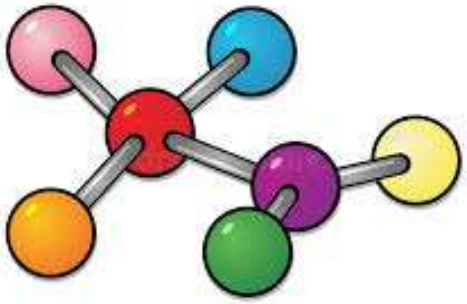
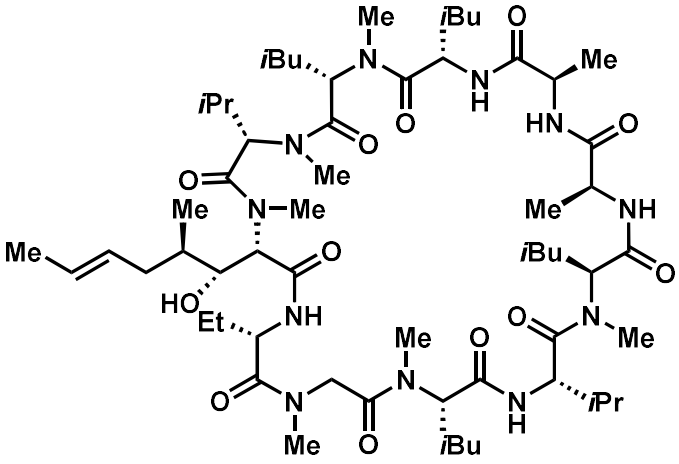
Molecular Glues



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Sorensen Lab
Literature Talk
Sam He
5/2/25

Molecular Glues

- market size estimated at 3.23 billion in 2022, forecasted to increase to 6.07 billion by 2032

from marketresearchfuture.com, https://finance.yahoo.com/news/molecular-glues-market-register-stunning-214600511.html

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- as of 2023, only 3 synthesized molecular glues were FDA-approved, and ~20 currently in clinical trials
  - emerging market with billions of Big Pharma investment into molecular glues

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BIOTECH

Sticky, sticky, sticky: Neomorph tacks on another Big Pharma glue degrader deal with $1.6B AbbVie pact

By **Gabrielle Masson** · Jan 23, 2025 9:58am

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By **Darren Incorvaia** · Oct 30, 2024 10:50am

Lilly joins molecular glue field with Magnet deal worth up to $1.25B



Max Gelman
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Another day, another molecular glue deal in the biopharma world.

This time around, it's Eli Lilly partnering with the private startup Magnet Biomedicine on the ...

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Why are molecular glues so hot in drug discovery?

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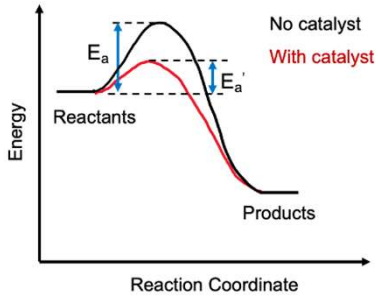
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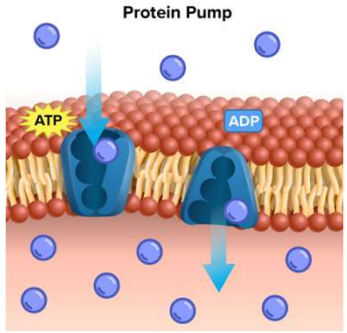
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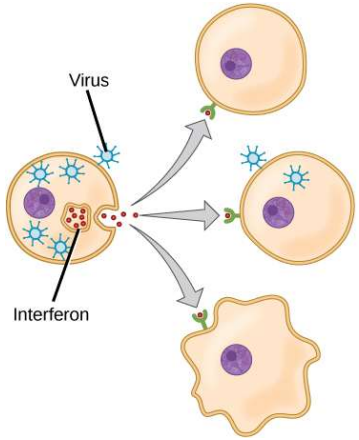
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Protein-Protein Interactions

- at a molecular level, proteins have variety of functions – catalysts, transportation, or immune response



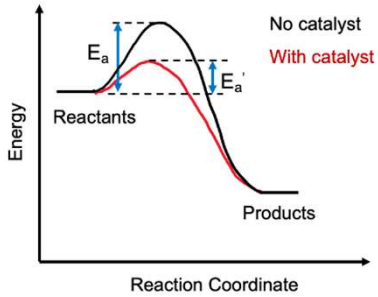


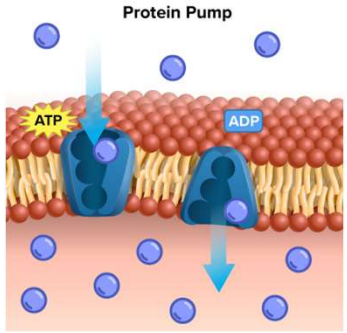


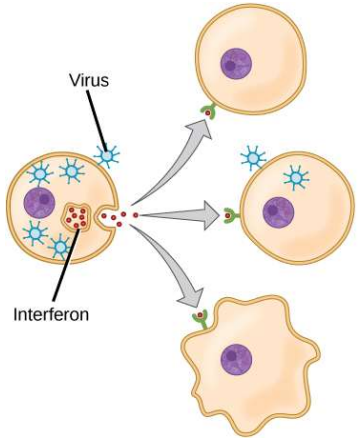
Signal Transduction and Targeted Therapy, **2020**, *5*, 213

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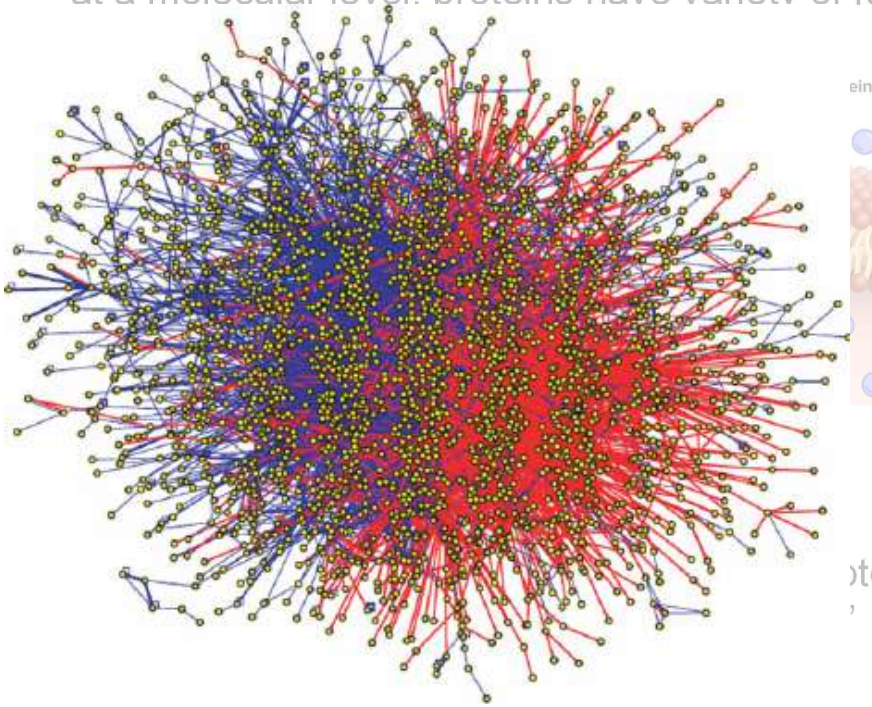


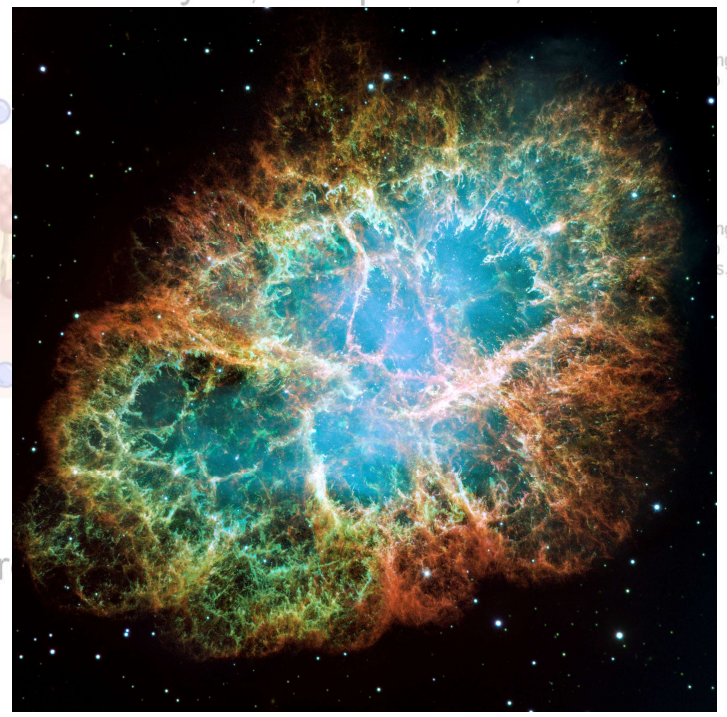
- such biological activities are regulated by protein-protein interactions (PPIs), which form a complex network known as the “interactome”

