The use of the 3d-qsar.com portal to derive ligand-based and structure-based models from scratch. Application on tyrosine kinase 2 protein inhibitors

Experimental Thesis
in
Medicinal Chemistry (CHIM08)

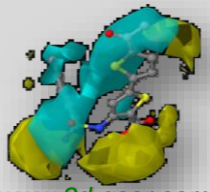
SAPIENZA
UNIVERSITÀ DI ROMA

Pharmacy and Medicine Faculty
Degree Course in
Bioinformatics

Candidate:
Amedeo Antoci (Matr. 1615797)

Tutor:
Prof. Rino Ragno

Accademic Year 2019/2020



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The aim of the project

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Journal of Medicinal Chemistry

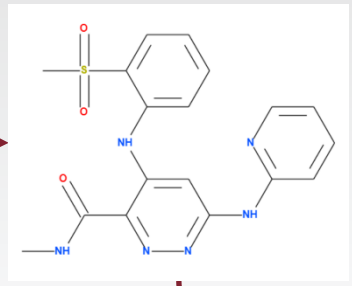
Identification of *N*-Methyl Nicotinamide and *N*-Methyl Pyridazine-3-Carboxamide Pseudokinase Domain Ligands as Highly Selective Allosteric Inhibitors of Tyrosine Kinase 2 (TYK2)

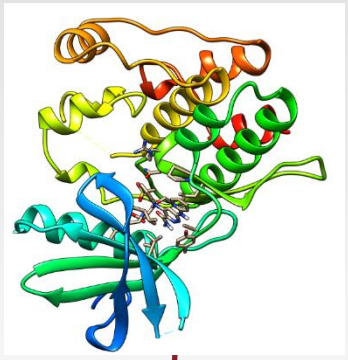
Ryan Moslin,[*,†] Yanlei Zhang,[†] Stephen T. Wrobleski,[†] Shuqun Lin,[†] Michael Mertzman,[†] Steven Spergel,[†] John S. Tokarski,[§] Joann Strnad,[‡] Kathleen Gillooly,[‖] Kim W. McIntyre,[‡] Adriana Zupa-Fernandez,[‡] Lihong Cheng,[‡] Huadong Sun,[#] Charu Chaudhry,[⊥] Christine Huang,[⊥] Celia D'Arienzo,[⊥] Elizabeth Heimrich,[‡] Xiaoxia Yang,[‖] Jodi K. Muckelbauer,[§] ChiehYing Chang,[§] Jeffrey Tredup,[§] Dawn Mulligan,[§] Dianlin Xie,[§] Nelly Aranibar,[#] Manoj Chiney,[#] James R. Burke,[‖] Louis Lombardo,[†] Percy H. Carter,[†] and David S. Weinstein[†]

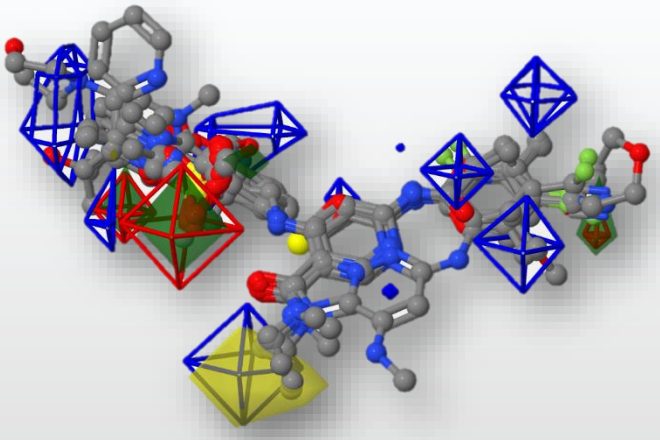
2018

Highly Selective Inhibition of Tyrosine Kinase 2 (TYK2) for the Treatment of Autoimmune Diseases: Discovery of the Allosteric Inhibitor BMS-986165

Stephen T. Wrobleski,[*,†] Ryan Moslin,[*,†] Shuqun Lin,[†] Yanlei Zhang,[†] Steven Spergel,[†] James Kempson,[‡] John S. Tokarski,[§] Joann Strnad,[‖] Adriana Zupa-Fernandez,[‖] Lihong Cheng,[‖] David Shuster,[‖] Kathleen Gillooly,[‖] Xiaoxia Yang,[‖] Elizabeth Heimrich,[‖] Kim W. McIntyre,[‖] Charu Chaudhry,[⊥] Javed Khan,[§] Max Ruzanov,[§] Jeffrey Tredup,[§] Dawn Mulligan,[§] Dianlin Xie,[§] Huadong Sun,[#] Christine Huang,[#] Celia D'Arienzo,[#] Nelly Aranibar,[#] Manoj Chiney,[#] Anjaneya Chimalakonda,[#] William J. Pitts,[†] Louis Lombardo,[†] Percy H. Carter,[†] James R. Burke,[‖] and David S. Weinstein[†]







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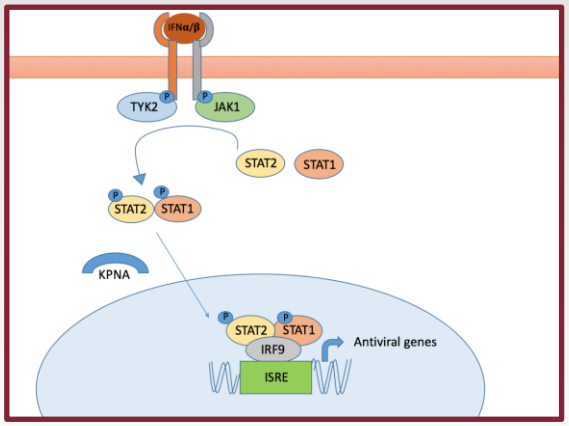
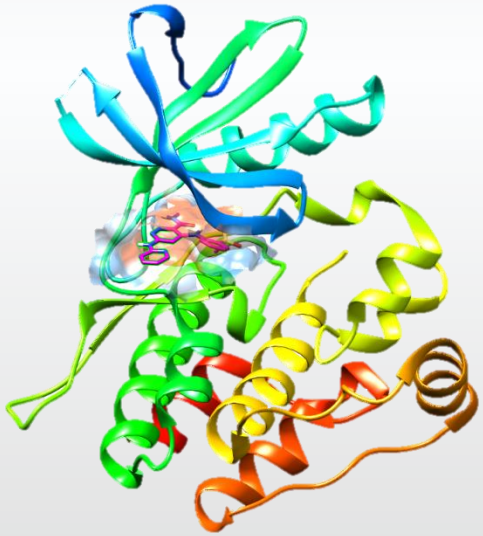
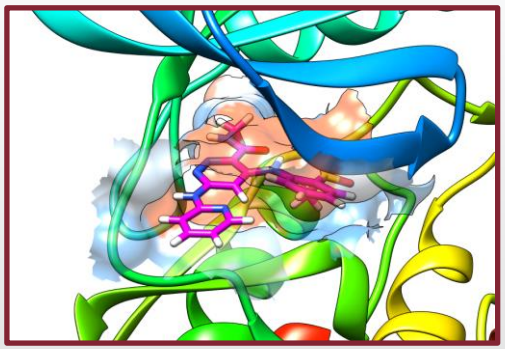
The biological target Tyrosine Kinase 2
The JH2 pseudokinase domain



