Small Molecule Drug Discovery

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FDA Approved Drugs by Modalities

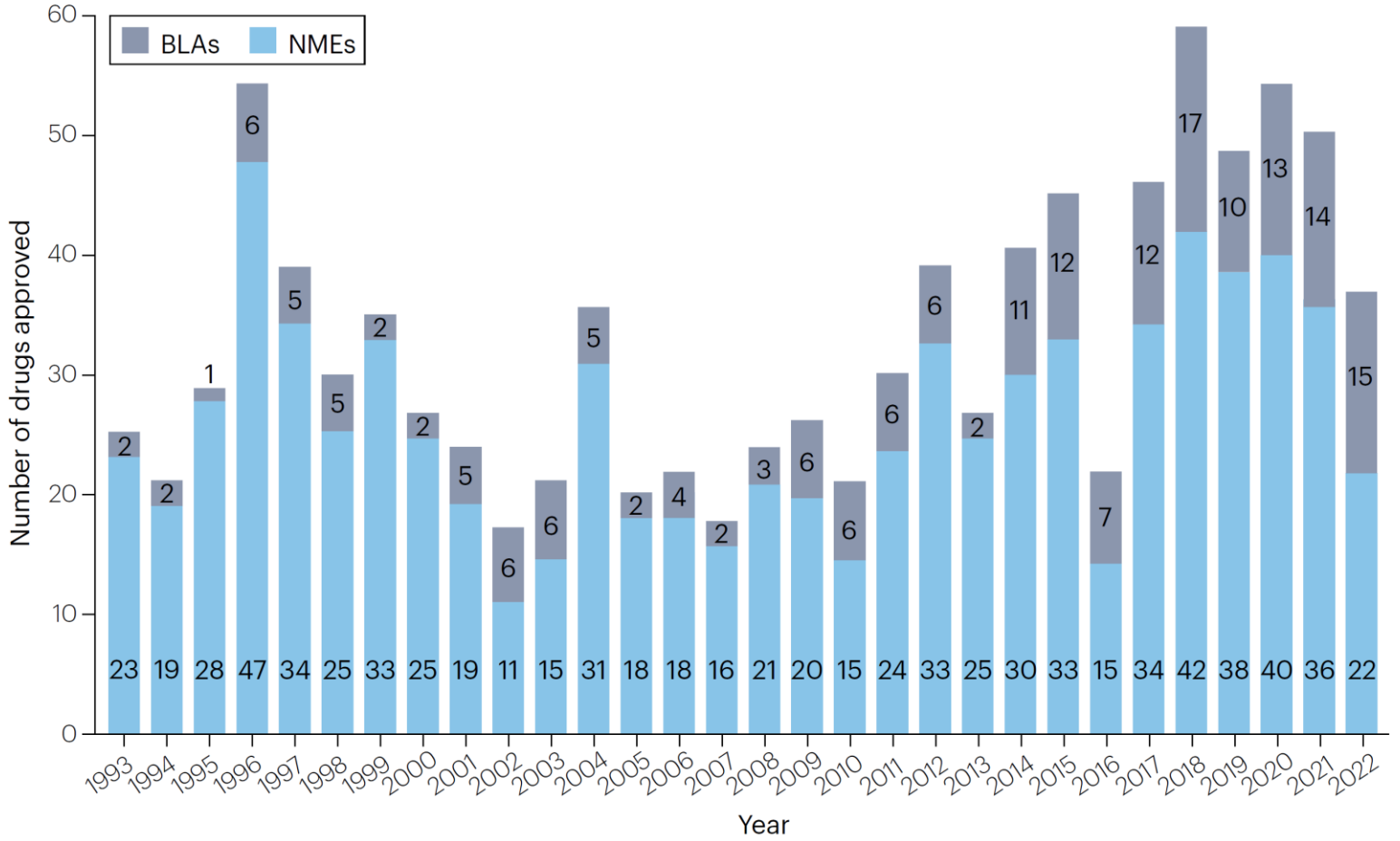
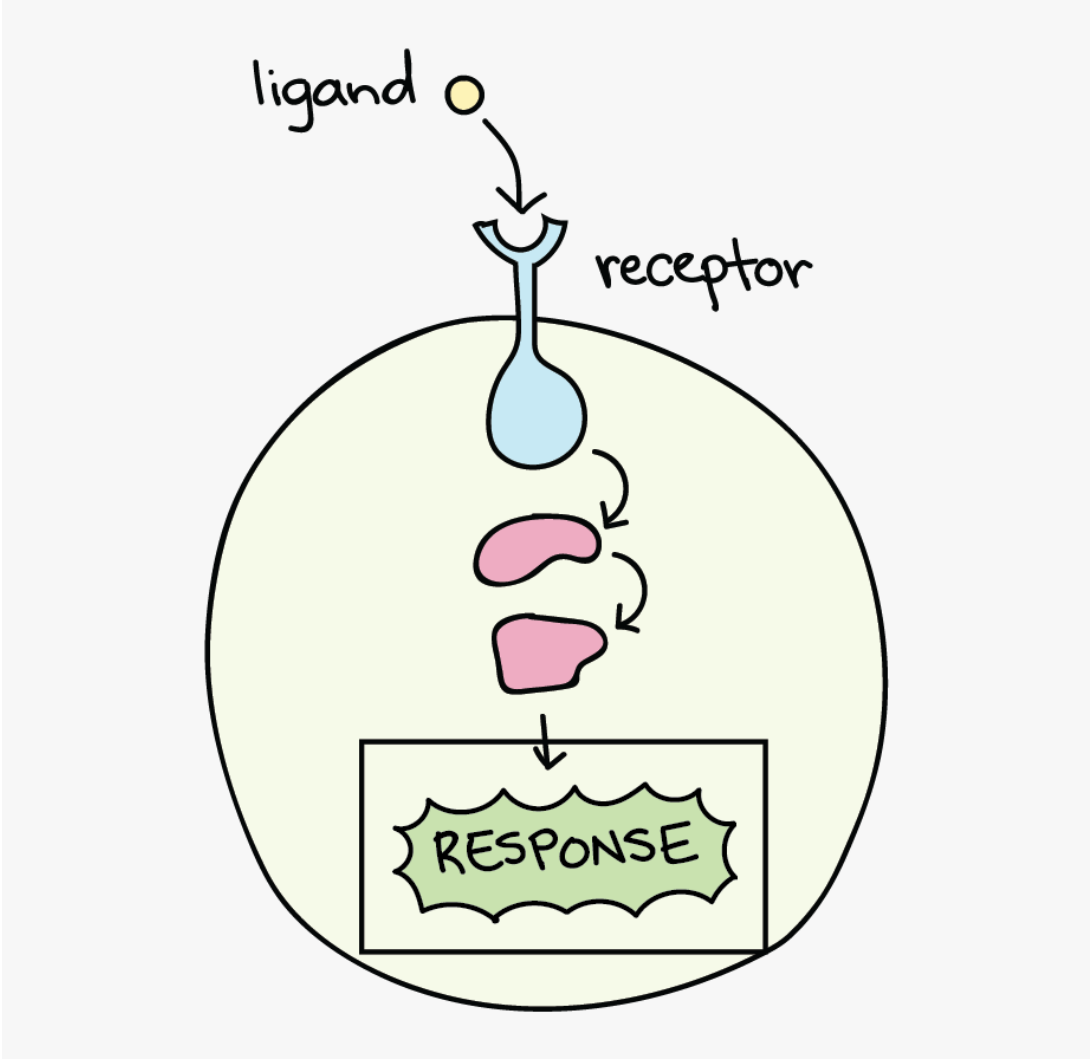


