MOLECULAR FIELD TOPOLOGY ANALYSIS AS AN ADVANCED TOOL FOR QSAR/QSPR STUDIES

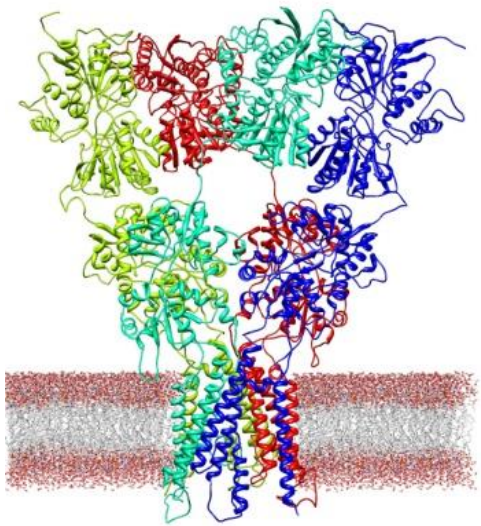
Vladimir A. Palyulin,
Eugene V. Radchenko,
Nikolay S. Zefirov

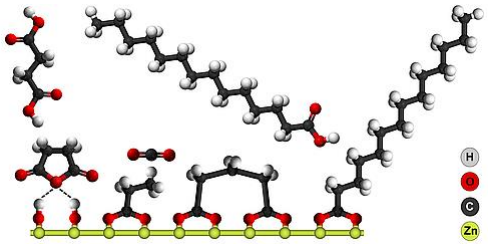
Department of Chemistry,
Lomonosov Moscow State University,
Moscow, 119991 Russia

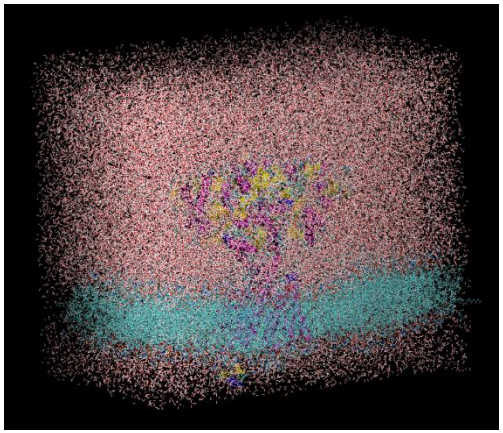
Design of Compounds/Materials with Required Activities/Properties:

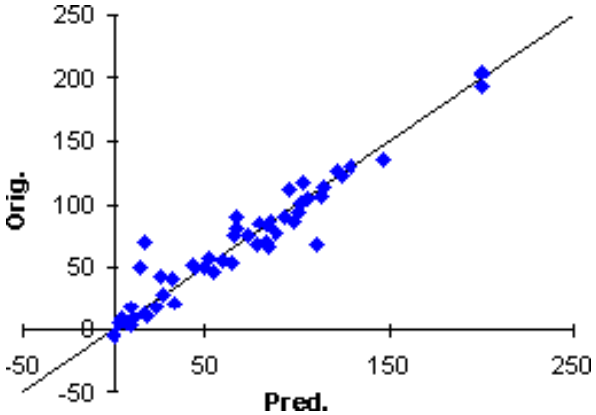
Molecular Modelling, Docking, Molecular Dynamics

QSAR/QSPR

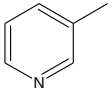
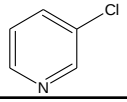
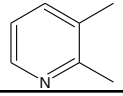
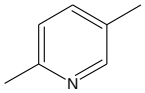
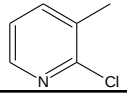
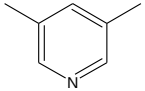
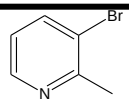
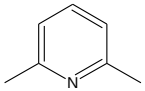








QSAR/QSPR: General Approach

	A	Structure	Descriptors			
Training	–		–	–	–	–
	–		–	–	–	–
	–		–	–	–	–
	–		–	–	–	–
Test	–		–	–	–	–
	–		–	–	–	–
New	?		–	–	–	–
	?		–	–	–	–

Model

F: *A*=F(*S*)

Predictivity

Δ*A*

Prediction

PROPERTIES

Physico-chemical properties:

Boiling points, melting points, density, viscosity, surface tension, solubility in various solvents, lipophilicity, magnetic susceptibility, retention indices, enthalpy of formation, etc.

Biological activity:

IC_{50}, EC_{50}, LD_{50}, MEC, ILS, etc.

DESCRIPTORS (“global” and “local”)

Topological indices

Quantum-chemical

Physico-chemical

Fragmental

Solvation Index. Prediction of Non-Specific Solvation Enthalpy of Organic Compounds

Solvation enthalpy (kJ/mol)

$$\Delta H_{solv}^{A/Y} = 4.52 + 9.04\,{}^{1}\chi^{S}$$

n **= 141** ***R*** **= 0.985** ***s*** **= 2.1**

Vaporization enthalpy (kJ/mol)

$$\Delta H_{vap}^{A} = 4.13 + 9.52\,{}^{1}\chi^{S} + 0.827\,\mu^{2}$$

n **= 528** ***R*** **= 0.989** ***s*** **= 2.0**

μ – dipole moment

${}^{1}\chi^{S}$ – 1-st order solvation topological index

Z_i – period number (measure of atom size)

δ_i – number of non-hydrogen neighbors

$$ {}^{1}\chi^{S} = \frac{1}{4}\sum_{(bonds)} \frac{Z_i Z_j}{\sqrt{\delta_i \delta_j}} $$

