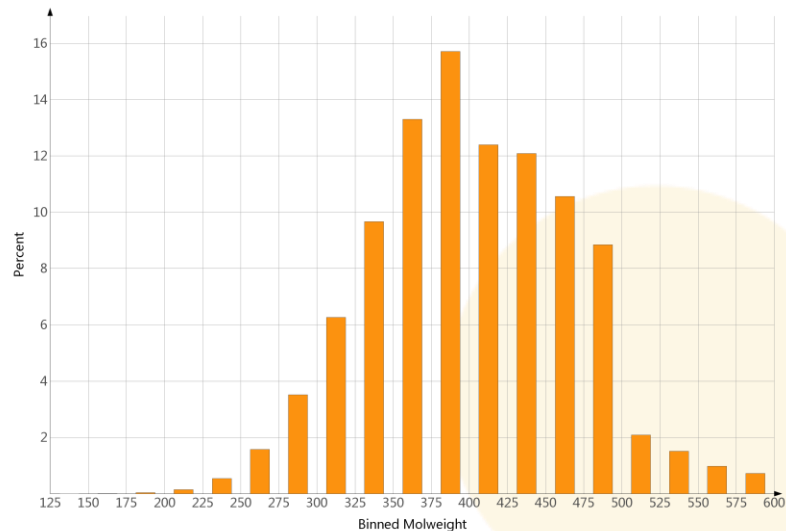




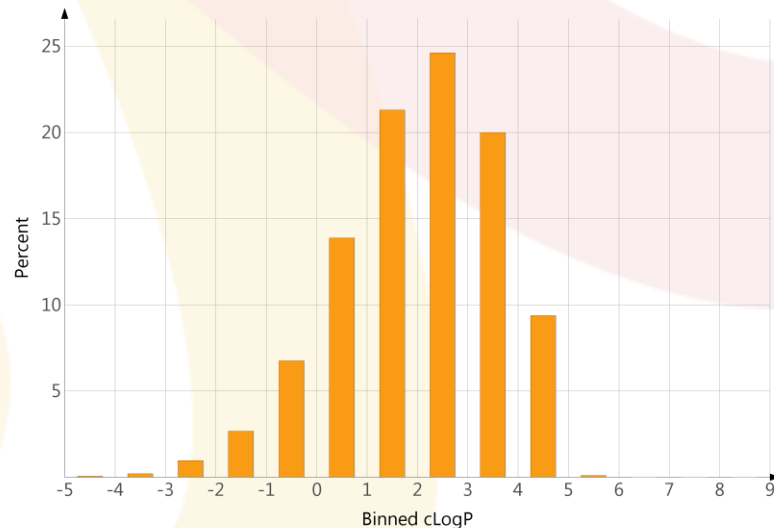
# EDEN (EDELIRIS DISCOVERY ENGINE)



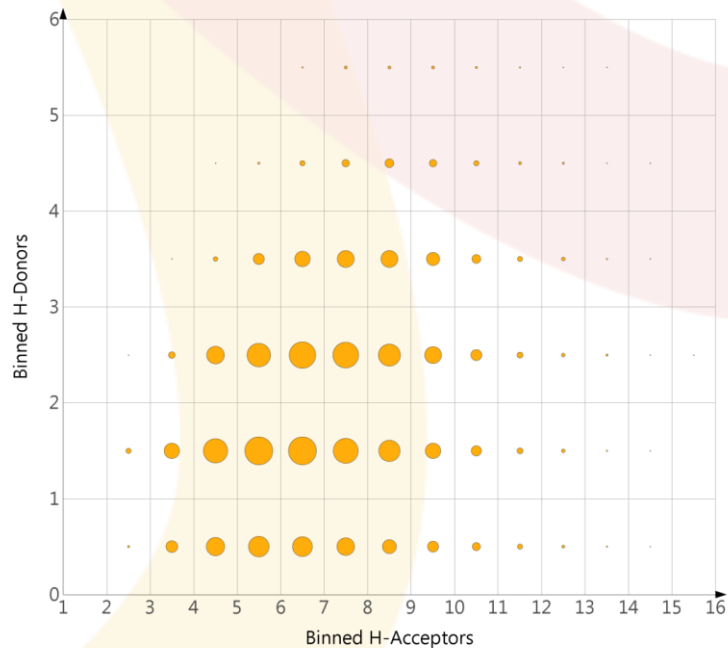
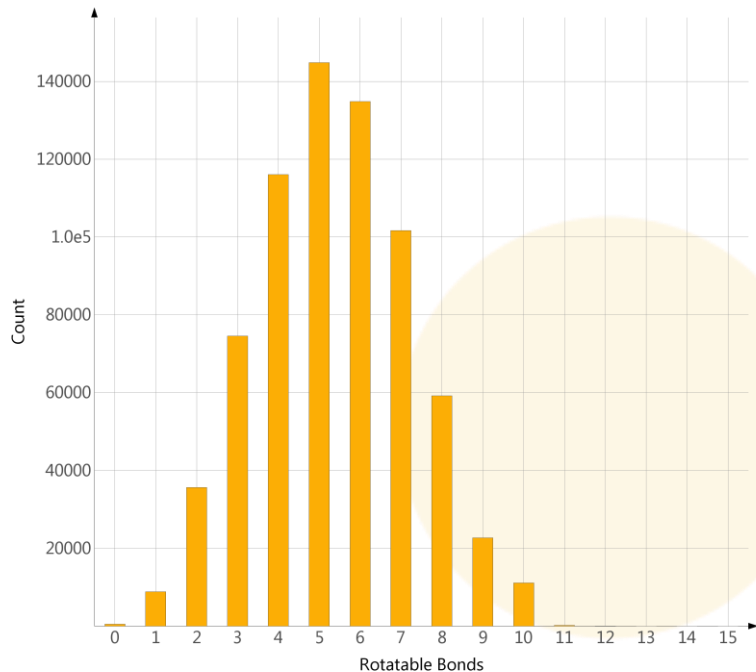
# KEYMICAL SPACE™ PHYSCHEM PROPERTIES 1/2