Signal Transduction and Targeted Therapy, **2020**, *5*, 213

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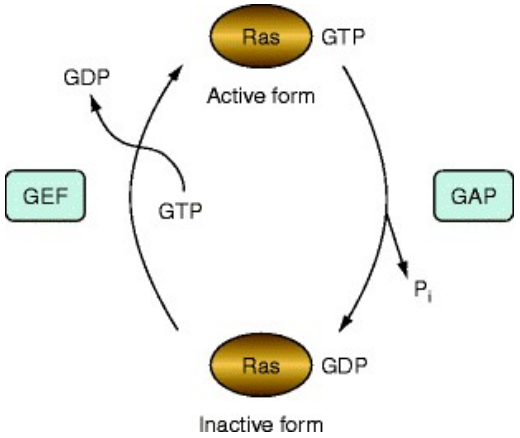


Signal Transduction and Targeted Therapy, **2020**, *5*, 213

“Interactome” and Connection to Human Disease

- aberrant PPIs are often the cause of common major diseases

- Ras proteins [regulated by **guanine nucleotide exchange factors** and **GTPase-activating proteins**]
  - “switched on” Ras leads to the “switching on” of genes controlling cell growth, thus aberrant Ras function linked to *cancer*



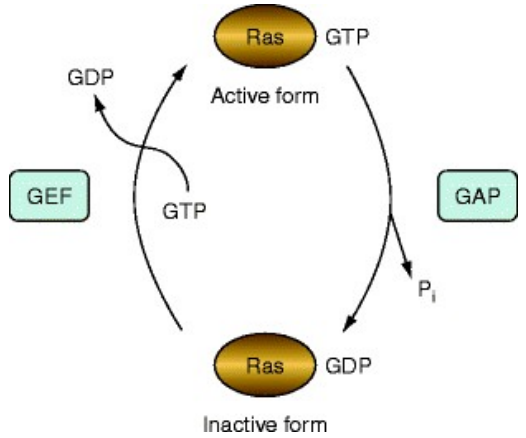
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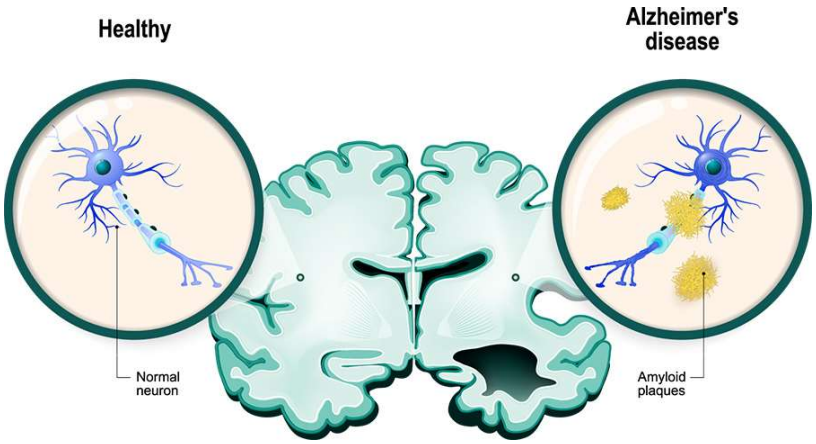
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- *β*-amyloid protein oligomerization is the initial process of Alzheimer’s – normally minimal interactions

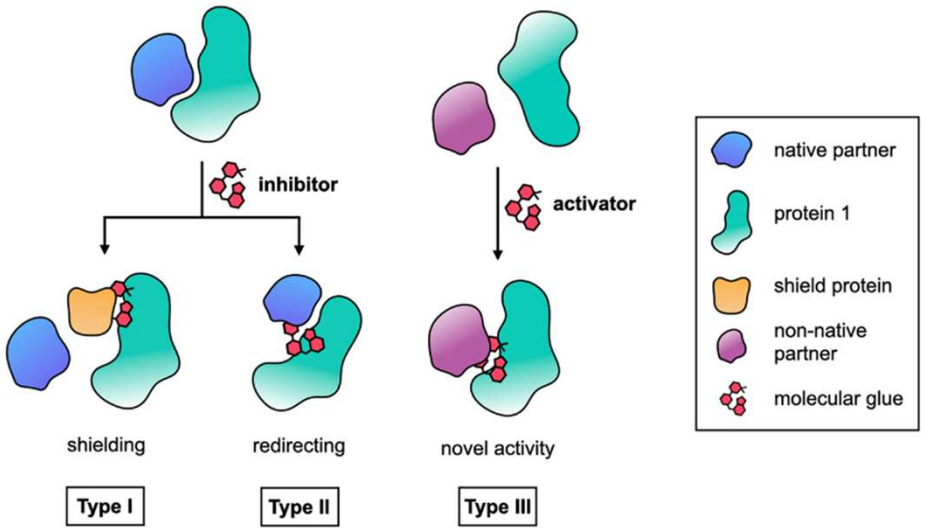




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Introduction to Molecular Glues

- molecular glues – small molecules that stabilize endogenous PPIs or induce non-native ones
  - classified into 3 distinct categories dependent on binding modes

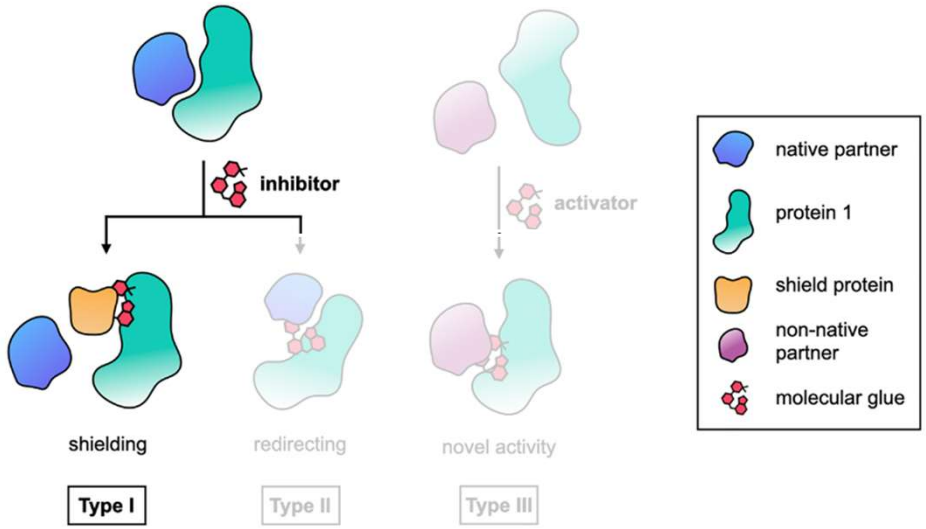


J. Med Chem., **2023**, *66*, 9278-9296

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Type I – *shielding* – induce a non-native PPI via endogenous PPI inhibition, which physically "blocks" the target protein's activity



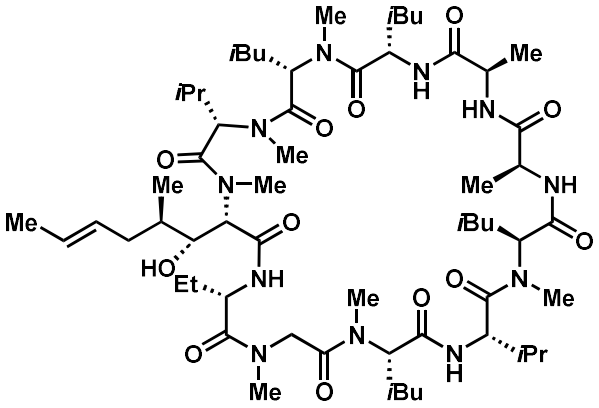
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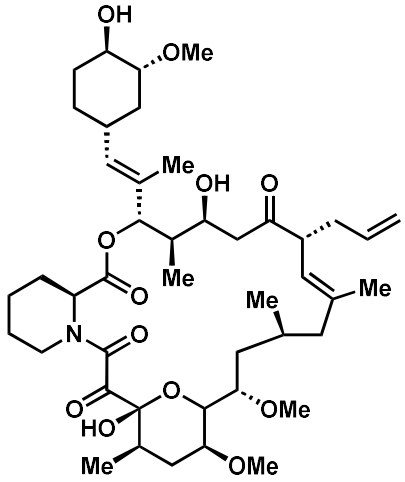
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examples: cyclosporine A and tacrolimus (FK506) – both are selective inhibitors of *calcineurin*, which regulates T-cell activation, and thus used as immunosuppressants



