Simona Cotesta

IASOC, September 19, 2026

Computational Chemistry in Drug Discovery

NOVARTIS



The drug discovery pipeline: from target identification to development candidate



- Link the target to the disease mechanism
- Confirm that modulation gives the desired phenotype
- Assess tractability and early safety liabilities
- Agree the target product profile and key questions

- Develop assays and set up the screening cascade
- HTS, DEL, fragment and focused-library screening
- Confirm hits: purity, structure and activity
- Establish first SAR and triage chemotypes

- Improve potency and demonstrate robust SAR
- Build selectivity against anti-targets
- Early ADME: solubility, permeability, metabolic stability
- Secure the IP position and define the lead series

- Balance potency, selectivity, PK and safety
- In vivo efficacy and PK/PD understanding
- De-risk hERG, Ames, CYP and early tox
- Scalable route, form selection and clinical candidate nomination

Development candidate selection

Computational methods impact every stage of drug discovery

Where computer-aided drug design adds value, phase by phase

Target identification and validation

- Protein structure prediction, co-folding
- Cavity and binding-site detection
- Target druggability assessment
- Analysis and proposal of mechanisms of action

Hit finding

- Virtual screening
- Docking and high-throughput docking
- Pharmacophore and shape-based searching
- De novo ligand design, including generative chemistry

Hit to lead

- Iterative structure-based and ligand-based optimization
- Use of AI/ML and physics-based models for property predictions
  - Binding affinity, selectivity and anti-target profiling
  - Physical chemical and ADME predictions

Lead optimisation

Development candidate selection

Throughout the talk I will illustrate the impact of computational chemistry across these stages, drawing on examples from my own experience and my team in Novartis

Assessing ligandability of new targets

Can a compound of the required potency realistically bind in this pocket?

1
Structural input
X-ray structure, homology model or co-folding model of the target

2
Cavity detection
Pockets identified on the protein surface; site defined by residues within 6 Å of a bound ligand where available

3
Pocket property analysis
For example, SiteMap (Schrodinger) profiles size, enclosure and the balance of hydrophobic and polar character

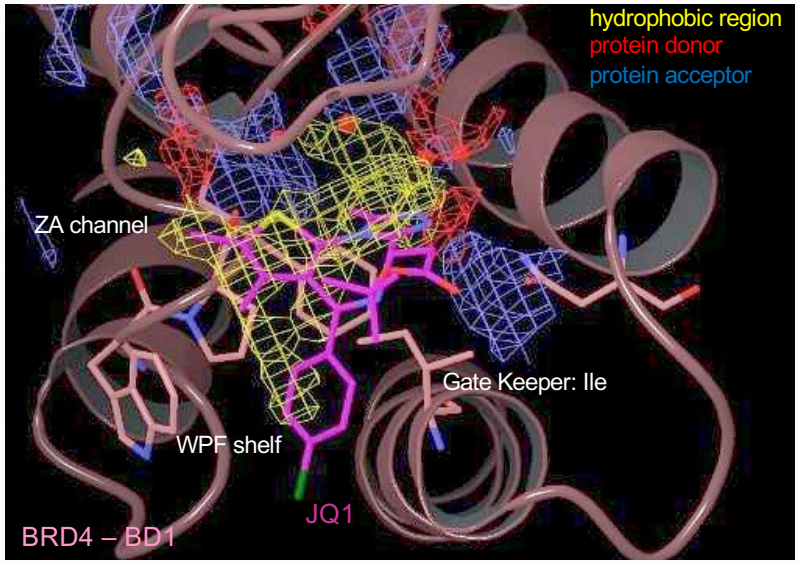
4
Ligandability call
SiteScore and DScore, with visual inspection, give a High / Medium / Low ranking and rank ordering of pockets

Druggable DScore ~ 1.1 | **Difficult DScore ~ 0.9** | **Undruggable DScore ~ 0.6**

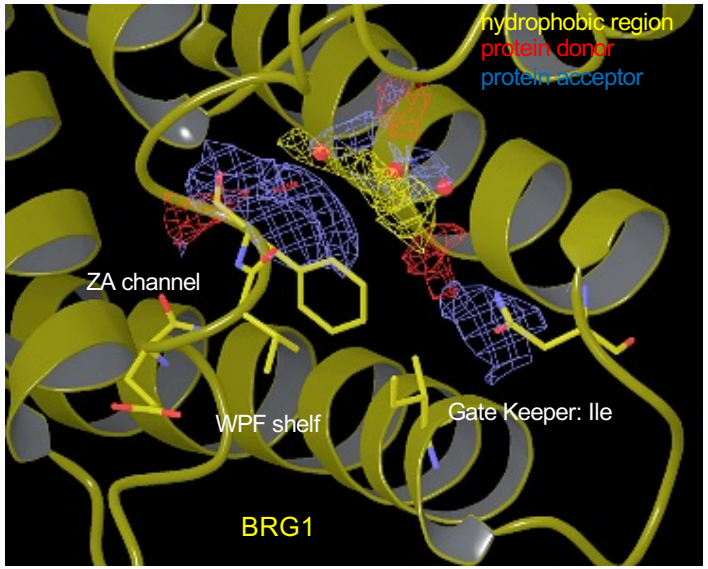
DScore combines site size, enclosure and hydrophilicity (Halgren, J. Chem. Inf. Model. 2009, 49, 377)

> *The score guides, it does not decide:* ***apo structures often understate a pocket, and drug-like potency has been reached on sites scored as difficult or undruggable***

Ligandability assessment: the Bromodomain family



BRD4 – Dscore 1.1 → ligandable
PDB code: 3mxf



BRG1 – Dscore 0.8 → Difficult or not ligandable?
PDB code: 3mxf

- It has been possible to identify potent ligand for both targets, however for BRG1 it has been more difficult