Fig. 1 | Novel FDA approvals since 1993. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's CDER. See Table 1 for new approvals in 2022. Products approved by CBER, including vaccines and gene therapies, are not included in this drug count (Table 2). Source: FDA.

https://doi.org/10.1038/d41573-023-00001-3

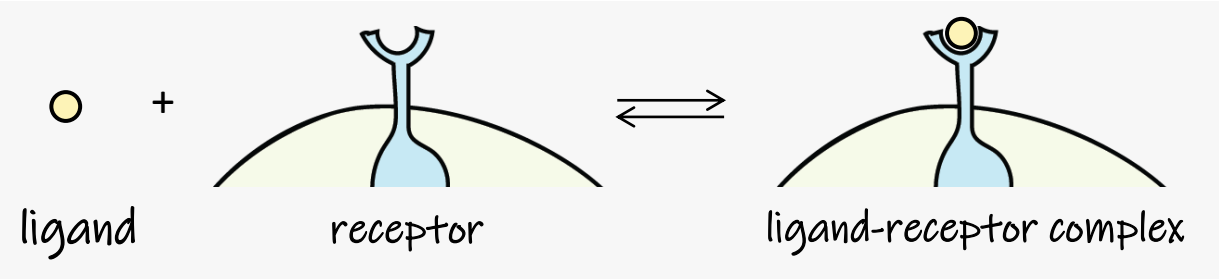
Ligand Receptor Theory

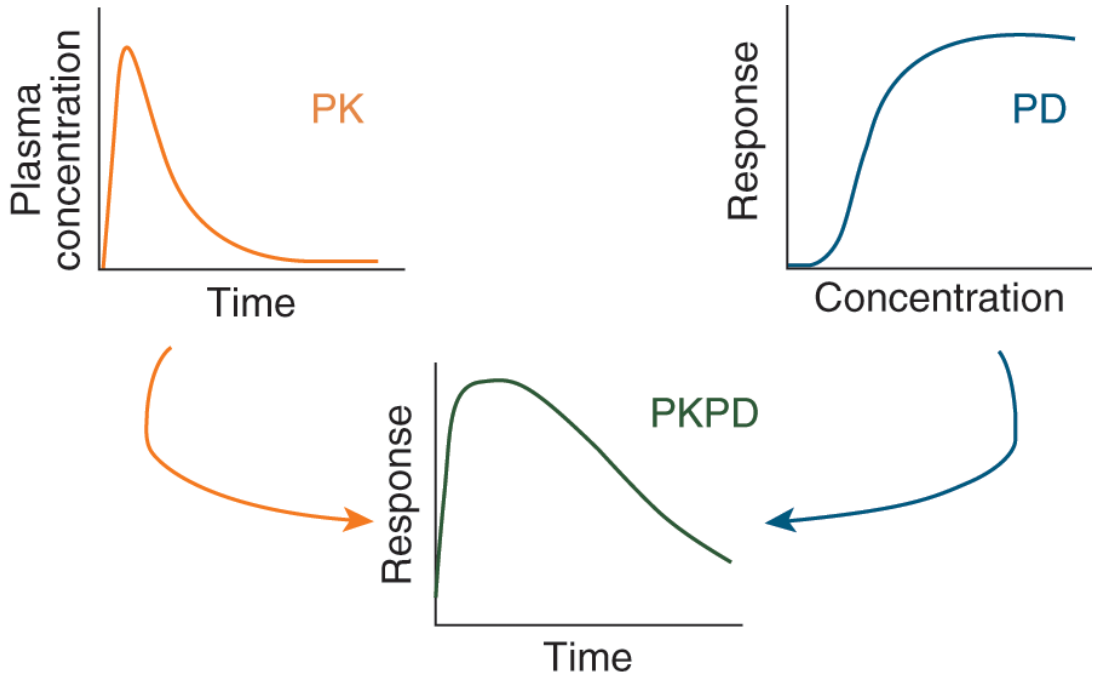


https://www.netclipart.com/isee/xJbiJx_generalized-diagram-of-receptor-ligand-binding-intracellular-response/

Reversible Inhibitors

- Ligands bind to receptors reversibly through non-covalent interactions.
- An equilibrium is established between the free ligand and ligand-receptor complex.
- Activity of the receptor is fully restored on removing ligands through dialysis.
- Occupancy based.
- PD tightly correlates with PK.





