NAVIGATING IN NATURAL PRODUCT INSPIRED KEYMICAL SPACE™ WITH EDELRIS DISCOVERY ENGINE (EDEN)

- BioSolveIT DrugSpace Symposium
  22 April 2021

Hugues Lemoine

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MEDICINAL KEYMISTRY

EDELRIS

> Innovative Drug Discovery CRO company

- Founded in 2005

> Expertises

- Chemical Libraries Synthesis
- Medicinal and Organic Chemistry
- Analytical Chemistry and Compound Management
- Screening Technologies

> Currently 50 employees (60% with Ph.D.)

> 1700 m^2 brand new facility located in Lyon

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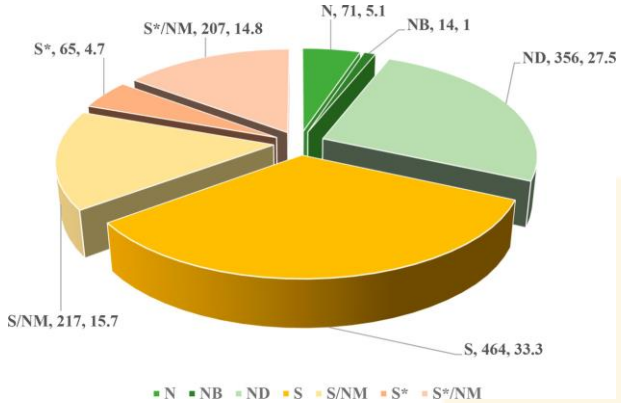
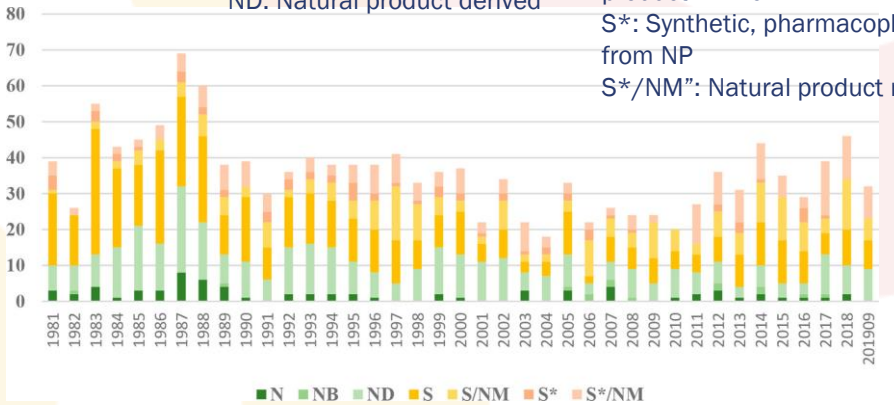
NATURAL PRODUCTS: A CONSTANT SOURCE OF NEW DRUGS



All small-molecule approved drugs 01JAN81 to 30SEP19; *n* = 1394.

N: Natural product
NB: Natural product "Botanical"
ND: Natural product derived

S: Totally synthetic drug
S/NM: Synthetic drug Natural product mimic
S*: Synthetic, pharmacophore from NP
S*/NM": Natural product mimic



Small-molecule approved drugs 01JAN81 to 30SEP19; *n* = 1394.

> **Over the last 4 decades, >66% of approved drug are NP or NP derived**

> **This ratio increased over the last 20 years**

Newman & Cragg, *J. Nat. Prod.* **2020**, 83, 3, 770-803

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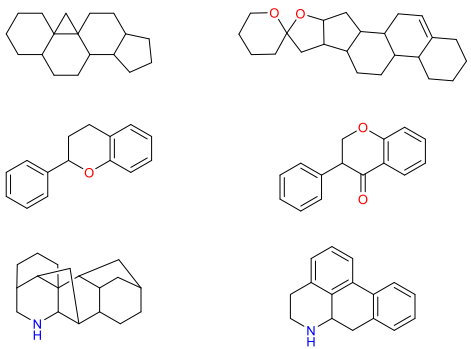
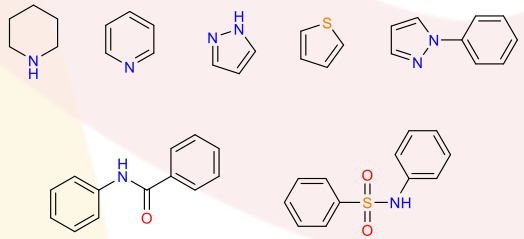
BUT SPARSELY REPRESENTED IN SYNTHETIC LIBRARIES