A story worth telling

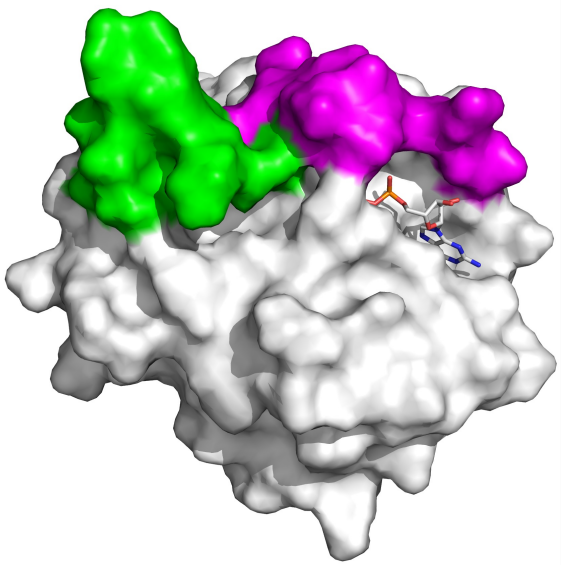
For thirty years, RAS was the target nobody could drug

Then, through the discovery of an induced pocket, everything changed

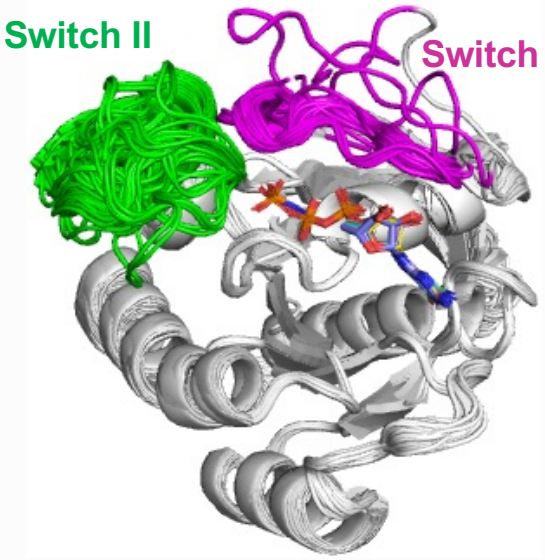
NOVARTIS

KRAS is highly flexible GTPase with no obvious ligandable binding site beside the nucleotide pocket

No ligandable pocket visible beside GDP (or GTP) binding site

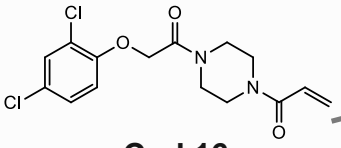


Switch I and II region are very flexible

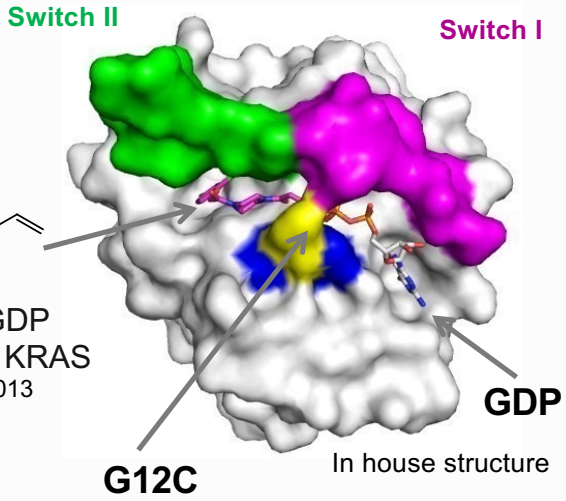


Due to the **high protein flexibility**, it is plausible that several conformations exist in solution, including those with a **ligandable pocket**

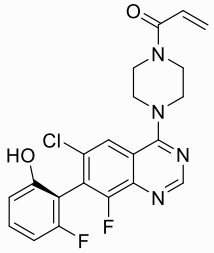
Focusing on KRAS^{G12C} and the discovery of the allosteric pocket under switch II delivered multiple clinical candidates and approved drugs



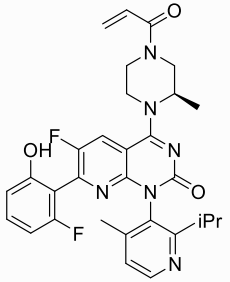
Cpd 16
Modify KRAS^{G12C}-GDP
No modification of WT KRAS
Ostrem et al., *Nature,* 2013



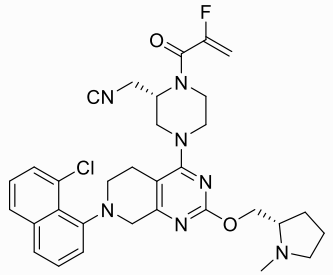
In house structure



ARS-1620 (Araxes)
Tool cmpd achieving *in vivo* PoC in mouse models
Janes et al, *Cell*, 2018



AMG-510 (Amgen)
Lumakras (Sotorasib) US approval: May 2021
Lanman et al, *J Med Chem*, 2019



MRTX-849 (Mirati)
Krazati (Adagrasib) US approval: Dec 2022
Fell et al, *J Med Chem*, 2020

- Cpd 16, an irreversible covalent inhibitor binding to C12 in an allosteric site under switch II
- **Mode of Action**
  - Irreversible trapping of KRAS^{G12C} in the inactive GDP bound conformation

Hit identification: three case studies

01

KRAS G12C example

Structure-based de novo design to identify novel chemotypes in the switch II pocket

02

Bcr-Abl example

Starting from a small fragment hit, pharmacophore searches deliver a new hit that could be optimized towards a development candidate

03

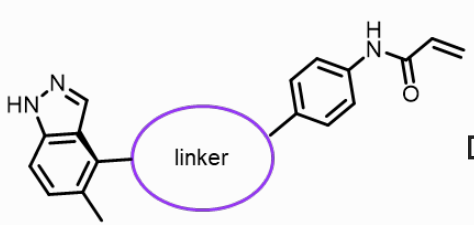
YAP/TEAD

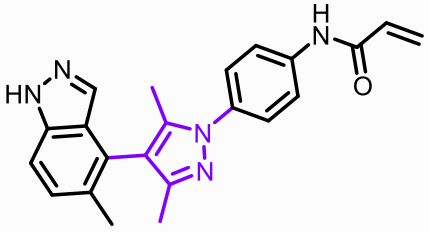
High-throughput docking to identify a starting point for blocking the YAP–TEAD protein–protein interaction