Small Molecule Induced Folding of IDPs

Molecular Basis of Small-Molecule Binding to α-Synuclein

Paul Robustelli, Alain Ibanez-de-Opakua, Cecily Campbell-Bezat, Fabrizio Giordanetto, Stefan Becker, Markus Zweckstetter,* Albert C. Pan,* and David E. Shaw*

Cite This: https://doi.org/10.1021/jacs.1c07591

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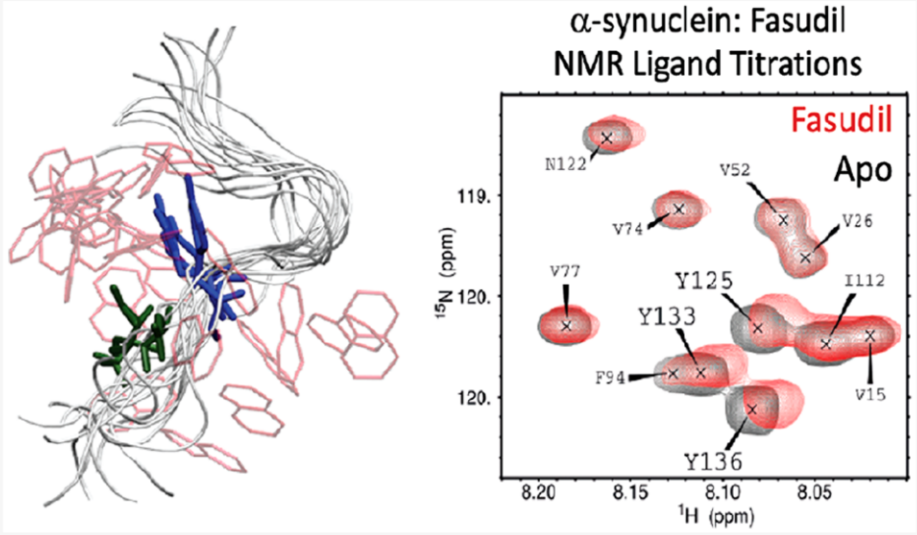
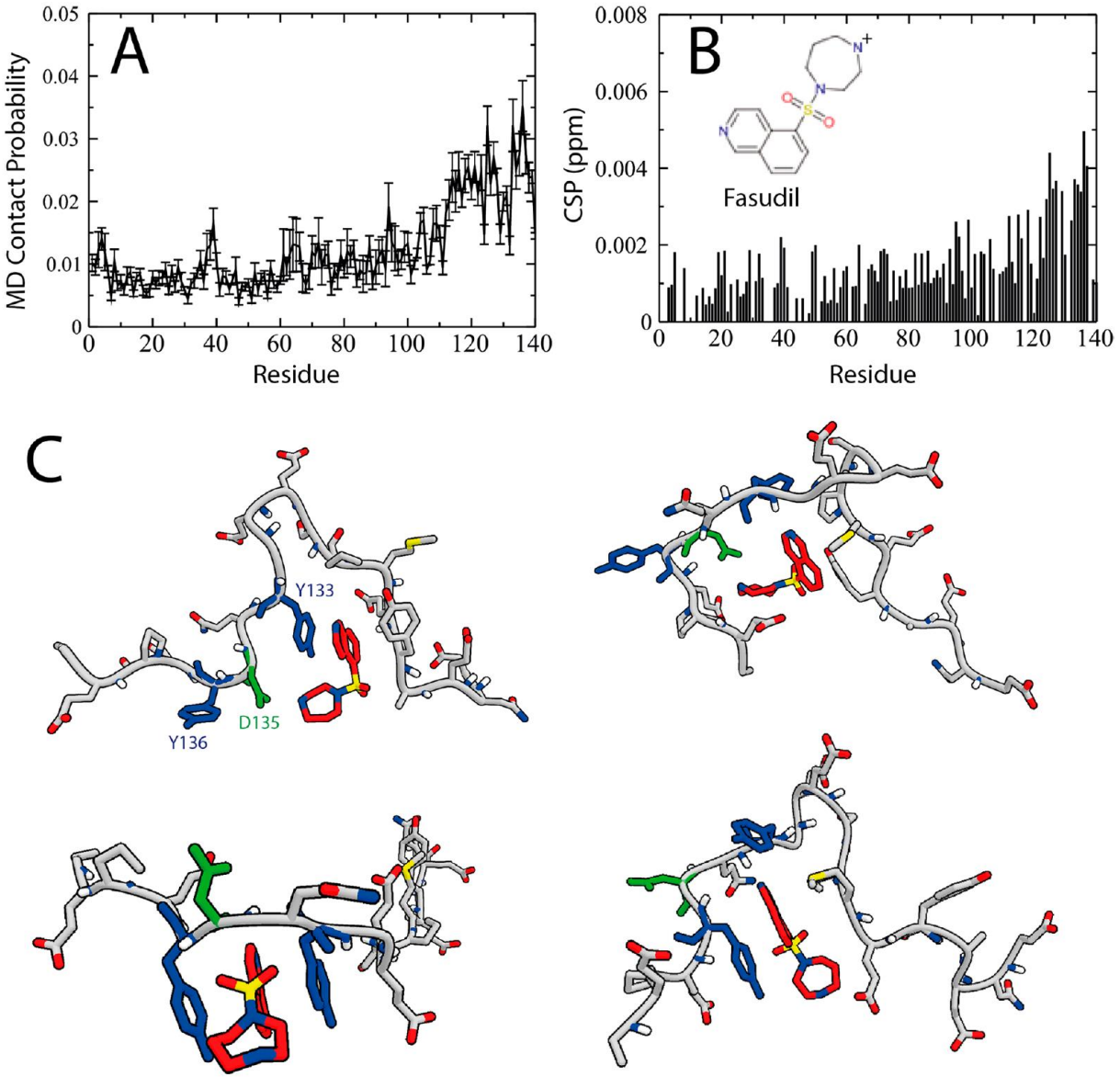
ABSTRACT: Intrinsically disordered proteins (IDPs) are implicated in many human diseases. They have generally not been amenable to conventional structure-based drug design, however, because their intrinsic conformational variability has precluded an atomic-level understanding of their binding to small molecules. Here we present long-time-scale, atomic-level molecular dynamics (MD) simulations of monomeric α-synuclein (an IDP whose aggregation is associated with Parkinson's disease) binding the small-molecule drug fasudil in which the observed protein−ligand interactions were found to be in good agreement with previously reported NMR chemical shift data. In our simulations, fasudil, when bound, favored certain charge−charge and π-stacking interactions near the C terminus of α-synuclein but tended not to form these interactions simultaneously, rather breaking one of these interactions and forming another nearby (a mechanism we term *dynamic shuttling*). Further simulations with small molecules chosen to modify these interactions yielded binding affinities and key structural features of binding consistent with subsequent NMR experiments, suggesting the potential for MD-based strategies to facilitate the rational design of small molecules that bind with disordered proteins.