Parameters for the 1000 most common scaffolds derived from plants and synthetic molecules	Plants	synthetic molecules
% of heteroatoms in scaffolds	11,2	21,4
average number of stereocenters in scaffold	2,9	0,1
% scaffolds containing aromatic ring	49,9	98,1
% scaffolds containing macrocycles	6,4	0
% scaffolds containing spiro system	18,9	0,2
% of scaffolds with 7 or 8 membered rings	10,1	1
% scaffolds being hydrocarbons	16,3	2
% scaffolds containing oxygen	75,8	80,7
% scaffolds containing nitrogen	17,9	92,9

P. Ertl, T. Schuhmann, *Molecular Informatics* (**2020**), 39, 2000017



> Natural products contains more asymmetric centers, mid-sized and spiro rings and less nitrogen and aromatic rings than synthetic compounds

> 83% of rings found in NP are not commercially available

Need for NP derived chemical space

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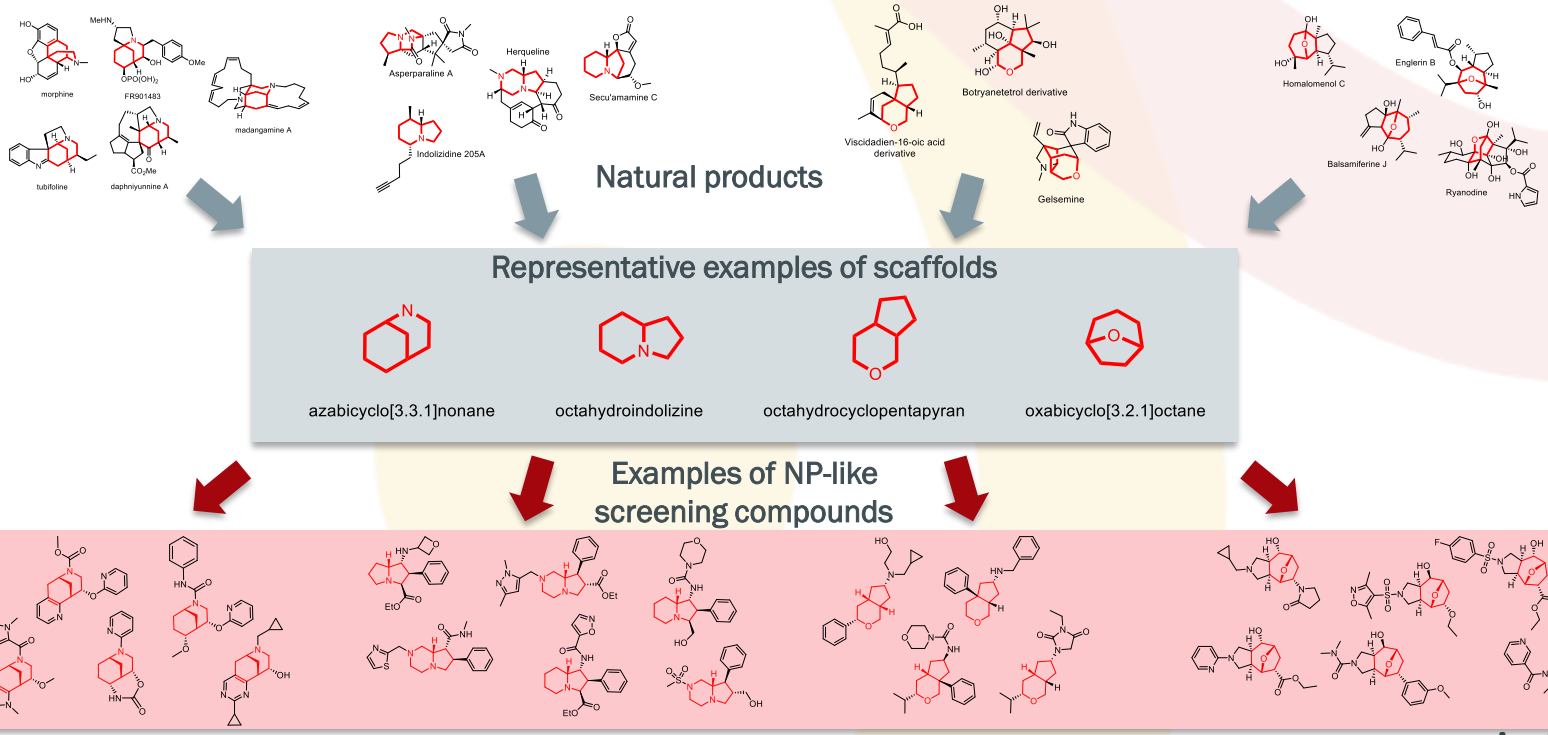
UNIQUE KEYMICAL SPACE™ EXPLORATION