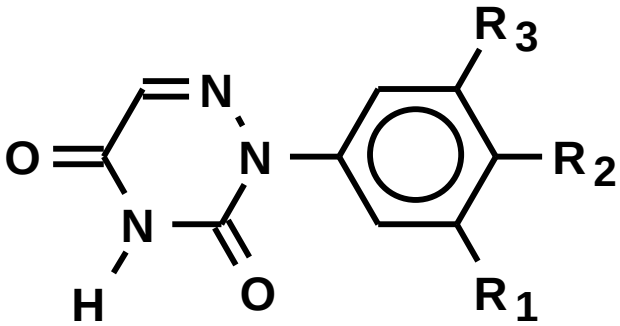
I.S.Antipin, N.A.Arslanov, V.A.Palyulin, A.I.Konovalov, N.S.Zefirov
Dokl. Akad. Nauk,1993, 331(2), 173-176.

Fragmental Descriptors

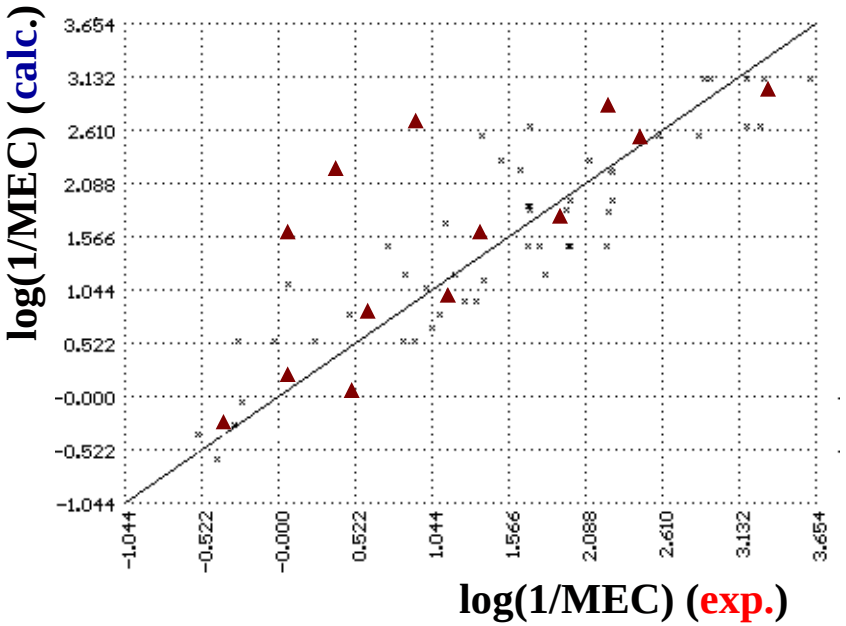
The numbers of fragments of various kind and various size (chains, cycles, branched fragments) in a molecule with several levels of classification of atoms. For each molecule hundreds of fragmental descriptors can be computed.

Good correlations with various physico-chemical properties (enthalpy of formation, boiling points, density of organic liquids, surface tension, lipophilicity, etc.), could be used for prediction of mutagenicity, logBB, etc.

Fragmental Approach: Anticoccidial Activity of Triazines



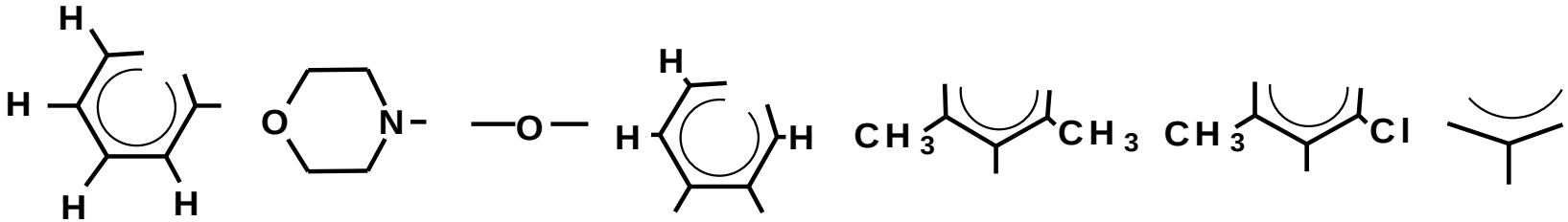
Training and Test (▲) sets:



log(1/MEC) = -0.258 Fr1 + 0.594 Fr2 - -0.734 Fr3 - 0.255 Fr4 - 0.558 Fr5 - -0.452 Fr6 + 0.639Fr7 -0.728,

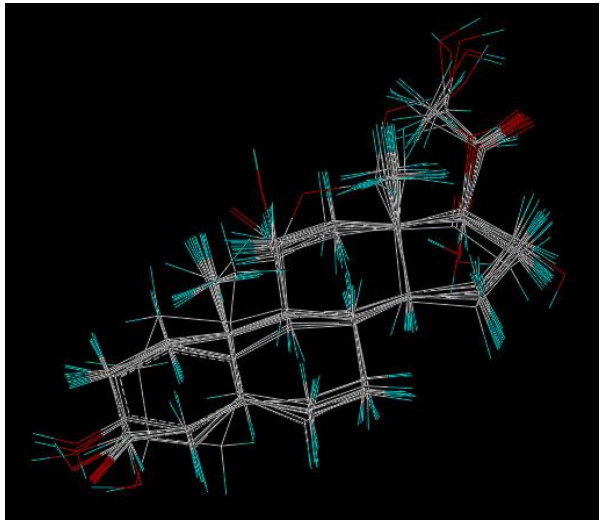
n=54, R=0.90, s=0.48

where Fr i - the number of the fragments :