Fasudil Binding to α-Synuclein



Rationally Optimized Ligands of α-Synuclein

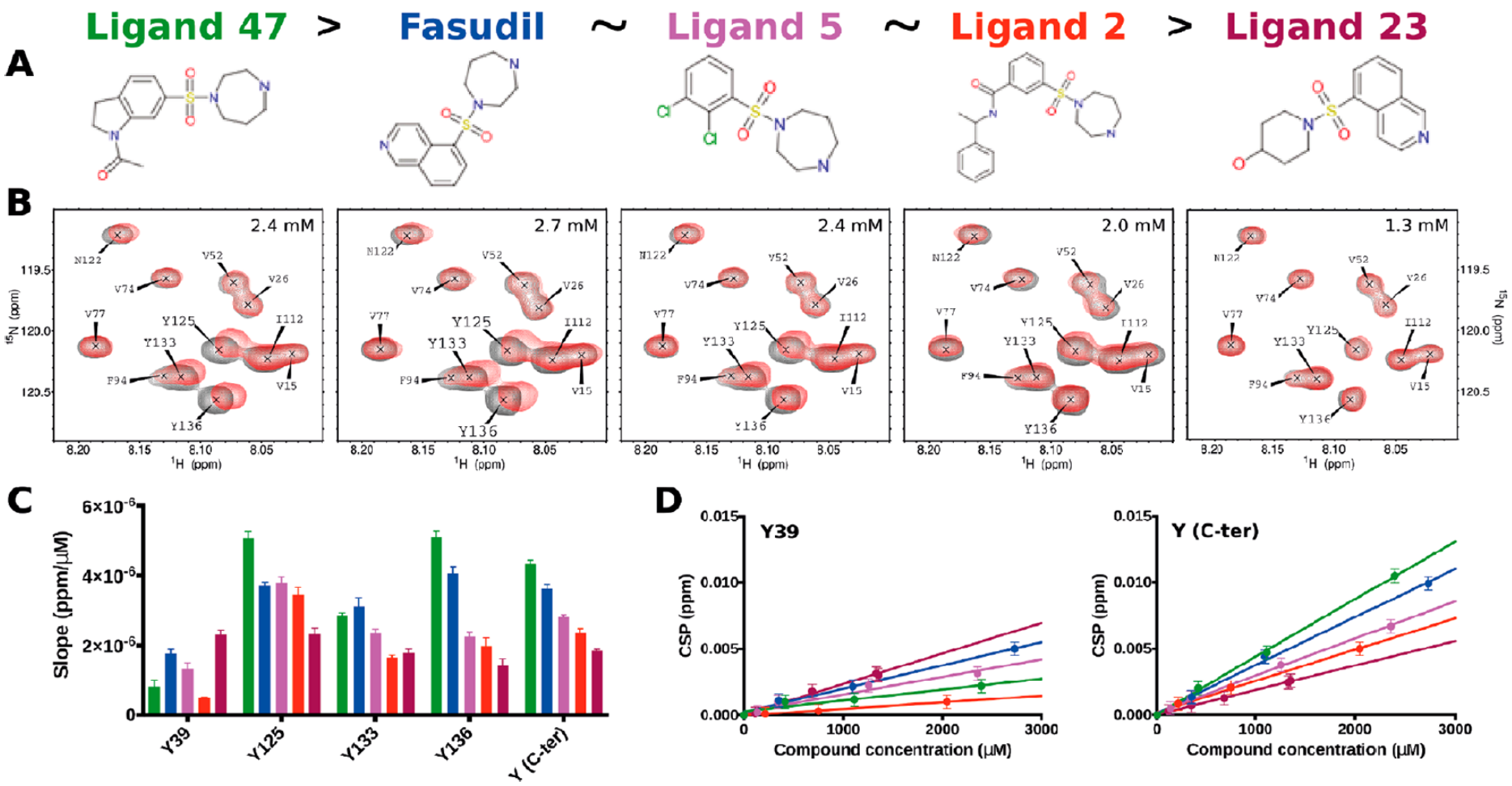
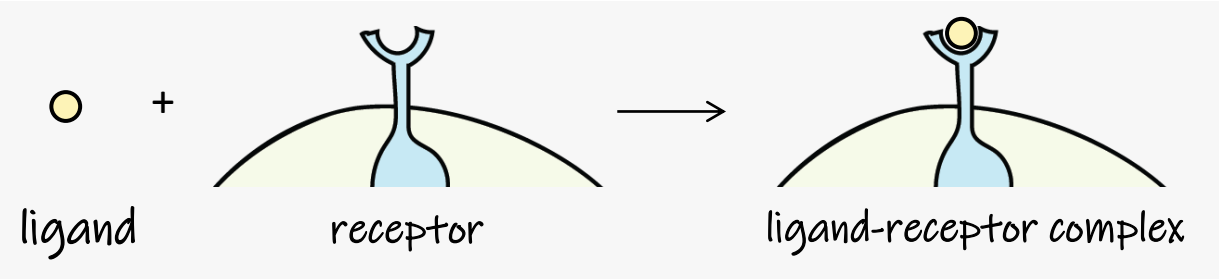
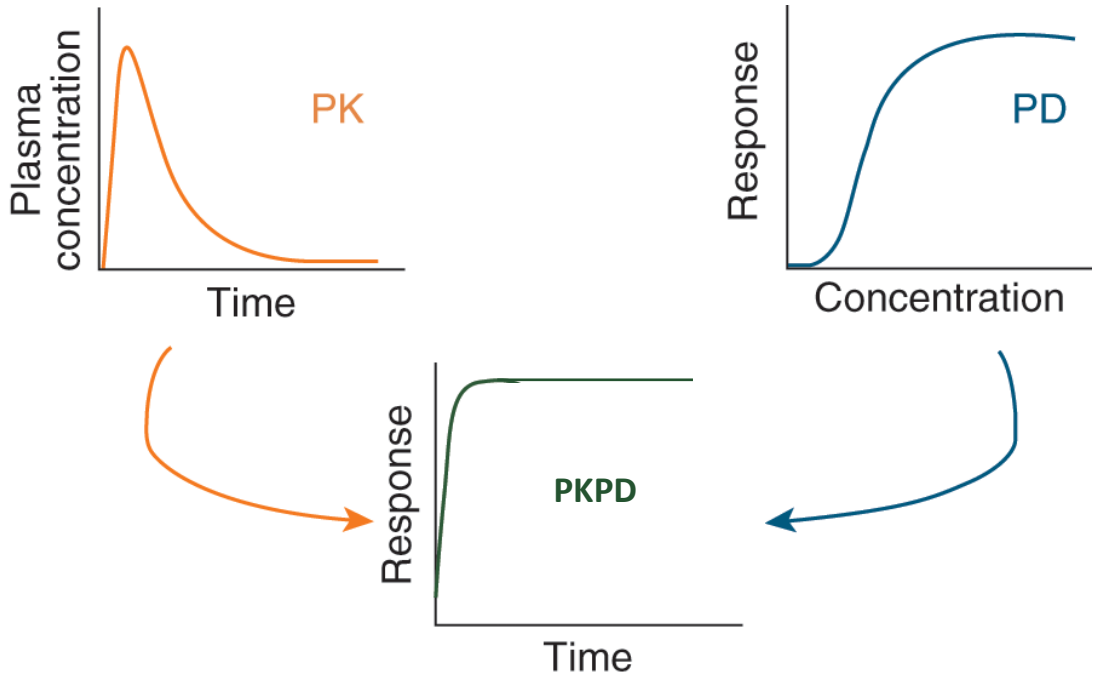