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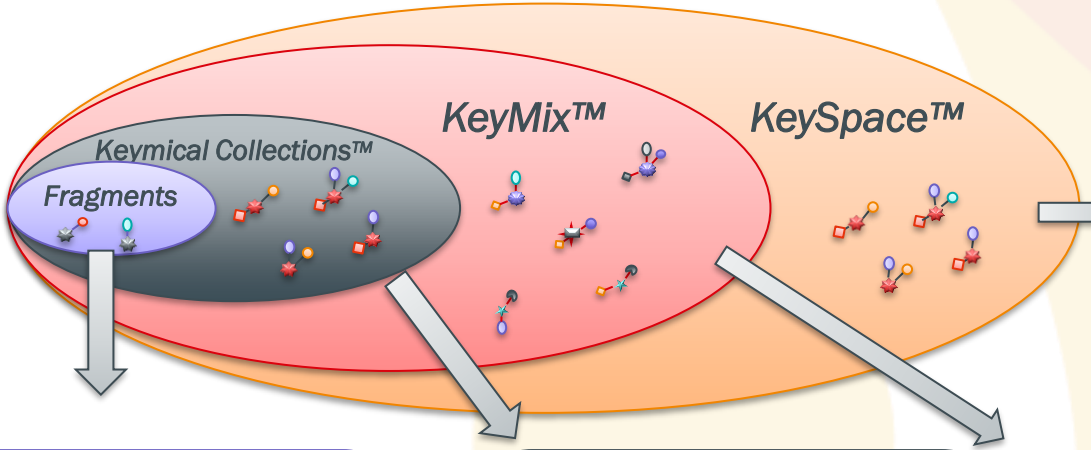
NAVIGATING THE KEYMICAL SPACE™



- For Virtual Screening
- Exclusive to the EDEN offer
- Based on >350 unique Edelris Scaffolds
- Enumerated on tractable chemistry
- VS with LeadIT, SeeSAr, Recore platform
- *> 20M compounds*

- For FBS
- Non-exclusive
- 3D-fragments enriched
- Ro3 compliant
- *~2 000 compounds*

- For HTS
- Non-exclusive
- Leadlike libraries
- Ro5 compliant
- *~30 000 compounds*
- Custom library synthesis capabilities of 20k/year

- For AS-MS
- Exclusive to the EDEN offer
- Ligand identified by Affinity Selection /MS
- Ro5 compliant
- *2 000 000 compounds*