- Tyrosine Kinase 2 (TYK2) plays a central role in mediating signals in type I Interferon pathways
- Inhibition of TYK2 is a sought-out target for treatment of inflammatory and autoimmune diseases where we have type I IFN overproduction
- JAK Homology 2 (JH2) pseudokinase domain offers a promising target for selective allosteric inhibition of TYK2





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The biological target Tyrosine Kinase 2
The Ligands

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Journal of Medicinal Chemistry

Identification of *N*-Methyl Nicotinamide and *N*-Methyl Pyridazine-3-Carboxamide Pseudokinase Domain Ligands as Highly Selective Allosteric Inhibitors of Tyrosine Kinase 2 (TYK2)

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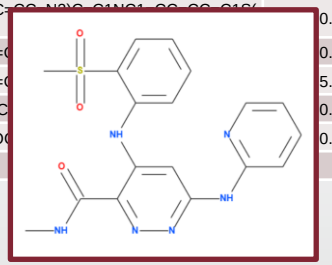
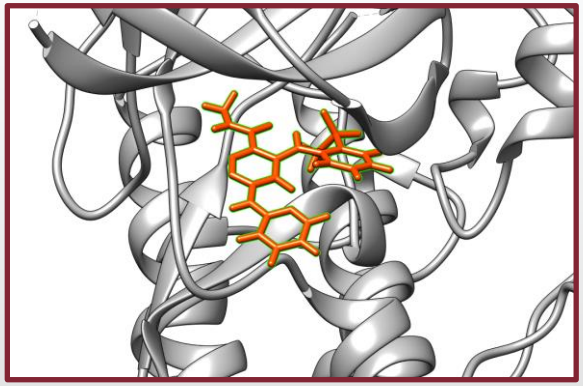
Highly Selective Inhibition of Tyrosine Kinase 2 (TYK2) for the Treatment of Autoimmune Diseases: Discovery of the Allosteric Inhibitor BMS-986165

Stephen T. Wrobleski,*,† Ryan Moslin,*,† Shuqun Lin,† Yanlei Zhang,† Steven Spergel,† James Kempson,‡ John S. Tokarski,§ Joann Strnad,∥ Adriana Zupa-Fernandez,∥ Lihong Cheng,∥ David Shuster,∥ Kathleen Gillooly,∥ Xiaoxia Yang,∥ Elizabeth Heimrich,∥ Kim W. McIntyre,∥ Charu Chaudhry,⊥ Javed Khan,§ Max Ruzanov,§ Jeffrey Tredup,§ Dawn Mulligan,§ Dianlin Xie,§ Huadong Sun,# Christine Huang,# Celia D'Arienzo,# Nelly Aranibar,# Manoj Chiney,# Anjaneya Chimalakonda,# William J. Pitts,† Louis Lombardo,† Percy H. Carter,† James R. Burke,∥ and David S. Weinstein†

ID	Smiles string	TYK2 JH2 IC50 (nM)
I_11	[2H]C([2H])([2H])NC(=O)C1=NN=C(NC(=O)C2CC2)C=C1NC1=CC=CC(C2=NN(C)C=N2)=C1OC	0.2
I_12	[2H]C([2H])([2H])NC(=O)C1=NN=C(NC2=CC=CC=N2)C=C1NC1=CC=CC(C2(C)C)=O)=O	0.5
I_13	CNC(=O)C1=CN=C(NC2=NC=C(F)C=C2)C=C	0.9
I_14	CNC(=O)C1=CN=C(NC2=NC=C(F)C=C2)C=C	5.2
I_15	CNC(=O)C1=C(NC2=CC=CC(C#N)=C2OC)C	0.9
I_16	CNC(=O)C1=C(NC2=CC=CC(C(O)=O)=C2O	0.9
…	…	



- **Molecules were obtained from two scientific articles from Journal of Medicinal Chemistry**
- **62 Small-molecule allosteric TYK2 Inhibitors form the training set of to generate our 3D-QSAR models**
- **6 Molecules were available co-crystallized with TYK2**



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The 3d-qsar.com web portal

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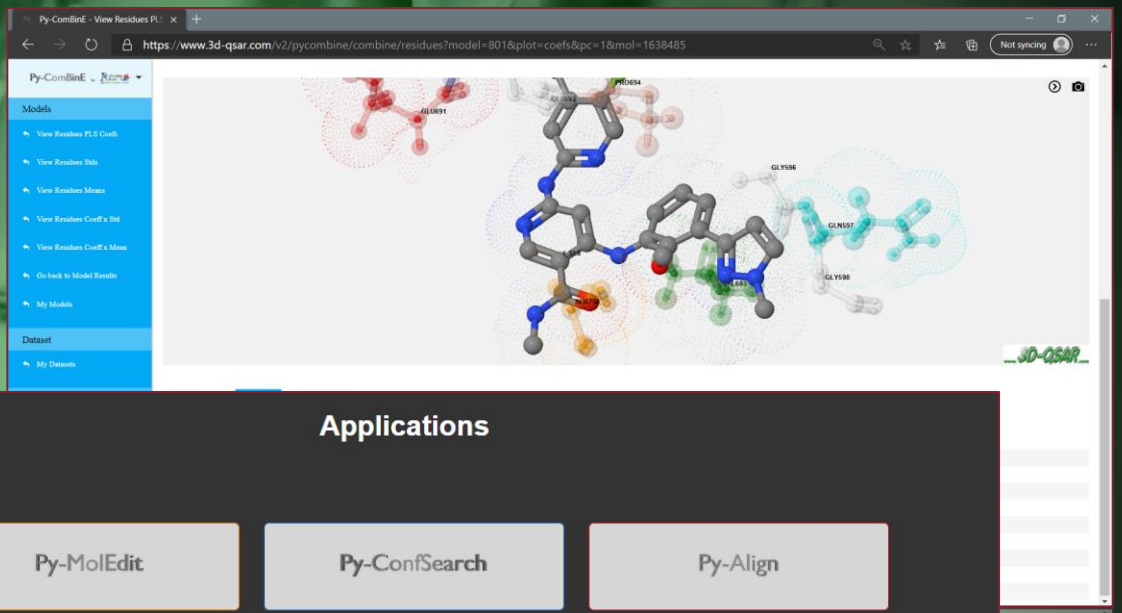
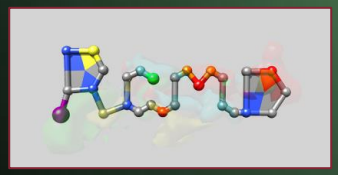
Build predictive models using a simple and intuitive interface on any device.



