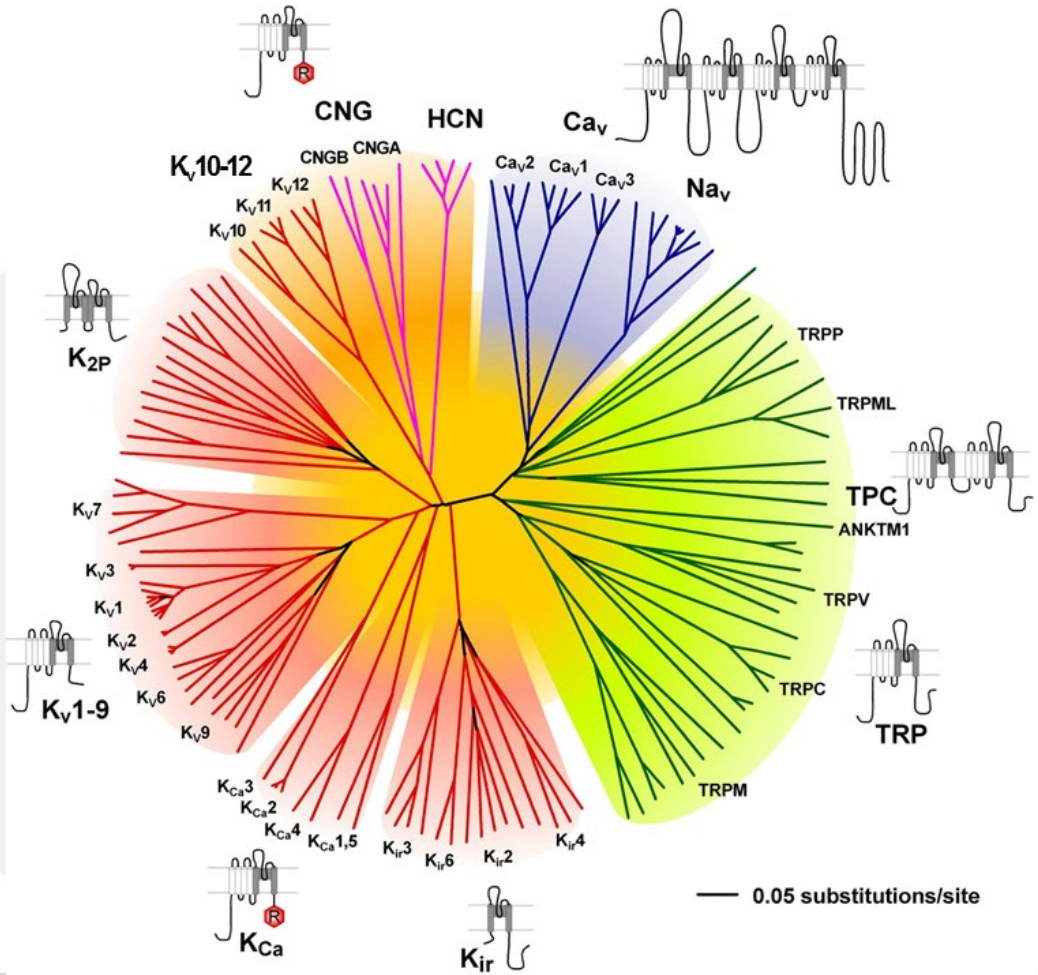
Библиотеки, фокусированные по разным типам ионных каналов

Ion Channels

Focused Library

26,000 Compounds

Selection



We improve the quality of life by creating new medicines

Ion Channels Focused Library Selection

- Ion channels are pore-forming proteins that allow the flow of ions across membranes
- Physiologically the Ion Channels are regulated by
  - voltage, e.g. most Na, K, Ca and some Cl channels are “voltage-gated ion channels”
  - intracellular and/or extracellular mediators, e.g. some K and Cl channels, TRP channels, GABA(A) and P2X receptors are “ligand-gated ion channels”
- Ion channels are well recognized as important therapeutic targets for diseases of
  - the central nervous system (CNS), e.g. sleep disorders, anxiety, epilepsy, pain
  - the peripheral nervous system, e.g. anticonvulsant, analgesic, anti-inflammatory
  - the cardiovascular system, e.g. ischemia, hypoxic conditions, stroke

A unique collection of small molecule compounds selected for Ion Channels protein targets

- ❑ Therapeutically relevant 57 ion channels (119 protein sub-families/units targets in total)
- ❑ Recent literature data from 509 research papers and patents published since 2014
- ❑ The most recent (2019 and 2020) X-Ray and Cryo-EM structures from PDB
- ❑ Comprehensive Ion Channels Platform Library : 26,000 compounds

Virtual Screening Methodology

Swiss-Prot Protein Targets and PDB X-Ray, Cryo-EM Structures Search

Training Sets – ChEMBL 25, PubMed, Current Patent Literature (CAS, Integrity)

Machine Learning Data Curation :

a) KNIME/RDKit, kNN classifier, Distance in BitVector Cosine Space, FCFP12 (10,240 bit) fingerprints

- Bajusz D. et al J. Cheminform. 2015;7:20.

b) Hybrid 2D QSAR/Fingerprint Model - Kernel Chemical Classification/Regression (kcc)

3D Shape Similarity Virtual Screening :

- APF® MolSoft, Lam et al J. Comp Aided. Mol. Design (2017, 2018 & 2019); APF- Totrov Chem Biol Drug Des. (2008)

Structure-Based (Ligands, Fragments, Covalent Fragments) Docking / Virtual Screening :

a) Multiple Receptor Conformation (MRC) 4D Docking; ICM-Pro MolSoft, Bottegoni et al (2009) J. Med. Chem. 52:397

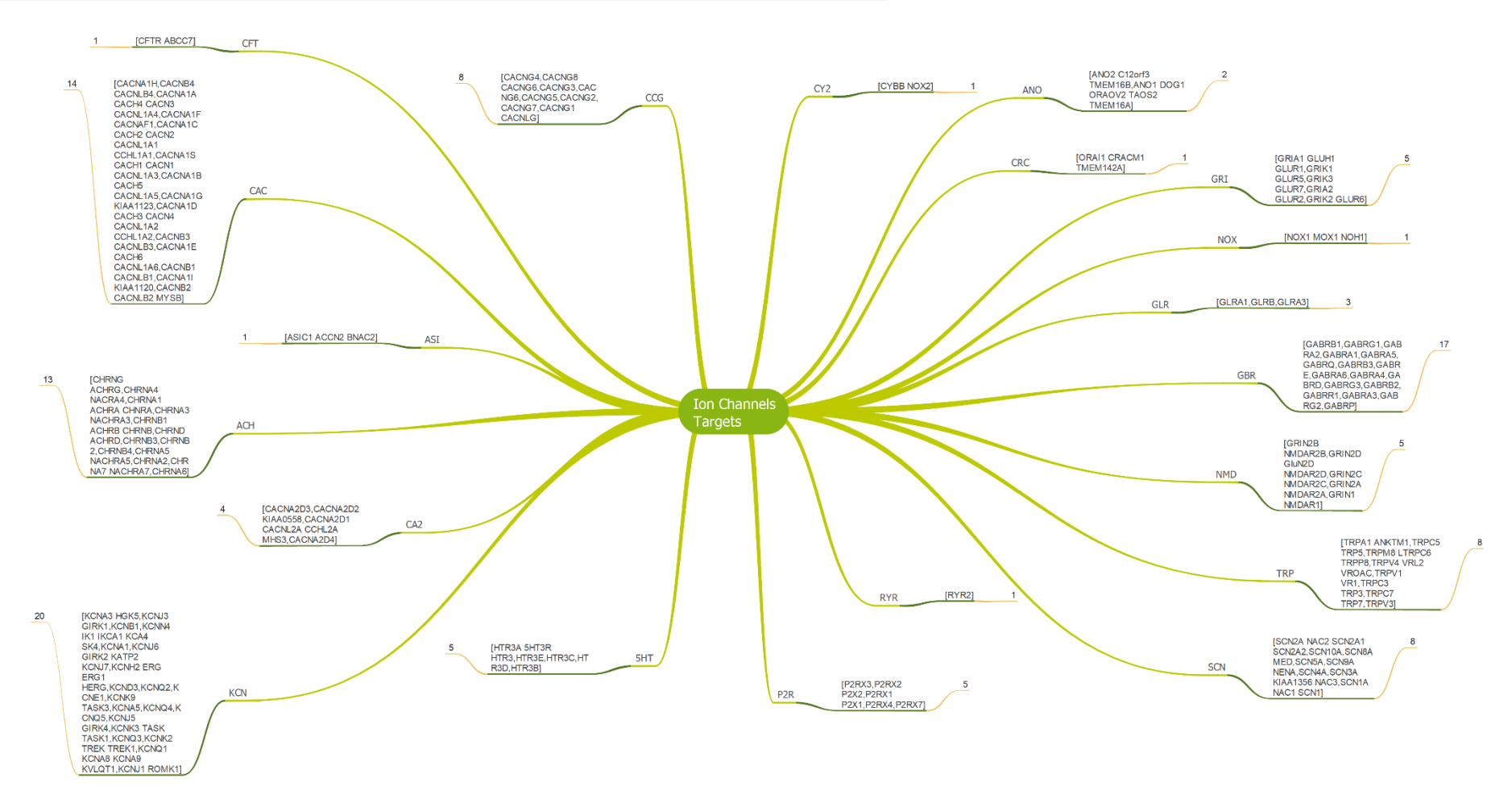
b) Ligand-Biased Ensemble receptor Docking (LigBEnD); ICM-Pro MolSoft, Lam et al J. Comp Aided. Mol. Design (2018)

REOS, MedChem & PAINS Filters - Removal of reactive, toxic, promiscuous, and other undesirable structural motifs

Diversity Picking (Tanimoto) : RDKit implementation of the MaxMin algorithm - Ashton, M. et. al., Quant. Struct.-Act. Relat., 2002, 21, 598-604.