cyclosporin A



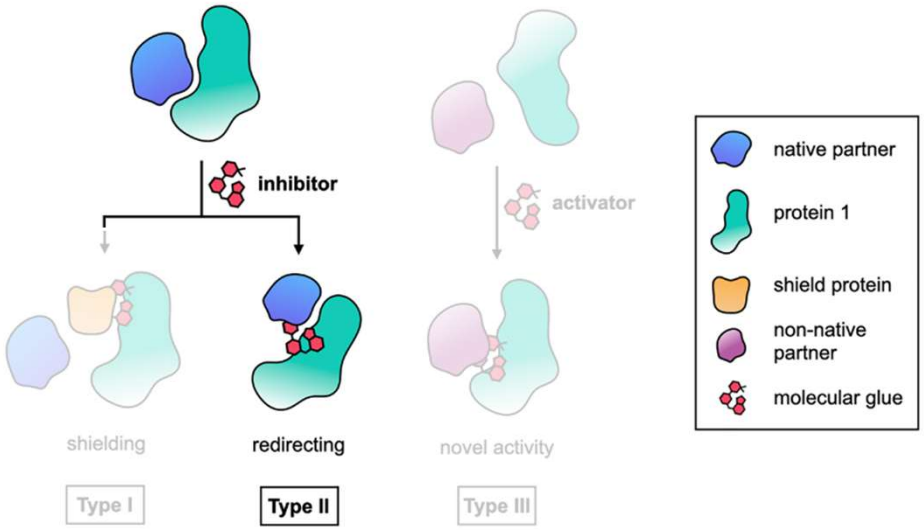
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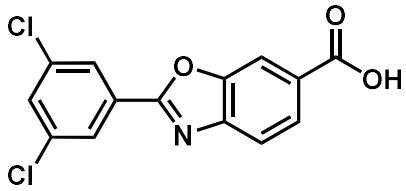
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examples: tafamidis – stabilizes transthyretin (transport protein in blood and CSF) tetramers via PPI binding, which is used to treat TTR amyloidosis



tafamidis

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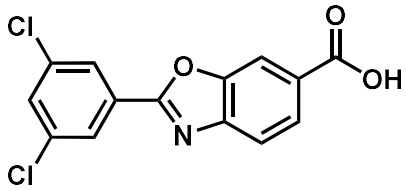
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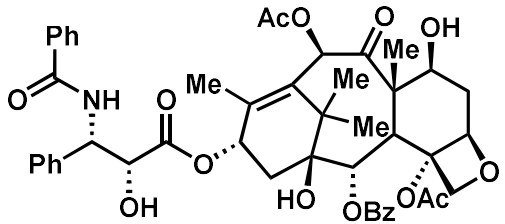
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TAXOL! – stabilizes the PPI of tubulin heterodimers, which prevents microtubule disassembly



tafamidis



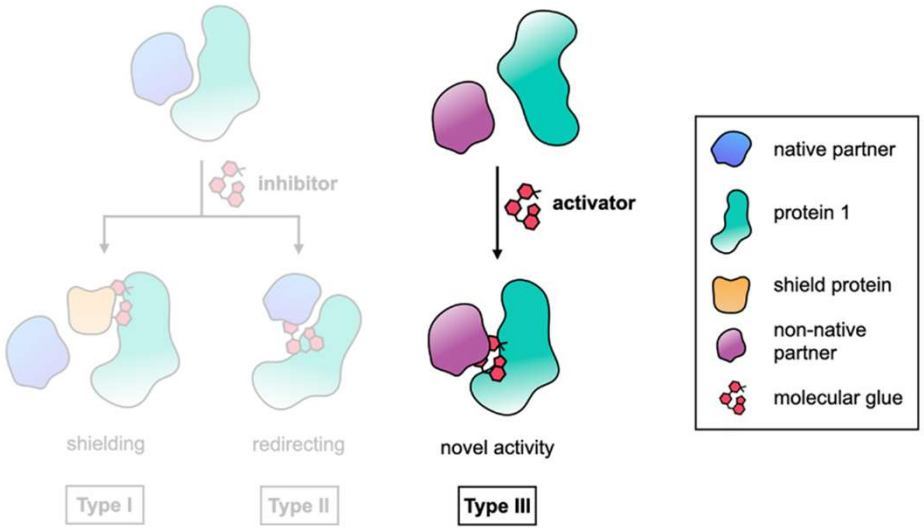
taxol

J. Med Chem., **2023**, *66*, 9278-9296

Introduction to Molecular Glues

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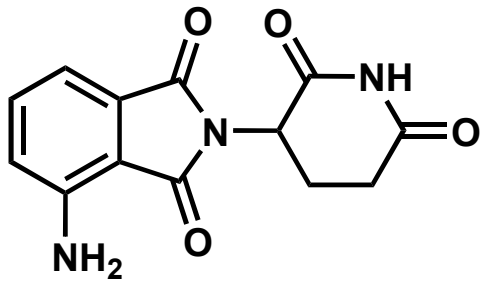
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Type III – *novel activity* – induction of a non-native PPI to enable novel activity between the proteins

example: pomalidomide – induces interaction between E3 ubiquitin ligase cereblon and various non-native proteins, including lymphoid transcription factors, helps treat multiple myeloma



pomalidomide

J. Med Chem., **2023**, *66*, 9278-9296

History of Molecular Glues

First Discoveries from Natural Products

- cyclosporin A first serendipitously discovered from a soil sample collected in Norway (1971), began use in patients as immunosuppressant in 1979

- FK506 discovered by Japanese pharmaceutical company Fujisawa in 1987 through antimicrobial screening

Cell, **2021**, *184*, 3-9
J. Am. Chem. Soc., **1990**, *112*, 5583-5601.

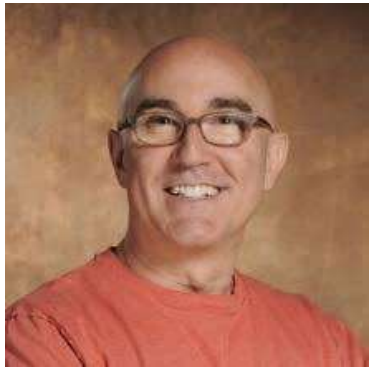
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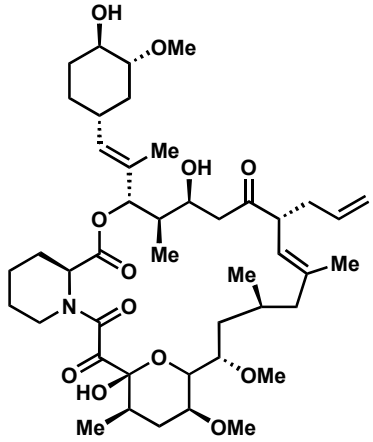
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- Schreiber and his lab became greatly interested in investigating FK506 and its mechanism of action… first completed a total synthesis of FK506 in 1989!



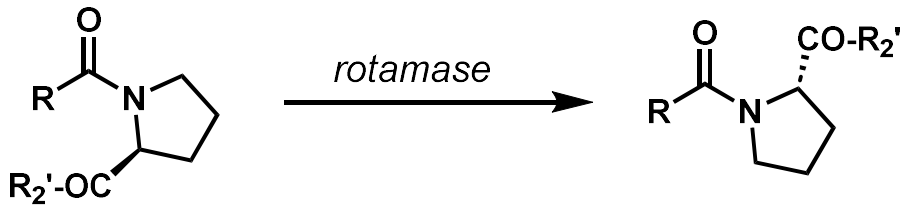


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History of Molecular Glues

Investigation into Mechanism of Action



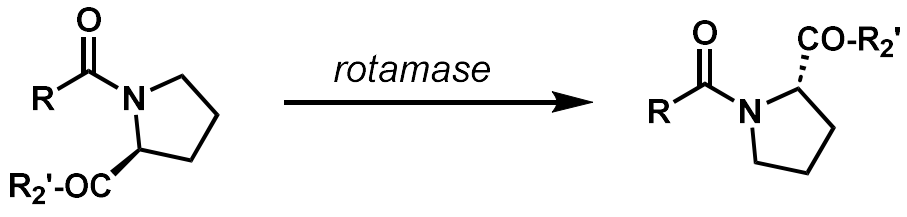
- Schreiber's lab determined FK506 to act as an inhibitor for *trans-cis* peptidyl-prolyl isomerase FKBP (FK-binding proteins)

- Takahashi, Hayano, and Suzuki also determined CsA was an inhibitor of cyclophilin [another peptidyl-prolyl isomerase]