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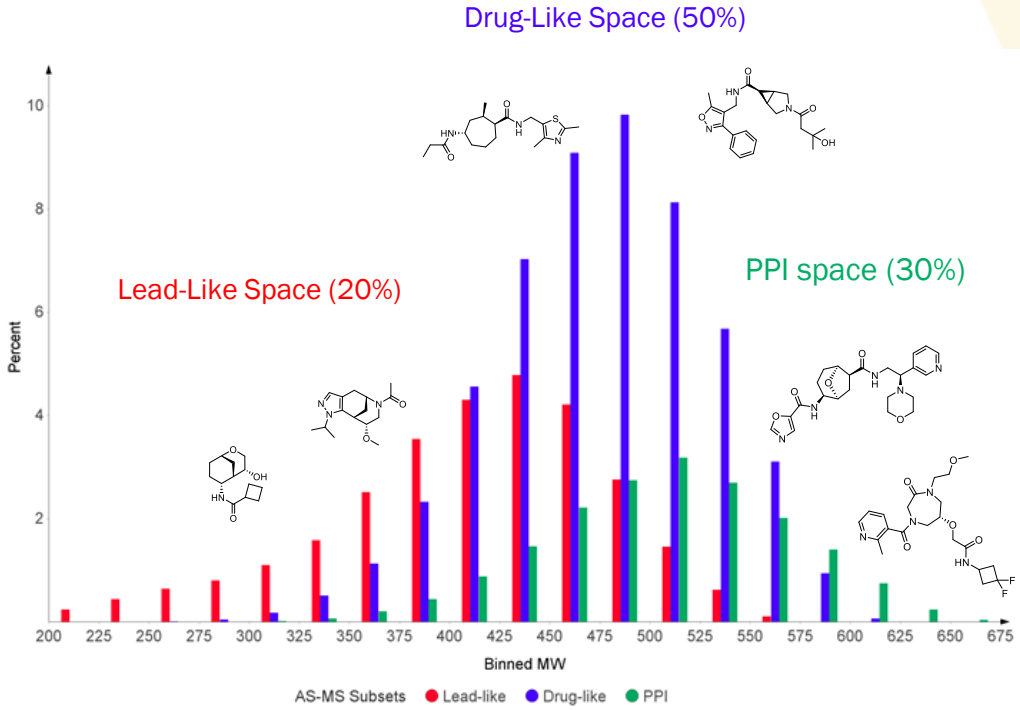
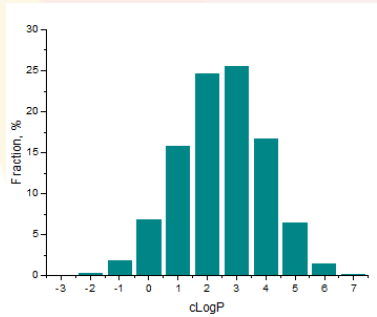
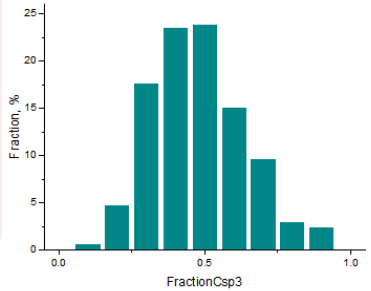
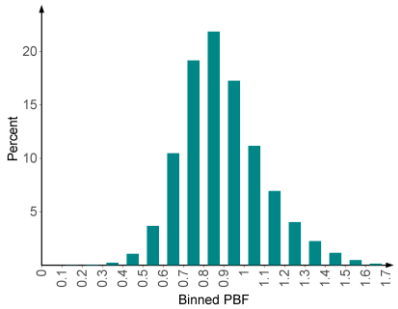
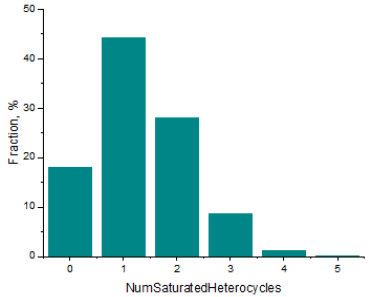
KEYMIX LIBRARY PHYS-CHEM PROPERTIES