Applications

Py-MolEdit	Py-ConfSearch	Py-Align
Py-CoMFA	Py-ComBinE NEW!	Py-Docking NEW!



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The 3d-qsar.com web portal
The Tools

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- **Py-MolEdit**
  - JVME
- **Py-Align**
  - Balloon
  - RDKit
  - OpenBabel
- **Py-ConfSearch**
  - RDKit
  - Shaep
- **Py-Docking** NEW!
  - SMINA
    - Vinardo
    - Vina
    - ad4_scoring
  - PLANTS
    - plp
    - plp95
    - chemplp
- **Py-CoMFA**
  - CoMFA
- **Py-ComBinE** NEW!
  - COMBINE

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Overview of the study
The big picture

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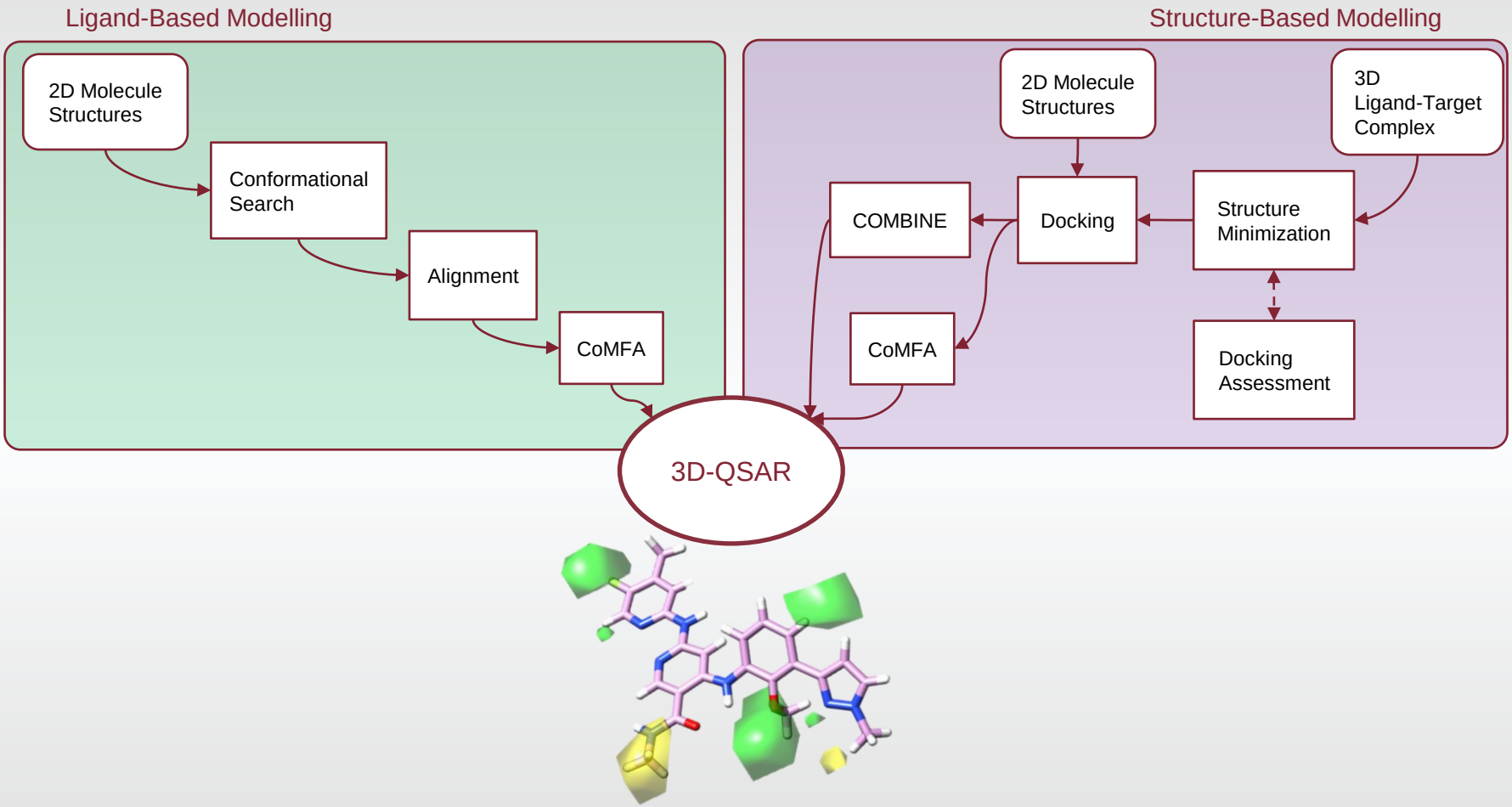

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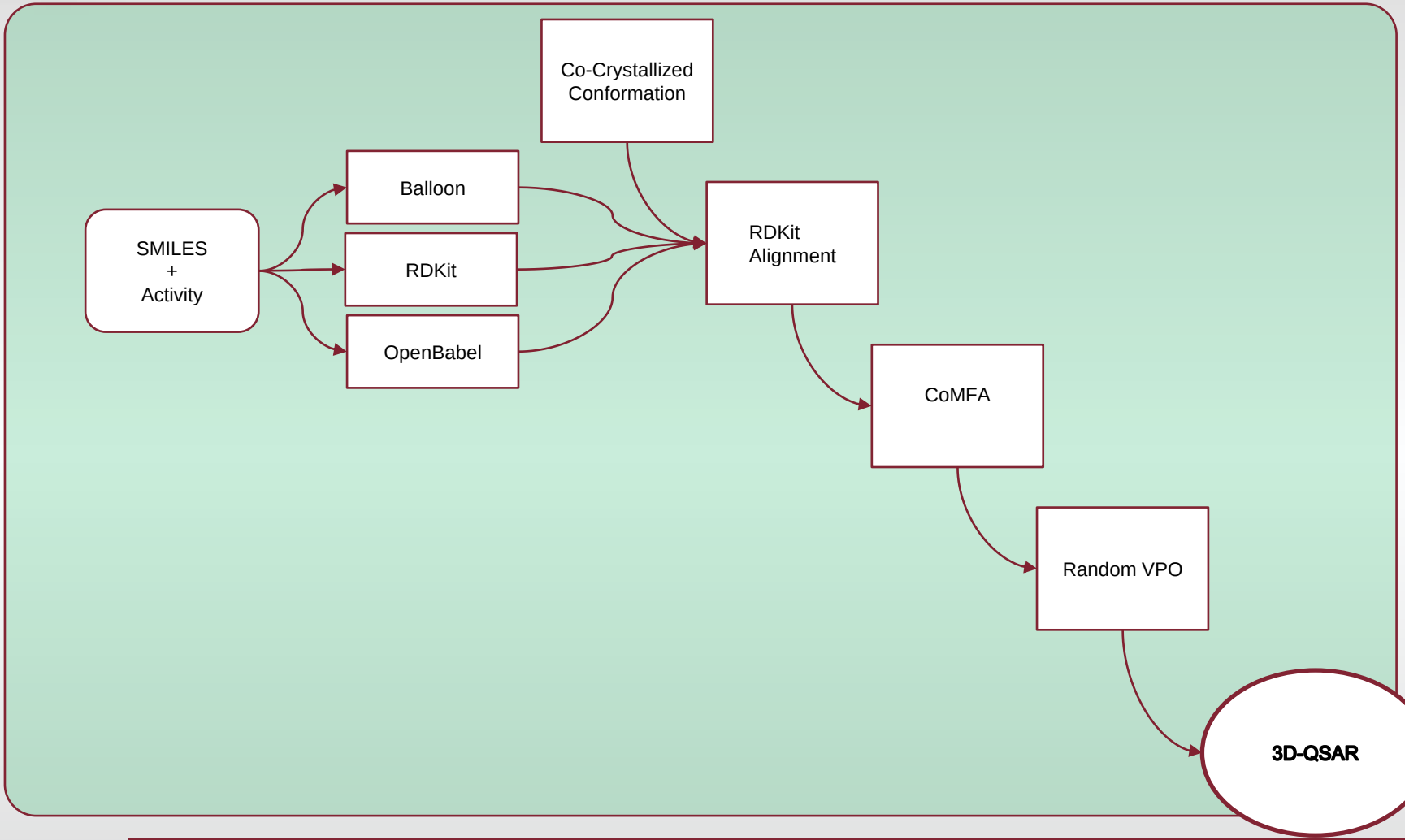
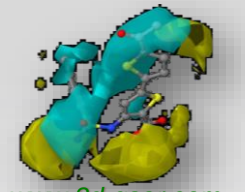
Ligand-Based Modelling