Figure 4. Predicted binding affinities of fasudil analogues with α-synuclein from simulation are in line with subsequently measured chemical shift perturbation titrations from NMR. (A) Structures of fasudil and tested analogues, with ligand 47 having the highest affinity for α-synuclein and ligand 23 the lowest. (B) NMR chemical shift titration curves of the aromatic residues of the C-terminal region of α-synuclein with the five ligands depicted in panel A. (C) Slope of titration curves for each tyrosine residue in α-synuclein, and the average of all tyrosine residues in the C-terminal region of α-synuclein (Y125, Y133, Y136). (D) Titration curves of each compound for Y39, and for the average of all tyrosine residues in the C-terminal region of α-synuclein. Individual titration curves for Y125, Y133, and Y136 are shown in Figure S10. The CSP errors are based on the resolution of the spectra.

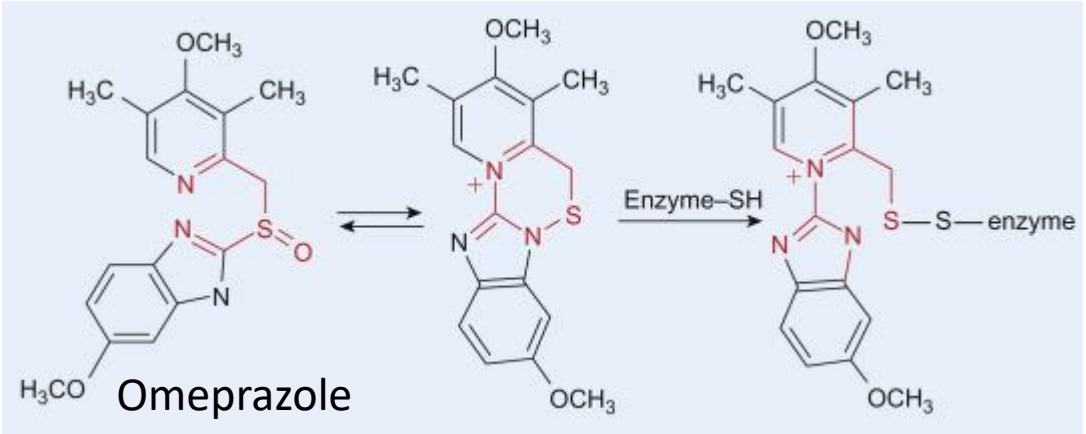
Irreversible/Covalent Inhibitors

- Ligands form covalent bonds with receptors through reacting with amino acid side chains, such as cysteine, lysine, tyrosine, and serine.
- Activity of the receptor is not restored on removing ligands through dialysis.
- Occupancy based.
- PD decouples from PK and is dependent on the resynthesis rate of the target protein.