Ion Channels Focused Library Selection

Library Targets by Families



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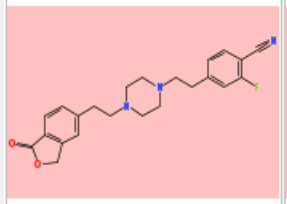
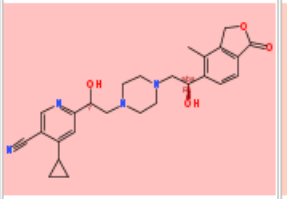
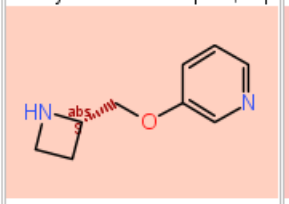
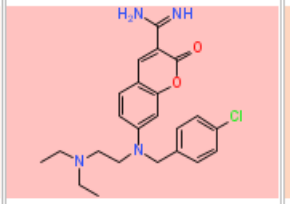
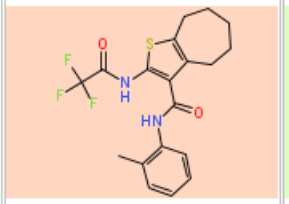
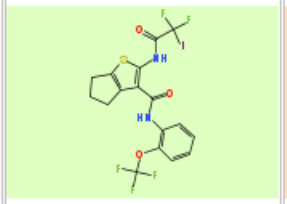
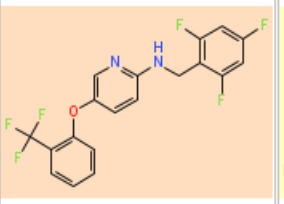
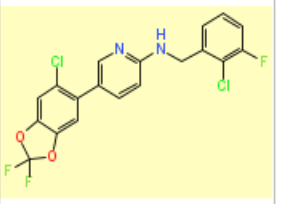
Training Set – ChEMBL 25, Examples

CHEMRAR group of companies

ATP-sensitive inward rectif	ATP-sensitive inward rectif	Acetylcholine receptor; alp	Amiloride-sensitive cation c	Anoctamin-1	Anoctamin-1	ORAI1/STIM1	ORAI1/STIM1
							
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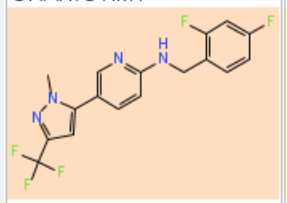
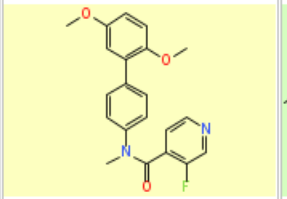
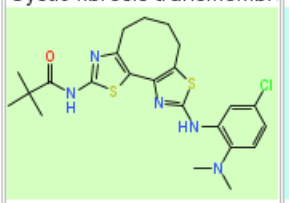
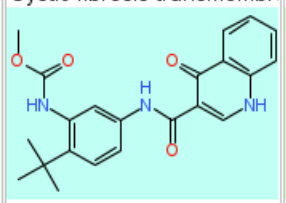
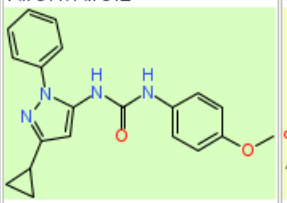
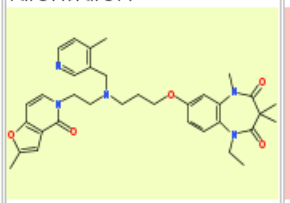
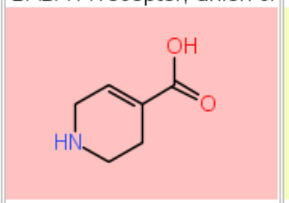
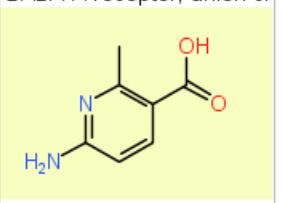
ORAI1/STIM1	Calcium release-activated	Cystic fibrosis transmembr	Cystic fibrosis transmembr	Kir3.1/Kir3.2	Kir3.1/Kir3.4	GABA-A receptor; anion ch	GABA-A receptor; anion ch
							
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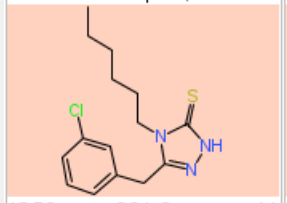
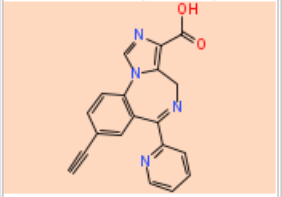
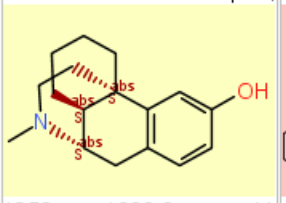
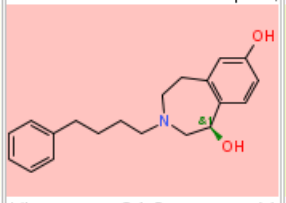
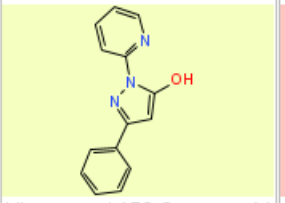
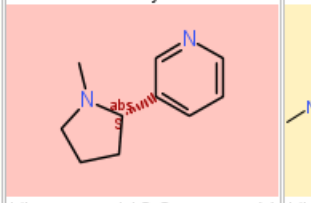
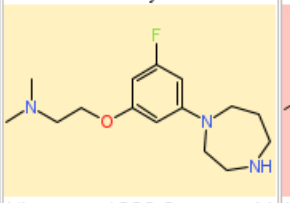
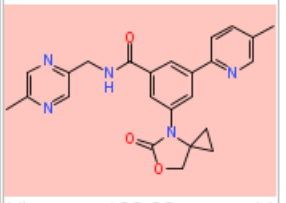
GABA-A receptor; anion ch	GABA-A receptor; alpha-3/	Glutamate NMDA receptor;	Glutamate NMDA receptor;	NADPH oxidase 1	Neuronal acetylcholine rec	Neuronal acetylcholine rec	P2X2/P2X3 heterotrimeric r
							
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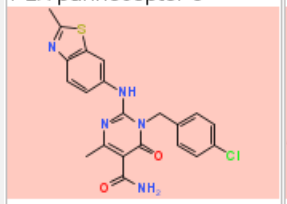
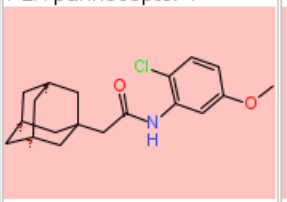
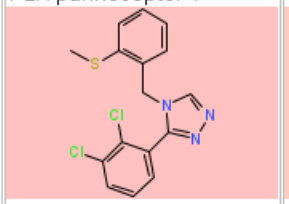
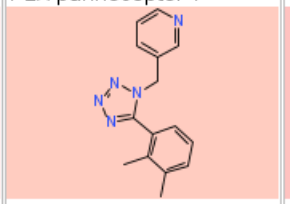
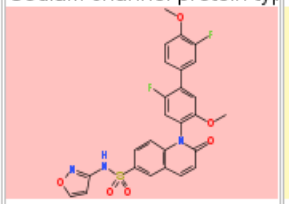
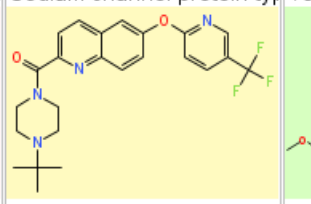
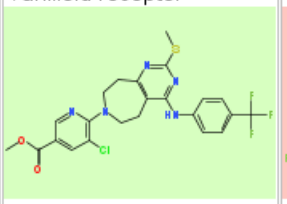
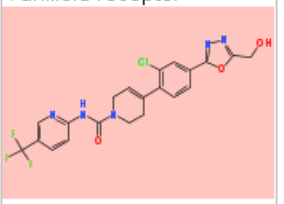
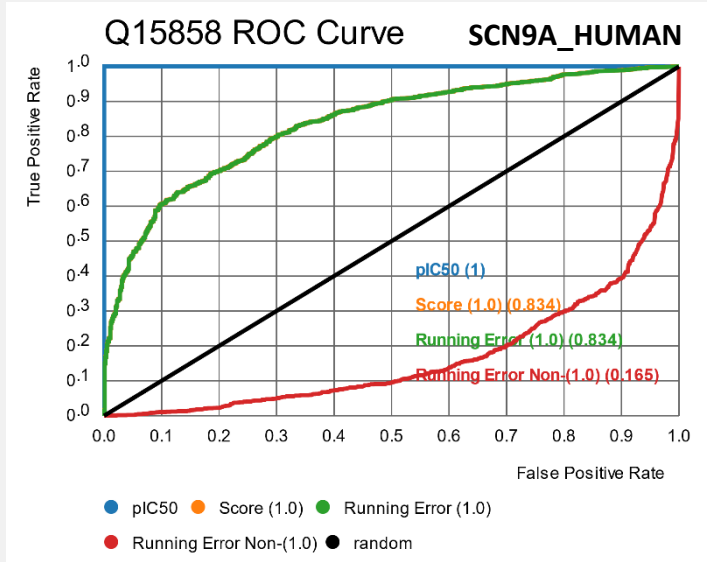
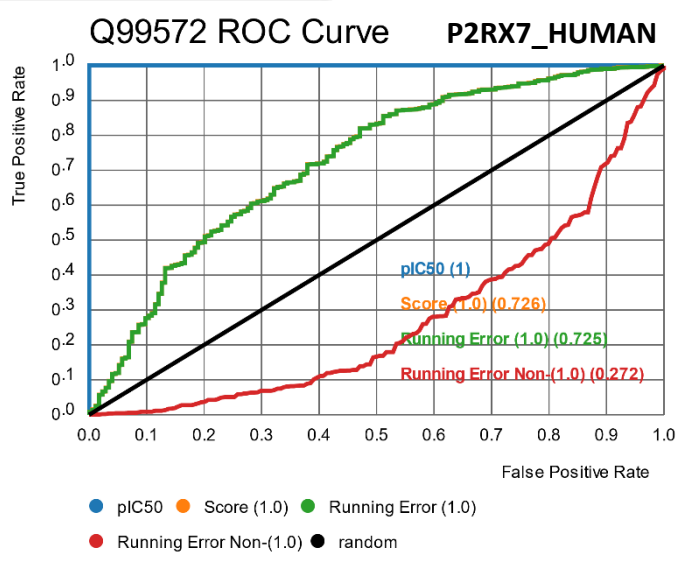
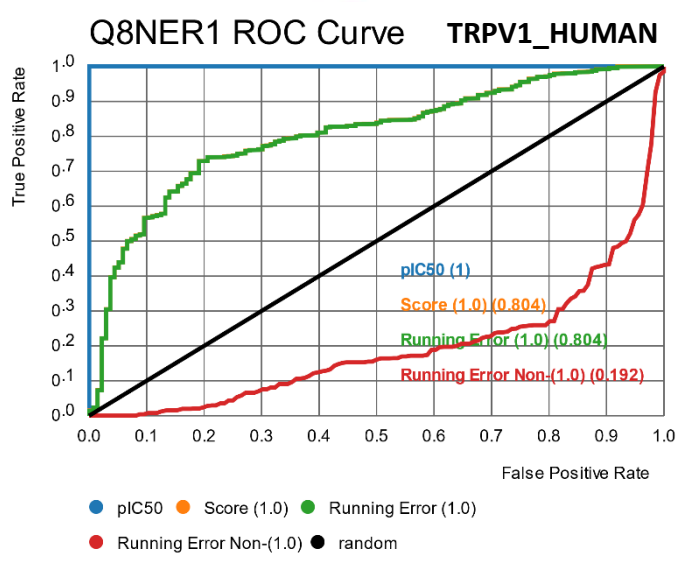
P2X purinoceptor 3	P2X purinoceptor 7	P2X purinoceptor 7	P2X purinoceptor 7	Sodium channel protein typ	Sodium channel protein typ	Vanilloid receptor	Vanilloid receptor
							