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Results
Ligand-Based Modelling

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https://www.3d-qsar.com/v2/pycomfa/comfa/compare?data_set=43649&

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Py-CoMFA

Models
- My 3-D QSAR Models

Dataset
- My Datasets

User
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Compare 3-D QSAR Models for Dataset and its children: TYK2_jmedchem.9b00444 (3

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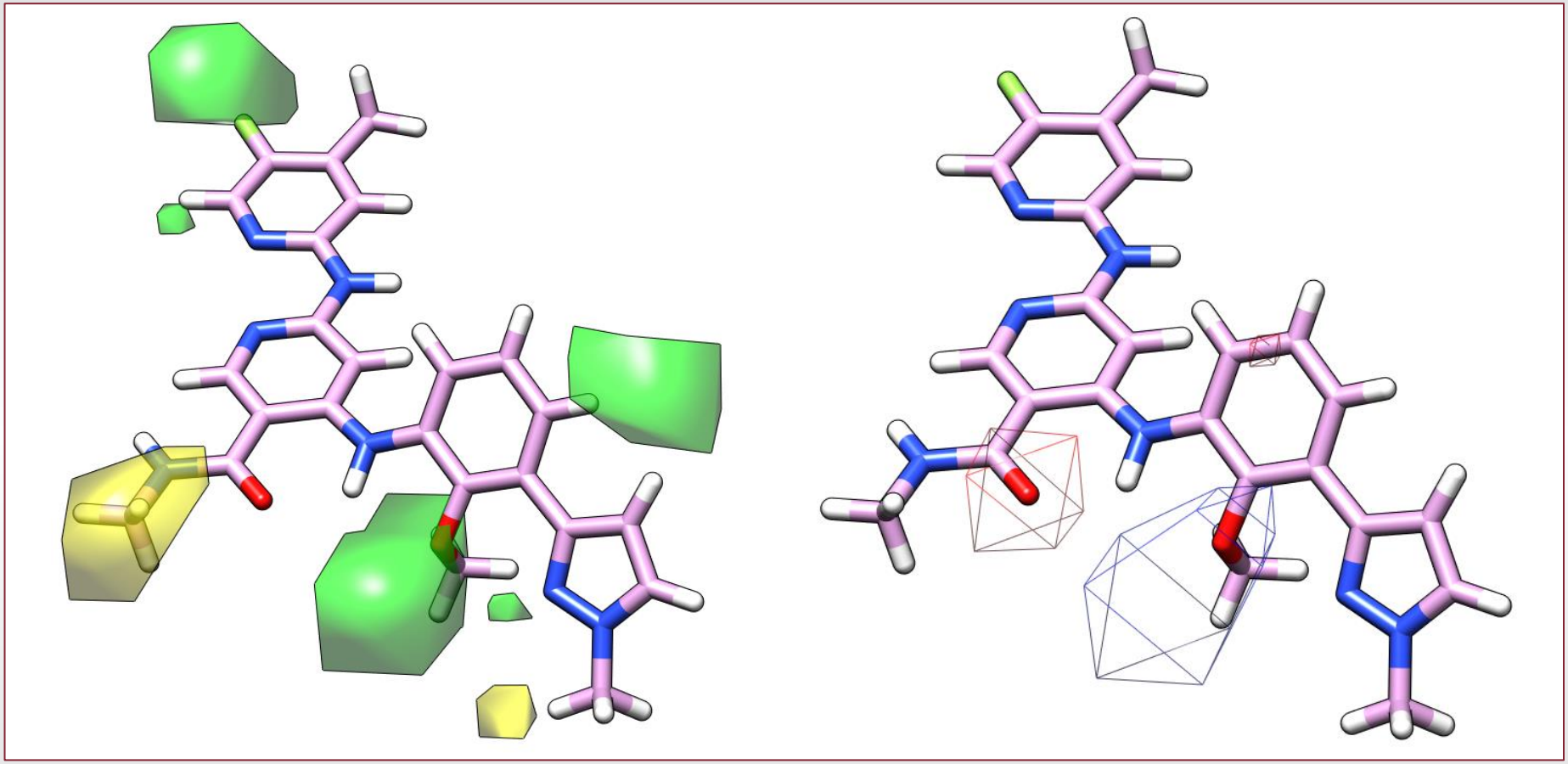
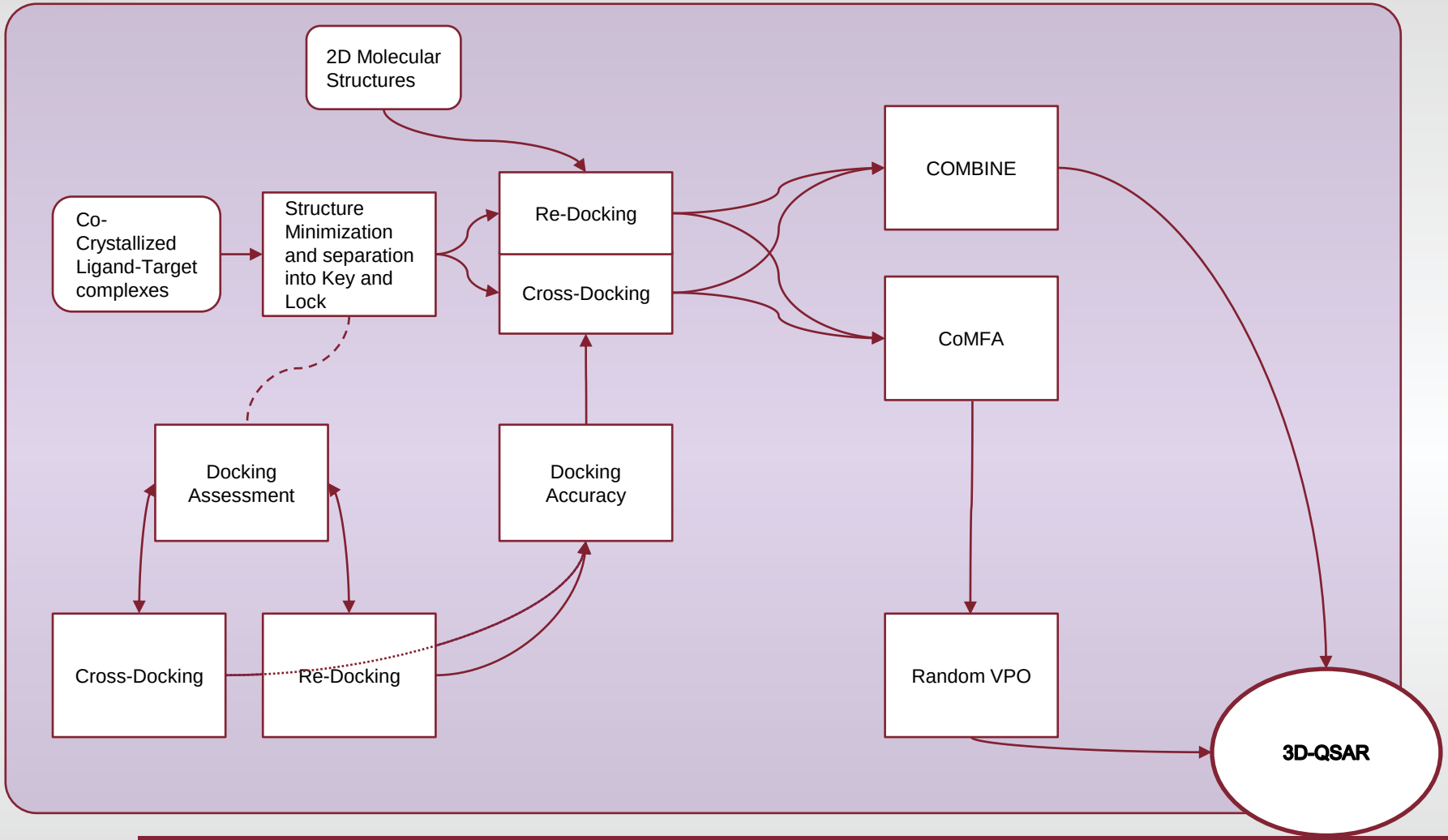
Model ID	Dataset	Status		Maps	nTrMols	External Pred	r^2 STE(PC)	q^2 STE(PC)	r^2 ELE(PC)	q^2 ELE(PC)	r^2 BOTH(PC)	q^2 BOTH(PC)	Probe	Probe Charge
191420	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Available	62	False	0.853 (3)	0.583 (3)	0.497 (3)	0.316 (3)	0.933 (3)	0.605 (3)	O.2	1
193003	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.882 (4)	0.616 (4)	0.299 (1)	0.206 (1)	0.874 (4)	0.549 (4)	N.2	1
193007	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.882 (4)	0.616 (4)	0.288 (1)	0.202 (1)	0.874 (4)	0.549 (4)	N.2	1
193009	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.885 (4)	0.615 (4)	0.297 (1)	0.205 (1)	0.877 (4)	0.549 (4)	N.2	1
193037	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.885 (4)	0.615 (4)	0.349 (2)	0.238 (2)	0.877 (4)	0.549 (4)	N.2	1
193010	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.886 (4)	0.614 (4)	0.343 (2)	0.235 (2)	0.877 (4)	0.548 (4)	N.2	1
192997	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.888 (4)	0.613 (4)	0.290 (1)	0.203 (1)	0.879 (4)	0.545 (4)	N.2	1