KRAS^{G12C}: a pyrazole chemotype discovered by structure-based *de novo* design

Design principle

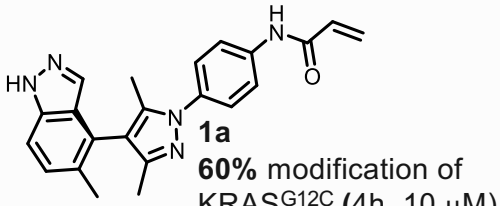
- Maximize diversity to known chemo-types
- Ligands locked in bioactive conformation



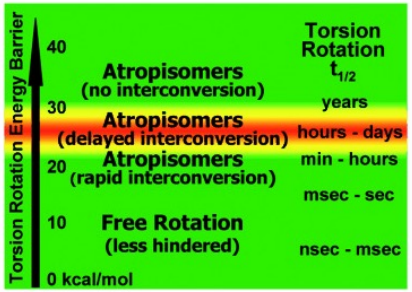


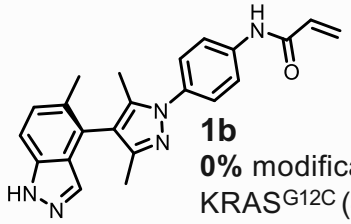
atropisomers?

QM calculation: ΔE_{rot} (kcal/mol) =31.6



1a
60% modification of KRAS^{G12C} (4h, 10 μM)

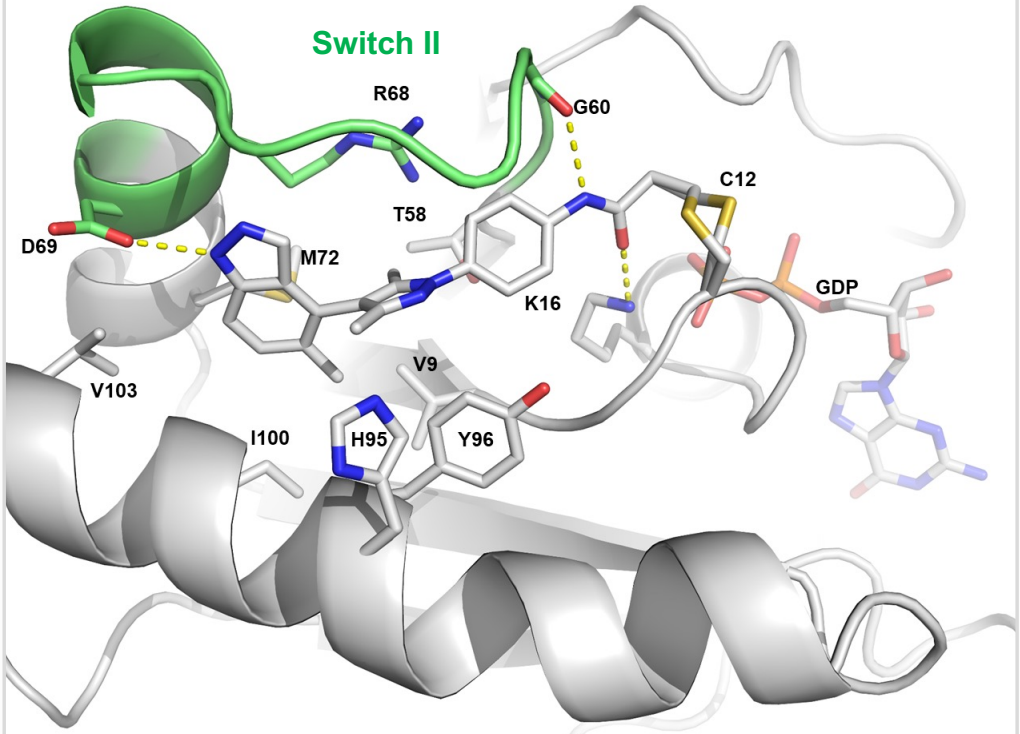




1b
0% modification of KRAS^{G12C} (4h, 10 μM)

La Plante et al, *ChemMedChem*, 2011

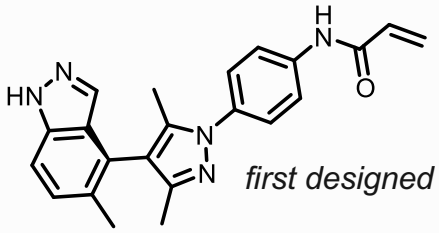
Co-crystal structure of 1a with KRAS^{G12C}



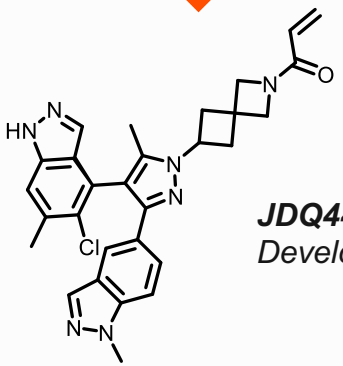
PDB: 7R0Q, Weiss et al, *Cancer Discovery*, 2022