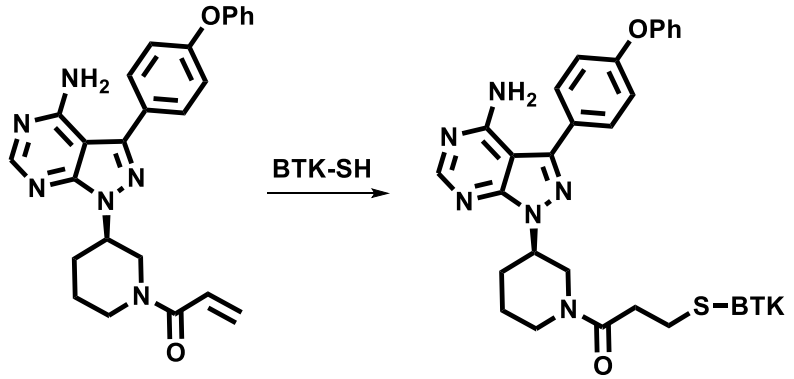




Irreversible Inhibitors

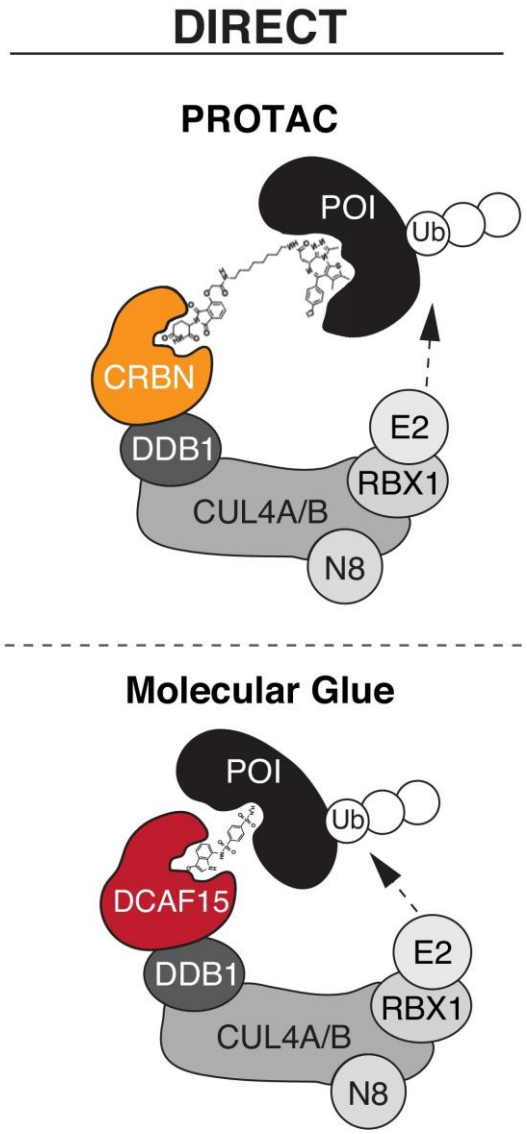


Omeprazole

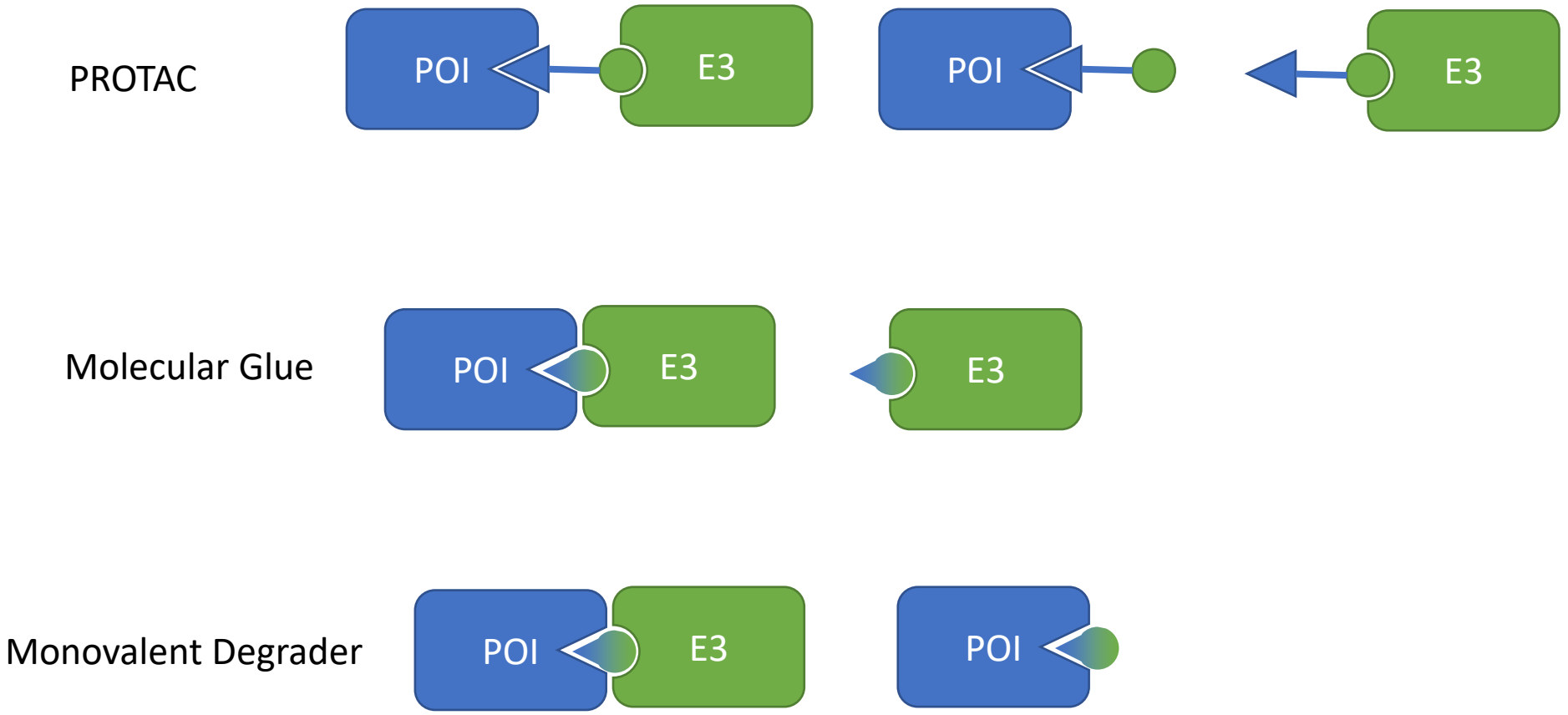


Ibrutinib

Small Molecule Induced Protein Degradation

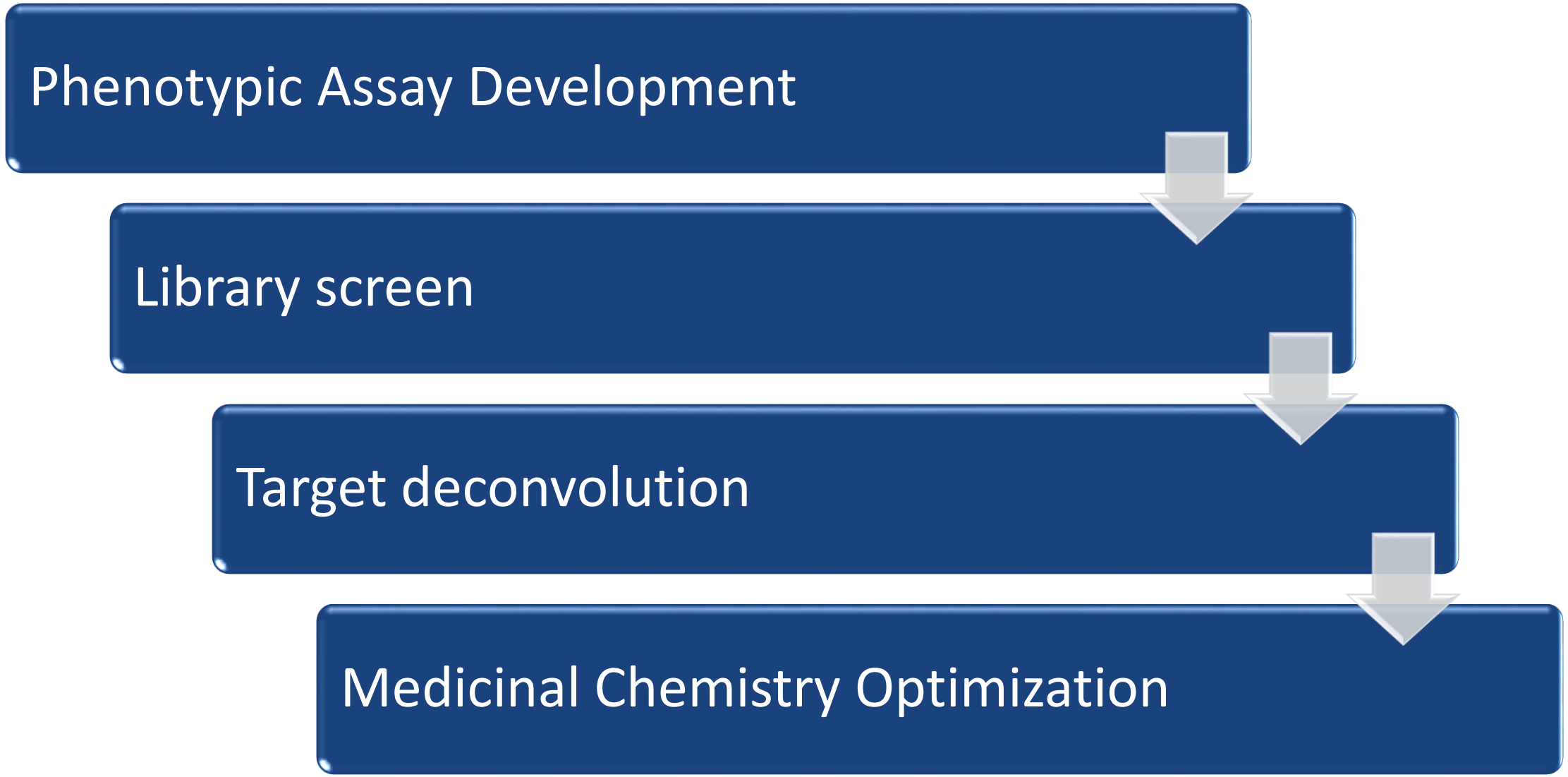


Mayor-Ruiz and Winter, 2019

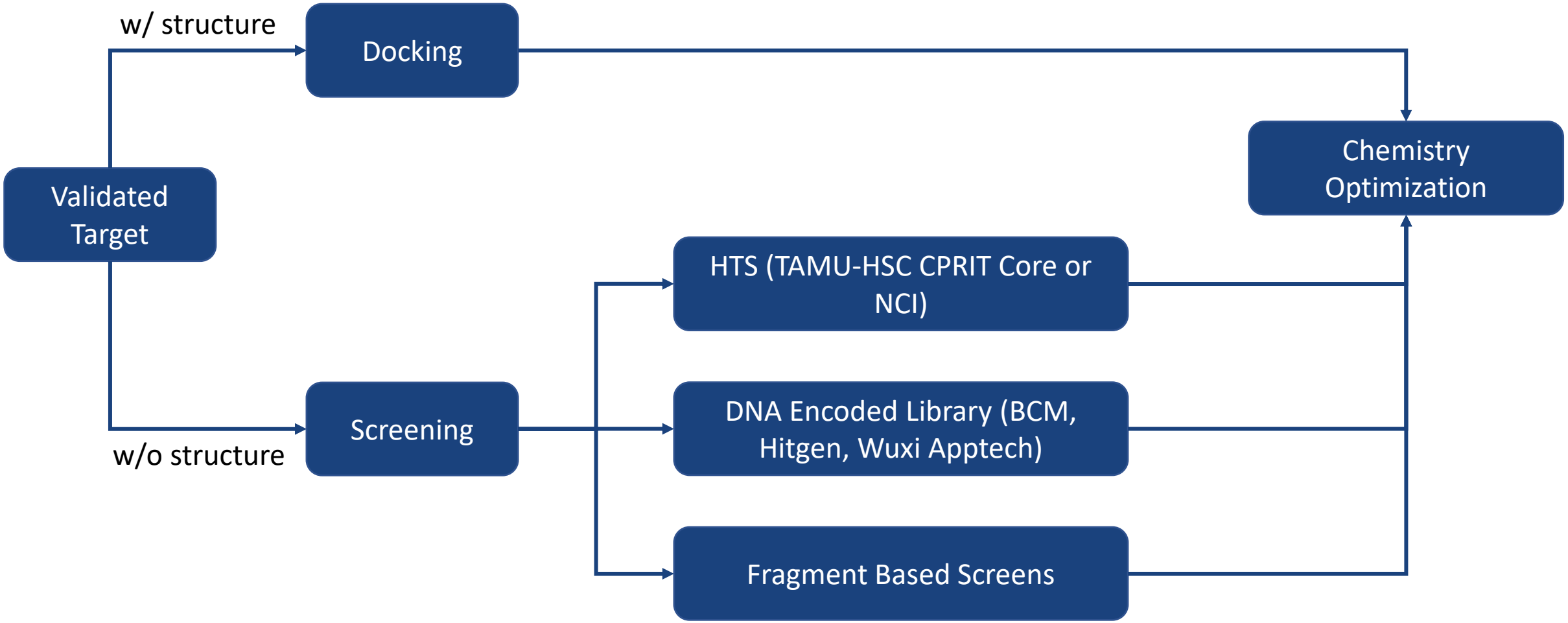


Ning Zheng, https://www.youtube.com/watch?v=f0YYXe18nuA