192980	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.888 (4)	0.601 (4)	0.338 (2)	0.235 (2)	0.882 (4)	0.537 (4)	N.2	1
193047	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.888 (4)	0.607 (4)	0.288 (1)	0.201 (1)	0.878 (4)	0.537 (4)	N.2	1
193022	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.885 (4)	0.604 (4)	0.299 (1)	0.206 (1)	0.875 (4)	0.535 (4)	N.2	1
192998	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.912 (5)	0.576 (5)	0.000 (1)	-0.033 (1)	0.887 (5)	0.533 (5)	O.2	1
191418	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.914 (5)	0.591 (5)	0.329 (2)	0.220 (2)	0.880 (5)	0.530 (5)	C.3	1
192958	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.913 (5)	0.581 (5)	0.339 (2)	0.243 (2)	0.885 (5)	0.524 (5)	O.2	1
189776	43669.TYK2_jmedchem.9b00444_most_active	completed	Results	Missing	62	False	0.795 (3)	0.496 (3)	0.652 (4)	0.434 (4)	0.757 (3)	0.520 (3)	C.3	1
192962	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.874 (4)	0.550 (4)	0.623 (4)	0.360 (4)	0.928 (4)	0.519 (4)	O.2	1
192984	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.890 (4)	0.568 (4)	0.551 (3)	0.344 (3)	0.863 (4)	0.518 (4)	N.2	1
192999	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.890 (4)	0.568 (4)	0.605 (4)	0.355 (4)	0.863 (4)	0.518 (4)	N.2	1
193042	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.813 (3)	0.528 (3)	0.307 (1)	0.214 (1)	0.786 (3)	0.518 (3)	N.2	1
193001	44129.TYK2_jmedchem.9b00444_most_rigid	completed	Results	Missing	62	False	0.808 (3)	0.524 (3)	0.308 (1)	0.214 (1)	0.785 (3)	0.517 (3)	N.2	1