IC50 182.0 nM P56373 CHEMBL3886979	IC50 63.1 nM Q99572 CHEMBL131241	IC50 48.98 nM Q99572 CHEMBL245561	IC50 251.19 nM Q99572 CHEMBL3108814	IC50 41.0 nM Q15858 CHEMBL3900290	IC50 1150.0 nM Q15858 CHEMBL3897701	IC50 2030.0 nM Q8NER1 CHEMBL3956727	IC50 100.0 nM Q8NER1 CHEMBL3956326

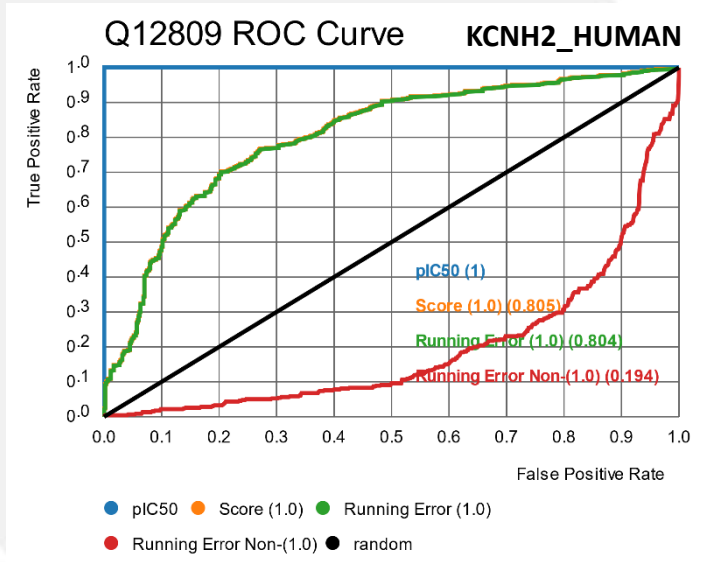
Machine Learning Models, Examples

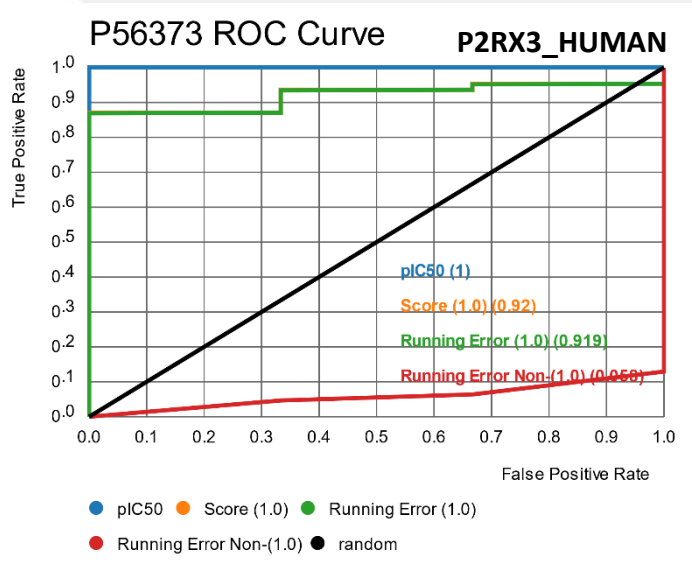
- Built for targets with validated QSAR data with over 300 compounds, 22 ML models in total

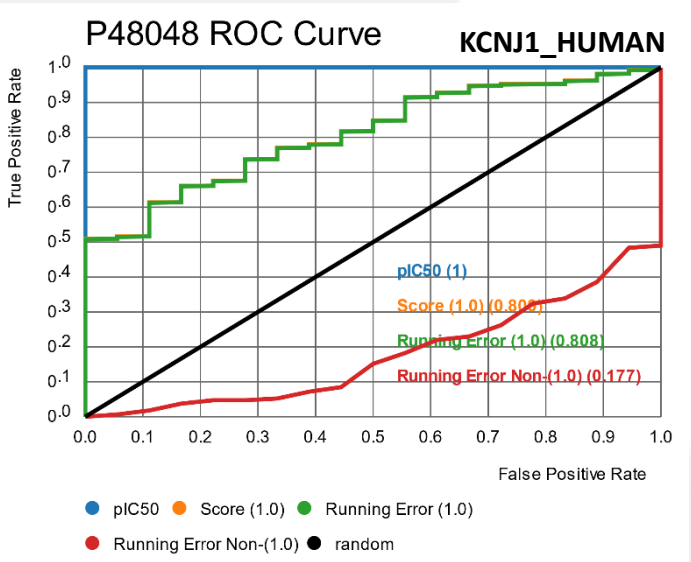






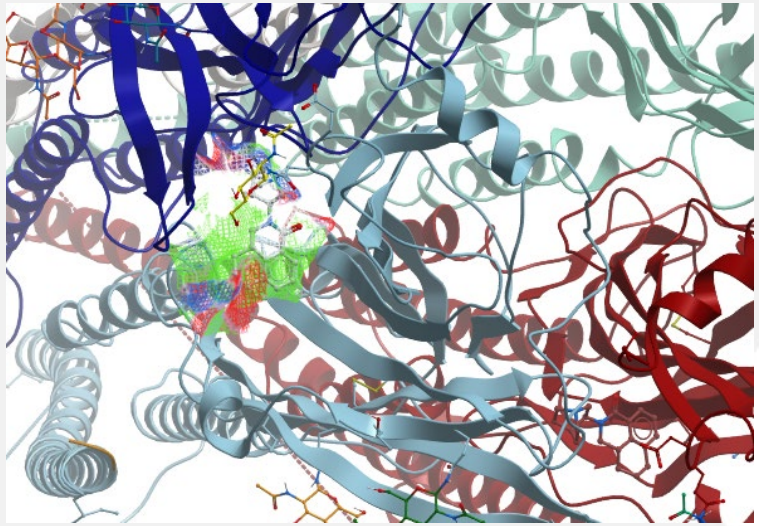


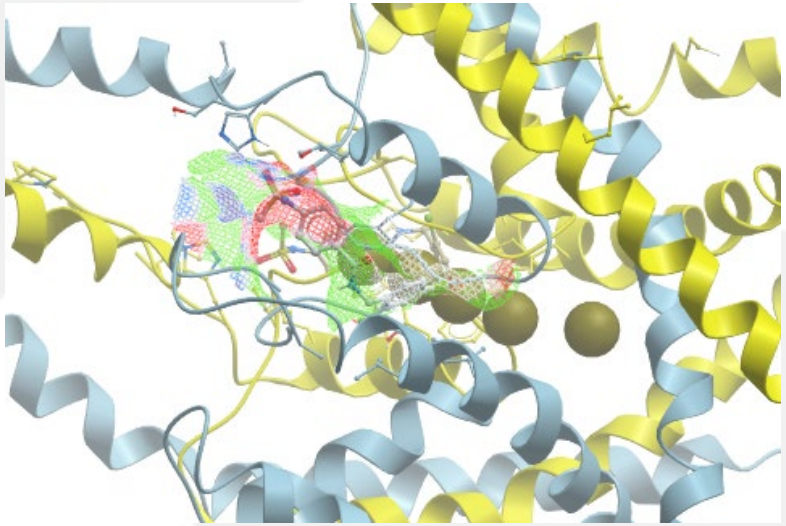


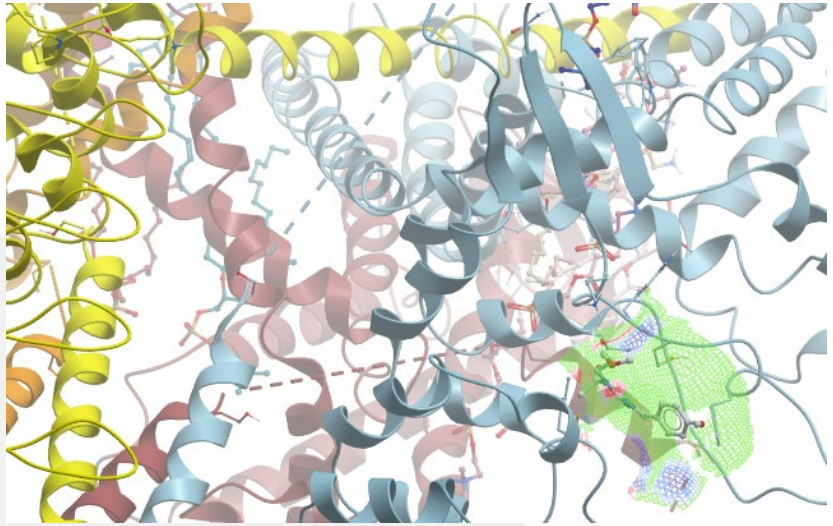


Structure-Based Templates – Recent PDB publications

3D Ligand-Based Atomic Property Fields virtual screening (APF® MolSoft) effectively reinforces selectivity, novelty, and physico-chemical profiles.