MedChem optimization delivered JDQ443, our development candidate

From first designed hit to development candidate

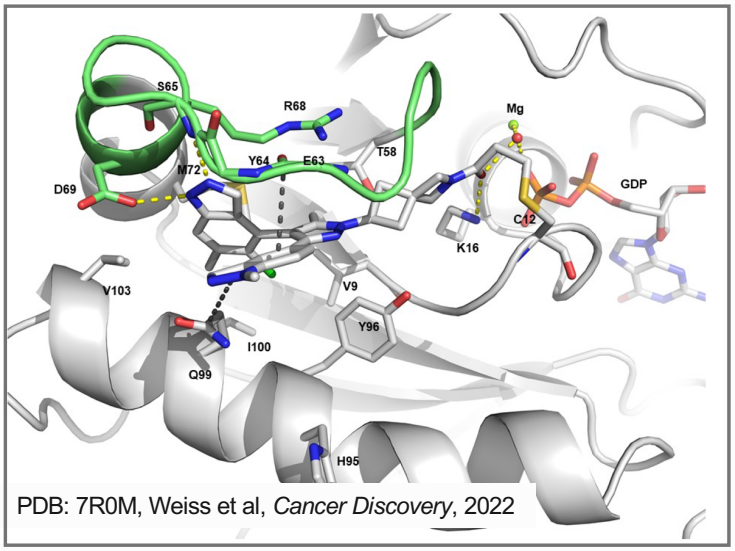


first designed hit



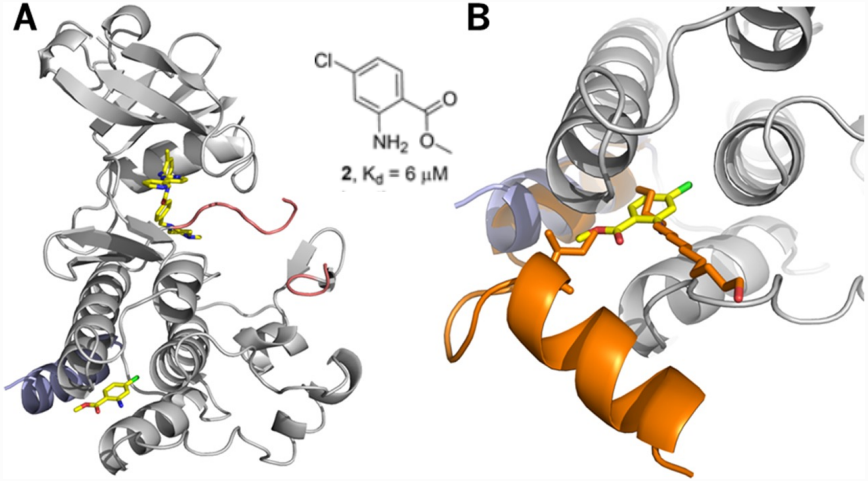
JDQ443 (Opnurasib)
Development candidate

Co-crystal structure of JDQ443 with KRAS^{G12C}

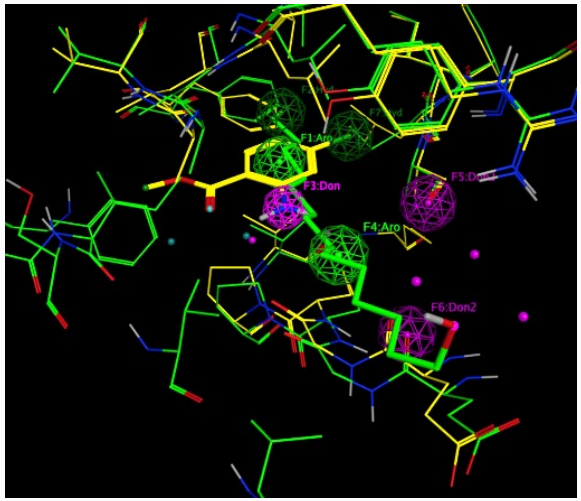


PDB: 7R0M, Weiss et al, *Cancer Discovery*, 2022

BCR-ABL: from a fragment hit to a new chemotype by pharmacophore searching and SBDD

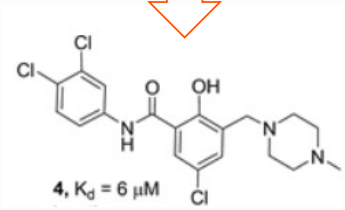


(A) Crystal structure of ABL1 kinase domain in complex with imatinib and fragment hit 2. (B) Structural detail, showing the position of 2 in the myristate pocket of ABL1 kinase. Superimposed from the structure of ABL1 kinase in complex with myristic acid (1opl) are the myristic acid ligand (orange) and helix-I (orange) (PDB code 3MS9, 1.80 Å).



Green and **purple** spheres: pharmacophore features
Yellow: yellow sticks fragment 2; **green sticks**: myristate

Pharmacophore search + hit expansion

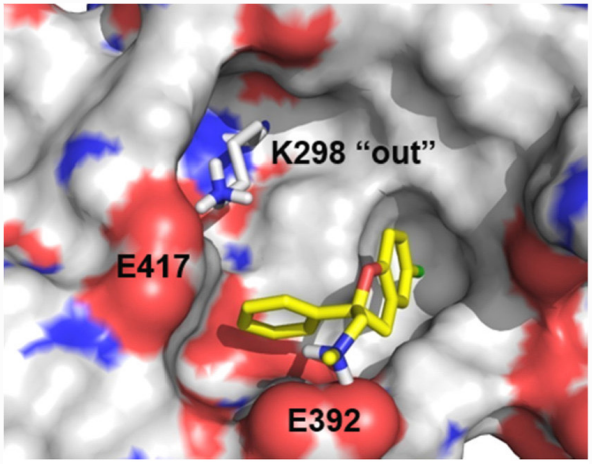


- Further optimization led to the discovery of Asciminib (Scemblix)

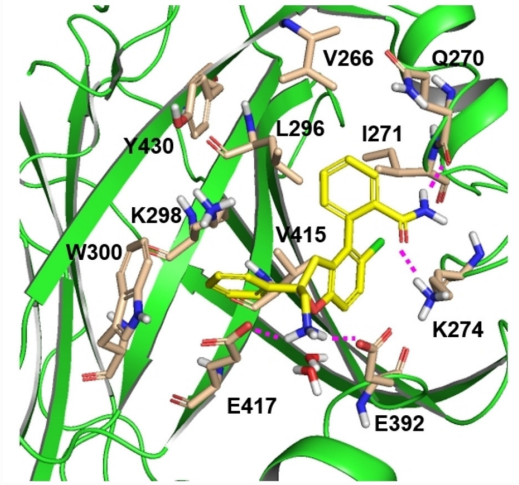
NOVARTIS *Schoepfer et al., J. Med. Chem., 2018, 61, 8120*