N=710190\_Diversity set



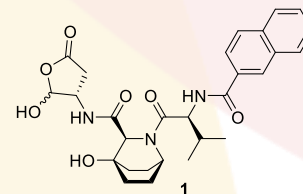
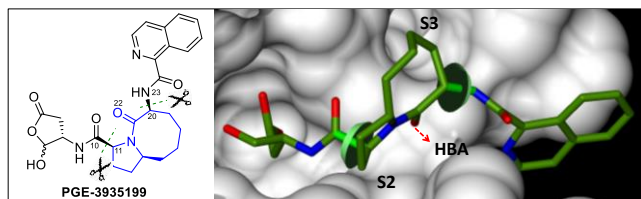
# KEYMICAL SPACE™ PHYSCHEM PROPERTIES 2/2



N=710190\_Diversity set

# RESCAFFOLDING STRATEGY: CASPASE-1 INHIBITORS

PLAYING AGAINST THE ODDS  
SCAFFOLD HOPPING FROM COMPLEX 3D FRAGMENTS



Inhibitor	PGE-3935199	VRT-043198	1
IC <sub>50</sub> (nM)	11	5	17

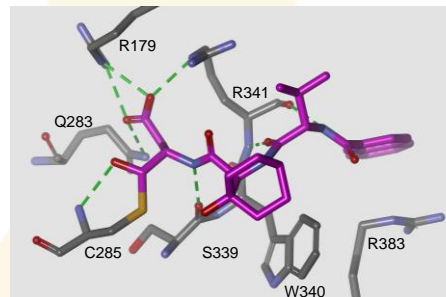
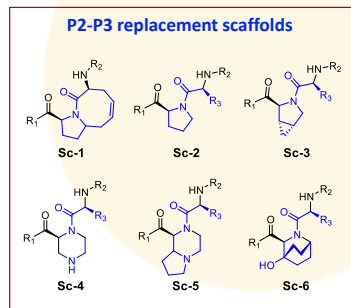
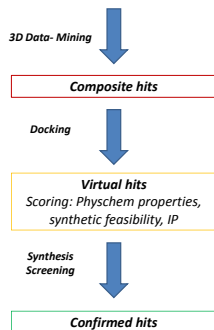


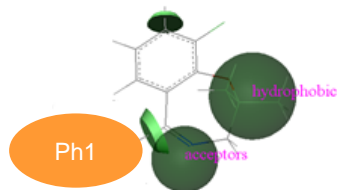
Figure 2: Scaffold hopping process implemented to identify new Caspase-1 inhibitors