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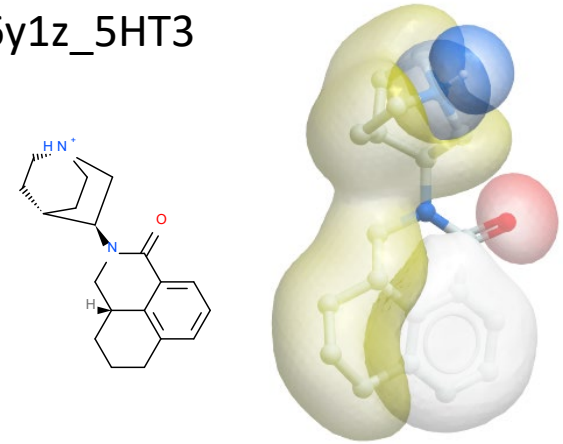

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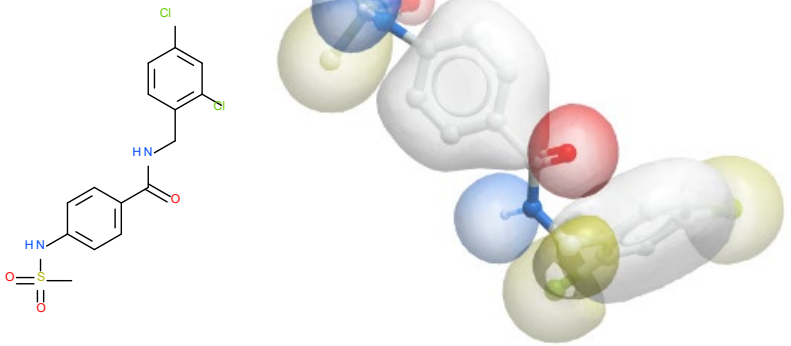
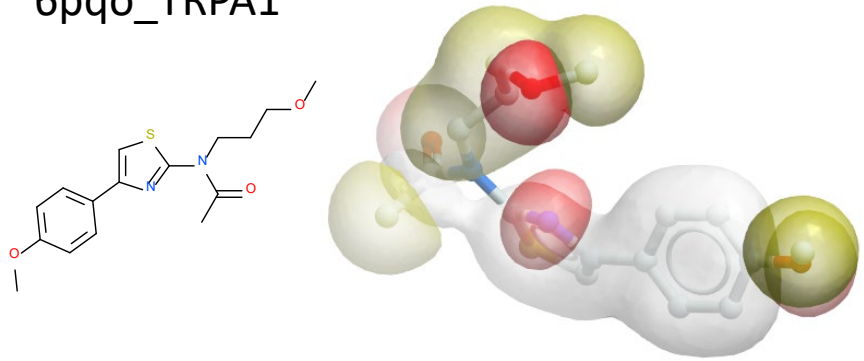


6pqo_TRPA1



Structure-Based Templates – Recent PDB publications

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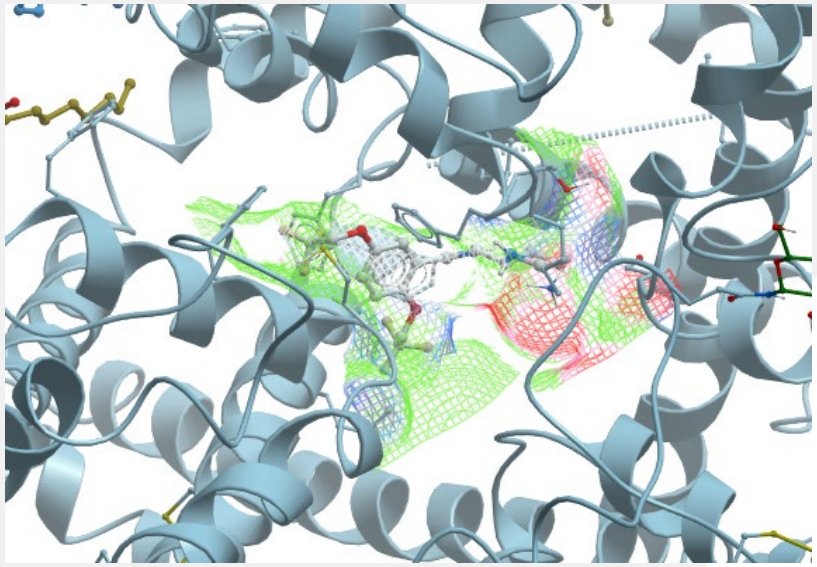

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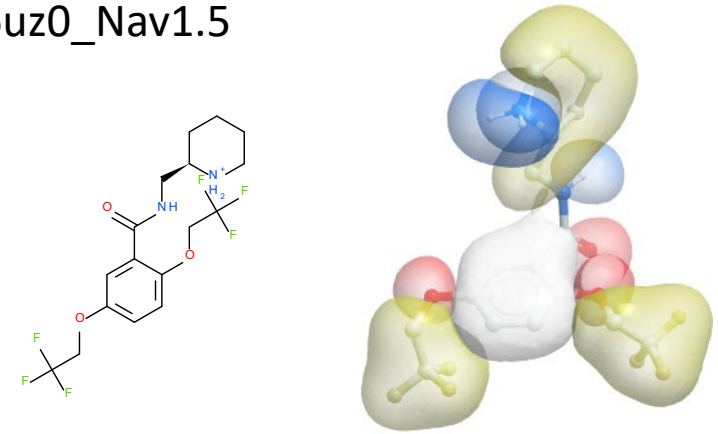

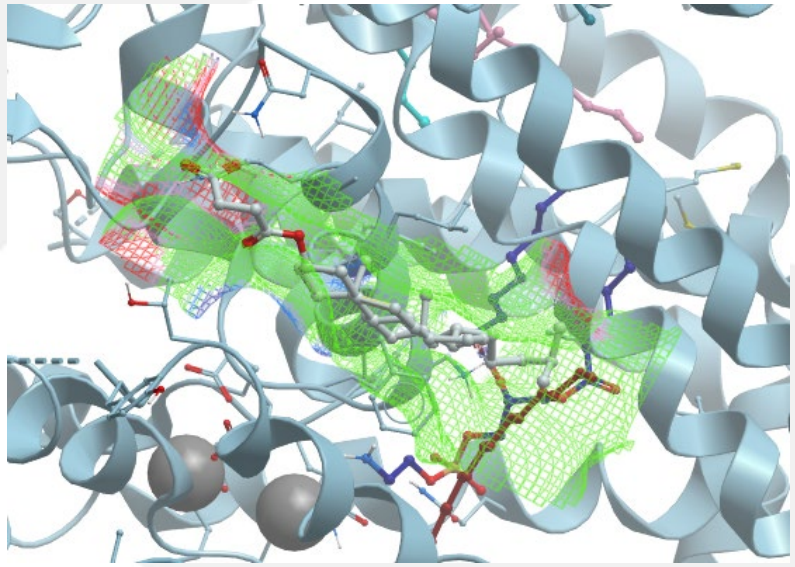

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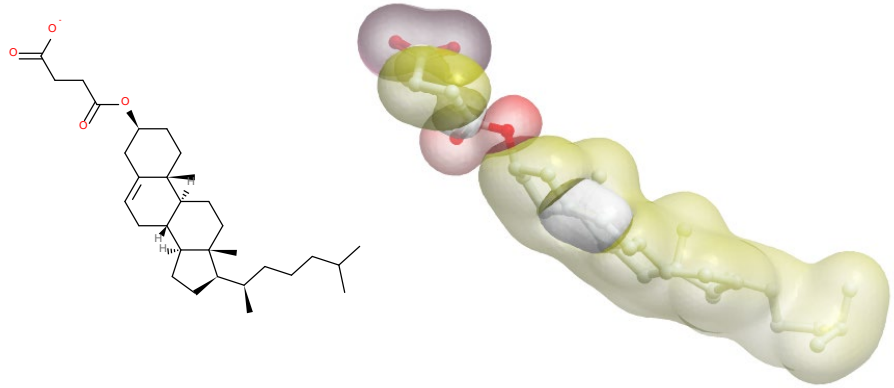

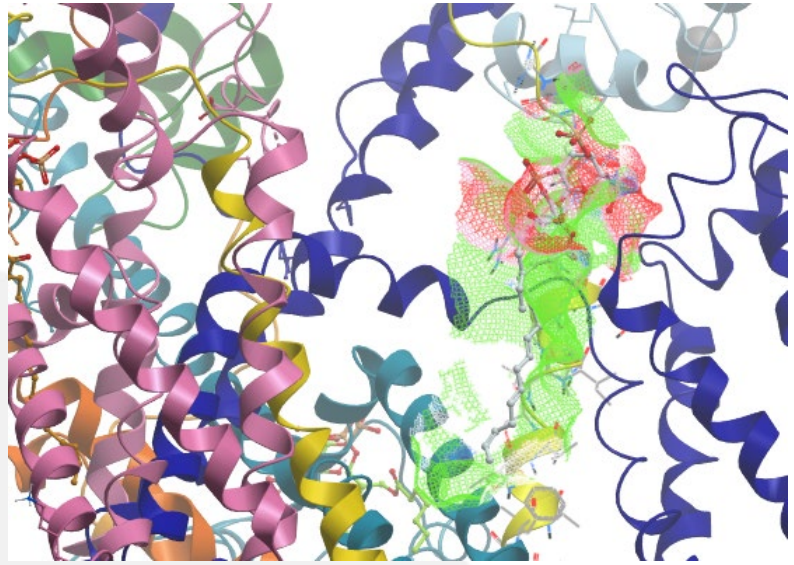

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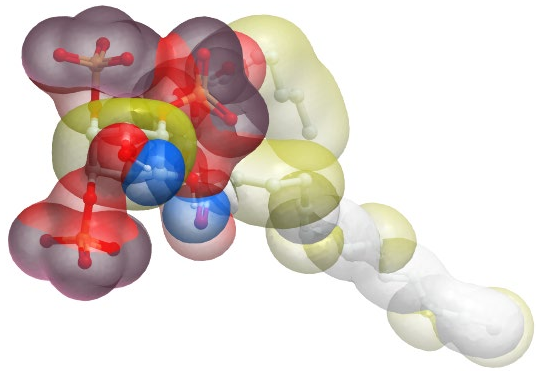