Nature, **1989**, *341*, 758-760.
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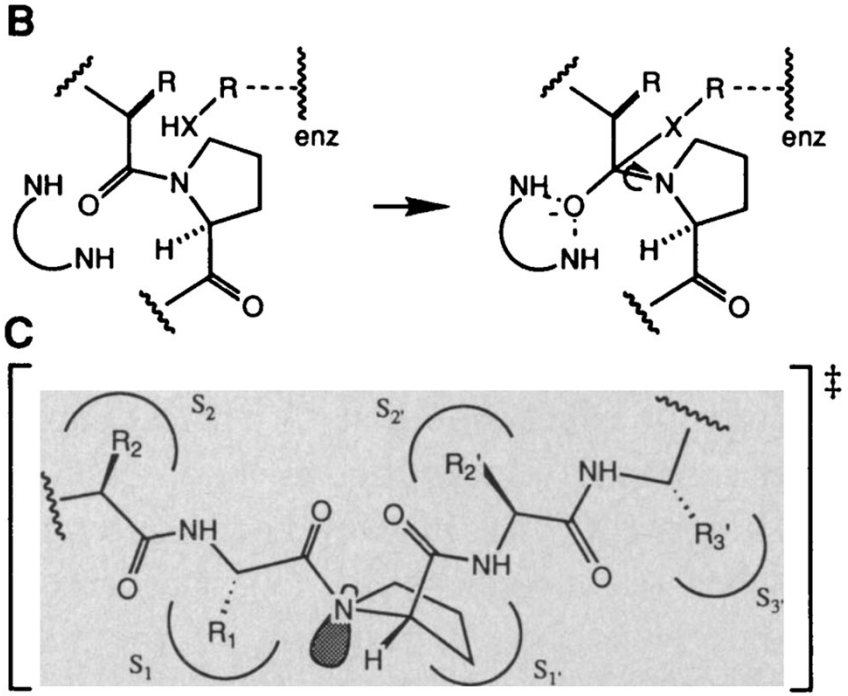
key insight: FK506 and CsA were highly selective, they *only* inhibited their respective proteins potently

additionally, these findings led to the discovery these immunophilins were involved in T-cell activation

Nature, **1989**, *341*, 758-760.
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History of Molecular Glues

Investigation into Mechanism of Action



- Schreiber sought out to determine the chemical mechanism operant – either B) tetrahedral adduct mechanism [via cysteine residues] or C) twisted amide mechanism
  - both mechanisms lead to loss of amide resonance, enabling rotation

Science, **1990**, *248*, 863-866.

History of Molecular Glues

Investigation into Mechanism of Action

- following complexation studies with FKBP, they concluded **no covalent bond** was forming, thus concluded the stabilization provided by FK506 derived from twisted peptidyl-prolyl amide bonds in the active site

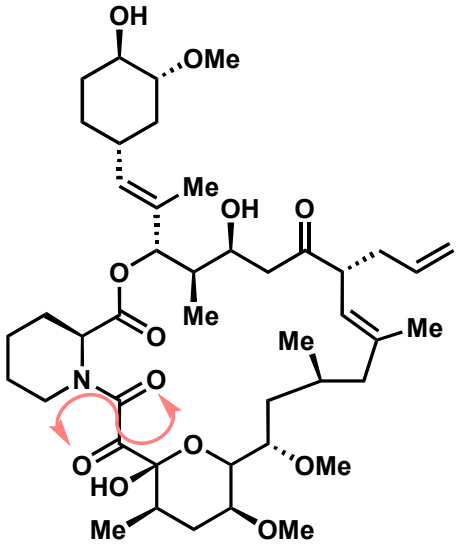
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- the C8/C9 *α*-keto amide carbonyls are forced to be orthogonal due to $A_{1,3}$ strain [normally ~180°] which *is* the ground state conformation
  - compared to a peptide with twisted amide (~15 kcal/mol less stable than ground state)



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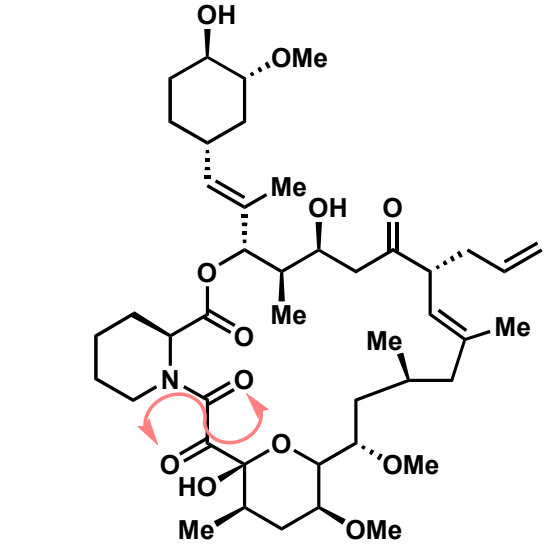
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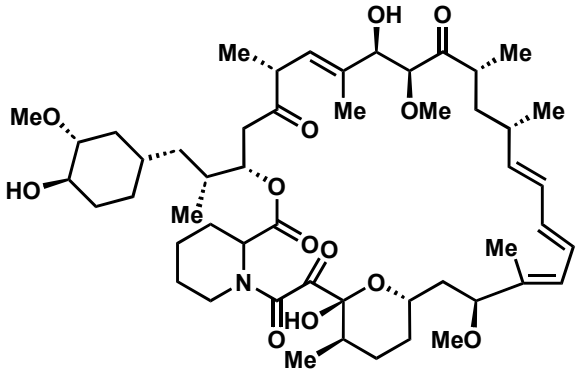
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- this energetic preference thus gives FK506 its potent inihibitory activity for FKBP and by extension, rapamycin too!





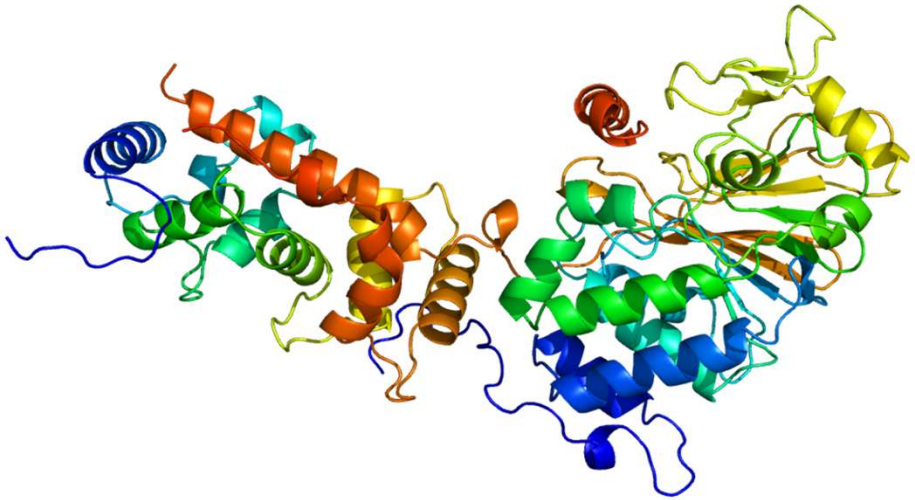
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History of Molecular Glues

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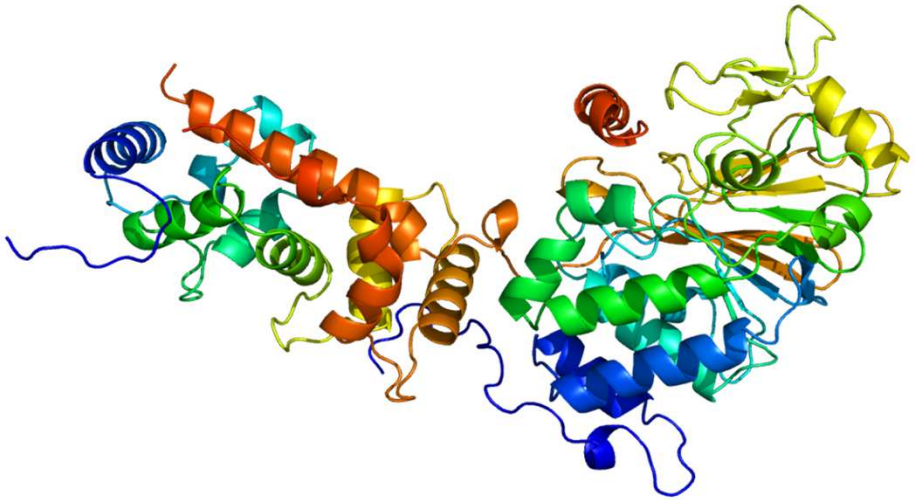