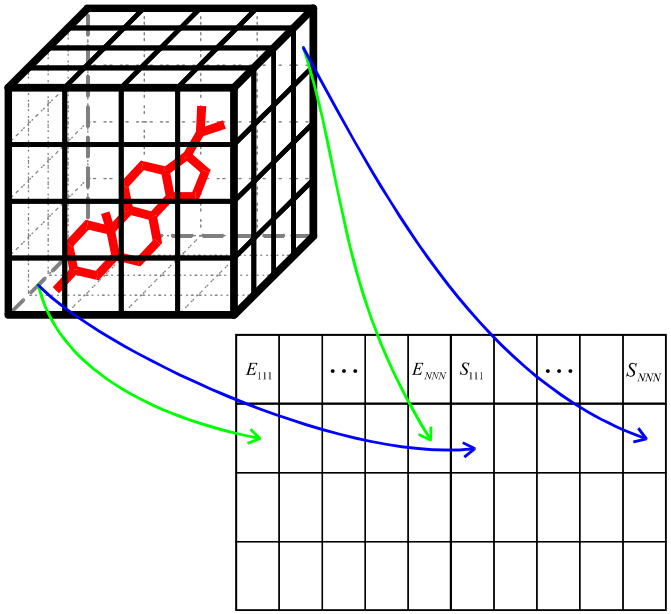
Fr1 Fr2 Fr3 Fr4 Fr5 Fr6 Fr7

Comparative Molecular Field Analysis (CoMFA)



$$E = \frac{1}{4\pi\varepsilon_0\varepsilon}\sum_i \frac{q_i\, q_p}{d_{ip}}$$

$$S = \sum_i \left[-\frac{A_{ip}}{d_{ip}^6} + \frac{B_{ip}}{d_{ip}^{12}} \right]$$



3D alignment could be difficult for flexible structures

Molecular Field Topology Analysis (MFTA)

The main steps of an MFTA study:

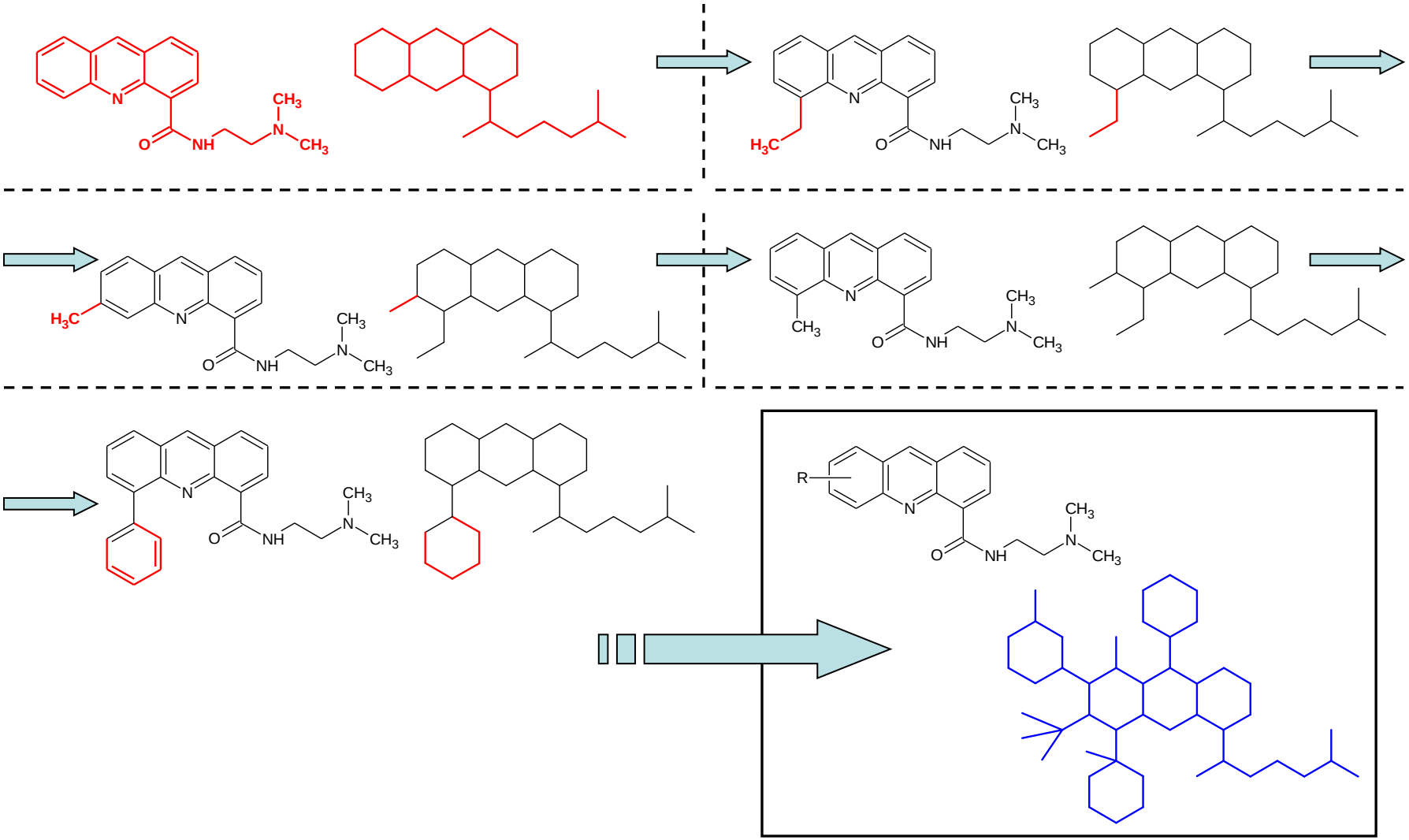
Construction of a ***molecular supergraph*** *(MSG)* that allows the superposition of any training set structure