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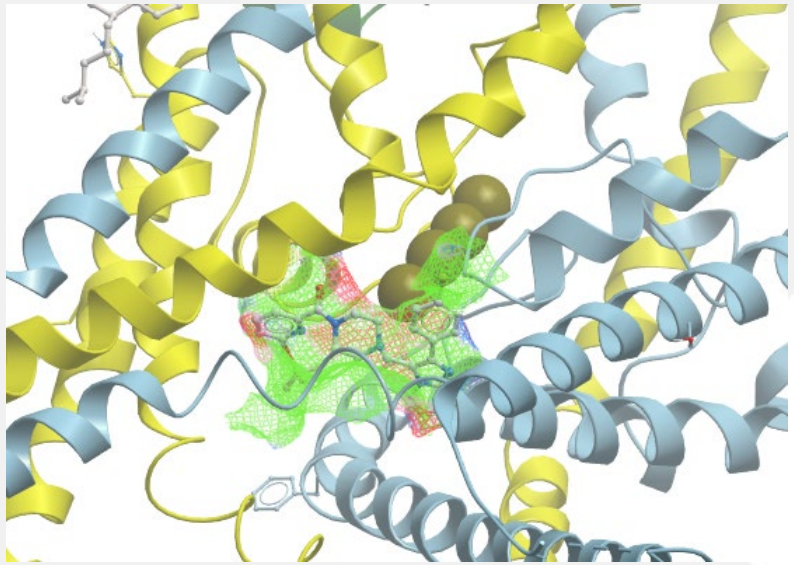

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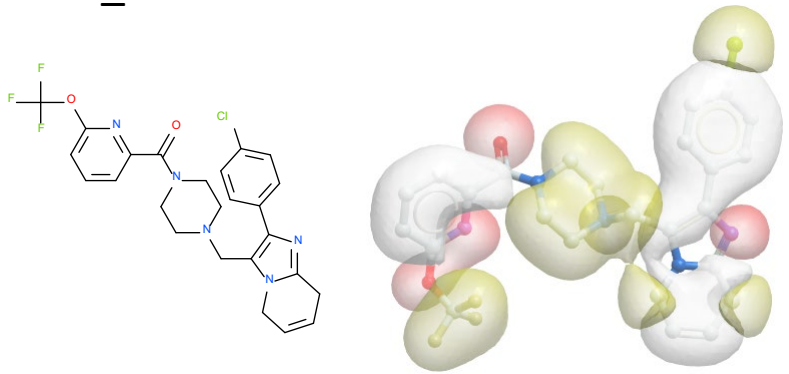

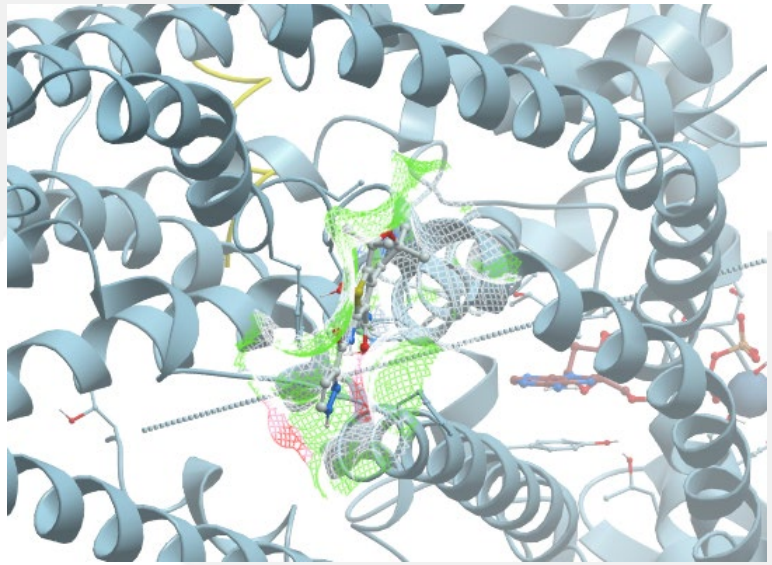

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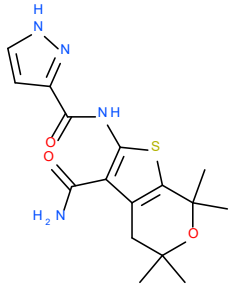

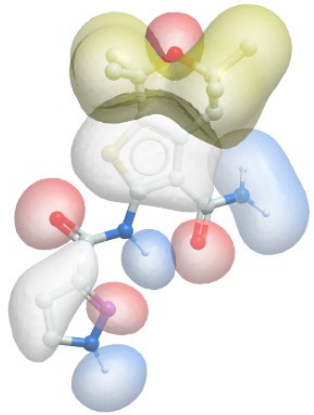

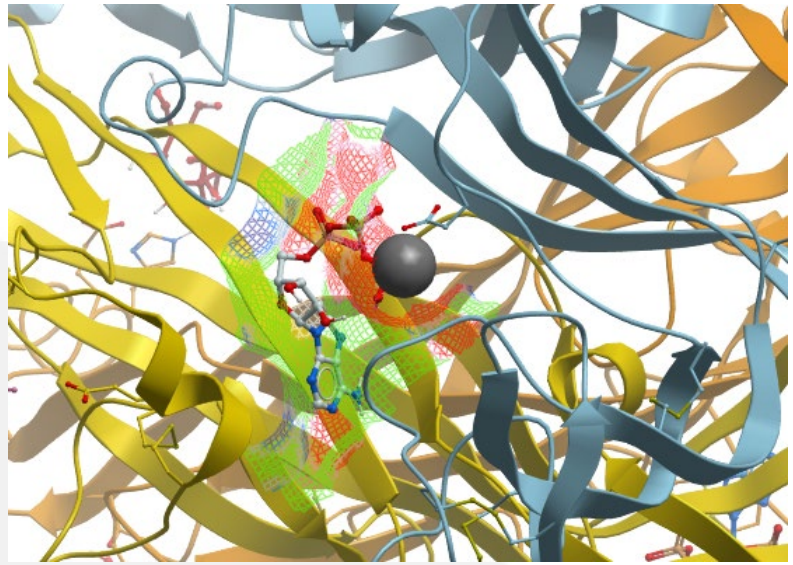

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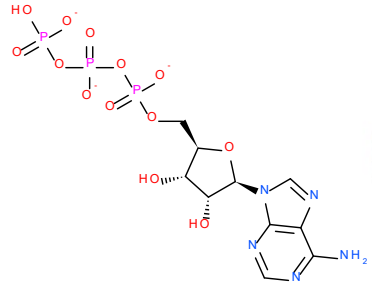

