Reaxys® Medicinal Chemistry

ELSEVIER

Helping Medicinal Chemists Discover New Opportunities during Lead ID and Optimisation

Leveraging ChemAxon's technology for future product developments

ChemAxon User Group Meeting

May 2019

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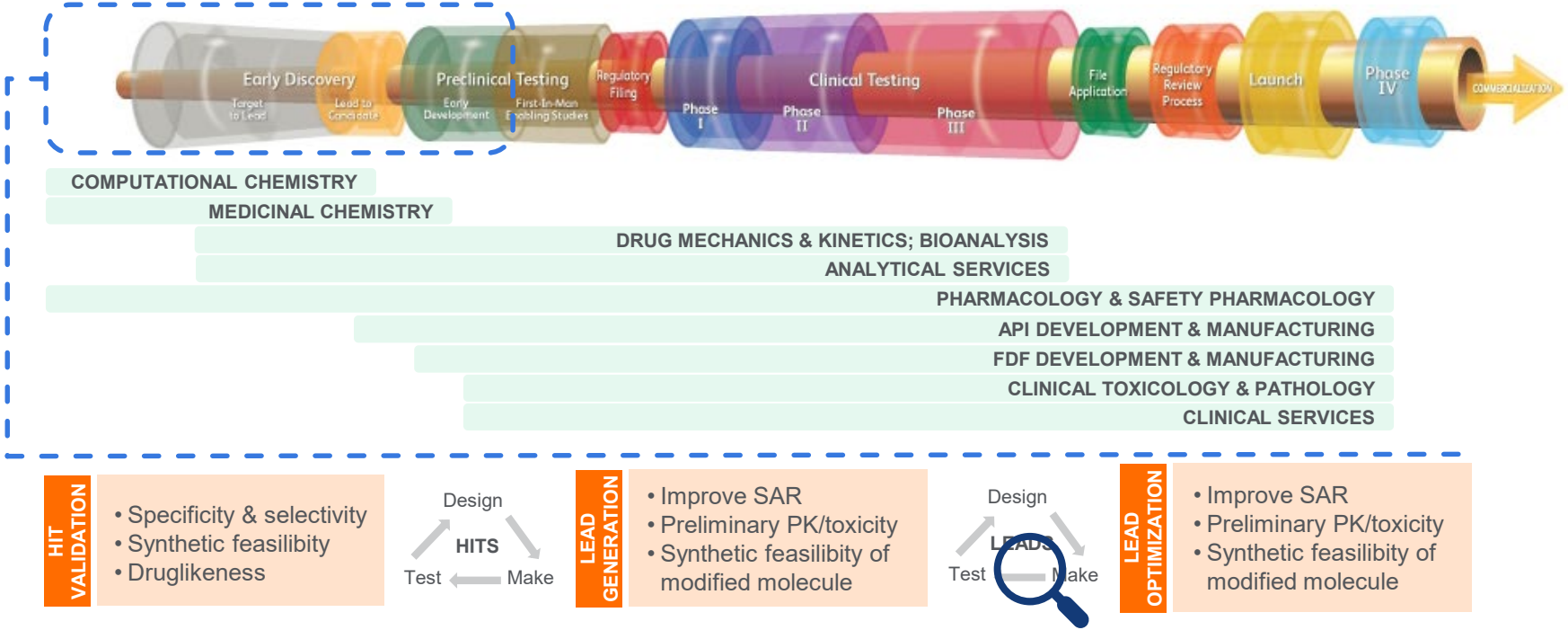
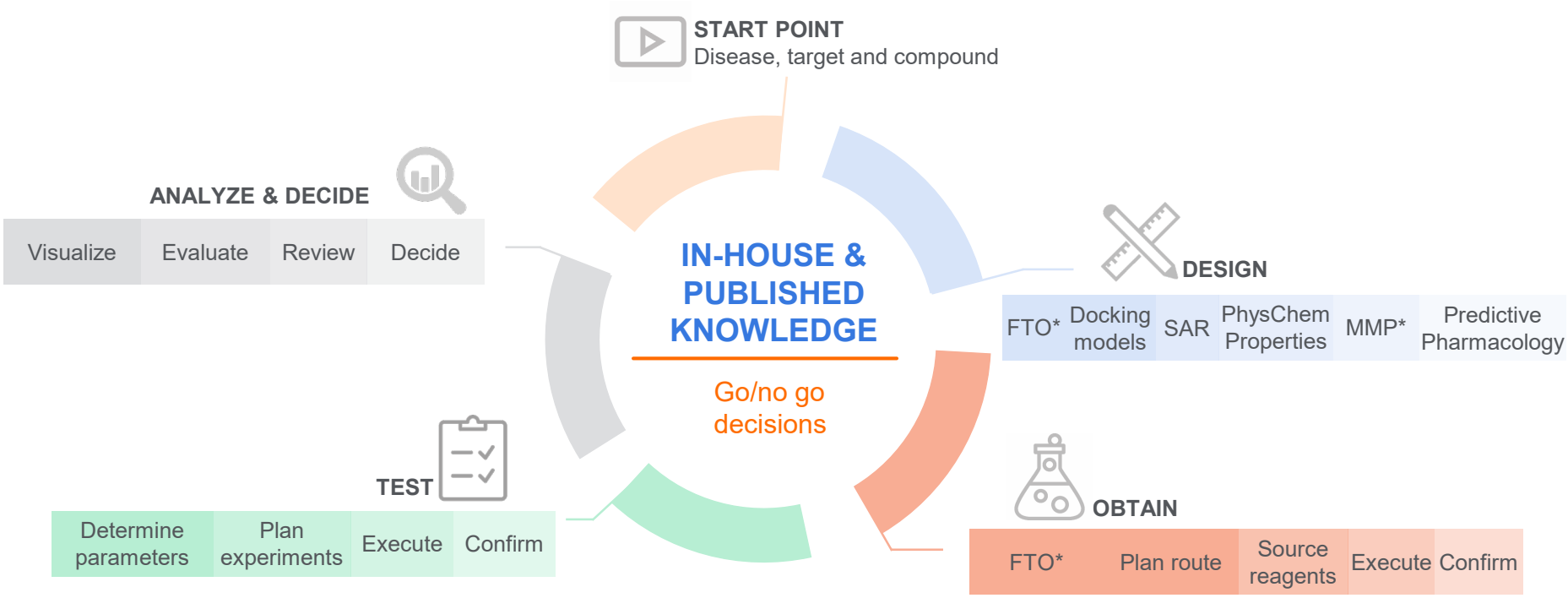
The requirements for effective drug discovery are complex and command a multi-disciplinary approach