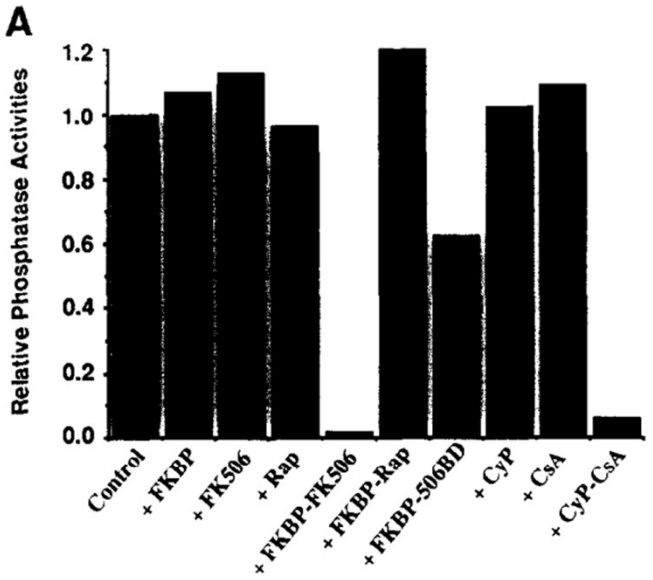
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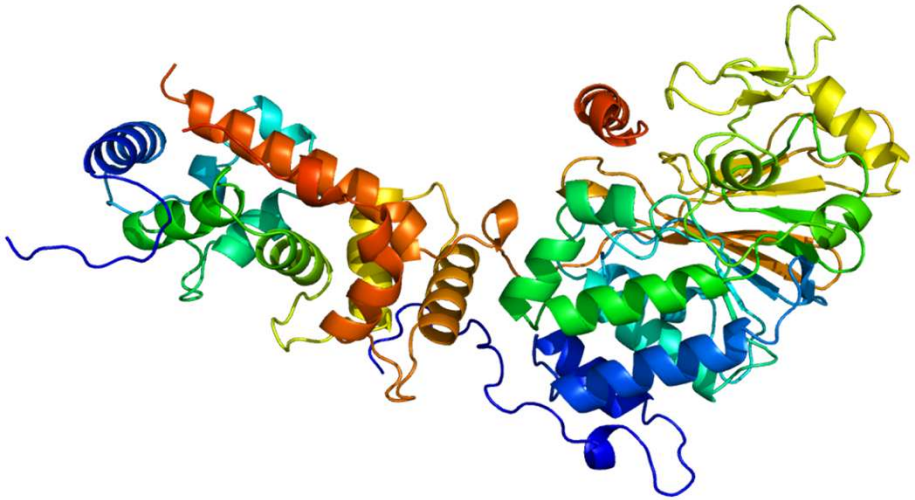


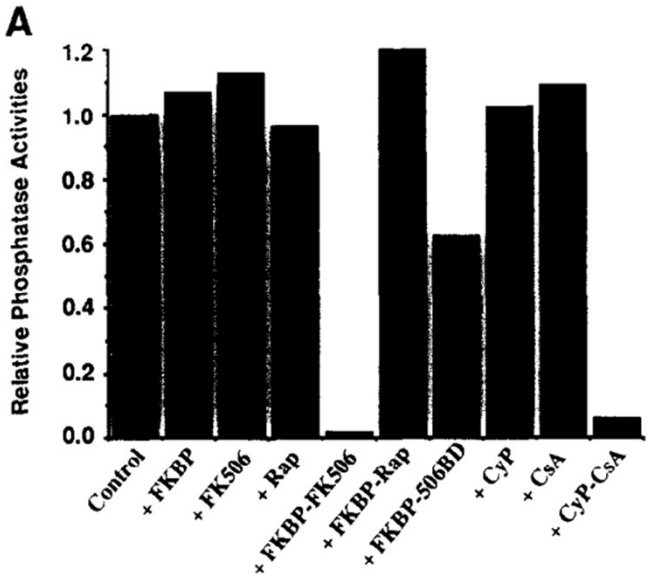
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  - later biological studies revealed calcineurin as a T-cell activator





Cell, **1991**, *66*, 807-815.

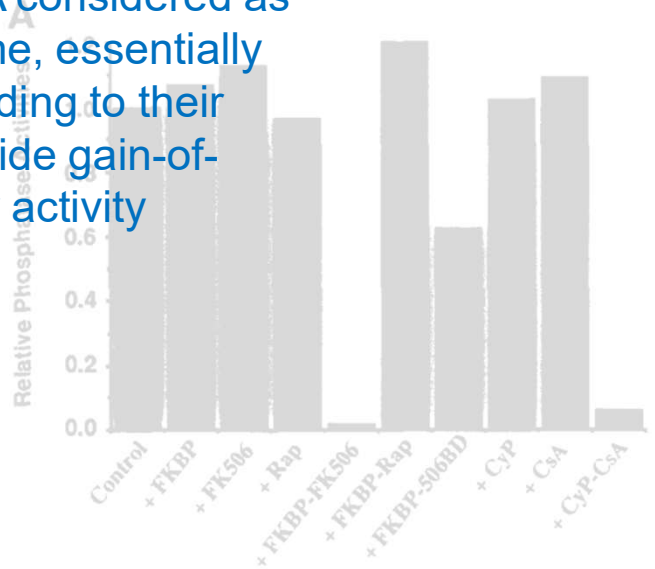
History of Molecular Glues

Investigation into Mechanism of Action

- further probing into the mechanisms of FK506 and cyclosporin A revealed calcineurin as a common target of both molecule!
  - affinity studies revealed FK506-FKBP and CsA-cyclophilin complexes ***both*** potently targeted calcineurin, which is a Ca^{2+}-dependent protein phosphatase
  - later biological studies revealed calcineurin as a T-cell activator – detection of increased cytoplasmic calcium levels leads to calcineurin activation => T-cell production

key conclusion: FK506 and CsA considered as "molecular glues" for the first time, essentially acting as prodrugs – once binding to their respective proteins, they provide gain-of-function to allow inhibitory activity





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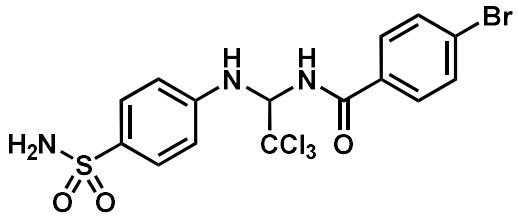
History of Molecular Glues

Chemistry and Biology, **2000**, *7*, 275-286.

History of Molecular Glues

Discovery of “Non-Natural” Molecular Glues

- around 2000, the Schreiber lab made their first discovery of a non-natural small molecule as molecular glue
  - until this point, all the molecules explored in the literature were largely ***natural product***-derived