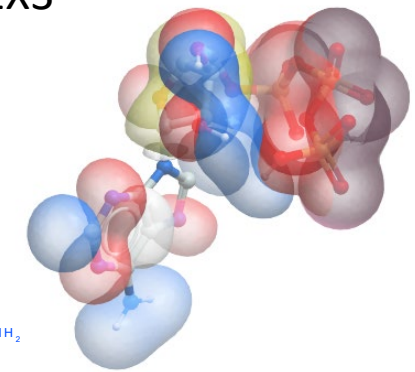

Distribution of Phys-Chem Properties

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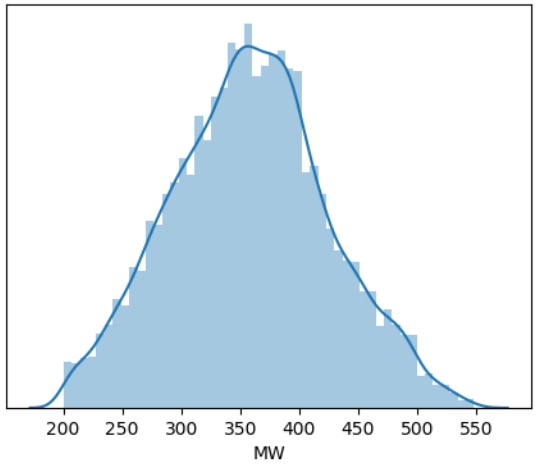
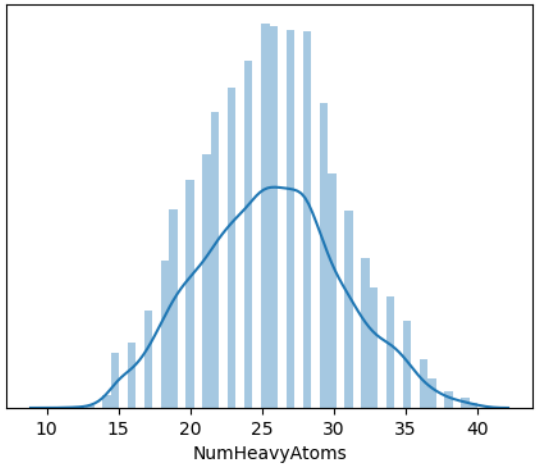
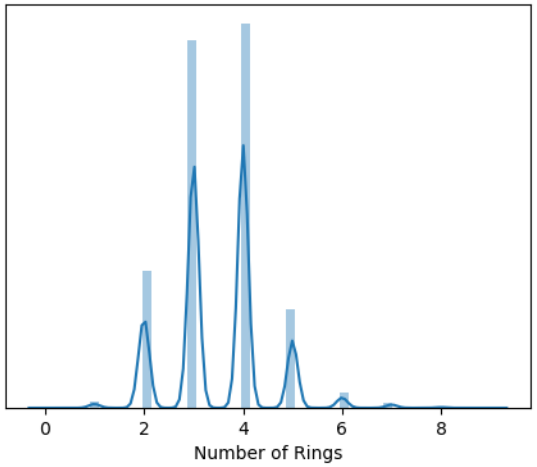
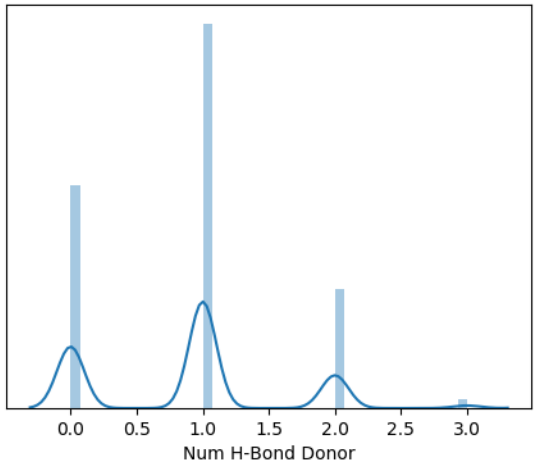
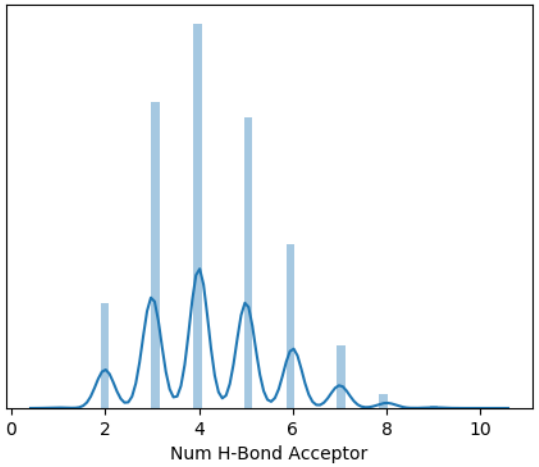
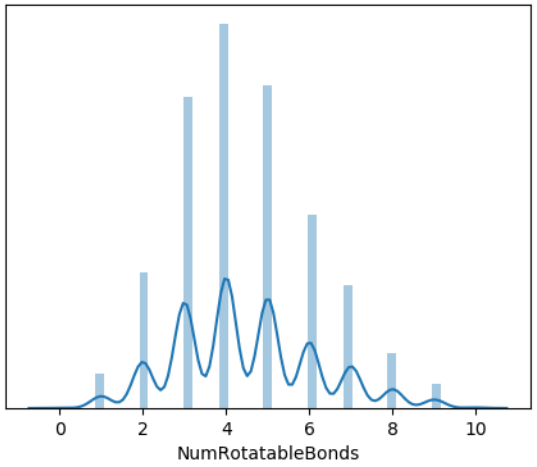