Drug design cycle leads to optimized candidates, but necessitates both in-house and published knowledge and data

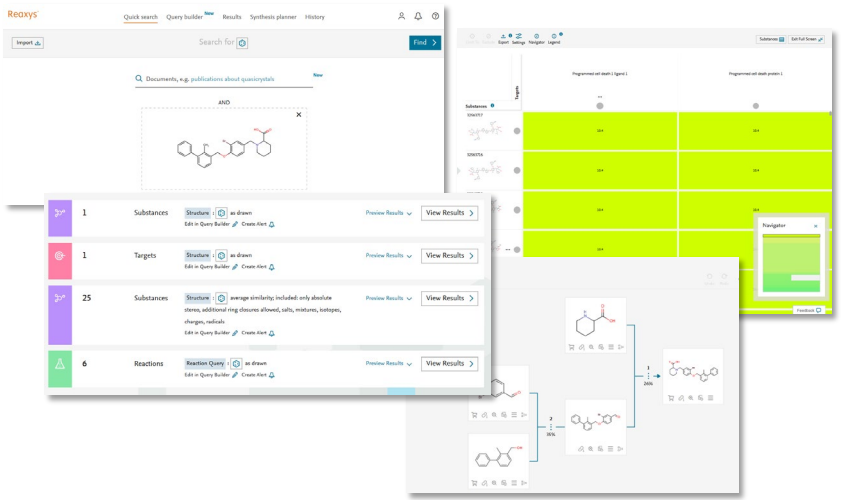


*Freedom to operate
*Matched Molecular Pairs

Reaxys aims to deliver actionable answers during the drug design cycle

Reaxys

- An integrated solution that augments understanding and catalyzes action in drug development
- One source of advanced approaches and best practices to reduce attrition
- Designed to help researchers identify and progress drug candidates as quickly and as safely as possible



		REAXYS & RMC
DESIGN	Docking models	
	SAR	
	Properties	
	MMP	
	Predictive pharmacology	
OBTAIN	Plan route	
	Source reagents	
	Execute	NA
	Confirm	
TEST	Determine parameters	
	Plan experiments	
	Execute	NA
	Confirm	
ANALYZE	Visualize	
	Evaluate	
	Review	
	Decide	NA

- Excellent support
- Good/fair support
- Limited support
- Currently under development

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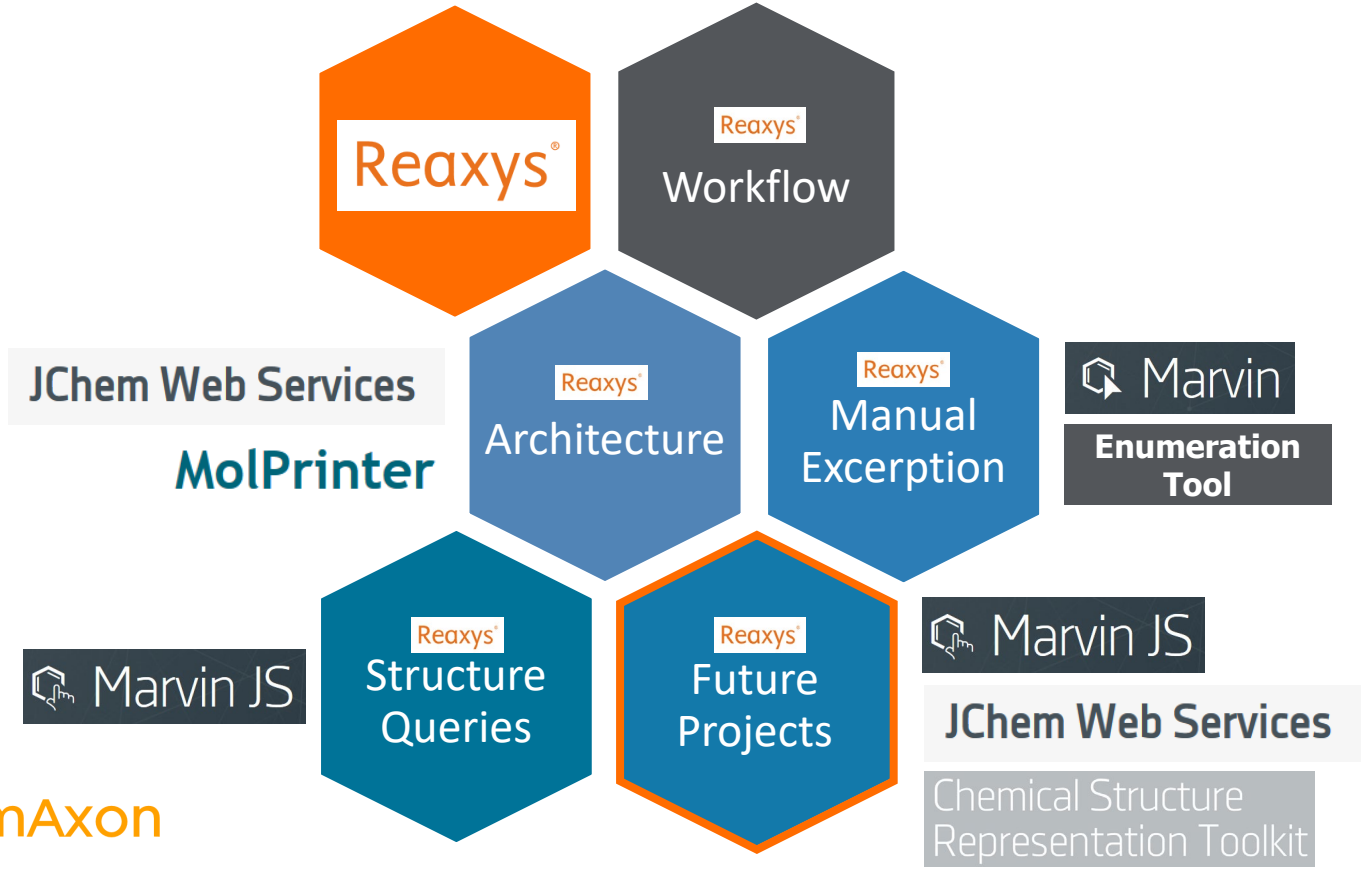
Reaxys' end-to-end processing workflow embeds and employs ChemAxon's technology in various stages and processes



ChemAxon

Development of new capabilities within Reaxys aim to enhance the ability to make informed and actionable decisions