Analysis of ***local physico-chemical molecular characteristics*** (atom and bond properties) in a uniform manner for all training set structures leading to a predictive PLS model

Radchenko E.V., Palyulin V.A., Zefirov N.S., in *Chemoinformatics Approaches to Virtual Screening*, ed. by A.Varnek, A.Tropsha, RSC, 2008, 150-181.

Palyulin V.A., Radchenko E.V., Zefirov N.S. J. Chem. Inf. Comp. Sci. 2000, 40, 659-667.

Molecular Supergraph



Local Molecular Descriptors

- **Electrostatic**
  - Atomic charge Q (electronegativity equalization approach: Gasteiger)
  - Absolute atomic charge $Q_a = abs(Q)$
- **Steric**
  - Van der Waals radius R (Bondi)
  - Group van der Waals radius R_g (atom+hydrogens)
  - Van der Waals radius of first environment R_e (atom+neighbours)
  - Exposed van der Waals surface of an atom S
  - Relative steric exposure $A=S/S_{free}$
- **Lipophilic**
  - Atomic lipophilicity contribution L_a (environment-dependent: Ghose, Crippen)
  - Group lipophilicity L_g (atom+hydrogens)
- **Hydrogen bonding**

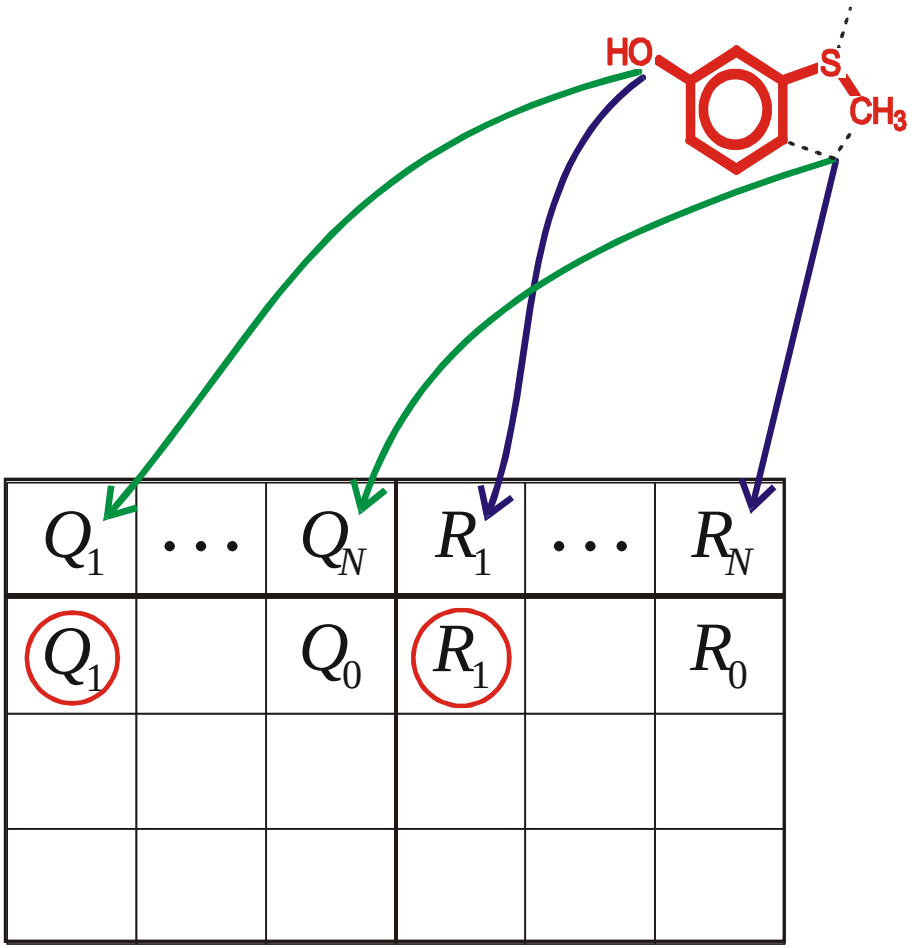
Hydrogen bond donor (H_d) and acceptor (H_a) ability of an atom (Abraham)

Construction of a Descriptor Matrix

Controlled by structure mapping to the supergraph

For the occupied positions: local property on a corresponding atom

For unoccupied positions: neutral value of local property



Statistical analysis

- Partial Least Squares Regression (PLS) Modelling
- Analysis of contribution to activity for each local property in every position of molecular supergraph
- Two-phase descriptor selection process

  Removal of low-variable descriptors

  Optional Q^2-guided selection of optimal descriptor subset using genetic algorithm
- Stable cross-validation (SCV) procedure to eliminate dependence on test set split and chance correlations

MFTA-Oriented Structure Generation

MFTA (and most other QSAR techniques) provide meaningful predictions only within the same general chemical class