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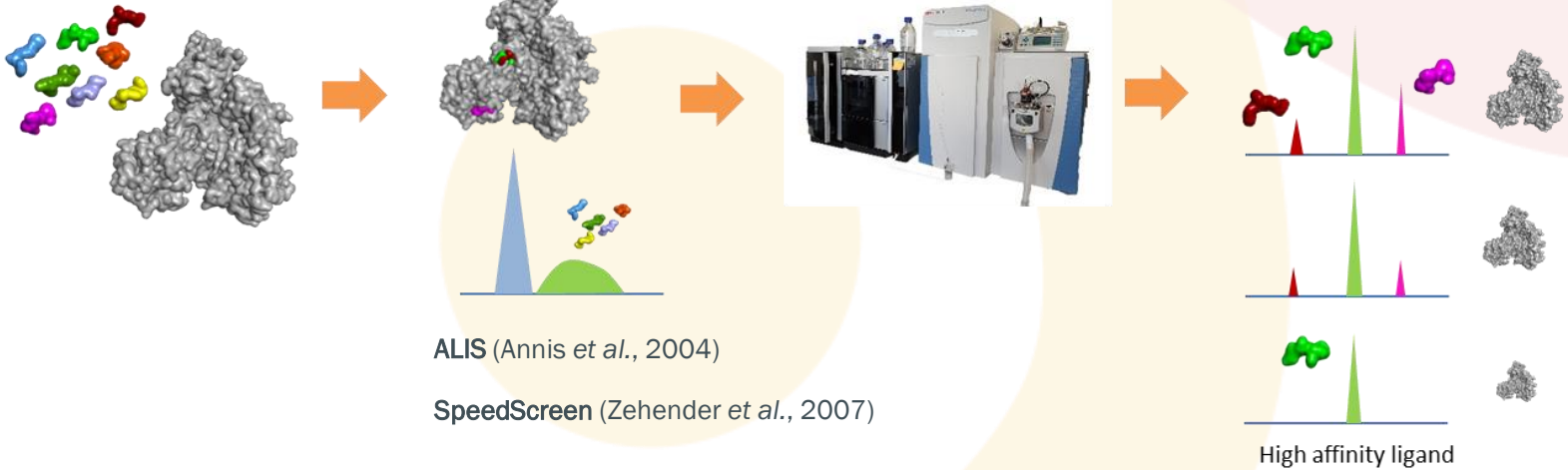
EDEN: AFFINITY SELECTION MASS SPECTROMETRY PLATFORM

1) Incubation

2) Separate protein-bound ligands

3) Denature protein complex & characterize ligands by HR-MS

4) Affinity ranking by decreasing protein concentration



ALIS (Annis *et al.*, 2004)

SpeedScreen (Zehender *et al.*, 2007)

High affinity ligand

Prudent, R., Annis, D.A., Dandliker, P.J. *et al.* Exploring new targets and chemical space with affinity selection-mass spectrometry. *Nat Rev Chem* (2020). https://doi.org/10.1038/s41570-020-00229-2

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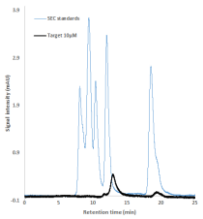
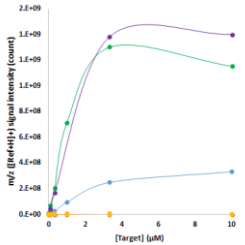
EDEN: CONFIRMED LIGANDS WITHIN 3 MONTHS