# RESCAFFOLDING STRATEGY: UNDISCLOSED TARGET



Marker bioactive  
conformation hypothesis



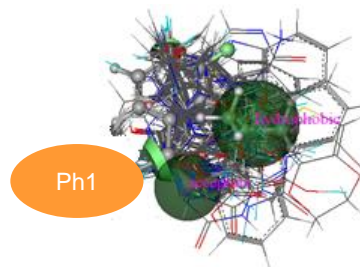
3D-data mining

EDEN



- Keyical Space™
- Zinc Lead-like
- PDB ligands

Privileged scaffolds



- Conformational stability
- Scoring
- SB ligand optimization

Synthesis@Edelris

Chemotype	pl50	LogD(2.3)
1	8.2	2.7
2	<5.0	2.7
3	8.0	3.4
4	6.1	2.0
5	5.6	1.8
6	5.4	1.8

> 6 new ligand chemotypes proposed

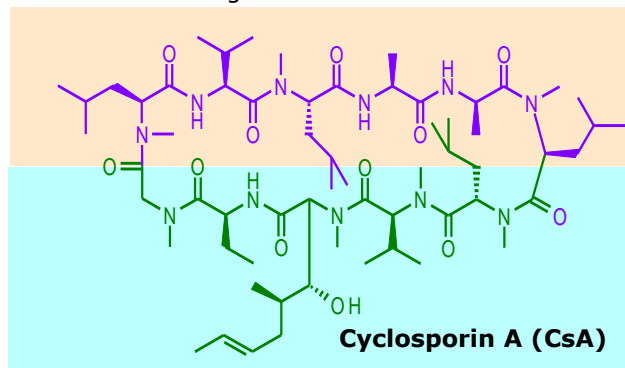
> 21 compounds prepared

> 2 chemotypes pl50 > 8

# FBDD TOWARDS LOW MW SELECTIVE CYCLOPHILIN D INHIBITORS



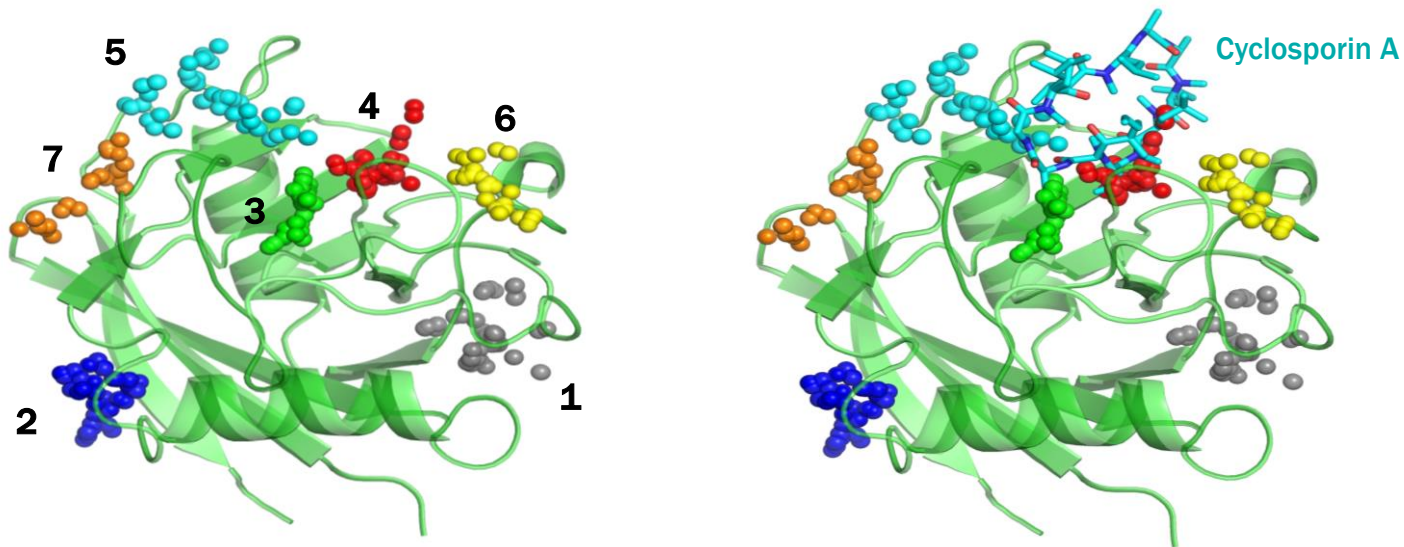
Calcineurin binding domain



Cyclophilin binding domain

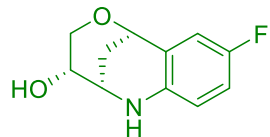
- > Cyclophilins are folding helper enzymes member of the Peptidyl Proline Isomerases (PPI) superfamily
- > Cyclosporin A (CsA) is a potent inhibitor of CypD
- > No SME disclosed as CypD inhibitor when work was initiated