Need for a specialized MFTA-oriented generation

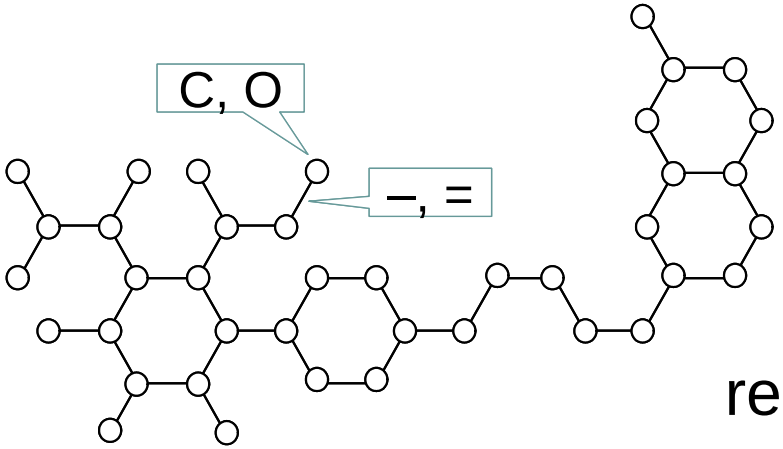
Structural constraints:

- The number of substituted positions in the central fragment
- Forbidden molecular fragments (“bad list”)
- Molecular mass

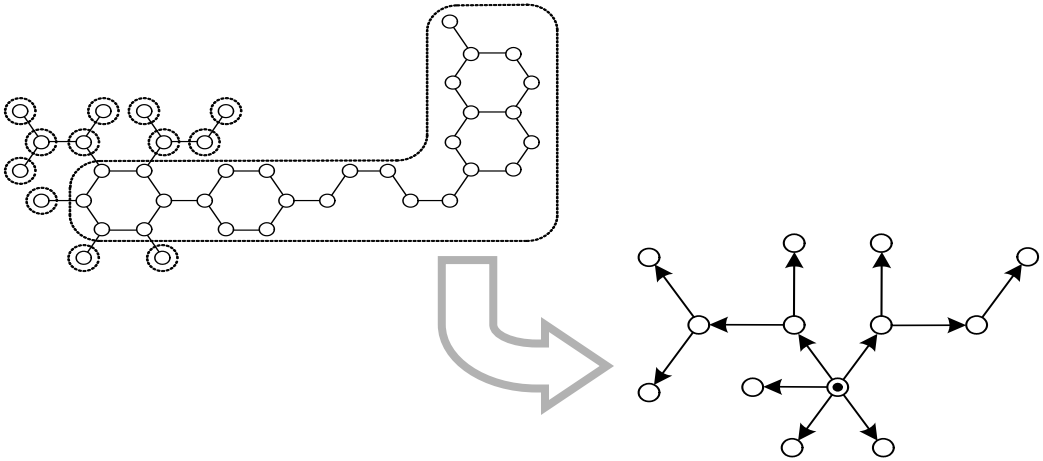
Generation modes: Deterministic or Stochastic

MFTA-Oriented Structure Generation

Analysis of a training set



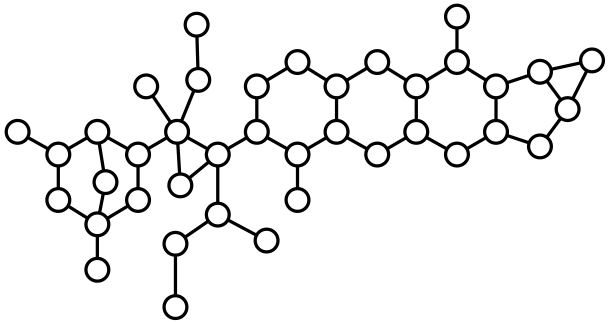
Fragmental supergraph – compact representation of all possible structures



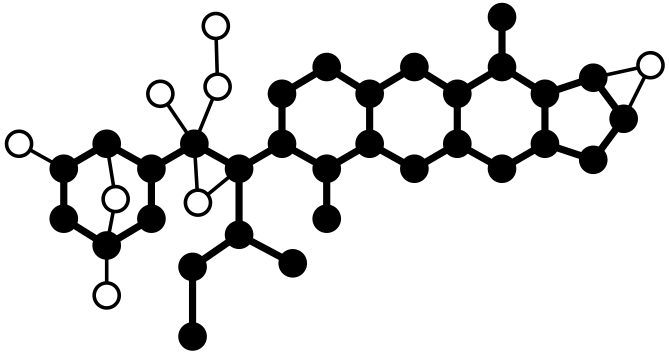
Positive AMPA receptor modulators. Benzotriazinone and benzopyrimidinone derivatives

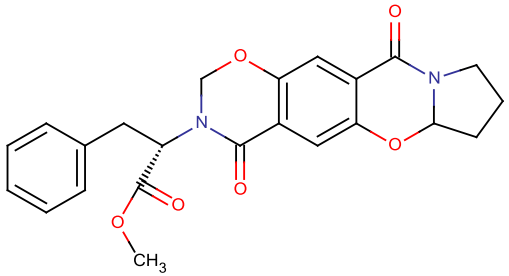
Total 37 compounds
Excluded 3 compounds with no or very low activity
Training set: 34 compounds of consistent stereochemistry
Endpoint: $pEC_{2x} = \log(1 / EC_{2x})$

Molecular Field Topology Analysis (MFTA)



Molecular supergraph





Example mapping

Muller R. et al., *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6170-6175.
Palyulin V.A., Radchenko E.V., Zefirov N.S., *J. Chem. Inf. Comput. Sci.*, **2000**, *40*, 659-667.