Results
Ligand-Based Modelling

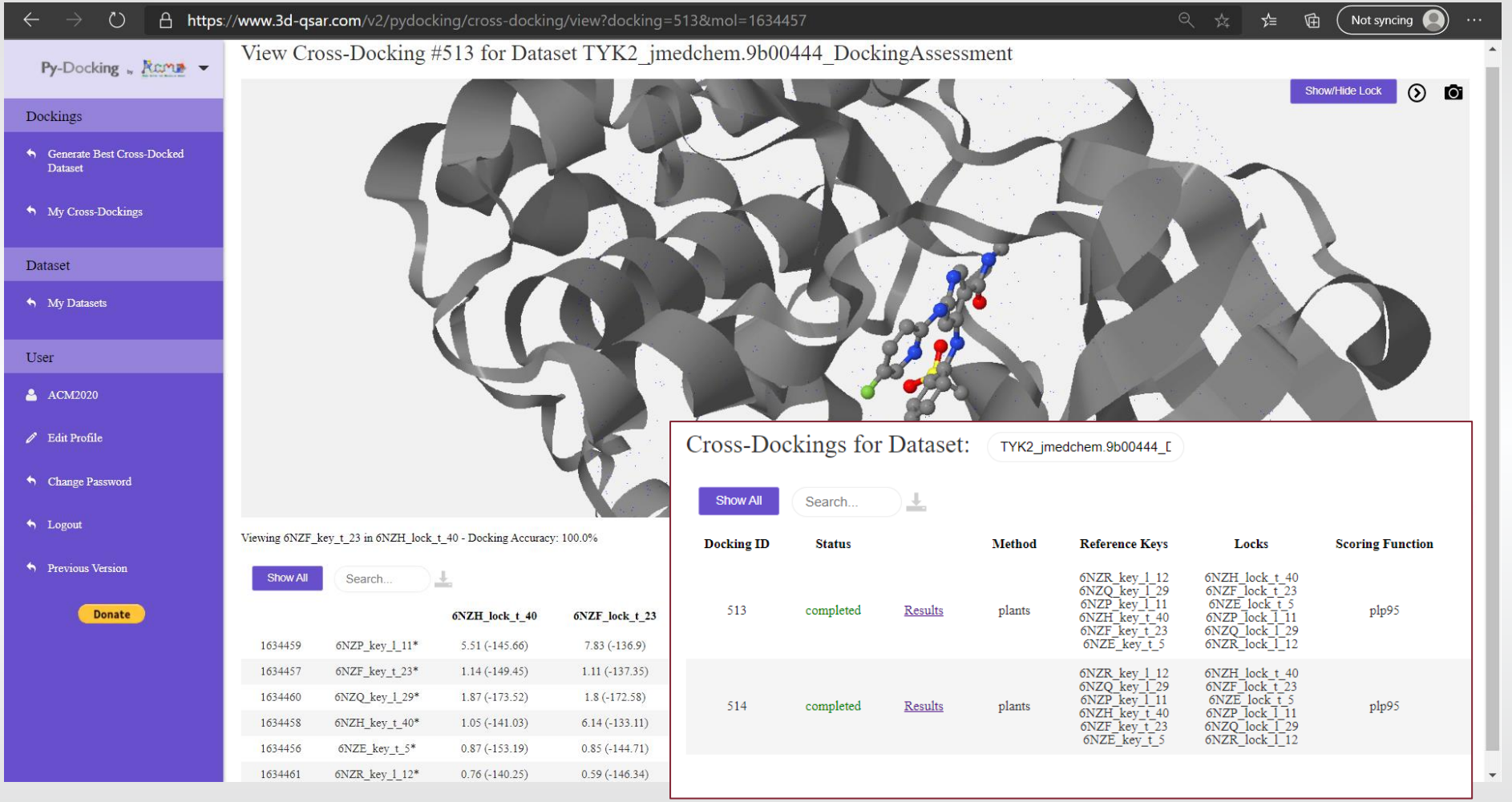


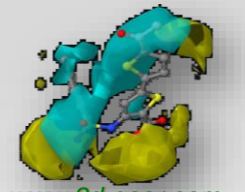
Structure-Based Modelling



The use of the 3d-qsar.com portal to derive ligand-based and structure-based models from scratch

Results
Structure-Based Modelling





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Results
Structure-Based Modelling

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https://www.3d-qsar.com/v2/pycomfa/comfa?data_set=44258

Not syncing

Py-CoMFA by RCMD

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3-D QSAR Models for Dataset: → 526.TYK2_jmedchem.9b0

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Model ID	Status		Maps	nTrMols	External Pred	r² STE(PC)	q² STE(PC)	r² ELE(PC)	q² ELE(PC)	r² BOTH(PC)	q² BOTH(PC)	Probe	Probe Charge	Min Sigma	Scaling	Max N Components
192205	completed	Results	Available	62	False	0.824 (4)	0.521 (4)	0.065 (1)	0.017 (1)	0.861 (5)	0.542 (5)	O.2	1	0.200	true	8
192535	completed	Results	Missing	62	False	0.939 (5)	0.595 (5)	0.442 (3)	0.171 (3)	0.935 (6)	0.514 (6)	C.3.H3	1	0.900	true	8
192531	completed	Results	Missing	62	False	0.932 (5)	0.538 (5)	0.735 (4)	0.326 (4)	0.897 (5)	0.513 (5)	C.3.H3	1	0.900	true	8
192828	completed	Results	Missing	62	False	0.937 (5)	0.539 (5)	0.786 (5)	0.289 (5)	0.958 (7)	0.512 (7)	N.2	1	0.700	true	8
192211	completed	Results	Missing	62	False	0.916 (5)	0.535 (5)	0.548 (3)	0.171 (3)	0.893 (5)	0.512 (5)	O.2	1	0.900	true	8
192181	completed	Results	Missing	62	False	0.940 (5)	0.491 (5)	0.738 (4)	0.315 (4)	0.906 (5)	0.487 (5)	O.2	1	0.800	true	8
192827	completed	Results	Missing	62	False	0.843 (4)	0.464 (4)	0.543 (4)	0.133 (4)	0.882 (5)	0.486 (5)	C.3.H3	1	0.500	true	8
192207	completed	Results	Missing	62	False	0.941 (5)	0.515 (5)	0.872 (6)	0.295 (6)	0.966 (7)	0.485 (7)	O.2	1	0.200	true	8
192550	completed	Results	Missing	62	False	0.942 (5)	0.493 (5)	0.776 (5)	0.326 (5)	0.903 (5)	0.485 (5)	N.2	1	0.400	true	8
192176	completed	Results	Missing	62	False	0.985 (8)	0.582 (8)	0.748 (5)	0.271 (5)	0.897 (5)	0.485 (5)	C.3.H3	1	0.300	true	8
192552	completed	Results	Missing	62	False	0.872 (4)	0.516 (4)	0.502 (3)	0.142 (3)	0.885 (5)	0.484 (5)	N.2	1	0.700	true	8
192507	completed	Results	Missing	62	False	0.873 (4)	0.516 (4)	0.390 (2)	0.127 (2)	0.886 (5)	0.483 (5)	O.2	1	0.700	true	8
192206	completed	Results	Missing	62	False	0.889 (4)	0.494 (4)	0.867 (6)	0.295 (6)	0.905 (5)	0.480 (5)	O.2	1	0.200	true	8
192202	completed	Results	Missing	62	False	0.988 (8)	0.533 (8)	0.929 (8)	0.479 (8)	0.904 (5)	0.479 (5)	O.2	1	0.500	true	8
192843	completed	Results	Missing	62	False	0.944 (5)	0.509 (5)	0.797 (5)	0.302 (5)	0.898 (5)	0.478 (5)	O.2	1	0.600	true	8
192197	completed	Results	Missing	62	False	0.942 (5)	0.488 (5)	0.804 (5)	0.286 (5)	0.903 (5)	0.478 (5)	O.2	1	0.500	true	8
192194	completed	Results	Missing	62	False	0.943 (5)	0.490 (5)	0.794 (5)	0.304 (5)	0.902 (5)	0.478 (5)	O.2	1	0.300	true	8
192210	completed	Results	Missing	62	False	0.860 (4)	0.456 (4)	0.070 (1)	0.014 (1)	0.881 (5)	0.476 (5)	O.2	1	0.400	true	8
192554	completed	Results	Missing	62	False	0.931 (5)	0.509 (5)	0.420 (2)	0.106 (2)	0.889 (5)	0.474 (5)	C.3.H3	1	0.400	true	8