		REAXYS & RMC
DESIGN	Docking models	
	SAR	
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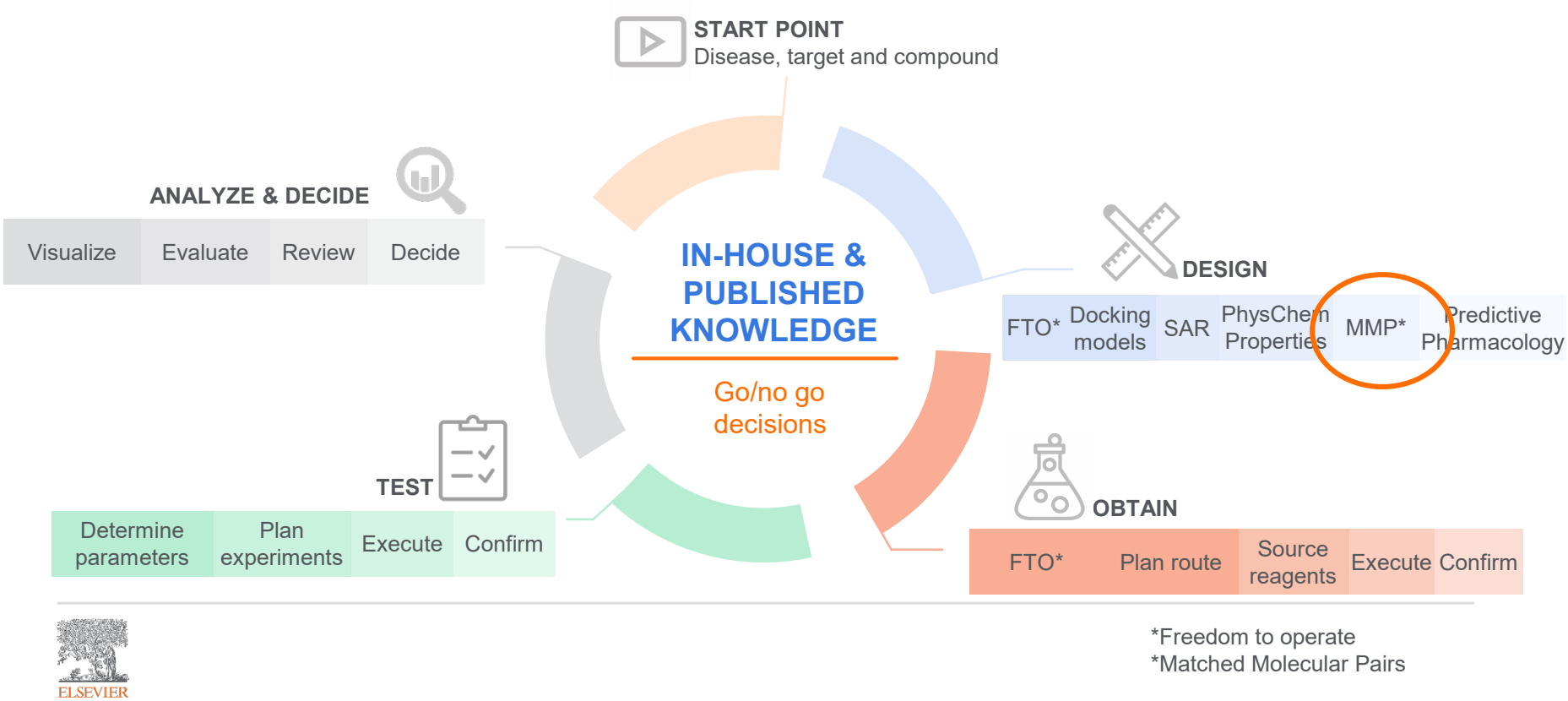
Using data from Reaxys we want to strengthening our support for the drug design cycle



*Freedom to operate
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Typical problems in lead optimization

Optimizing PK and ADME properties

"A part of my current lead structure is thought to be responsible for poor cell permeability. My plan is to **replace this substructure** with something that is:

a) chemically feasible and

b) likely keeping the activity against the primary target."

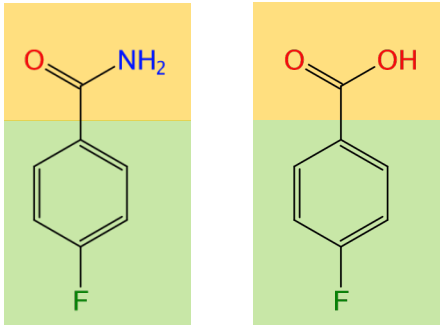
Researchers must identify, optimize and make lead compounds with **less PK and ADME issues** whilst **maintaining high affinity** for the identified target.

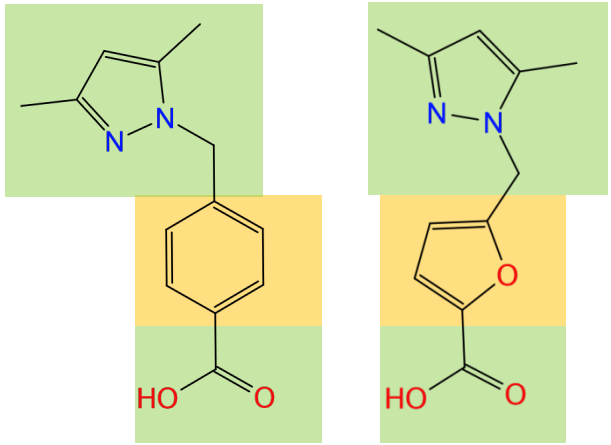
Critical to understand is **how to best modify a compound to achieve desired activity, PK or PD properties**

"What should we make next?"

Matched Molecular Pair (MMP) analysis

Pairs of compounds with a small sub-structural exchange





Used to understand the impact of sub-structural replacements on a given parameter of interest – particularly popular with bioactivity data

Hussain et al., *JCIM*, **2010**, 50, 339-348

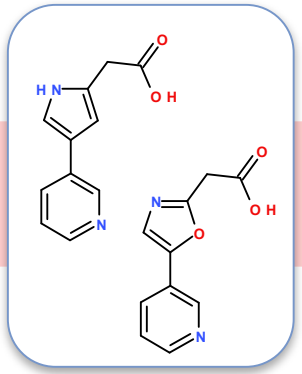
Matched Molecular Pair (MMP) analysis – a collaboration with the Swiss Institute of Bioinformatics using RMC data