YAP–TEAD: high-throughput docking finds a new chemotype

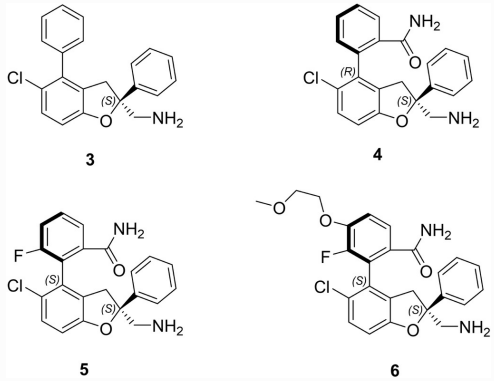
A docking-derived hit that could be optimised towards a development candidate



SBDD design



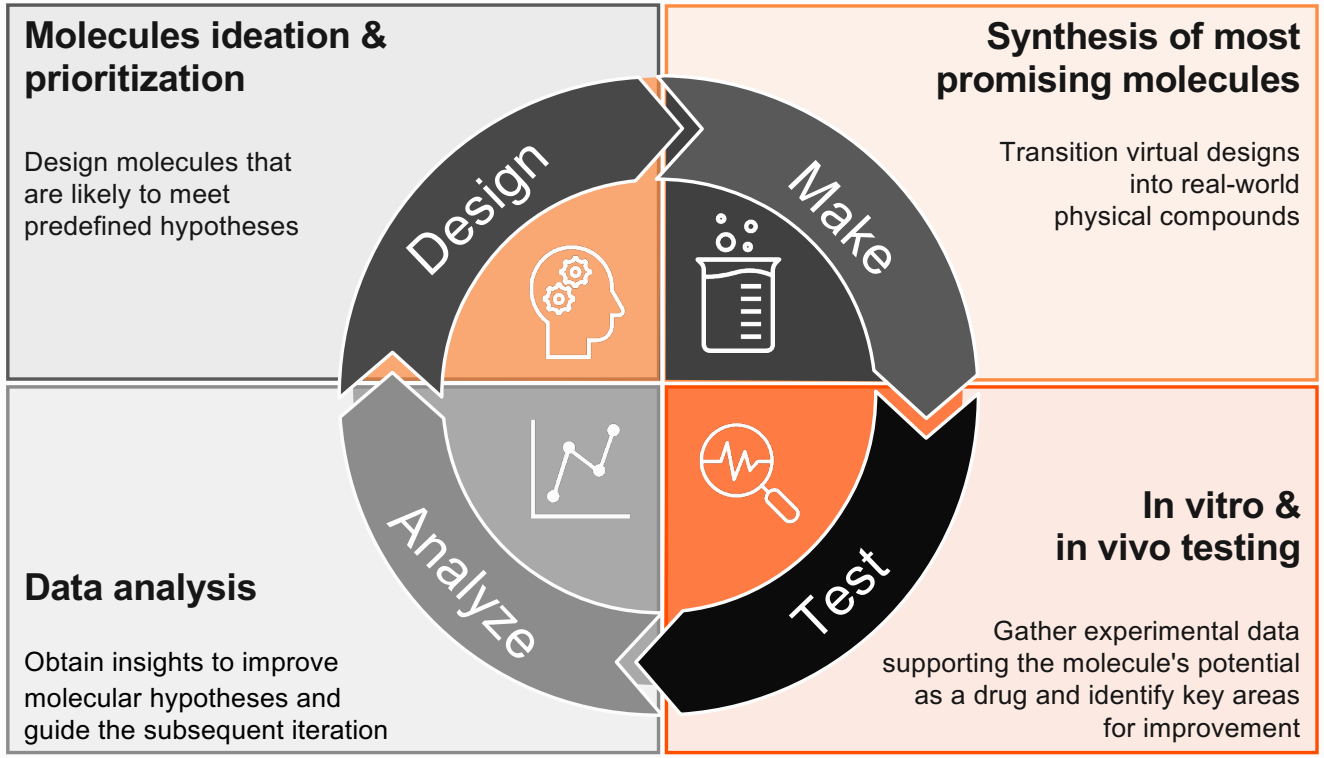
4 in yellow
IC_{50} = 150 nM (TR FRET)



6 IC_{50} = 3 nM (TR-FRET)
Atropisomerism to lock bioactive conformation and reduce entropy loss

Furet et al., ChemMedChem, 2022, 17, e202200303

Hit and lead optimization:
The Design Make Test Analysis (DMTA) cycle



Current bottlenecks

- Balancing novelty, synthesizability, and competing molecular properties
- Complex or slow synthesis routes
- Assay timelines (throughput limits), costs, variability, sparse data
- Slow decision making due to complex data, risk of confirmation bias

Can AI and computational methods help to accelerate the DMTA cycle?

Design Phase - In silico ideation & prioritization

Creative designs and generative models

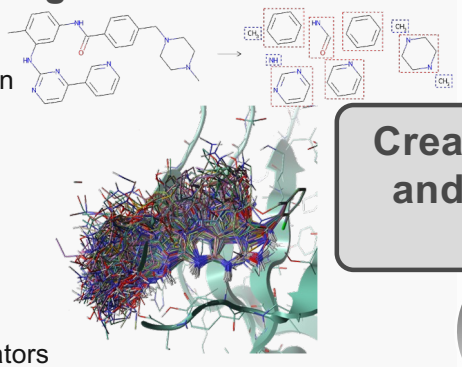
Examples:

- Structure Based Design
- Medicinal Chemistry

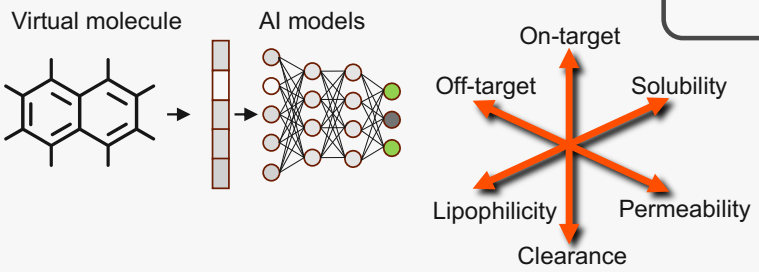
Multiple 2D generators

- Fragment and scaffold
- Library and decoration
- Molecule optimization
- Unconstrained