MFTA models of ampakine activity

Local molecular descriptors:

Q – **atomic charge** (electronegativity equalization approach)

R_e – **effective group van der Waals radius** (steric requirements of central atom and attached non-hydrogen atoms)

L_g – **group lipophilicity** (contributions of central atom and attached hydrogens)

H_d – **hydrogen bond donor ability**

H_a – **hydrogen bond acceptor ability**

Descriptors	N_F	R^2	*RMSE*	Q^2	*RMSEcv*
Q, R_e	2	0.73	0.54	0.44	0.74
Q, R_e, L_g	2	0.80	0.47	0.47	0.72
Q, R_e, H_d, H_a	2	0.73	0.54	0.45	0.73
Q, R_e, L_g, H_d, H_a	2	0.78	0.49	0.49	0.71

N = number of compounds, N_F = number of factors in the PLSR model,
R^2 = squared correlation coefficient, ***RMSE*** = root-mean-square error,
Q^2 = cross-validation parameter, ***RMSEcv*** = root-mean-square error of cross validation

Optimal MFTA model

Local molecular descriptors:

Q **– atomic charge**

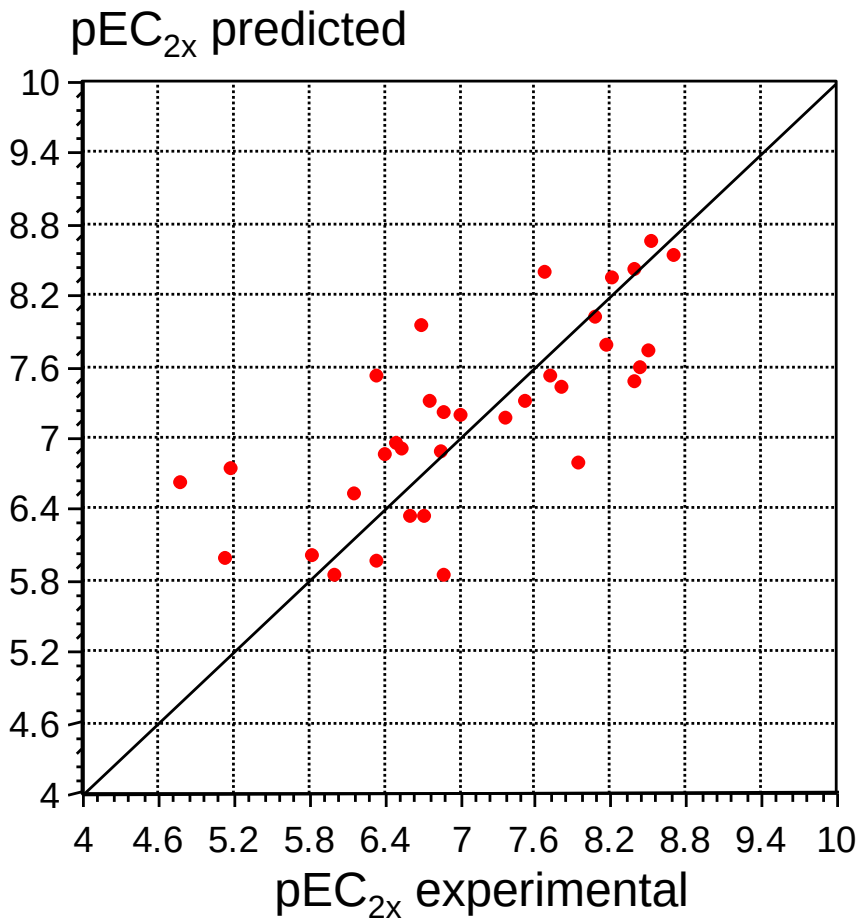
R_e **– effective group van der Waals radius**