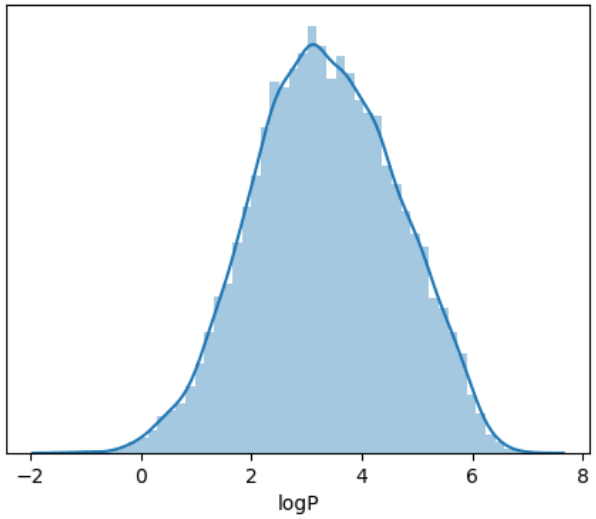


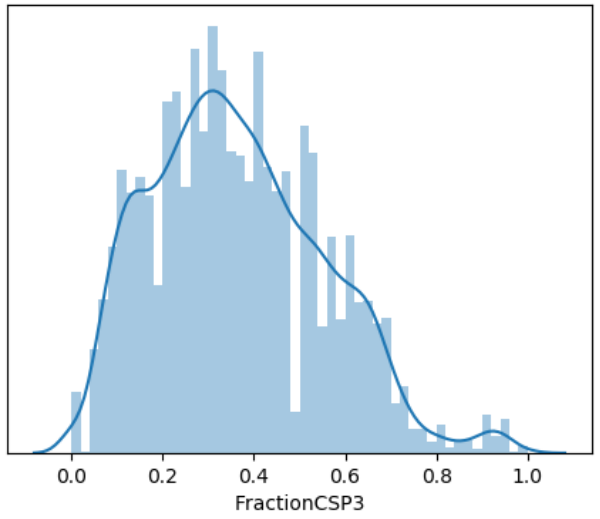


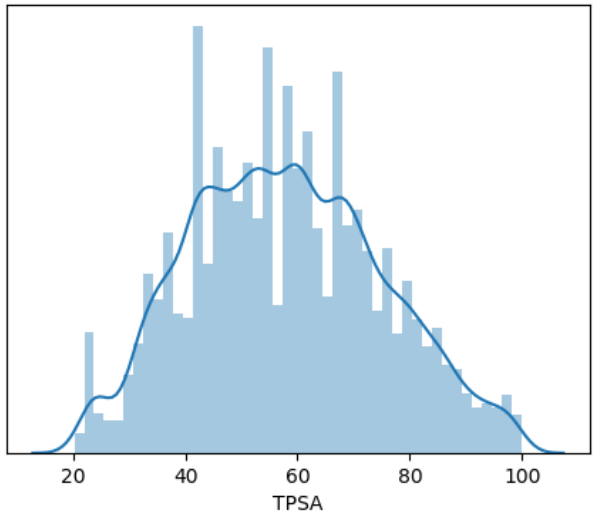


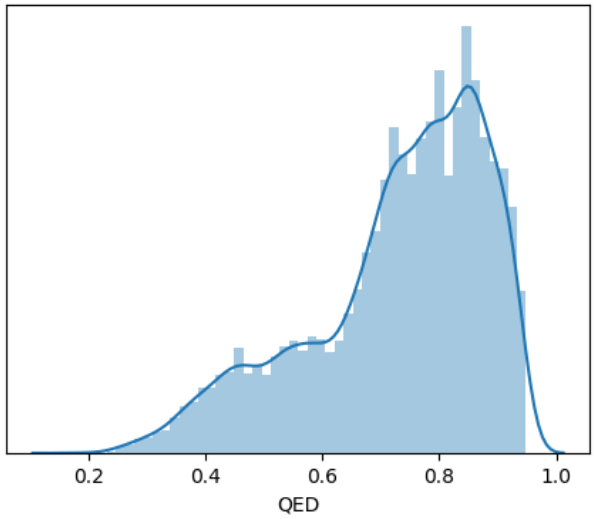


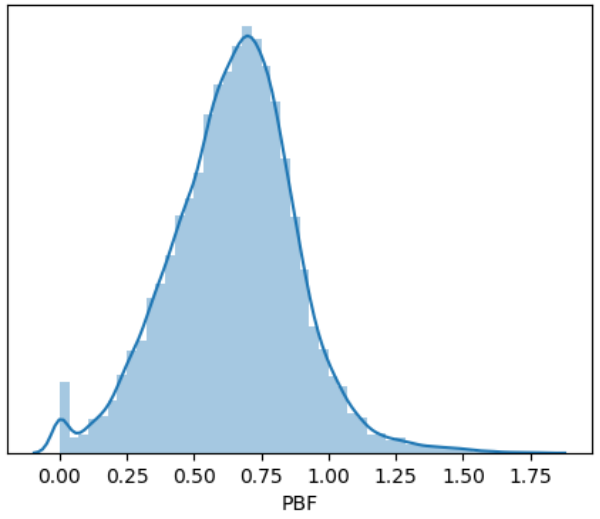
Distribution of Phys-Chem Properties

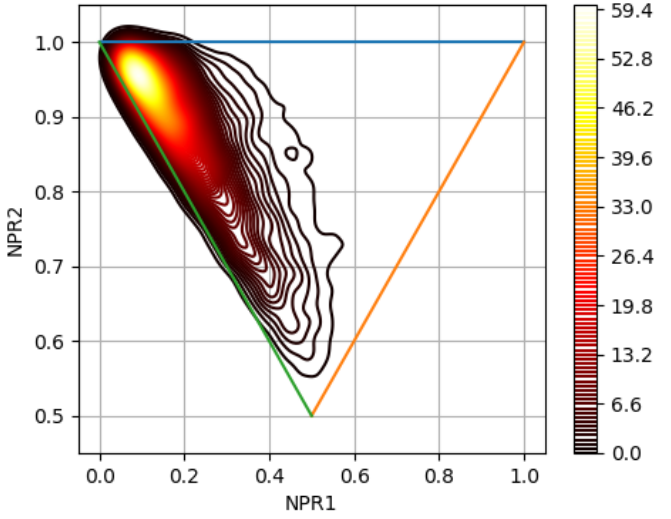












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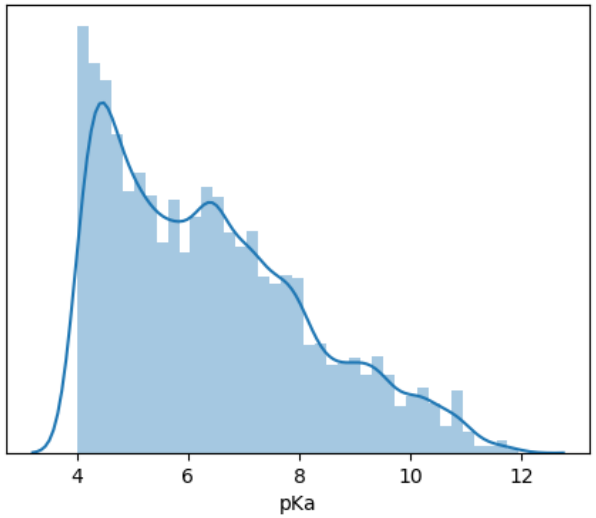
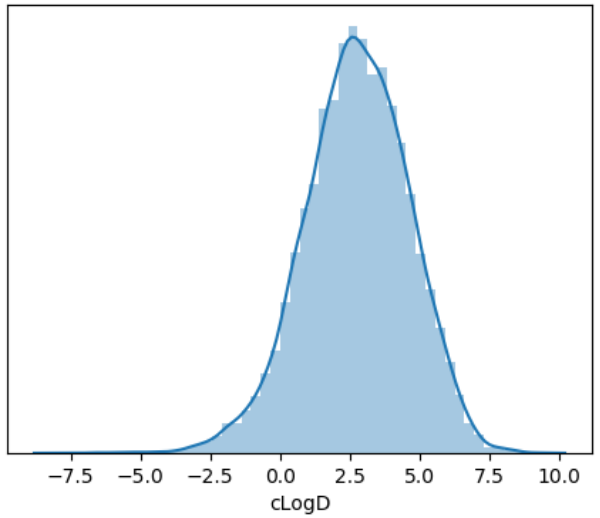
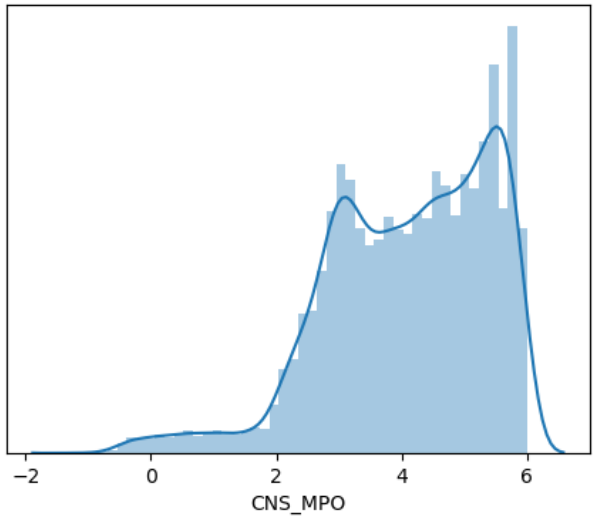
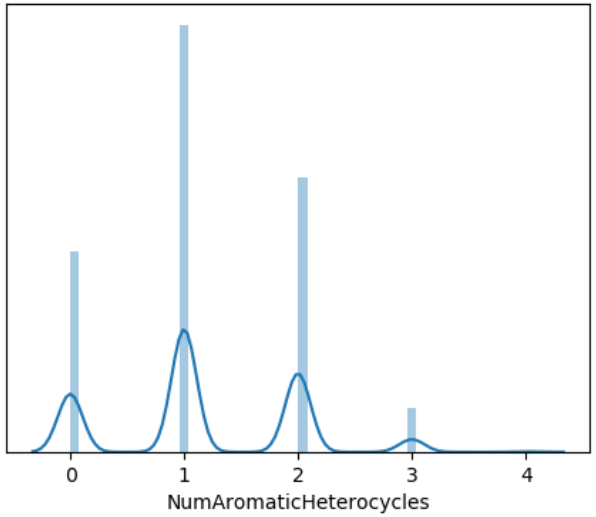
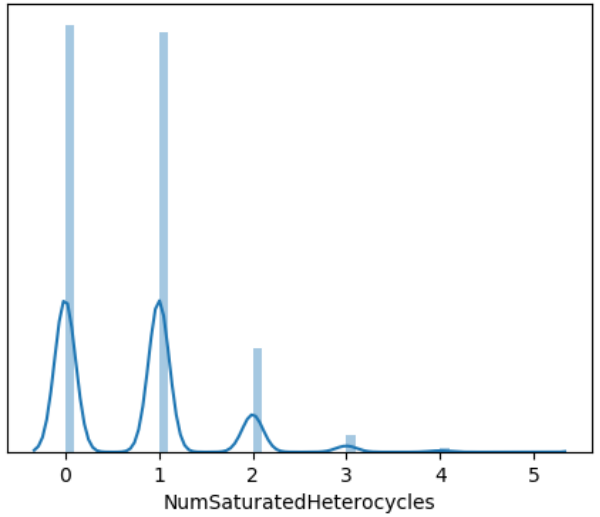
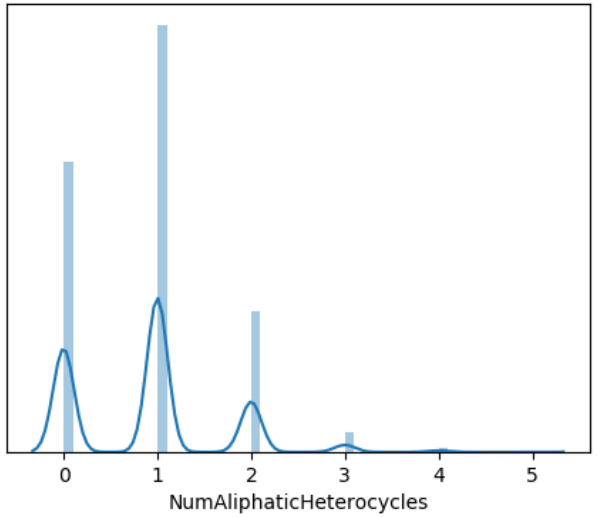