3D pocket-based generators



Multi-objective property optimization



Virtual ideation cycle

Creative designs and generative models

AI & physics-based models to prioritize best molecules

Selection of improved molecules

Predictive models to estimate drug relevant properties



Analysis ⇐ Test ⇐ Make

Digital workflow

Few 1000s virtual molecules

High throughput models phys-chem, ADME, drug likeness & synthesizability

3D assessment physics-based methods (SBDD & LBDD)

Low-throughput methods Quantum mechanics & free energy simulation



50-100 virtual molecules

Expert assessment and final decisions by MedChem team

Digital workflow used in KRAS^{G12C}

Global AI/ML models for
LogP, Solubility and Permeability

QM (ReSCoSS*)

- **Assessment of ligand conformations in solution** and comparison to co-crystal structures of known analogues
- Phys-chem calculations: **LogP, 3D-PSA, pKa**

Covalent Docking

- **Exploring novel interactions** in the binding pocket
- **Assessing new covalent warheads** and **novel linkers**
- Analysis of the predicted bound conformation



Prioritized compounds for synthesis



Digital workflow used in KRAS^{G12C}

Global AI/ML models for
LogP, Solubility and Permeability

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Covalent Docking

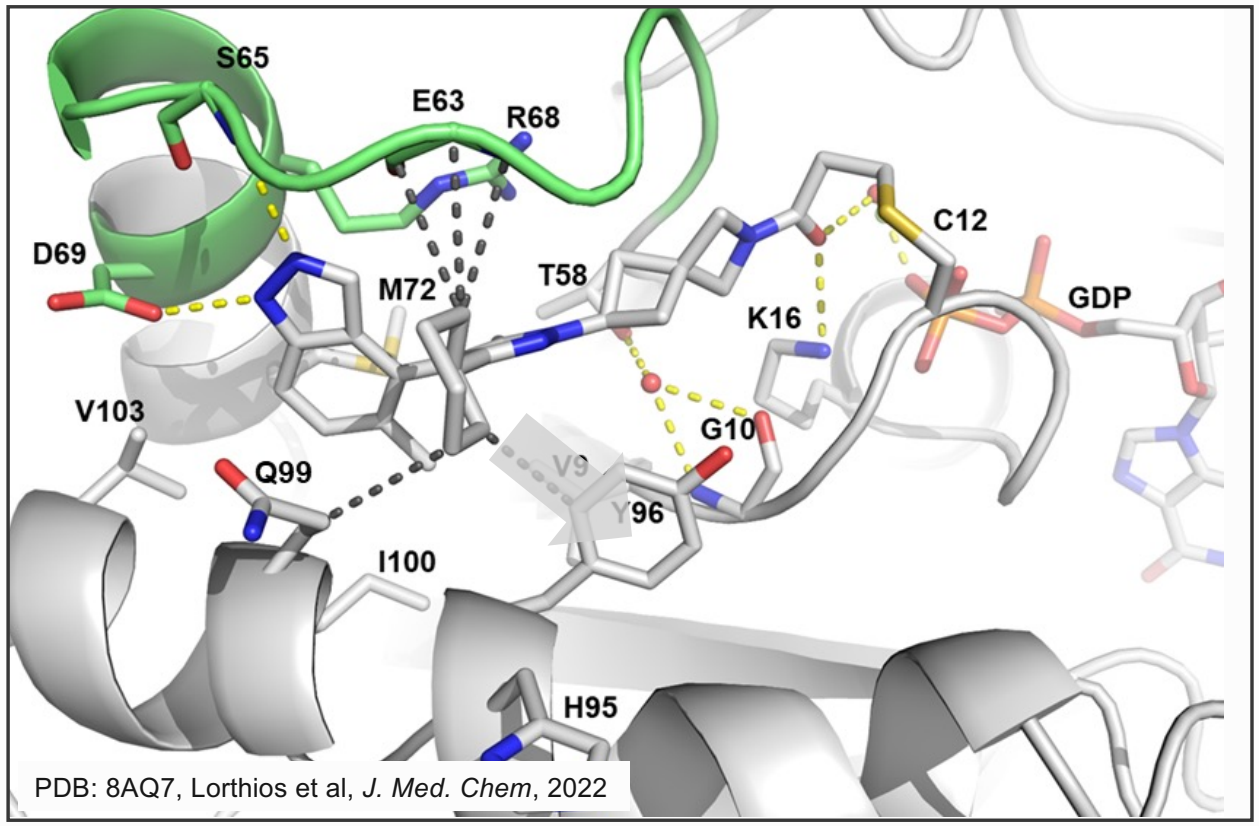
- **Exploring novel interactions** in the binding pocket
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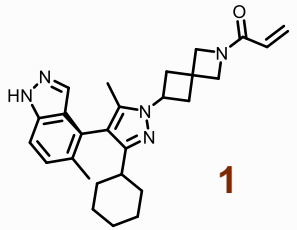
Prioritized compounds for synthesis



Can we optimize compound 1 to optimally interact with Y96?

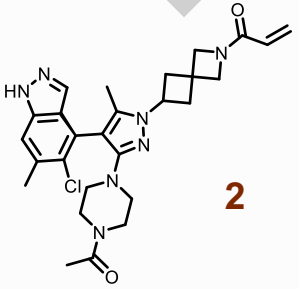


PDB: 8AQ7, Lorthios et al, *J. Med. Chem*, 2022



1

Rate constant
k_{inact}/K_I (mM^{-1} s^{-1}) 0.24

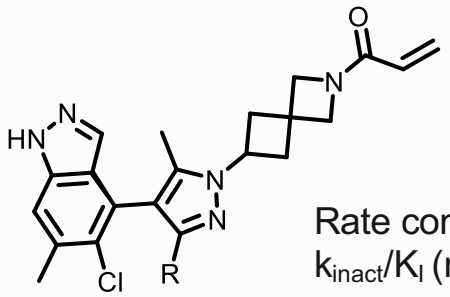


2

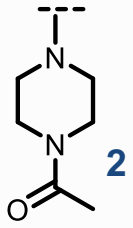
Rate constant
k_{inact}/K_I (mM^{-1} s^{-1}) 4.5