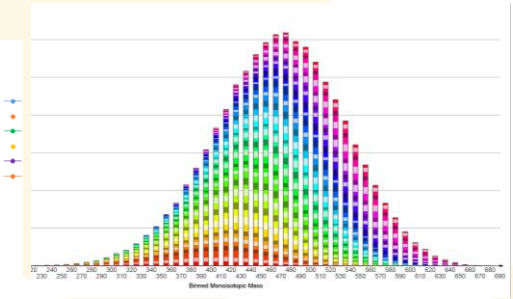
Target qualification
&
Pilot Screening

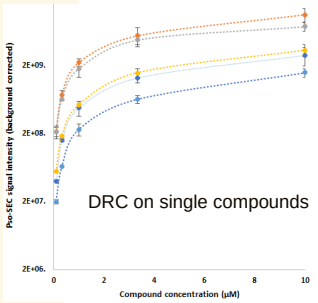
Full Screening
1.5 M compounds from
Edelris Keymical Space™

Hit confirmation
&
Deliverables









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SUCCESS STORIES FROM EDELRIS UNIQUE COMPOUNDS

> Mellitech

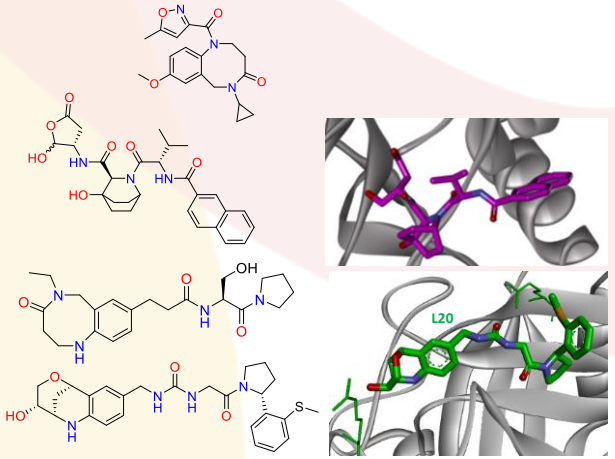
- [1,5]-Diazocin Derivatives. WO**2011**058193A1

> Nestlé Skin Health

- New Caspase-1 inhibitor. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5373-5377

> EMD Serono

- Compounds for the inhibition of cyclophilins and uses thereof. WO**2017**173048
- Compounds for the inhibition of cyclophilins and uses thereof. WO**2017**173049
- *Bioorg. Med. Chem Lett.* **2019**, *29*, 126717

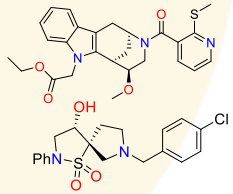


> Max Planck Institute - Pr. Waldmann

- Synthesis of Indomorphan Pseudo-Natural Product Inhibitors of Glucose Transporters GLUT-1 and -3. *Angew. Chem. Int. Ed.* **2019**, *58*, 2–12

> CNRS - Université Montpellier

- New inhibitors of bone resorption. WO**2019**197659A1
- *J. Med. Chem.* **2020**, *63*, 13680–13694 (DOCK5)



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CONCLUSIONS

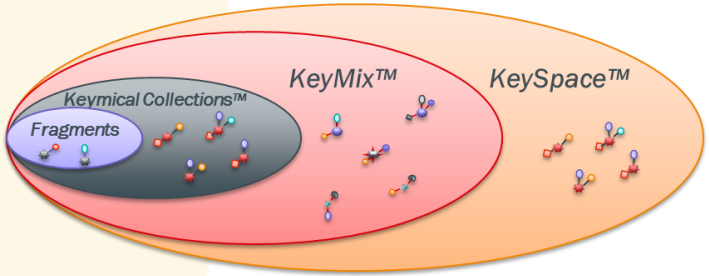
> NP remains an infinite source of chemical inspiration

azabicyclo[3.3.1]nonane | octahydroindolizine | octahydrocyclopentapyran | oxabicyclo[3.2.1]octane

> Edelris Keymical Space™ is a unique and innovative collection of tangible compounds inspired by natural products

> Hit Generation offers based upon Keymical Space™

- Keymical Fragments™ for FBS
- Keymical Collections™ HTS activities
- KeyMix library for a unique AS-MS screening platform
- Keymical Space™ for virtual screening



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ACKNOWLEDGMENTS

Edelris team

Thank you