Data Source

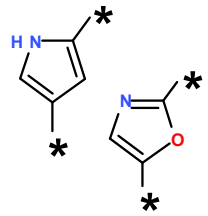
RMC

Reaxys Medicinal Chemistry

Pair Identification



Replacement Extraction



Activity Difference
Assay
Target
Target Class
Chemical Context

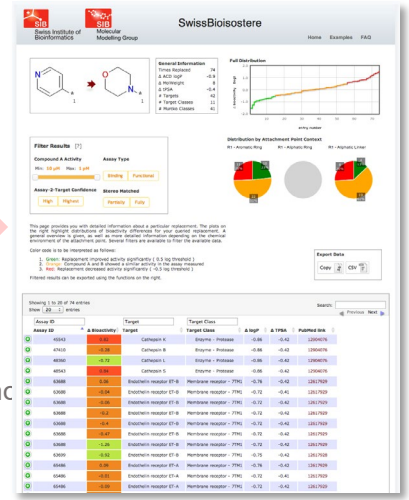
Database Storage

MMP

SIB

Matched Molecular Pair
The computational engine

Outcome



Back end: JChem

Front end: JChem Web Services

Marvin

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SIB Swiss Institute of Bioinformatics

With, M.; Zoete, V.*; Michielin, O.*; Sauer, W. H. B*. SwissBioisostere: a database of molecular replacements for ligand design. *Nucleic Acids Res.* **2013**, *41*, D1137–43.

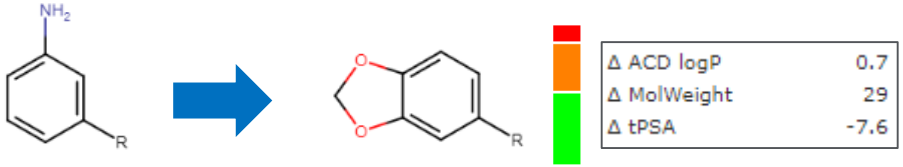
RMC data derived Matched Molecular Pair web application – user feedback

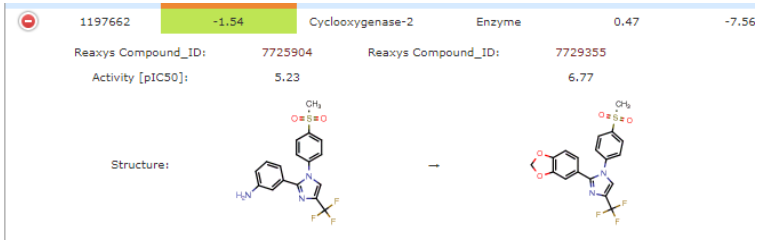
Medicinal Chemist in Pharma

- Used on a current drug design project
  - “Gave me new ideas and helped creativity”
  - New ideas were handed to my computational chemistry colleagues for docking and initiated further discussion

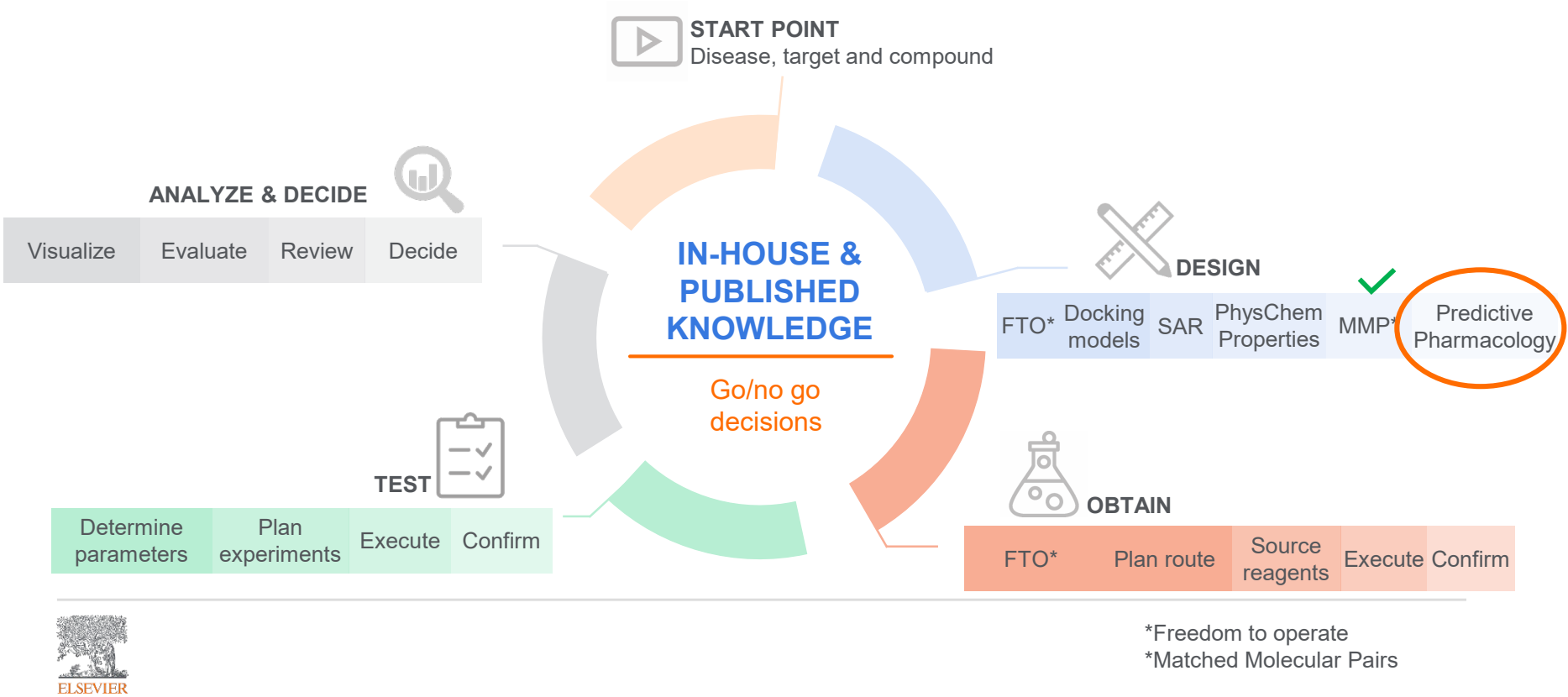
- Expected impact on research decisions:
  - Extend chemical space due to larger knowledge base
  - Trigger decisions more quickly when identifying and evaluating good/bad replacements

Illustrative example:





Using data from Reaxys we want to strengthening our support for the drug design cycle



*Freedom to operate
*Matched Molecular Pairs

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Typical problems in lead optimization

Safety pharmacology issues

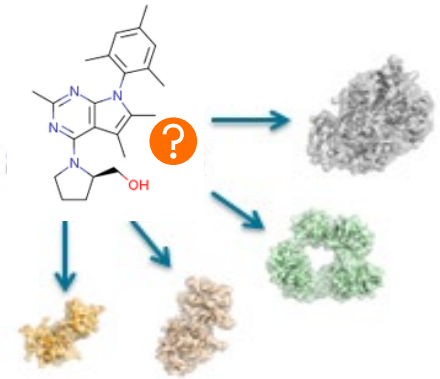
"I know my lead compound has good activity on my primary target but what other targets could it be active on? I need to understand if my compound could be responsible for any **unwanted effects** in a **safety assay**."