Starting point
for optimization

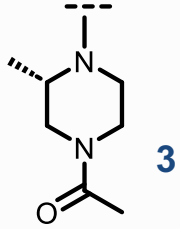
ReScoSS minimum conformation in water is close to the bound ligand conformation



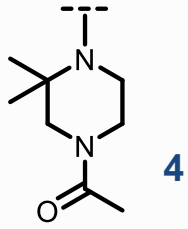
Rate constant
k_{inact}/K_I (mM^{-1} s^{-1})



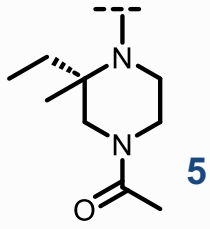
4.5



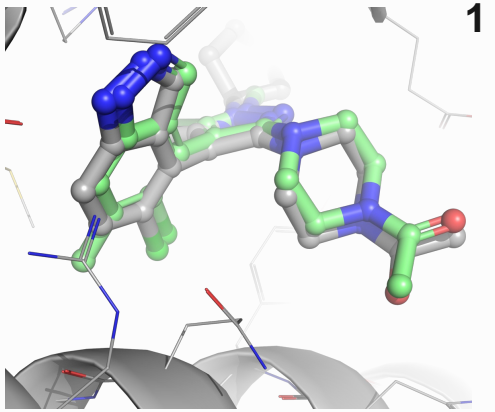
16.5 (3.6x)



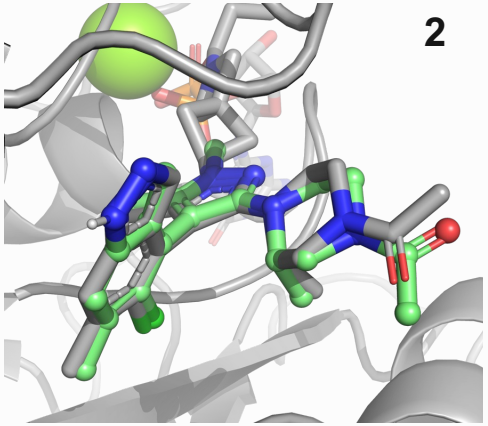
82 (5x)



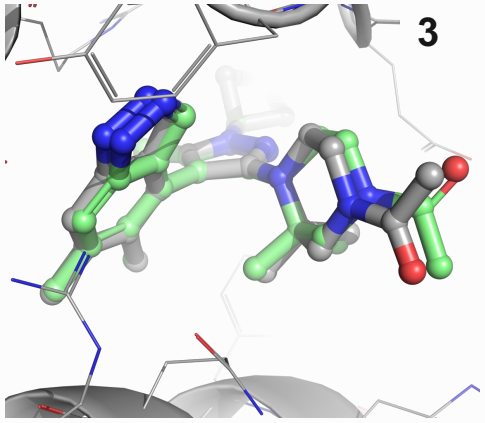
330 (4x)



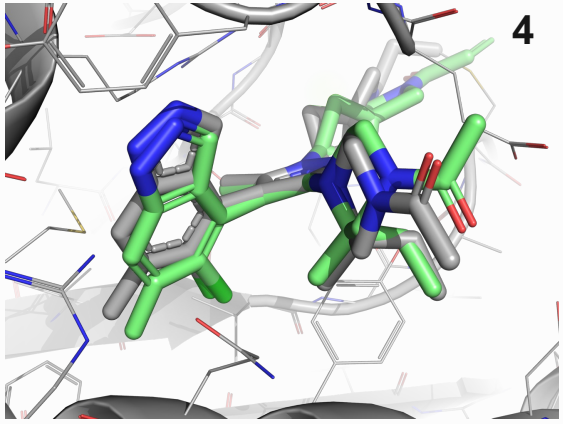
Conf. 0.9 kcal/mol from min / x-ray



Min conf. / x-ray
Methyl in hydrophobic region



Min conf. / x-ray
Piperazine perpendicular to pyrazole core and methyls in hydrophobic regions



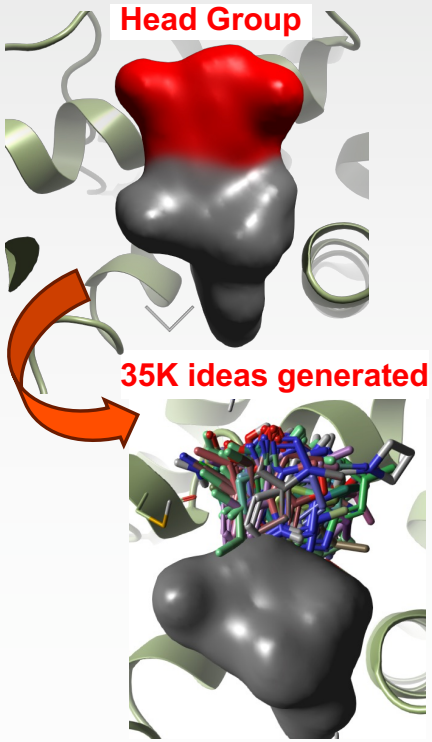
Min conf. / x-ray
Piperazine perpendicular to pyrazole core and ethyl reaches hydrophobic hotspot

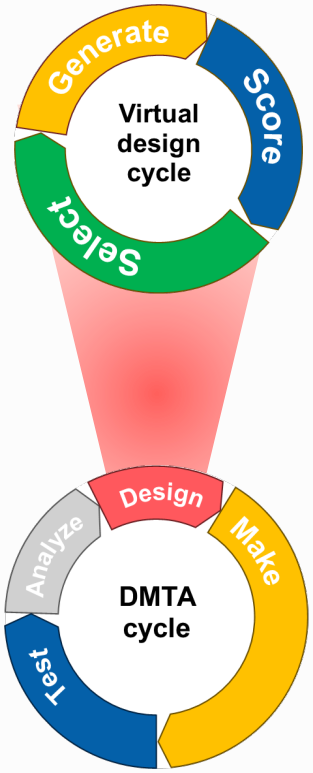
- Changing the piperazine orientation allowed reaching the hydrophobic hotspot, increasing k_{inact}/K_I