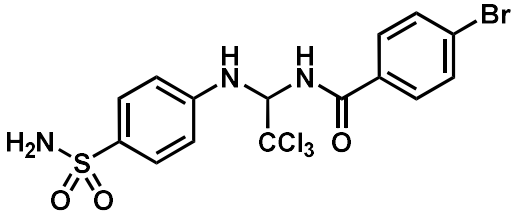


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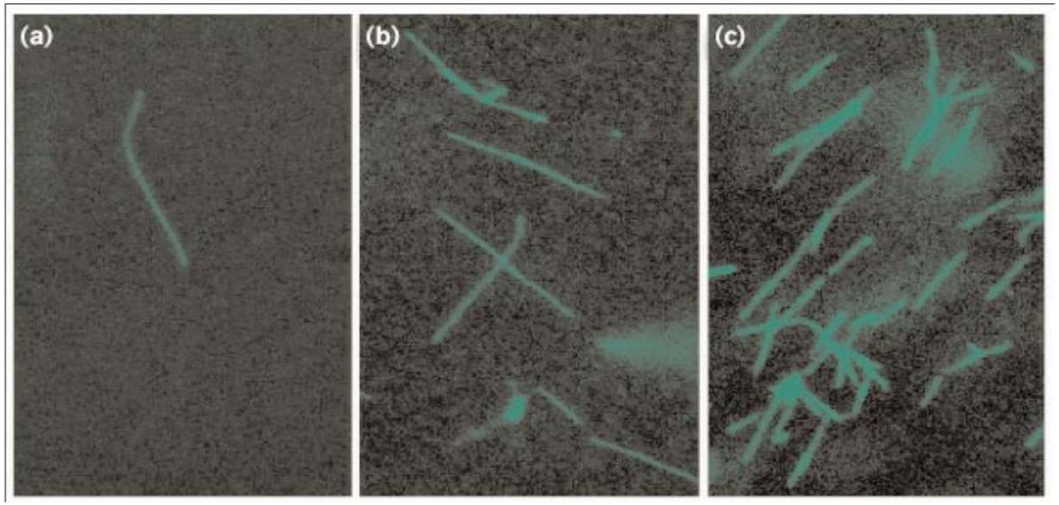
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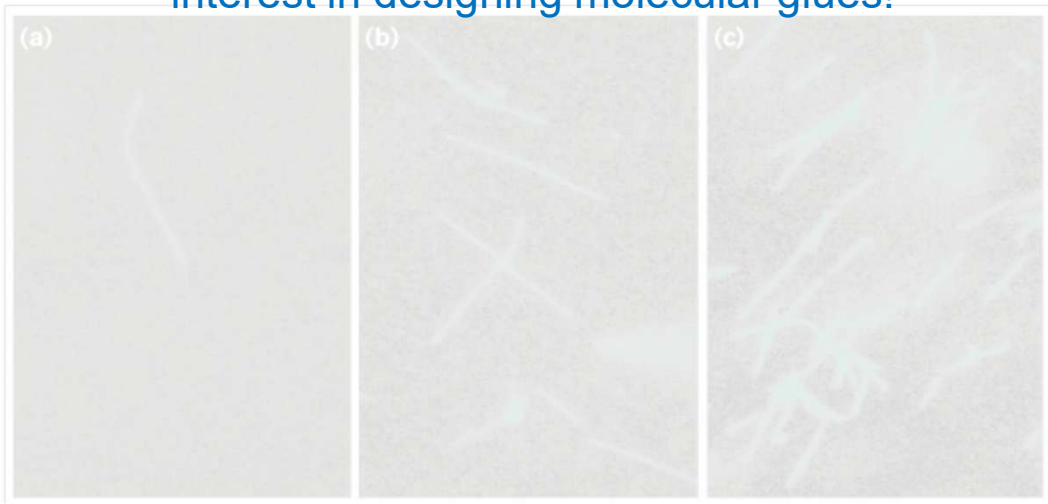
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Discovery of “Non-Natural” Molecular Glues

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key insight: natural products were not the only source of molecular glues – led to a boom of interest in designing molecular glues!

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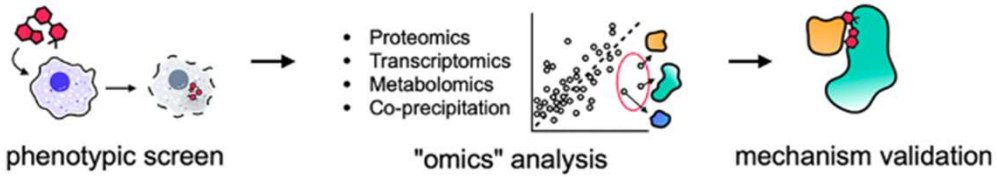


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Contemporary Work on Molecular Glues

Modern discovery of molecular glues can be split into two categories

activity-based methods

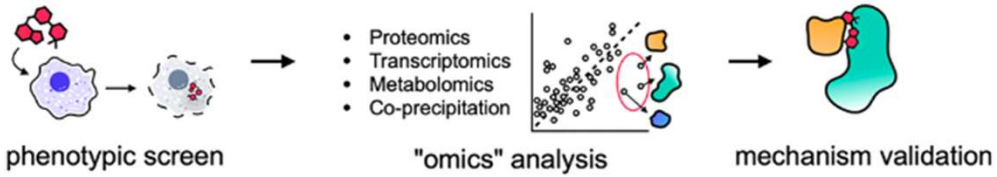


J. Med. Chem, **2023**, *66*, 9278-9296..

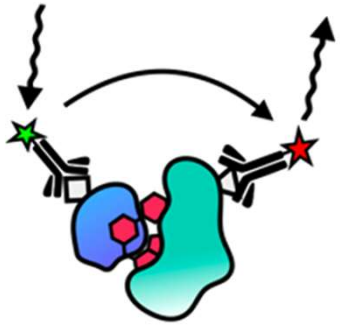
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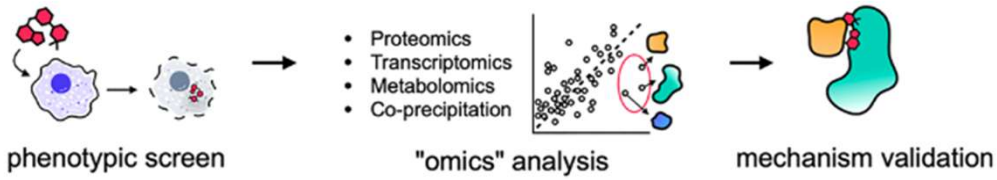


interaction detection methods



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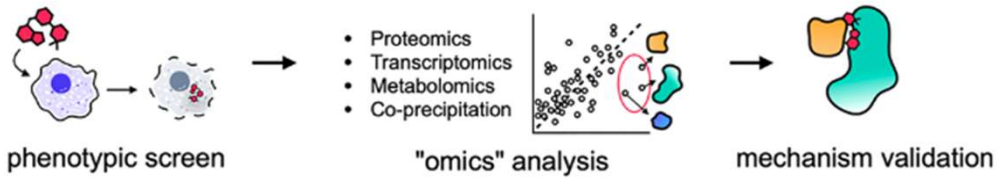
Activity-Based Methods



- ABMs are agnostic to the actual PPI that govern activity, and can enable discovery of novel biological pathways
  - without target-based screening, these methods do require more work to probe and validate the mechanism of action of hits

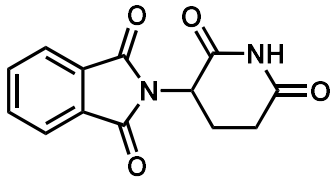
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Activity-Based Methods



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- ABMs the only screening method to lead to clinically approved molecular glues, including ***thalidomide***



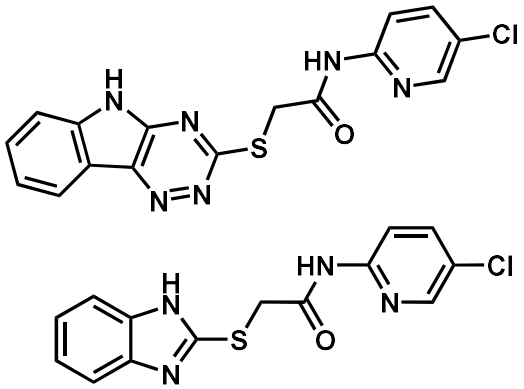
thalidomide

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Activity-Based Methods

Case Studies

- Mayor-Ruiz *et al.* conducted a screen of 2000 small molecules known to be cytotoxic and discovered a couple hits that killed cells via protein degradation

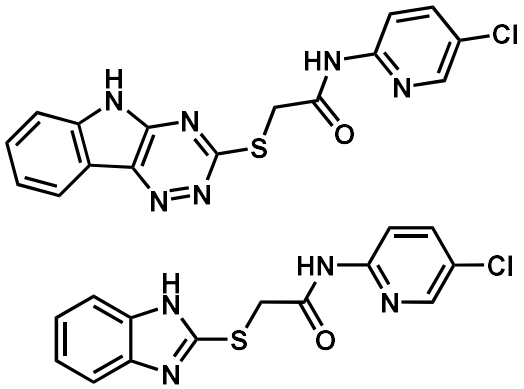


Nat. Chem. Bio, **2020**, *16*, 1199-1207.

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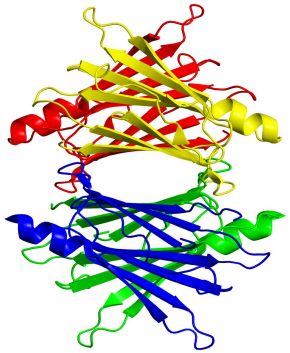
- Further experiments then revealed these molecules selectively degrade cyclin k, a transcription regulator – however, the mechanism of action has yet to be determined…

Nat. Chem. Bio, **2020**, *16*, 1199-1207.

Activity-Based Methods

Case Studies

- Transthyretin (TTR) is a homotetramer that misfolding and aggregation of was linked to amyloidosis

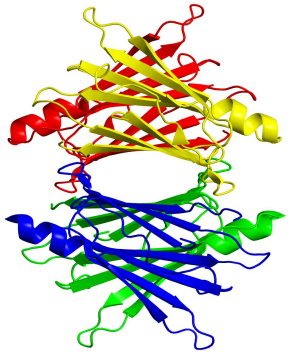


Angew. Chem. Int. Ed., **2003**, *42*, 2758-2761.