Researchers must identify, optimize and make lead compounds with **less toxicity or safety pharmacology issues** whilst **maintaining high affinity** for the identified target.

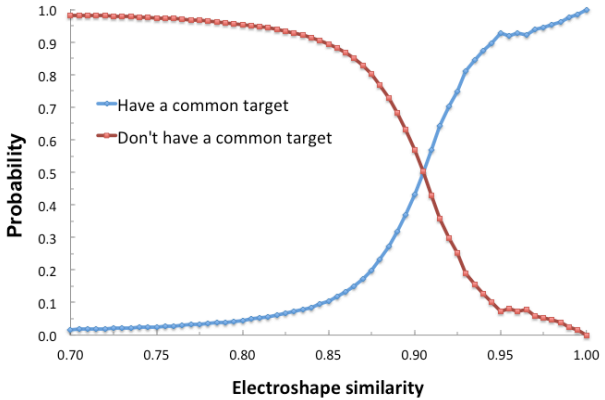
Critical to understand if a compound has potential to be active on **secondary targets** so that any **unwanted interactions/effects can be assessed and addressed**

"What can we expect from our compound?"

Target Prediction by molecular similarity



Assumption: if two molecules are very similar, they are more likely to be active on the same target



Target prediction (reverse screening):

Molecule with **unknown** target

Similarity

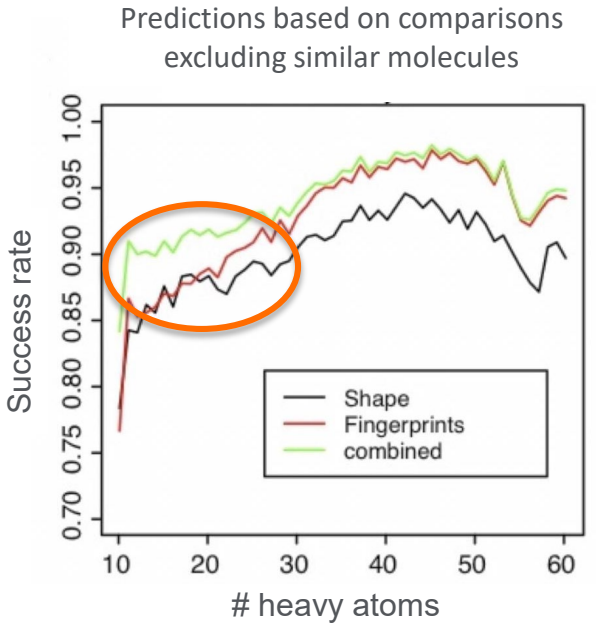
RMC

Library of molecules with **known** targets

List of possible **targets**

Target Prediction by molecular similarity

The dual scoring function, based on both 2D and 3D molecular similarity, gives high performing predictions



RMC data*	
Unique small molecules	521,445
Datapoints	745,106
Total protein targets included (human, rat & mouse)	2,590

* Only compounds having activity < 10 nM

Back end: JChem

Front end: Marvin

JChem Web Services

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SIB Swiss Institute of Bioinformatics

Gfeller, D.; Michielin, O.; Zoete, V. Shaping the Interaction Landscape of Bioactive Molecules. *Bioinformatics.* **2013**, *29*, 3073–3079.

Gfeller, D.; Grosdidier, A.; Wirth, M.; Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: a Web Server for Target Prediction of Bioactive Small Molecules. *Nucleic Acids Res.* **2014**, *42(Web Server issue)*, W32-8.

Gfeller D., Zoete V. Protein homology reveals new targets for bioactive small molecules. *Bioinformatics*. **2015**, *31*, 2721-7.

RMC data derived Target Prediction web application – user feedback

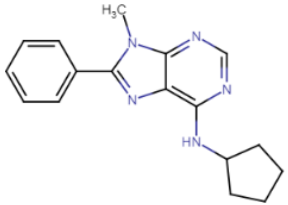
Medicinal Chemist in Pharma

- Used on a current drug design project
  - Looked for potential off-target pharmacology and assess safety
  - Used to priorit
  - "I took the predic
- Expected impact on r
  - Would be use
  - Doing drug sa later on
  - Doing the test

Target prediction

Target	Common name	Uniprot ID	Target Class	Probability*	Known actives (3D / 2D)
Adenosine receptor A2a	ADORA2A	P29274	Membrane receptor		584 / 465
Adenosine receptor A2b	ADORA2B	P29275	Membrane receptor		170 / 232
Adenosine receptor A1	ADORA1	P30542	Membrane receptor		488 / 591
Adenosine receptor A3	N/A	P33765	Membrane receptor		690 / 639
Neuropeptide Y receptor type 5	NPY5R	Q15761	Membrane receptor		299 / 149
Cannabinoid receptor 1	CNR1	P21554	Membrane receptor		1418 / 305
5-hydroxytryptamine receptor 2A	HTR2A	P28223	Membrane receptor		108 / 42
5-hydroxytryptamine receptor 2C	HTR2C	P28335	Membrane receptor		54 / 34
Cannabinoid receptor 2	CNR2	P34972	Membrane receptor		1633 / 133
Corticotropin-releasing factor receptor 1	CRHR1	P34998	Membrane receptor		216 / 123
Sodium-dependent serotonin transporter	SLC6A4	P31645	Transporter		12 / 33
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform	PIK3CD	O00329	Enzyme		100 / 135
Cathepsin L1	CTSL	P07711	Cysteine Protease		159 / 65
Epidermal growth factor receptor	EGFR	P00533	Tyr Kinase		674 / 53
Cyclin-dependent kinase 2	CDK2	P24941	Ser_Thr Kinase		160 / 518

Illustrative example:



Taken from Lan
Chem. 151 (20
adenosine rece

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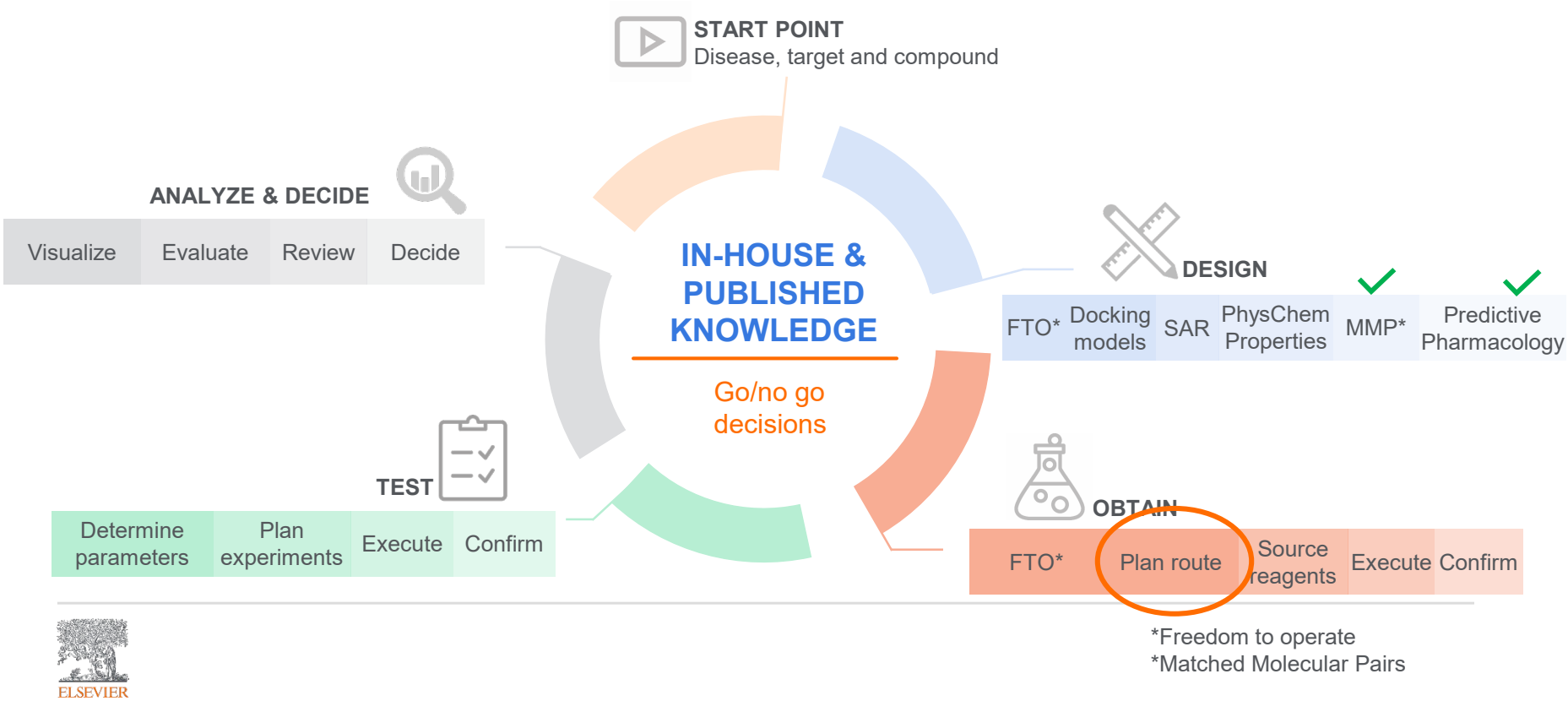

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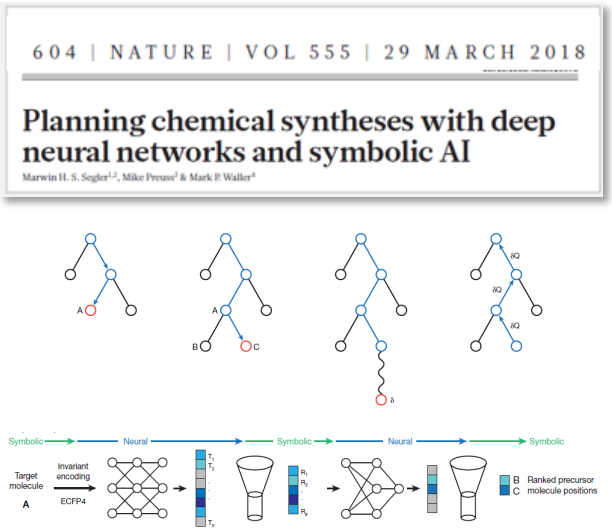
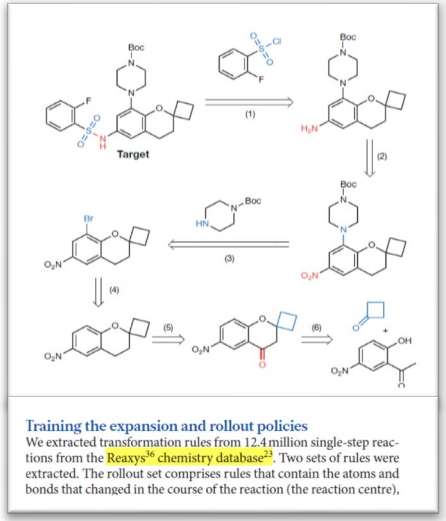
Predictive Retrosynthesis: rewiring chemistry and redesigning synthetic routes

The challenge: Merck quotes that 55% of the time, a benchmarked catalytic reaction fails to deliver the desired product*. Therefore a radical and innovative step change in synthesis is needed.





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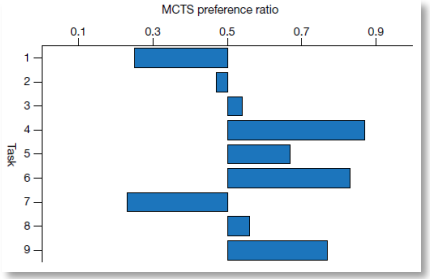
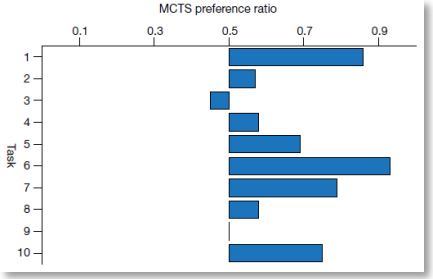


2)



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Science 02, Jan 2015

JChem Marvin

1) Performance vs literature routes
2) Performance vs other predictive models

Predictive Retrosynthesis: rewiring chemistry and redesigning synthetic routes

The solution: Reaxys will offer a new approach to retrosynthesis in 2019 using deep neural networks and symbolic AI in collaboration with Prof. Mark Waller. The new approach will extend syntheses of small organic molecules into predictive modeling of previously unpublished synthetic pathways

Retrosynthesis benefits…

Augment chemist knowledge
- Via scrutinization of millions of synthetic pathways and presenting a highly customized route to the researcher