# CYCLOPHILIN D LIGANDABILITY ASSESSMENT



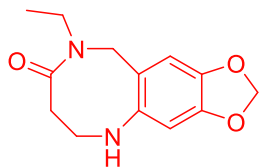
- > 7 Ligandable pockets identified (Fpocket)
- > Known inhibitor CsA binds mainly to pocket 4

# FRAGMENT X-RAYS



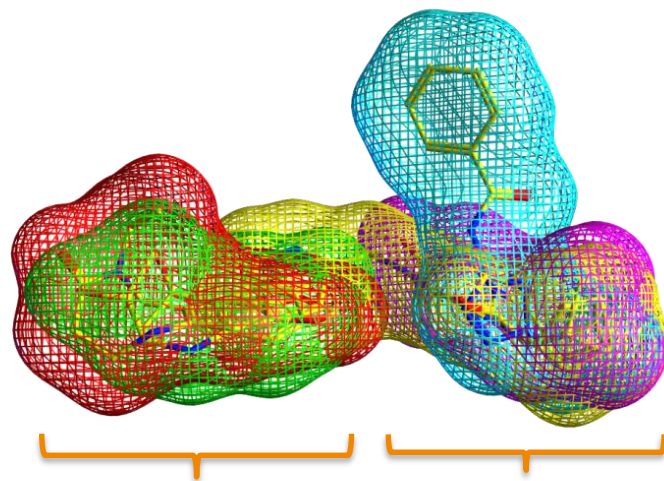
**Edelris 1**

$K_D = 7.1 \text{ mM}$  (LE = 0.2)



**Edelris 2**

$K_D = 7.5 \text{ mM}$  (LE = 0.16)



**Pocket 3**

**Pocket 4**

**Tetrazole**

$K_D = 3.9 \text{ mM}$

LE = 0.21

**Isoxazole**

$K_D = 22 \text{ mM}$

LE = 0.15

**Oxalylamide**

$K_D = 1.1 \text{ mM}$

LE = 0.22

**Succinimide**

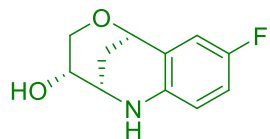
$K_D = 45 \text{ mM}$

LE = 0.11

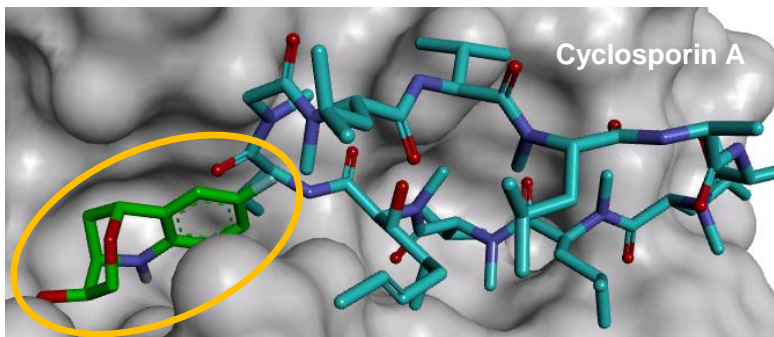
**Optimal space occupation for fragment growing and linking**



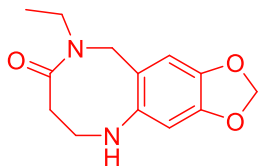
# EDELIRIS FRAGMENTS VERSUS CYCLOSPORIN A



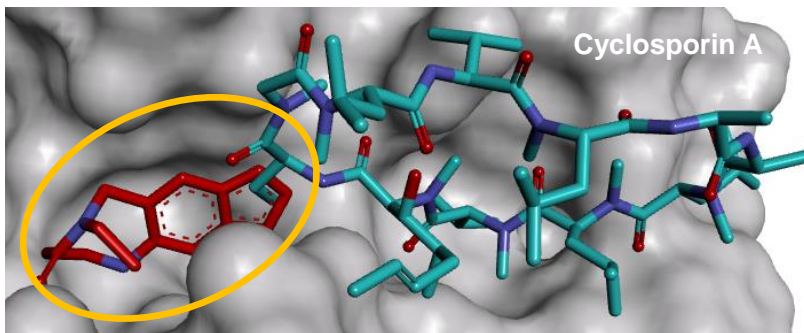
**Edelris 1** MW = 209  
**K<sub>D</sub> = 7.1 mM** clogP = 0.6  
**LE = 0.2** HAC = 15  
Fsp3 = 0.45