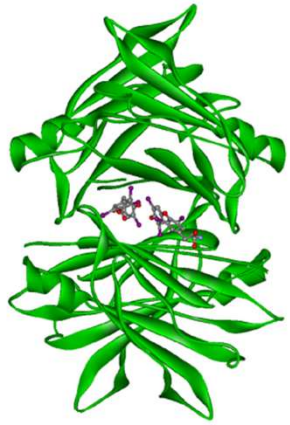
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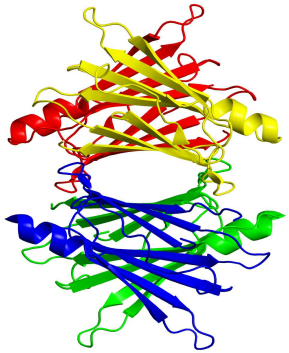


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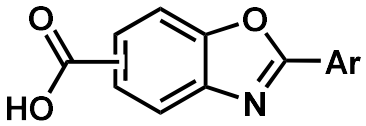
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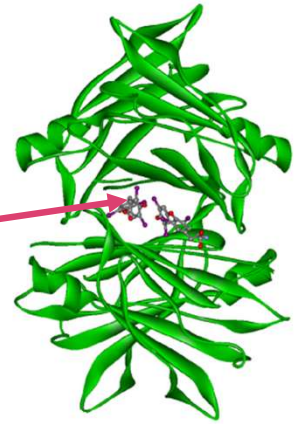
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- classes of small molecules that bound to an unoccupied thyroxine binding site stabilized the tetrameric ground state of TTR, and stabilizing amyloidosis
  - more specifically, it was discovered benzoxazoles with C4-C7 carboxylic acid and C2 aryl substitution could interact!



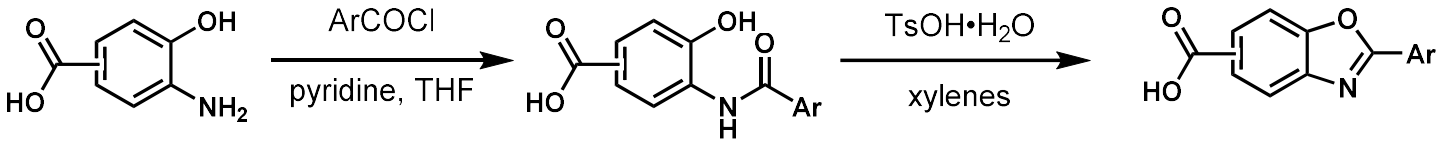


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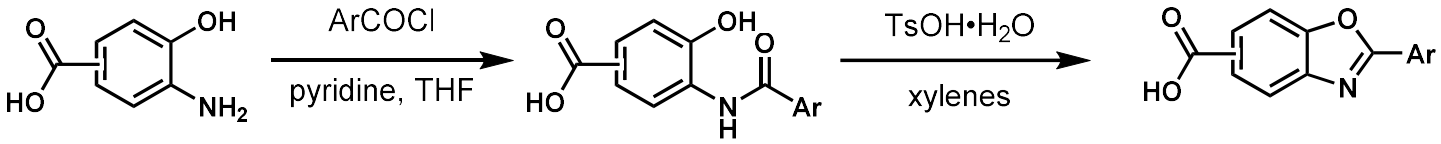


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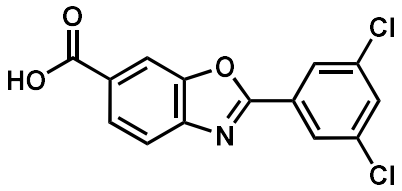
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tafamidis

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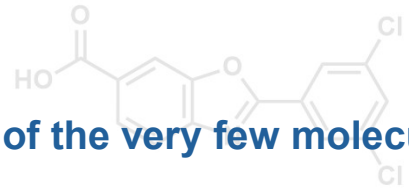
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tafamidis

However, tafamidis remains one of the very few molecular glues discovered by ABMs…

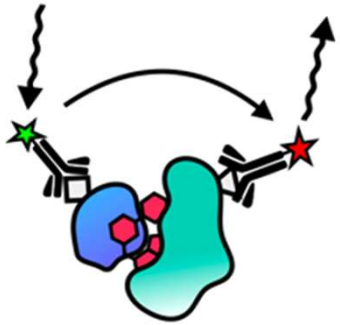
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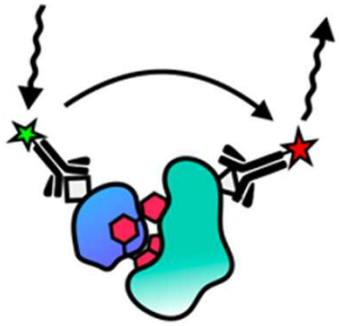
activity-based methods

interaction detection methods



J. Med. Chem, **2023**, *66*, 9278-9296..

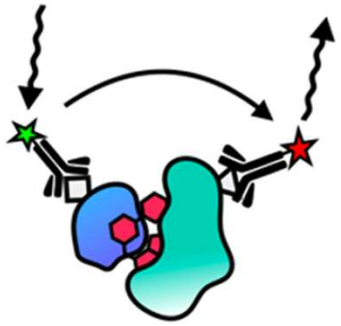
Interaction Detection Methods



- IDMs provide data that explicitly measures the interactions between two target proteins when a small molecule is added

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Interaction Detection Methods



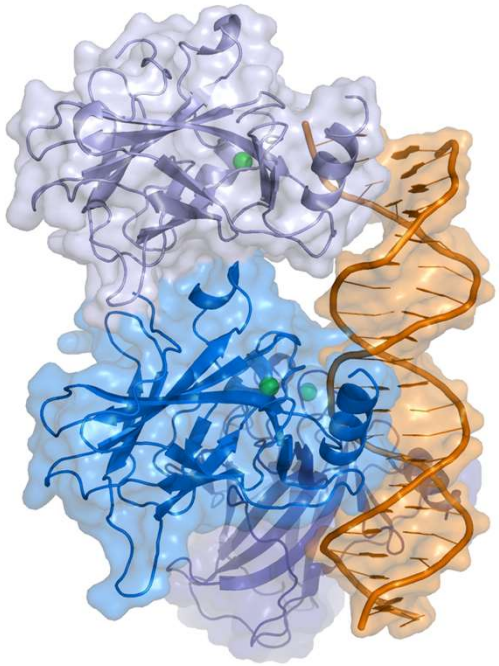
- IDMs provide data that explicitly measures the interactions between two target proteins when a small molecule is added
- some methods include: protein crystallization, mass spectrometry, time-resolved FRET
- more “intentional” experimentation to discover novel molecular glues as the protein interactions themselves are observed [as opposed to trying large libraries to see what hits]

J. Med. Chem, **2023**, *66*, 9278-9296..

Interaction Detection Methods

Case Studies

- PPI between tumor suppressor p53 and its negative regulators MDMX and MDM2 – which overexpression of leads to p53 being turned off and leading to tumor growth

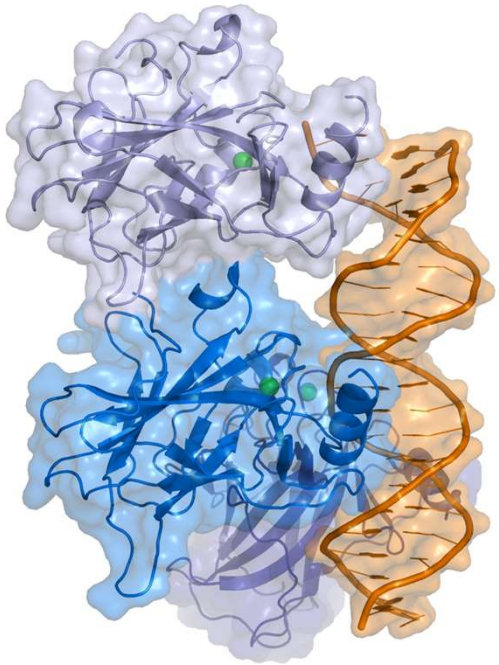


PNAS, **2012**, *109*, 11788-11793.