Project 1 | 3D-Aware GenChem accelerates lead optimization

Aim: Improve diversity

GenChem: Generate alternative head groups





35K ideas generated

Fit in allosteric pocket
by ensemble docking

Property predictions
by global **ML BR models** & **ReSCoSS**
for **LogD**, **permeability**, **PPB**, **pKa**, **deepPKu**

Udvarhelyi et al JCAMD (2021)

Activity predictions
Conformational analysis and ligand strain energy calculation by **QM**;
Binding affinity estimates by **FEP+**, MD

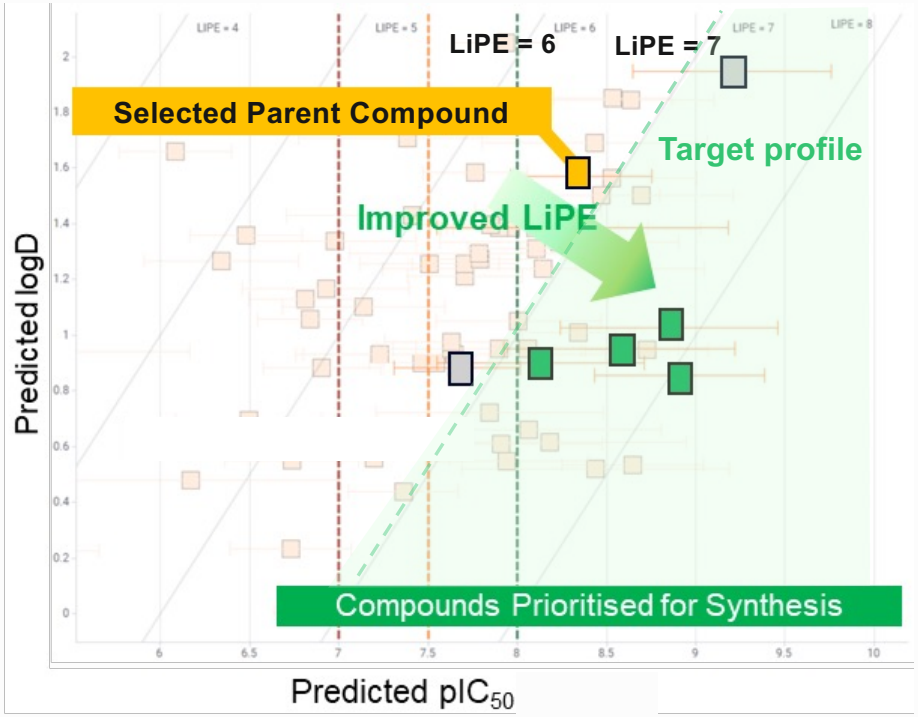
Prioritized compounds for synthesis

Physics based
Machine Learning

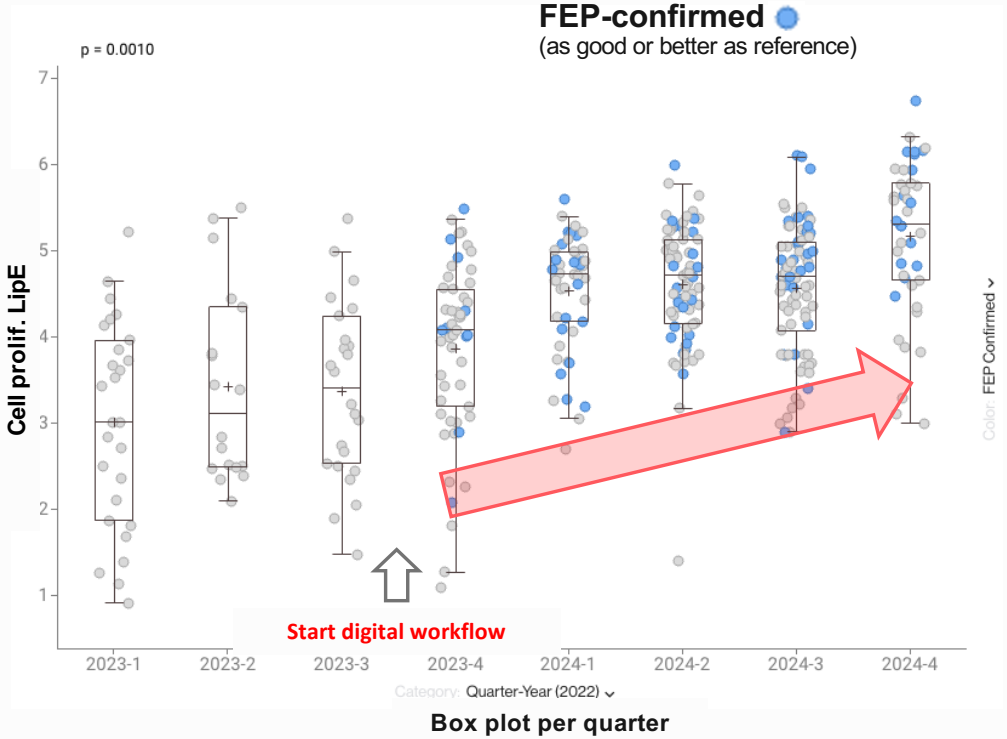
Project 1 | FEP-guided LIPE predictions enrich decision making

- Prior to selection for synthesis, compounds needed to show an increase in **predicted LiPE** (lipophilic efficiency)
  - Rational idea prioritization via the digital workflow **successfully enriched** LipE-efficient compounds

In silico lipophilic ligand efficiency (LiPE)



Evolution of cell proliferation LipE overtime



Conclusion

What computational chemistry contributed across the discovery cascade

Ligandability guides, it does not decide

Pocket detection and scoring rank targets, but KRAS show that sites called difficult can still be drugged.

Three routes to a new chemotype

De novo design (KRAS G12C), pharmacophore searching (BCR-ABL) and high-throughput docking (YAP–TEAD) each delivered novel starting points.

Digital workflows sharpen the DMTA cycle

Generative chemistry with AI/ML property models, docking, QM conformational analysis and FEP prioritize the molecules worth making.

Thank you!

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