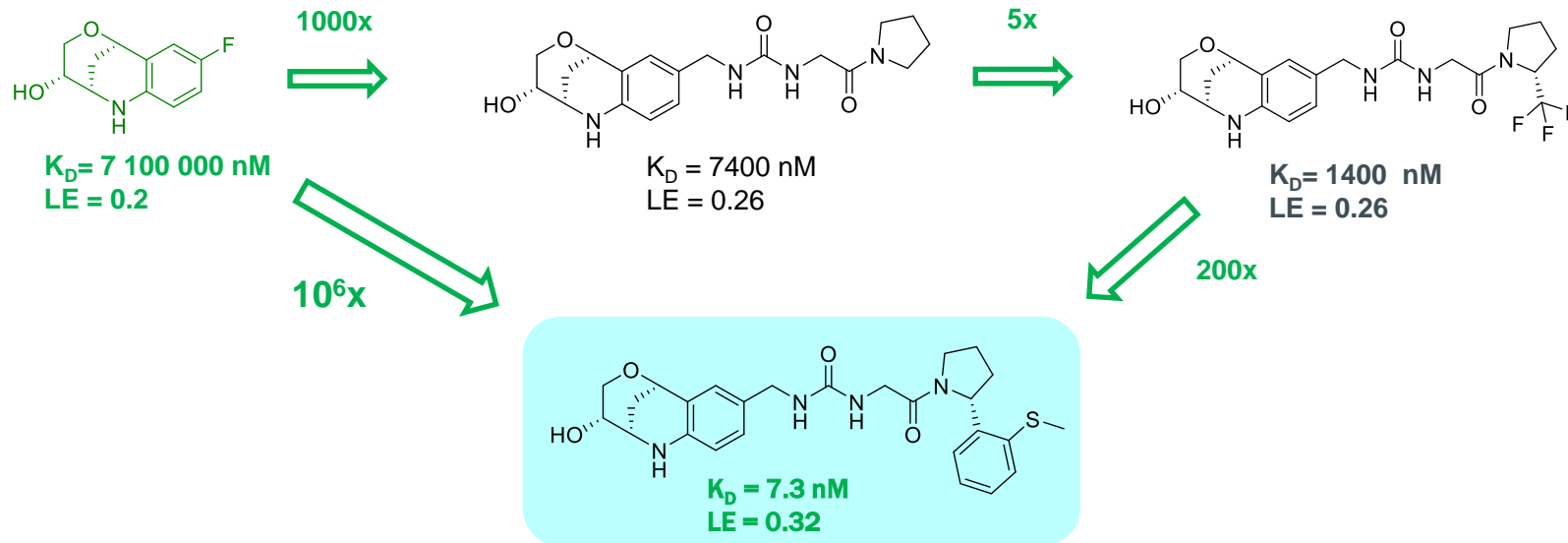
- > Fragment highly 3D (Fsp3 ↗)
- > Moderate Ligand efficiency (LE)
- > Optimal occupancy of pocket 3 unexplored by CsA



**Edelris 2** MW = 248  
**K<sub>D</sub> = 7.5 mM** clogP = 1.4  
**LE = 0.16** HAC = 18  
Fsp3 = 0.46

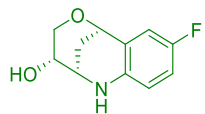


# A MILLION FOLD IMPROVEMENT OF AFFINITY IN 3 MONTHS



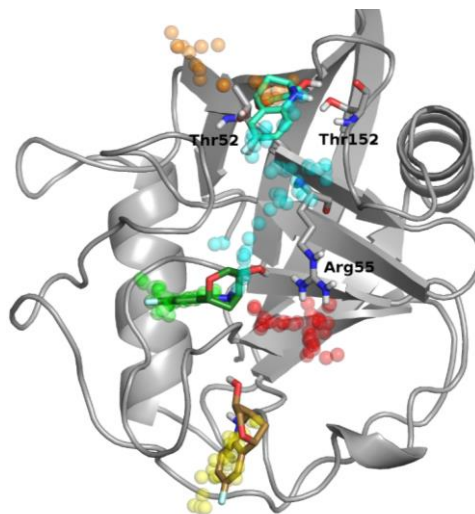
10<sup>6</sup> potency improvement in two optimization cycles through an optimized space occupancy of pocket 3 and the creation of interactions with two additional residues (Arg124 and Ser123)