Reduce time to discovery / development / synthesis
- Design successful synthesis pathway for novel molecules where previous attempts may have failed

Reduce cost
- Design improved lead series, reduce risk of late stage failure
- Design more efficient synthesis routes (improved yield, reduced production costs)

Support IP strategy
- Identify alternative synthesis routes to a patented route for a commercial product
- Identify novel synthesis routes for a new molecule

..leading to improved business outcomes

Improve speed to market

Embed / Leverage next-gen technology to out-compete

Increase productivity

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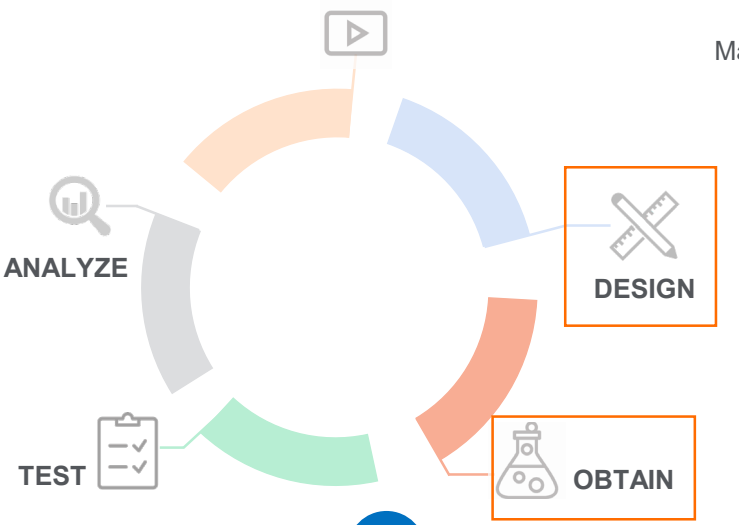
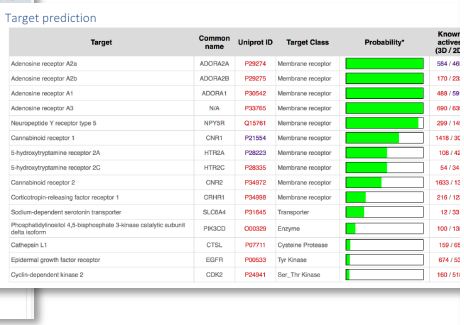
Summary and outlook

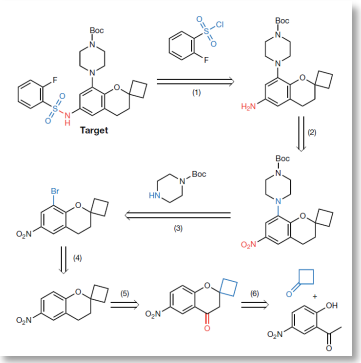


Matched Molecular Pair analysis

Target Prediction



Predictive Retrosynthesis



Curated, clean, linked and normalized Reaxys/RMC data underpins all three applications

AI in pharma – will enable researchers to focus on innovation

ChemAxon's technology and tools underpin these developments

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Acknowledgments

Antoine Daina
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Wallerlab

Pieder Caduff
Olivier Barberan
Ivan Kristic
Jürgen Swienty-Busch
Elena Herzog
Abhinav Kumar

For more information please contact Dr Rosalind Sankey
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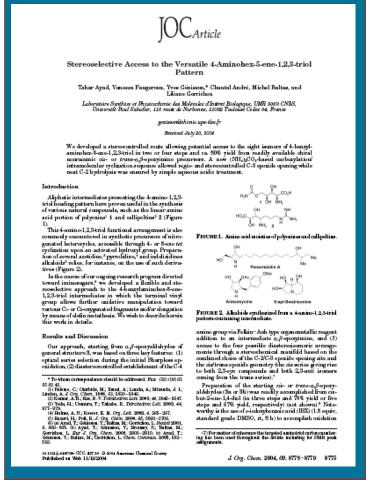
Additional Slides

Reaxys Workflow (simplified)

SOURCE → Automatic extraction of data → **Excerption program** → Database production → **Reaxys DATABASE**

Excerption program ↕ Manual excerption

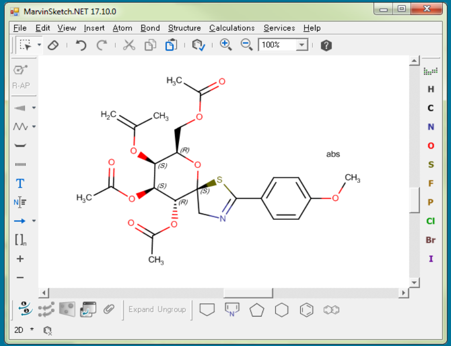
SOURCE ↕ **Paper or electronic file**


JOC Article

Stereoselective Access to the Versatile 4-Aminohex-5-ene-1,2,3-triol Pattern

Tahar Ayad, Vanessa Faugeroux, Yves Génisson,* Chantal André, Michel Baltas, and Liliane Gorrichon