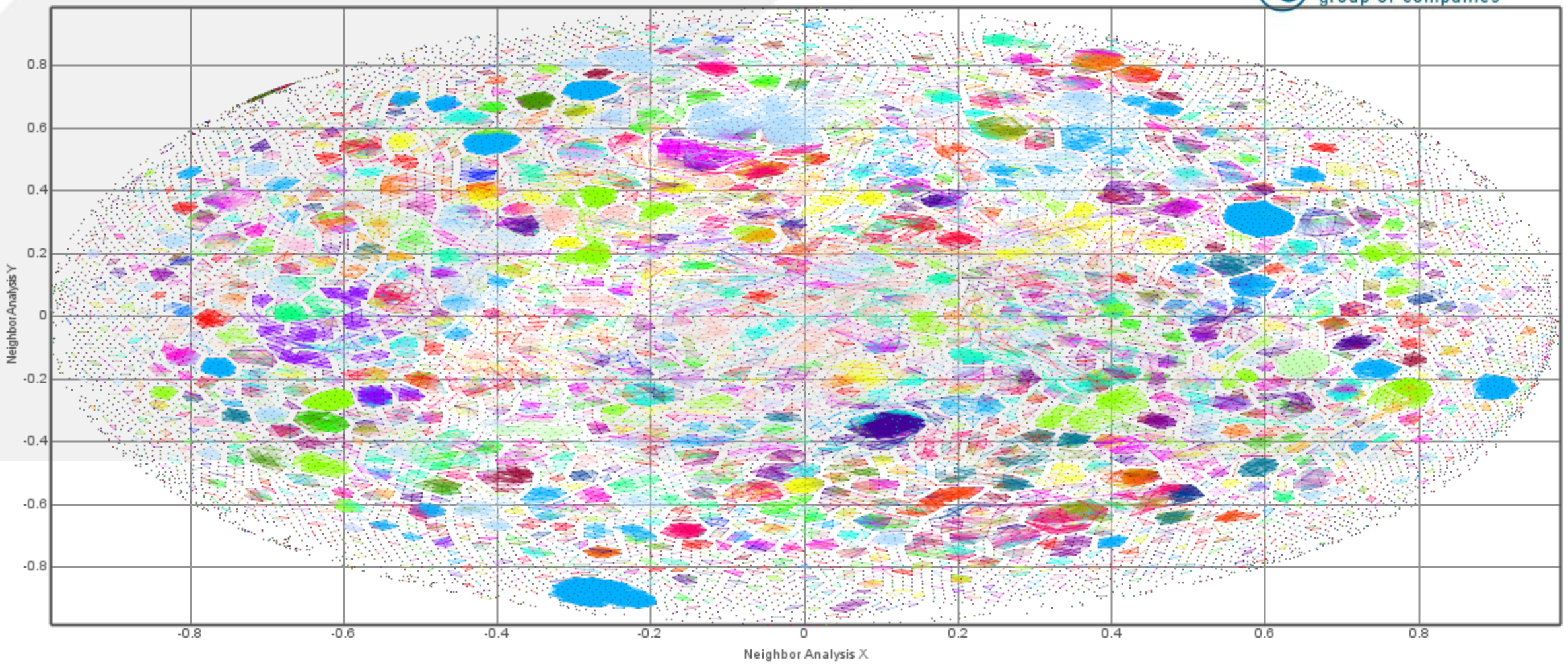




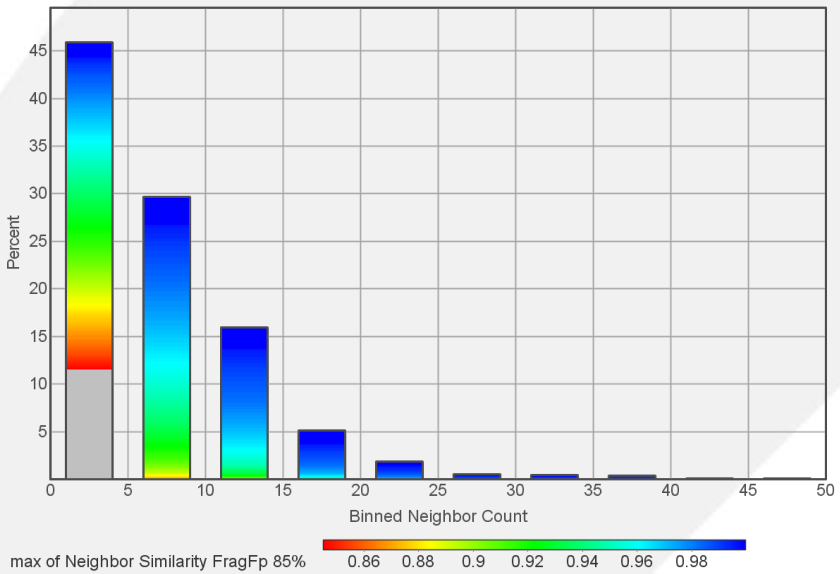


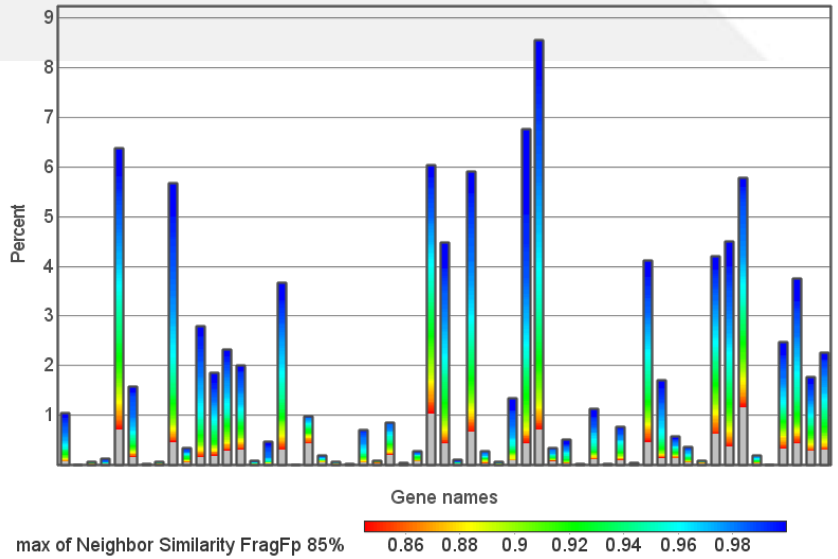


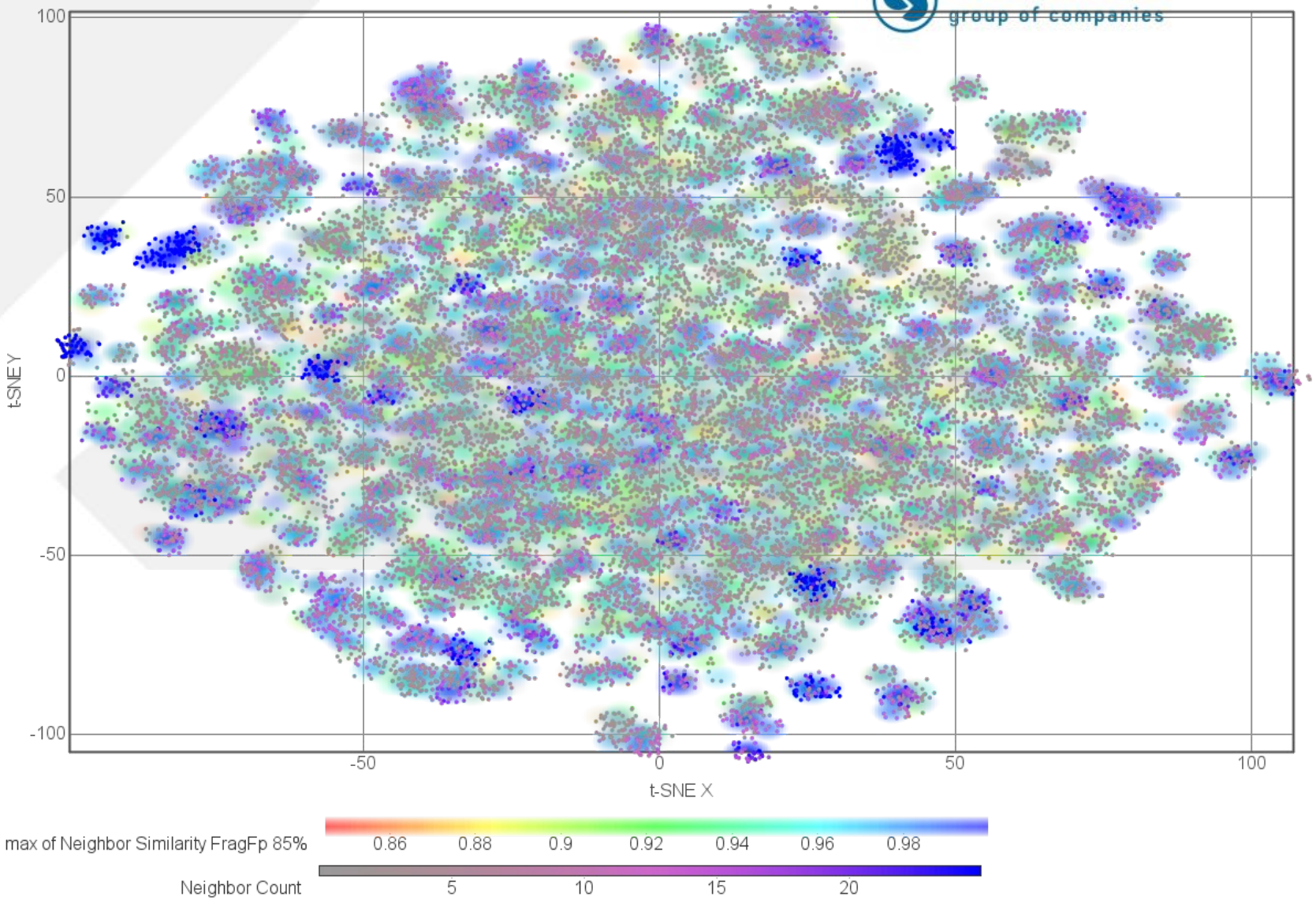
Structural Diversity



Structural Diversity







List of Selected Publications

1. J Med Chem 2018(61)8:3641-3659. Discovery of a Potent (4 R5 S)-4-Fluoro-5-methylproline Sulfonamide Transient Receptor Potential Ankyrin 1 Antagonist and Its Methylene Phosphate Prodrug Guided by Molecular Modeling. Chen H Volgraf M Do S Kolesnikov A Shore DG Verma VA Villemure E Wang L Chen Y Hu B Lu AJ Wu G Xu X Yuen PW Zhang Y Erickson SD Dahl M Brotherton-Pleiss C Tay S Ly JQ Murray LJ Chen J Amm D Lange W Hackos DH Reese RM Shields SD Lyssikatos JP Safina BS Estrada AA.
2. J Med Chem 2018(61)3:695-710. Targeting Acidic Mammalian chitinase Is Effective in Animal Model of Asthma. Mazur M Olczak J Olejniczak S […] Cousido-Siah A Fadel F Golebiowski A.
3. J Med Chem 2018(61)1:224-250. Novel Terminal Bipheny-Based Diapophytoene Desaturases (CrtN) Inhibitors as Anti-MRSA/VISR/LRSA Agents with Reduced hERG Activity. Li B Ni S Mao F Chen F Liu Y Wei H Chen W Zhu J Lan L Li J.
4. J Med Chem 2018(61)3:1355-1374. 3-((R)-4-(((R)-6-(2-Bromo-4-fluorophenyl)-5-(ethoxycarbonyl)-2-(thiazol-2-yl)-36-dihydropyrimidin-4-yl)methyl)morpholin-2-yl)propanoic Acid (HEC72702) a Novel Hepatitis B Virus Capsid Inhibitor Based on Clinical Candidate GLS4. Ren Q Liu X Yan G Nie B Zou Z Li J Chen Y Wei Y Huang J Luo Z Gu B Goldmann S Zhang J Zhang Y.
5. J Med Chem 2018(61)1:207-223. A Dipolar Cycloaddition Reaction To Access 6-Methyl-4567-tetrahydro-1H-[123]triazolo[45-c]pyridines Enables the Discovery Synthesis and Preclinical Profiling of a P2X7 Antagonist Clinical Candidate. Chrovian CC Soyode-Johnson A Peterson AA Gelin CF Deng X Dvorak CA Carruthers NI Lord B Fraser I Aluisio L Coe KJ Scott B Koudriakova T Schoetens F Sepassi K Gallacher DJ Bhattacharya A Letavic MA.
6. J Med Chem 2018(61)1:84-97. Phenotypic Optimization of Urea-Thiophene Carboxamides To Yield Potent Well Tolerated and Orally Active Protective Agents against Aminoglycoside-Induced Hearing Loss. Chowdhury S Owens KN Herr RJ Jiang Q Chen X Johnson G Groppi VE Raible DW Rubel EW Simon JA.
7. J Med Chem 2018(61)8:3685-3696. Discovery of a Novel Small-Molecule Modulator of C-X-C Chemokine Receptor Type 7 as a Treatment for Cardiac Fibrosis. Menhaji-Klotz E Hesp KD Londregan AT Kalgutkar AS Piotrowski DW Boehm M Song K Ryder T Beaumont K Jones RM Atkinson K Brown JA Litchfield J Xiao J Canterbury DP Burford K Thuma BA Limberakis C Jiao W Bagley SW Agarwal S Crowell D Pazdziorko S Ward J Price DA Clerin V.
8. J Med Chem 2018(61)1:251-264. 7-Phenoxy-Substituted 34-Dihydro-2H-124-benzothiadiazine 11-Dioxides as Positive Allosteric Modulators of Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptors with Nanomolar Potency. Goffin E Drapier T Larsen AP Geubelle P Ptak CP Laulumaa S Rovinskaja K Gilissen J Tullio P Olsen L Frydenvang K Pirotte B Hanson J Oswald RE Kastrup JS Francotte P.
9. J Med Chem 2017(60)22:9239-9250. Structure-Based Design and Discovery of New M2 Receptor Agonists. Fish I Stößel A Eitel K Valant C Albold S Huebner H Möller D Clark MJ Sunahara RK Christopoulos A Shoichet BK Gmeiner P.
10. ACS Med Chem Lett 2017(8)1:133-137. Development of 4-Heteroarylamino-1'-azaspiro[oxazole-53'-bicyclo[2.2.2]octanes] as Nicotinic Receptor Agonists. Hill MD Fang H King HD Iwuagwu CI McDonald IM Cook J Zusi FC Mate RA Knox RJ Post-Munson D Easton A Miller R Lentz K Clarke W Benitex Y Lodge N Zaczek R Denton R Morgan D Bristow L Macor JE Olson R.
11. J Med Chem 2017(60)16:7029-7042. Discovery of Clinical Candidate 4-[2-(5-Amino-1H-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-N-13-thiazol-4-ylbenzenesulfonamide (PF-05089771): Design and Optimization of Diaryl Ether Aryl Sulfonamides as Selective Inhibitors of NaV1.7. Swain NA Batchelor D […] Storer RI Stupple PA West CW.
12. 25-disubstituted-pyridyl nicotinic ligands and methods of use thereof 2016 US-9303017-B2
13. Substituted pyrazoles as N-type calcium channel blockers 2016 US-9434693-B2

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