# TOWARDS A FULLY NUMERICAL APPROACH ?

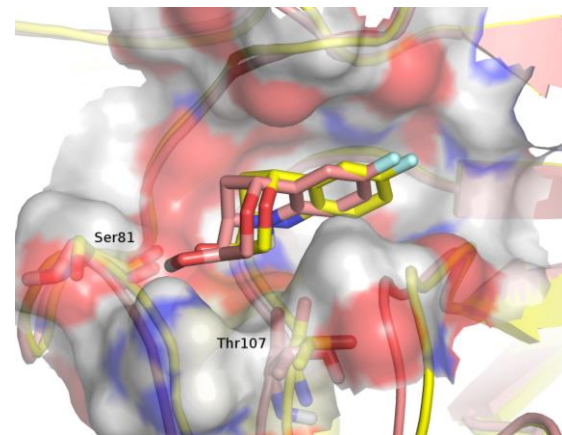


**Edelris 1**  
SPR :  $K_D = 7 \text{ mM}$

Docking



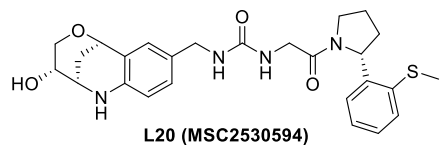
1  $\mu\text{s}$  MD



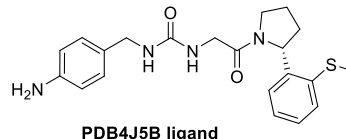
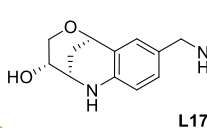
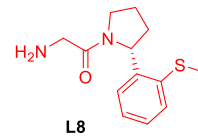
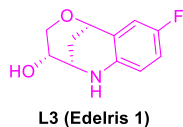
Frag	Pop(%)	BE	pocket	LE
Edelris 1	27	-5.44	5-7	0.363
	36	-5.06	6	0.337
	23	-4.62	3	0.308
	12	-4.40	5-7	0.290
	2	-4.36	4	0.291

> main populated cluster (pink)  
highly superimposable with X-Ray  
data (yellow)

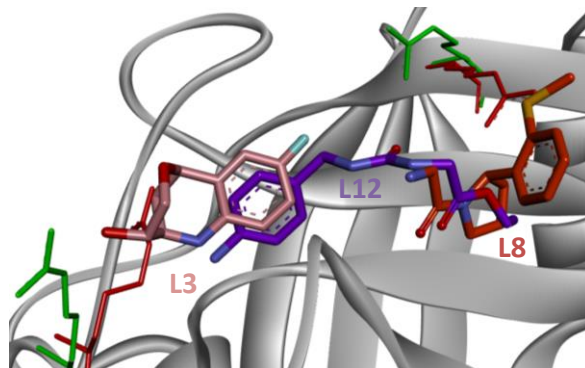
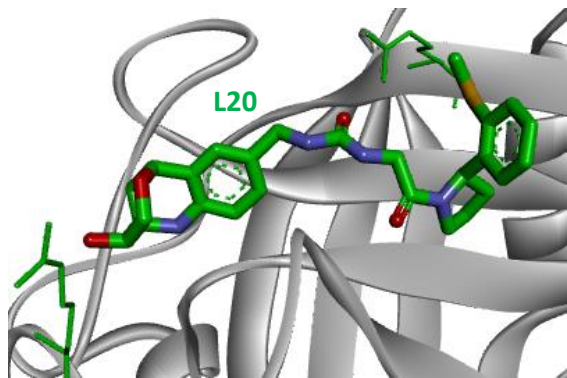
# MD HIGHLY PREDICTIVE OF FRAGMENT BINDING



fragmentation



2/ Docking  
3/ MD



# CONCLUSION

- 
- > Keyymical space™ has proved to be very valuable for SBDD (strong IP from hit series, drug like properties)
- > EDEN platform used successfully in biasing the unbiased
- > Scoring remains a key issue (accuracy of affinity prediction highly target dependant)
- > Molecular dynamics envisioned as a valuable approach to reduce false positives



AI ?

# ACKNOWLEDGMENTS



*Edelris team*



*C. Morgillo & J. M Lancelin*



Nestlé  
Skin  
Health

MERCK

***Thank you***

 **edelris**  
MEDICINAL KEYMISTRY