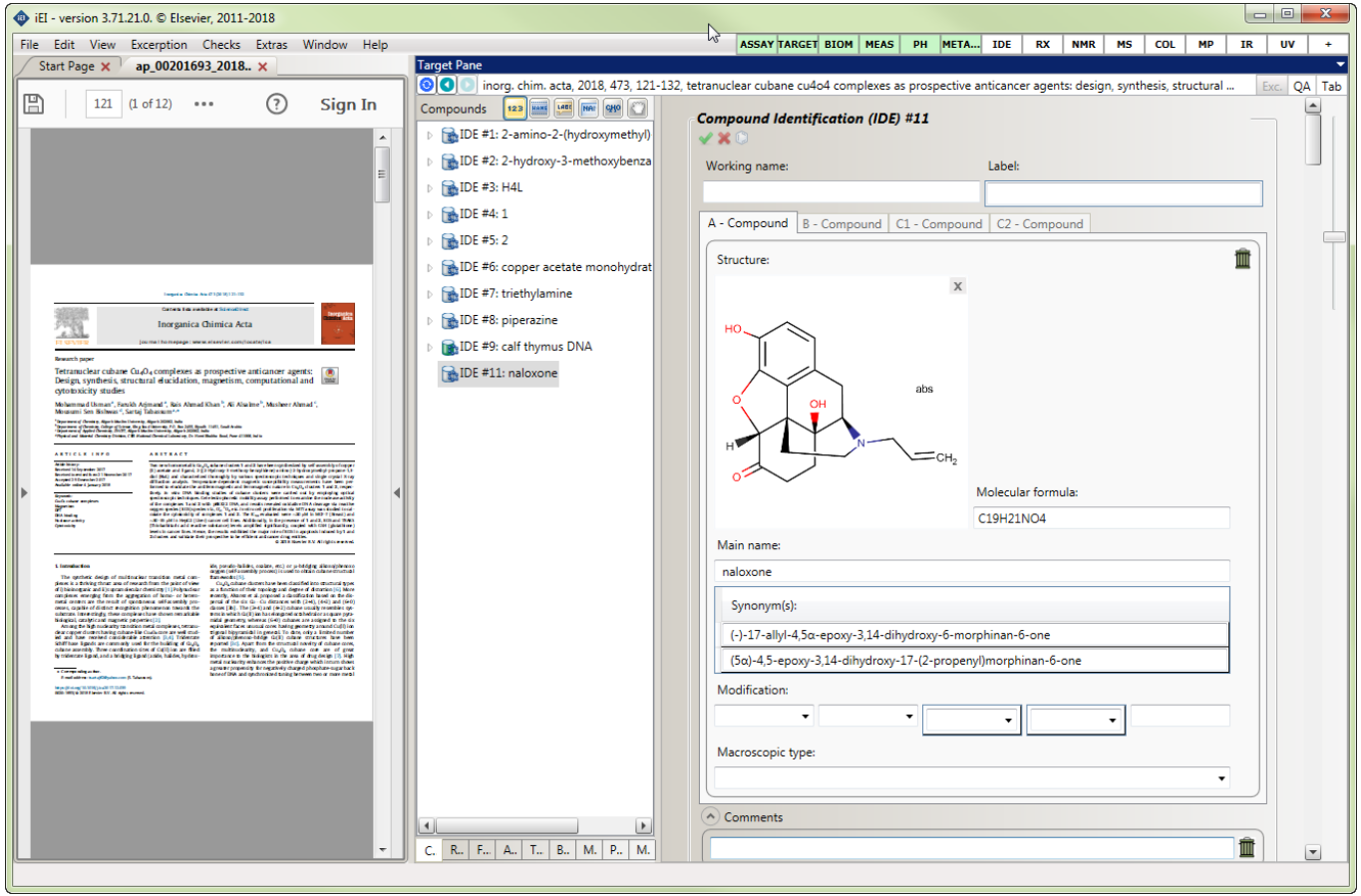
Structures, Markush, chemical names, NMR, IR, MP, USE, …
Reactions, temp., solvent,…
Targets, MedChem data



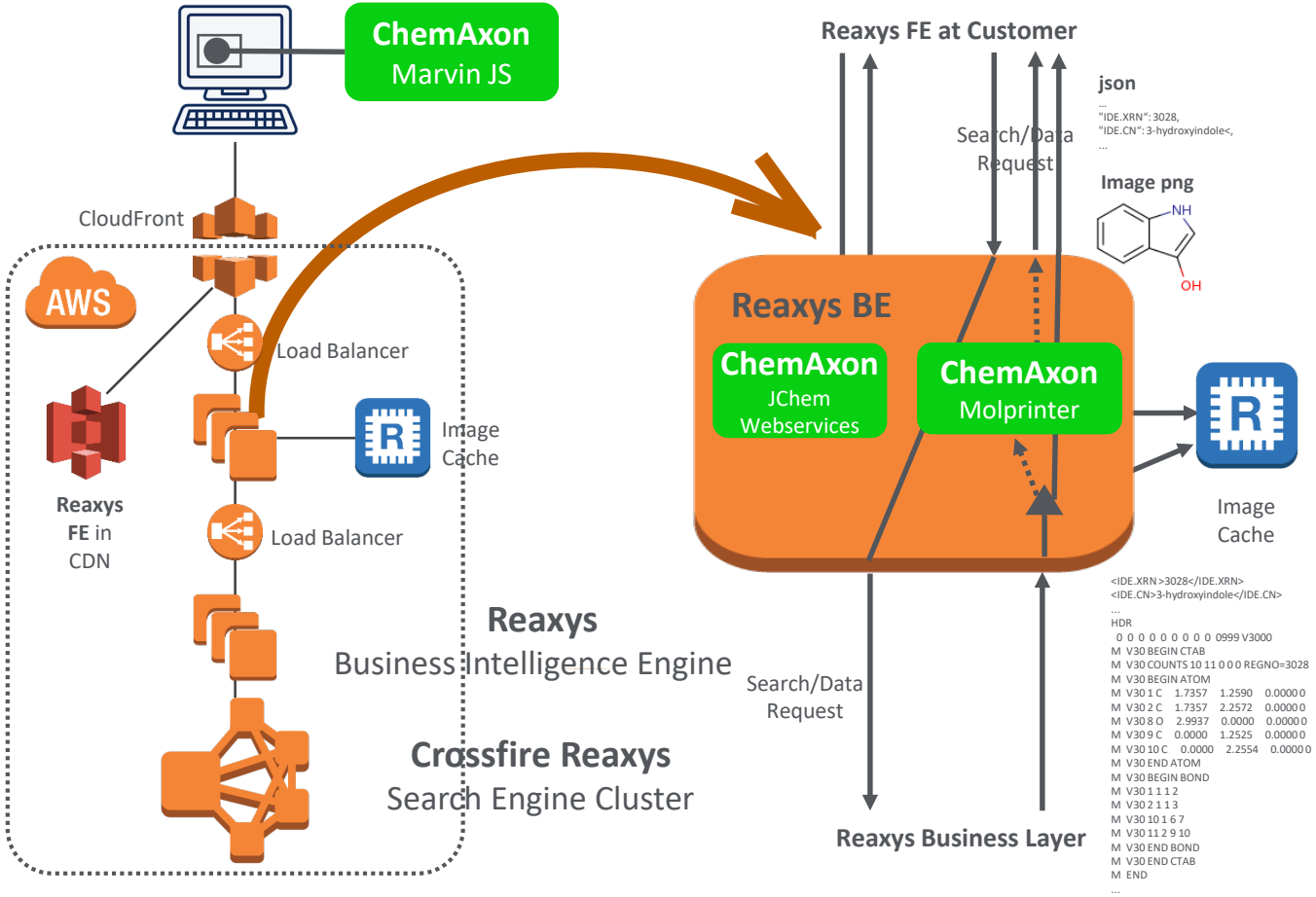
iEI (intuitive Excerption Interface)

Reaxys®

ChemAxon Marvin Sketch in Reaxys excerption



Reaxys Architecture Diagram (simplified)



Key Reaxys Use Case: Reaction Searching and Synthesis Planning

Using MarvinJS to enter even complex structure/reaction queries