Interaction Detection Methods

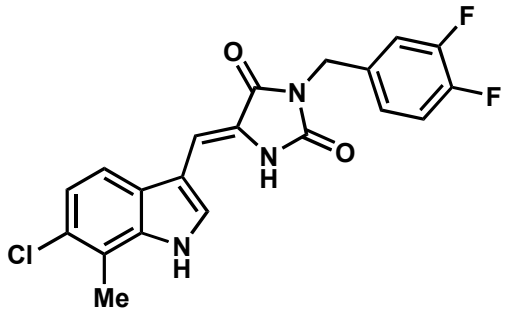
Case Studies

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- MDMX/MDM2 needed dual antagonists as sole antagonists for one protein or the other were not effective

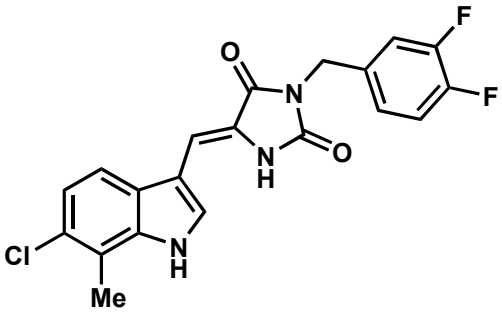
- using a time-resolved FRET assay to probe MDMX/p53 interactions, Roche studied 1 million molecules and found a hit with IC_{50} value of 33 nM to inhibit the MDMX/p53 binding

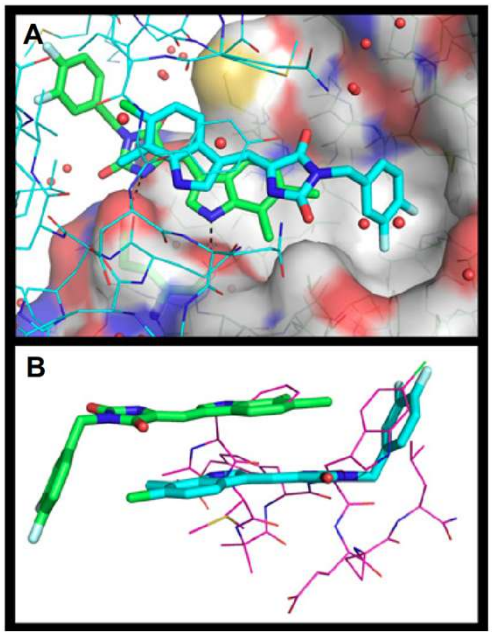


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Interaction Detection Methods

Case Studies



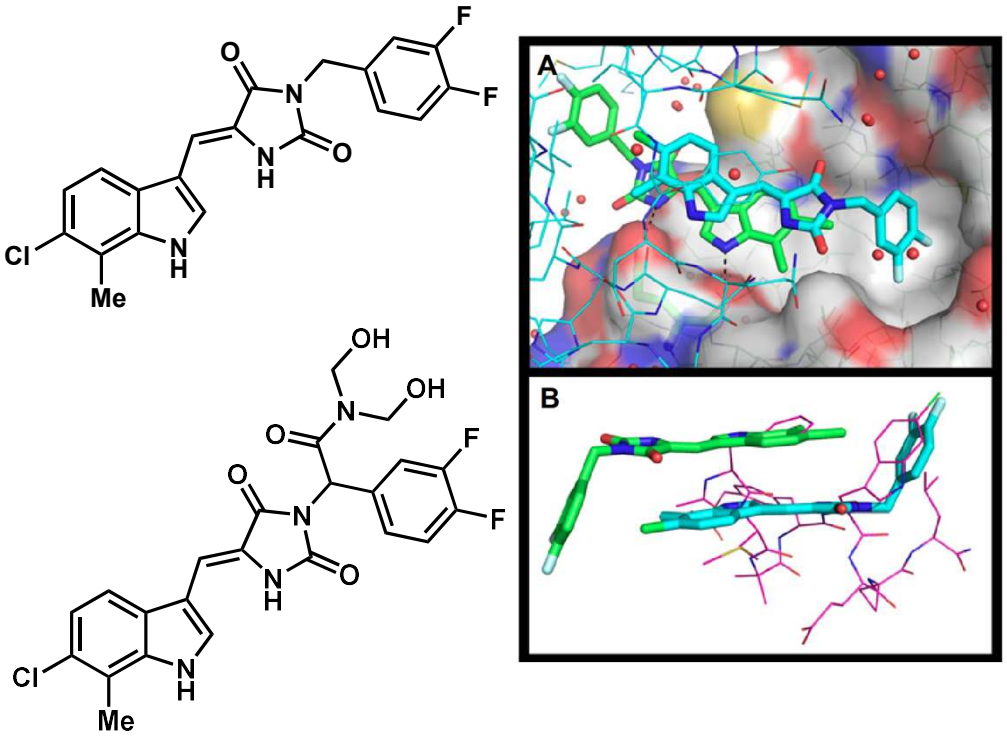


- after identifying the potent MDMX inhibitor, it was determined that the compound induced a dimerization of both MDMX and itself [2:2 ratio]

PNAS, **2012**, *109*, 11788-11793.

Interaction Detection Methods

Case Studies



- after identifying the potent MDMX inhibitor, it was determined that the compound induced a dimerization of both MDMX and itself [2:2 ratio]
- due to poor water solubility, modifications were made to enable further *in vivo* studies and boosted potency to IC_{50} of 17 nM
- the modified molecule showed effective activation of p53 via inhibition of p53/MDMX and MDM2 binding, including in MDMX-overexpressing cells [previously resistant to MDM2 antagonists]

PNAS, **2012**, *109*, 11788-11793.

Interaction Detection Methods

Case Studies

- with improvements in *in silico* technologies, researchers can make educated guesses experimentally via prediction software
  - utilized as an IDM as two proteins can be modeled by “docking” them and then identify small molecules that would be predicted to bind

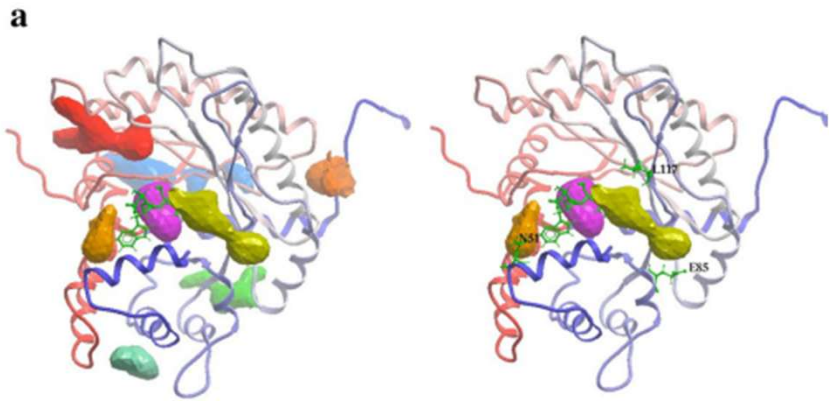
Malaria J., **2015**, *14*, 324.

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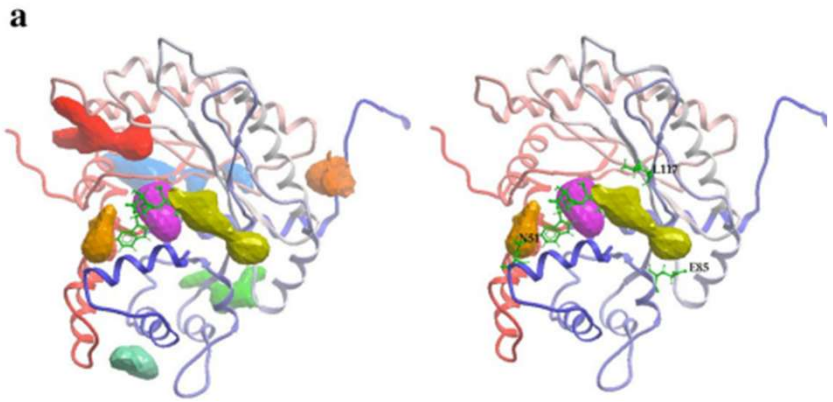
- Nemetski *et al*. locked *Plasmodium falciparum* aldolase with TRAP to prevent malaria infection and docked a library of ~300,000 small molecules to identify hits that showed predicted binding interactions with the protein complex



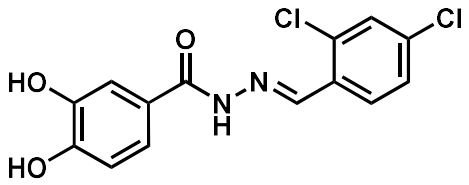
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Interaction Detection Methods

Case Studies



- from the docking, study only 60 compounds were biologically studied, and one compound was found via a crystal structure bind directly to the PPI surface of *P. falciparum* aldolase / TRAP



- by binding to the PPI, the molecule prevents further infection! [type II molecular glue]

Malaria J., **2015**, *14*, 324.

Interaction Detection Methods

Case Studies



Despite such recent advances in IDMs, there have been *no* clinically approved molecular glues discovered via these methods!

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Future Outlook…

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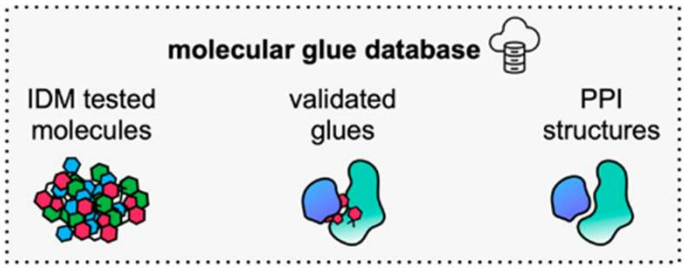




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