L_g **– group lipophilicity**

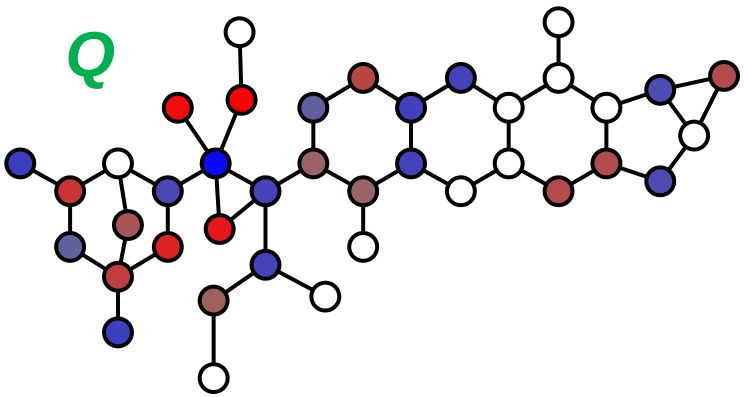
R^2 = 0.80

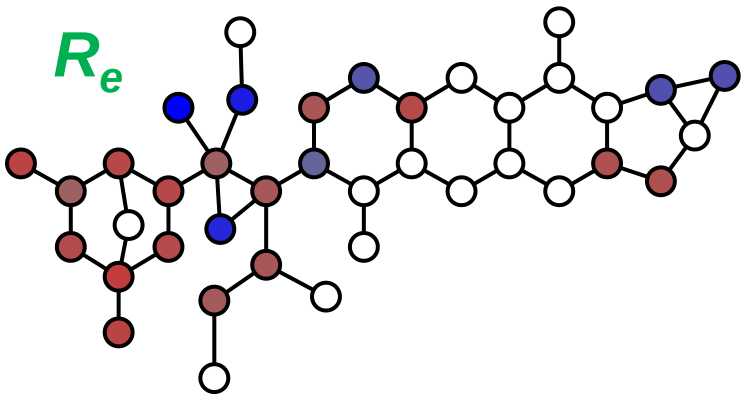
Q^2 = 0.47

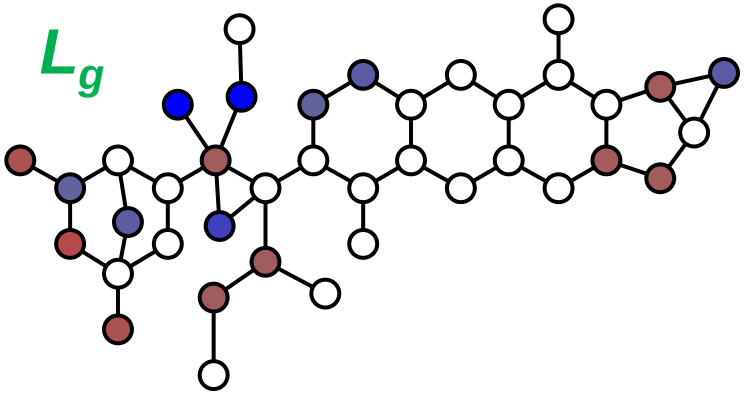
RMSEcv = 0.72



MFTA activity maps







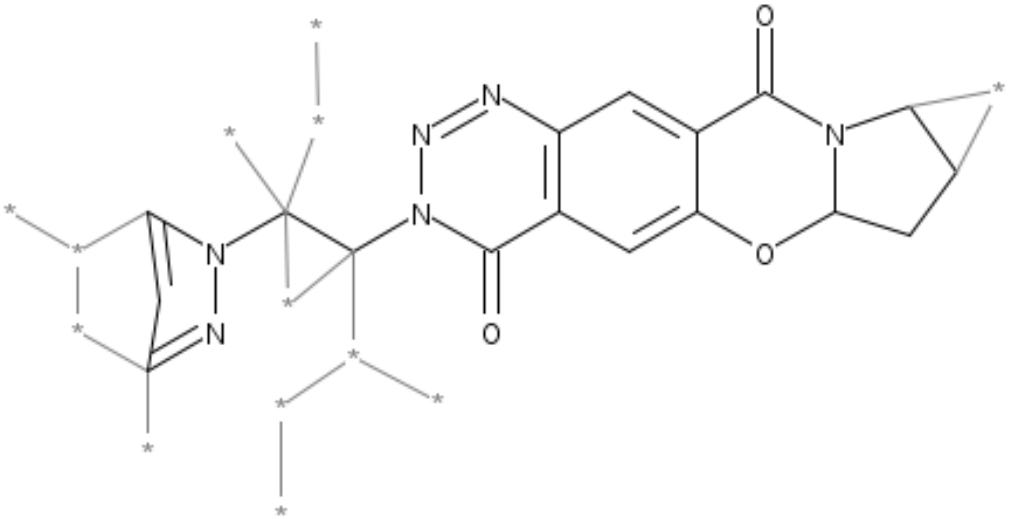
Activity is increased by F and other acceptor groups in phenyl group and α-position but not in β-position

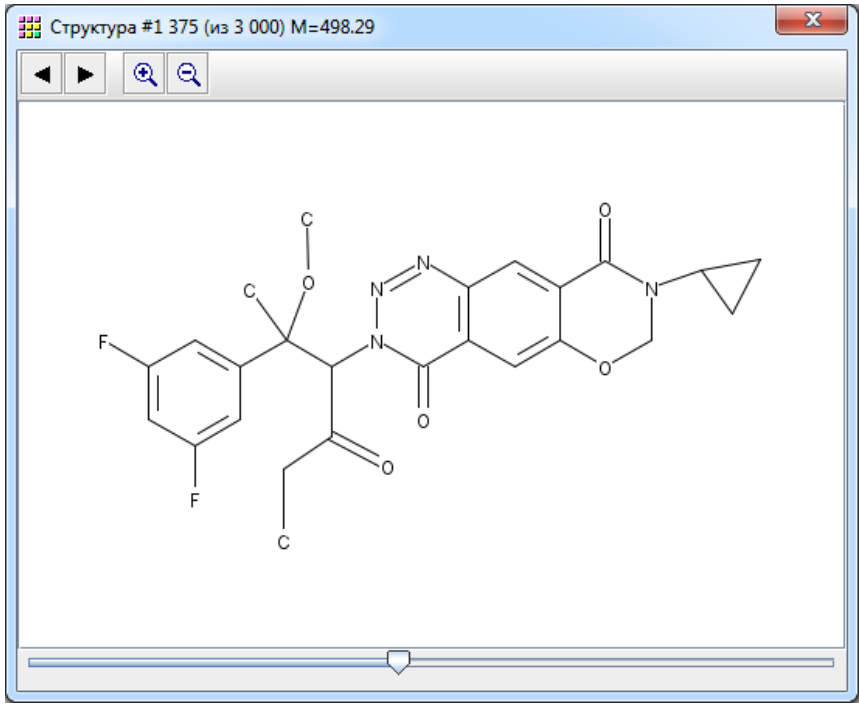
Cyclopropyl group is not desirable

Red: activity increases **Blue: activity decreases**

Molecular Design and Virtual Screening of Promising Structures

Generated structure library was built using specialized MFTA-oriented structure generator in stochastic mode – 3000 out of 14708 structures