The use of the 3d-qsar.com portal to derive ligand-based and structure-based models from scratch

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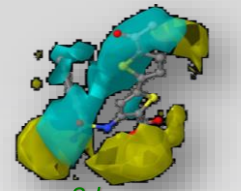

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Results
Structure-Based Modelling

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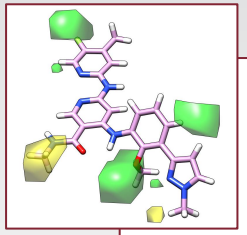

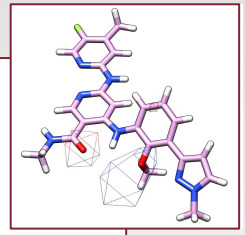

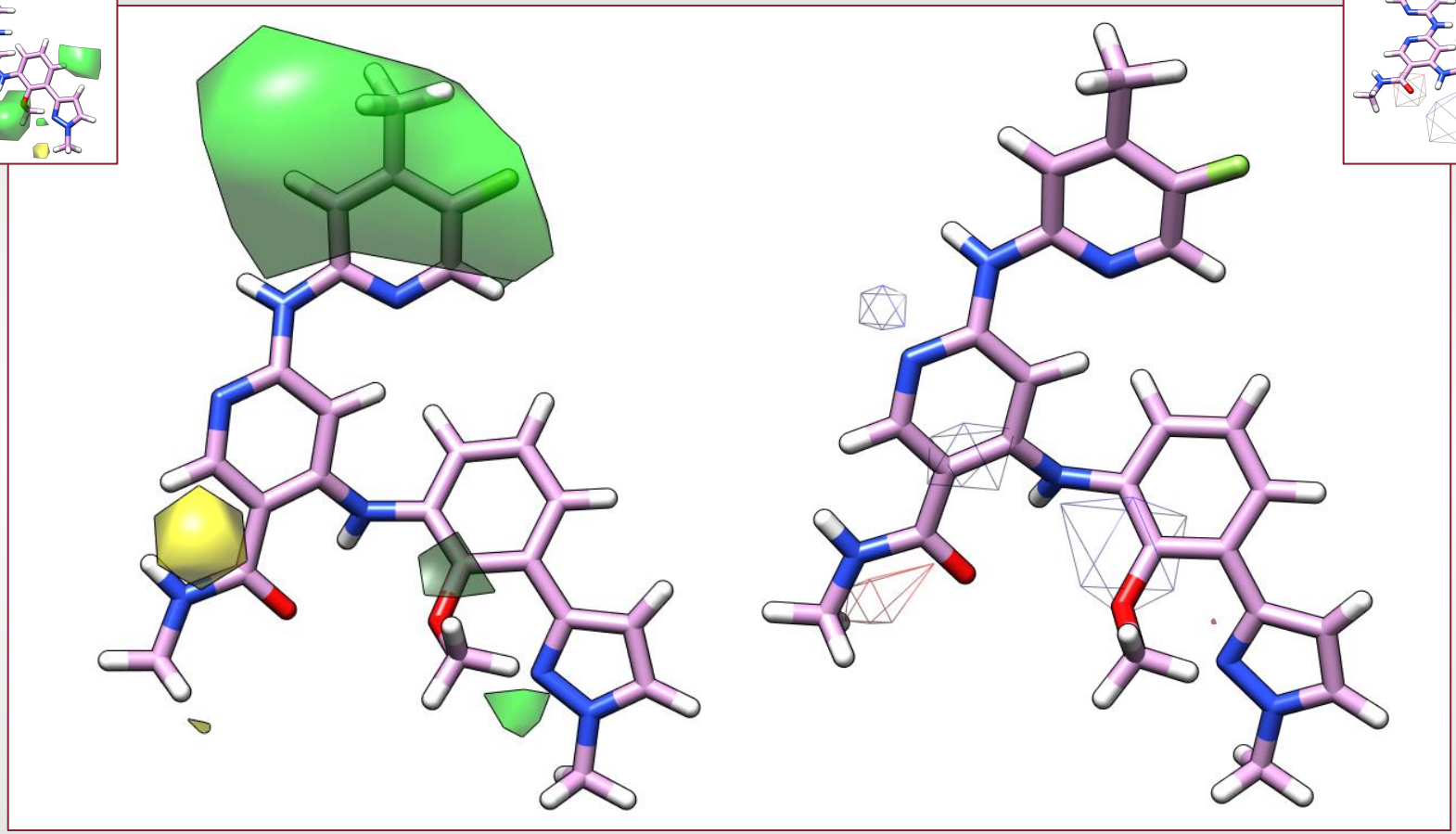

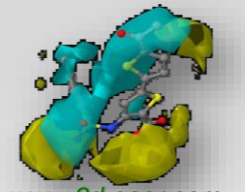

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https://www.3d-qsar.com/v2/pycombine/combine?data_set=44258