Phenotypic Screens



Target Based Drug Discovery



Drug Discovery Workflow

5-10 Compounds

Biochemical Assays

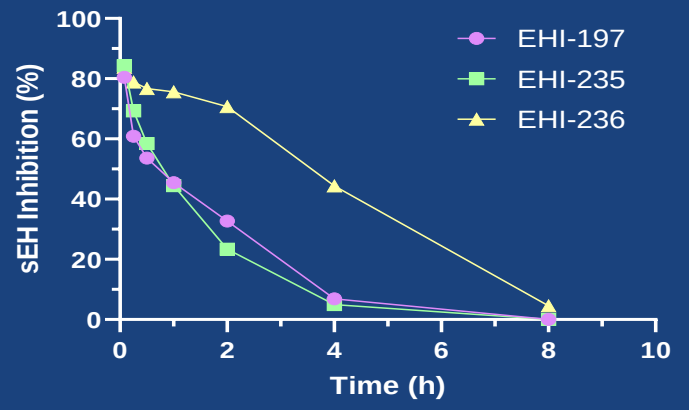
Cellular Assays

Metabolic Stabilities

B/P and PK in mice

Plasma/Tissue Binding

Brain PKPD



SAR Analysis

Compound Design

Computation Modeling

Some Lessons Learned

- Species difference
- Difficult to accurately measure high tissue binding compounds
- Re-evaluating assays and improve assay workflow

Modified Drug Discovery Workflow

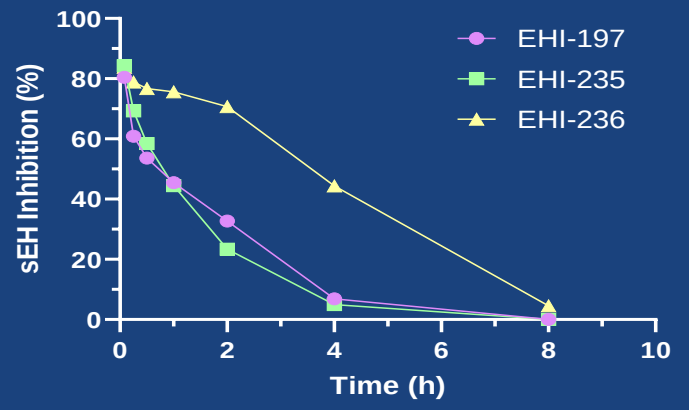
5-10 Compounds

Biochemical Assays

Inhibition and Binding in Brain Lysates

B/P and PK in mice

Brain PKPD



SAR Analysis

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