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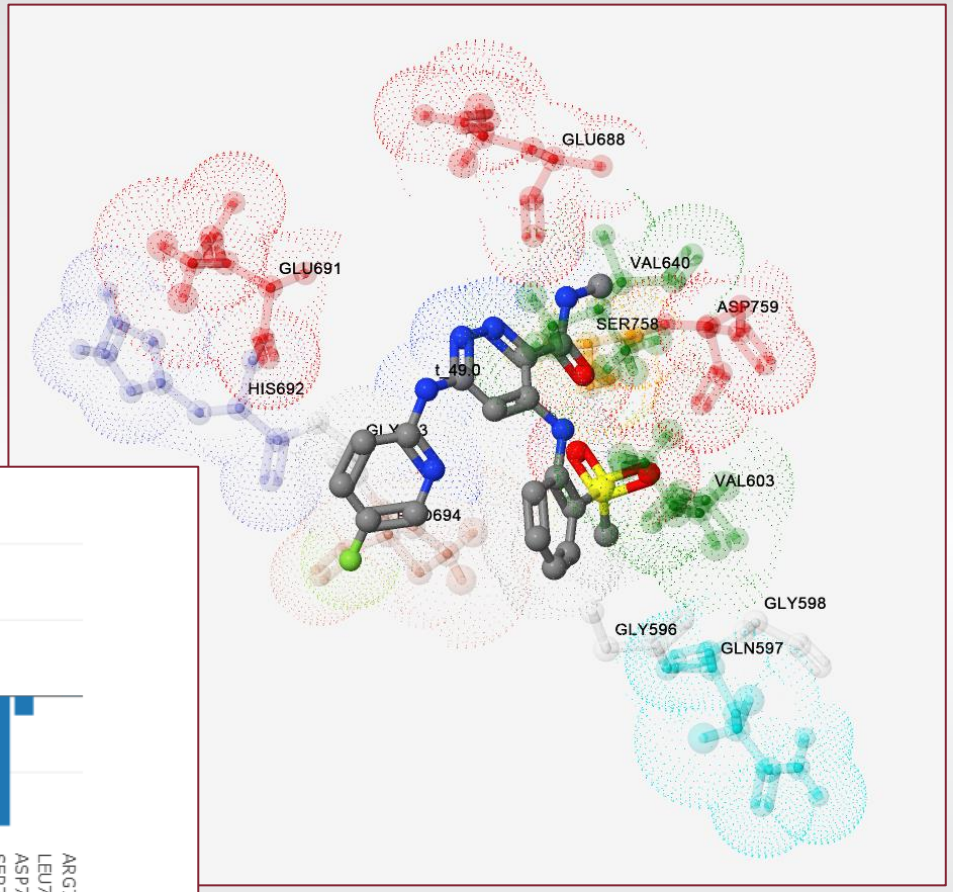
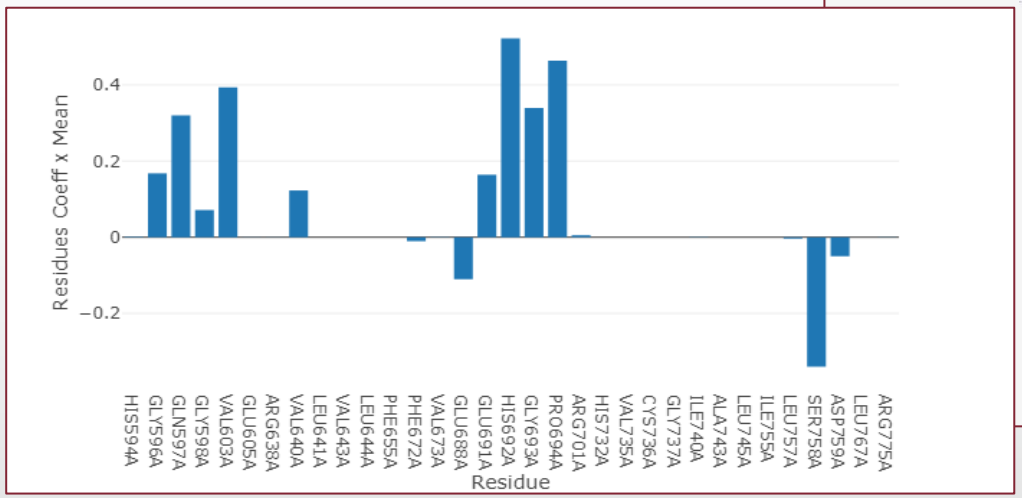
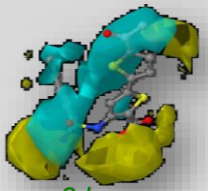
ID	Status		External Pred	Fields	r² (PC)	q² (PC)	SA Opt	Scaling	Max N Components	Score Func	CV Groups	CV Iterations	CV Random	Min SDEP Increment	Y-Scrambling	Y-S Iterati
801	completed	Results	False	STE	0.579 (5)	0.433 (5)	True	True	8	LOO	5	10	True	0	False	10
768	completed	Results	False	STE	0.53 (4)	0.291 (4)	False	True	8	LOO	5	10	True	0	False	10
807	completed	Results	False	STE	0.53 (4)	0.291 (4)	False	True	8	LOO	5	10	True	0	True	10
762	completed	Results	False	STE.DRY	0.664 (7)	0.282 (7)	False	True	8	LOO	5	10	True	0	False	10
766	completed	Results	False	DRY.HB	0.584 (5)	0.272 (5)	False	True	8	LOO	5	10	True	0	False	10
769	completed	Results	False	DRY	0.645 (8)	0.253 (8)	False	True	8	LOO	5	10	True	0	False	10
758	completed	Results	False	STE.ELE.DRY	0.606 (4)	0.218 (4)	False	True	8	LOO	5	10	True	0	False	10
764	completed	Results	False	ELE.DRY	0.525 (4)	0.195 (4)	False	True	8	LOO	5	10	True	0	False	10
761	completed	Results	False	STE.ELE	0.579 (4)	0.148 (4)	False	True	8	LOO	5	10	True	0	False	10
763	completed	Results	False	STE.HB	0.353 (1)	0.112 (1)	False	True	8	LOO	5	10	True	0	False	10
770	completed	Results	False	HB	0.274 (1)	0.066 (1)	False	True	8	LOO	5	10	True	0	False	10
723	completed	Results	False	STE.ELE.DRY.HB	0.238 (1)	0.064 (1)	False	True	8	LOO	5	10	True	0	False	10
760	completed	Results	False	ELE.DRY.HB	0.208 (1)	0.057 (1)	False	True	8	LOO	5	10	True	0	False	10
759	completed	Results	False	STE.ELE.HB	0.219 (1)	0.045 (1)	False	True	8	LOO	5	10	True	0	False	10
765	completed	Results	False	ELE.HB	0.187 (1)	0.038 (1)	False	True	8	LOO	5	10	True	0	False	10
767	completed	Results	False	ELE	0.102 (1)	0.004 (1)	False	True	8	LOO	5	10	True	0	False	10

Results
Structure-Based Modelling





The use of the 3d-qsar.com portal to derive ligand-based and structure-based models from scratch



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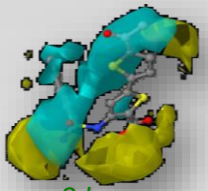
Conclusion and Perspectives
Where We Are

- 3d-qsar.com proved to be an effective platform for building LB and SB 3D-QSAR models
- A first almost-full LB and SB modeling profile was generated for 62 TYK2 JH2-binding inhibitors
- The models shed light on possible modifications to increase inhibition potency



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Conclusion and Perspectives
Where We Are Headed

The project will be expanded upon by an interfaculty team to:

- **make alignments using all alignment methods and scoring functions on all conformational analysis methods**
- **make alignments on the conformations**
- **make LB and SB pharmacophore alignments (ligand scout)**
- **make 3D-QSAR and COMBINE models with different methods of calculating interactions (3d-qsar.com 3.0)**

Thank You for Listening