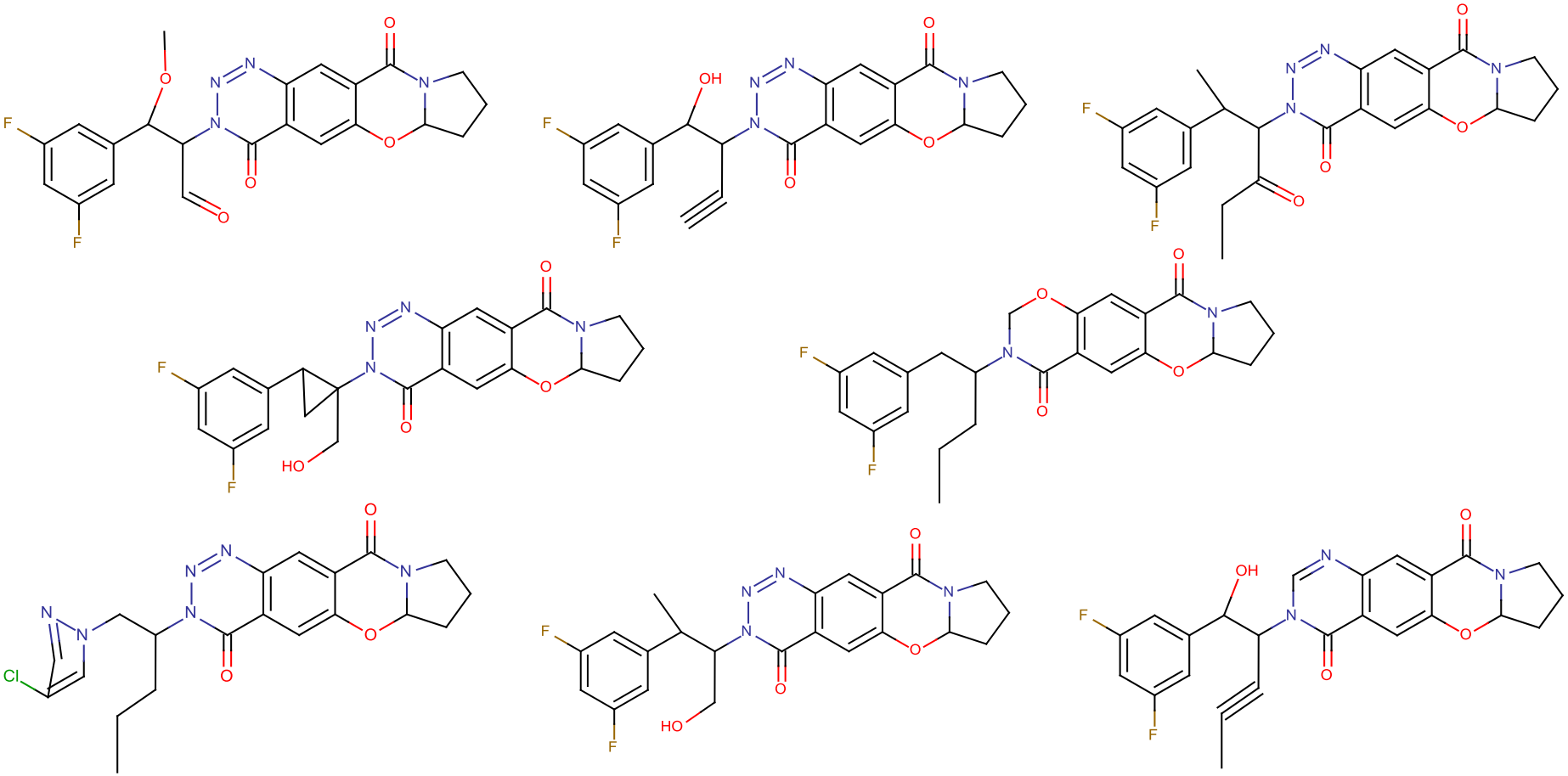
Melnikov A.A., Palyulin V.A., Radchenko E.V., Zefirov N.S. *Doklady Chemistry*, 2007, *415*, 196-199.
Radchenko E.V., Palyulin V.A., Zefirov N.S., in *Chemoinformatics Approaches to Virtual Screening*, ed. by A.Varnek, A.Tropsha, RSC, 2008, 150-181.

Molecular Design and Virtual Screening of Promising Structures

Selection of desired activity profile

– 49 structures have predicted $pEC_{2x} > 8$

Examples of proposed structures



Application Example

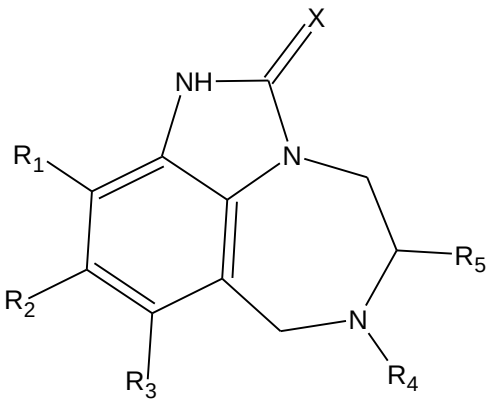
Anti-HIV Activity of Tetrahydroimidazobenzodiazepinone (TIBO) Derivatives: Reverse Transcriptase Inhibition

73 compounds

Kukla M.J. et al. *J. Med. Chem.* 1991, 34, 746-751

Ho W. et al. *J. Med. Chem.* 1995, 38, 794-802

Breslin H.J. et al. *J. Med. Chem.* 1995, 38, 771-793.



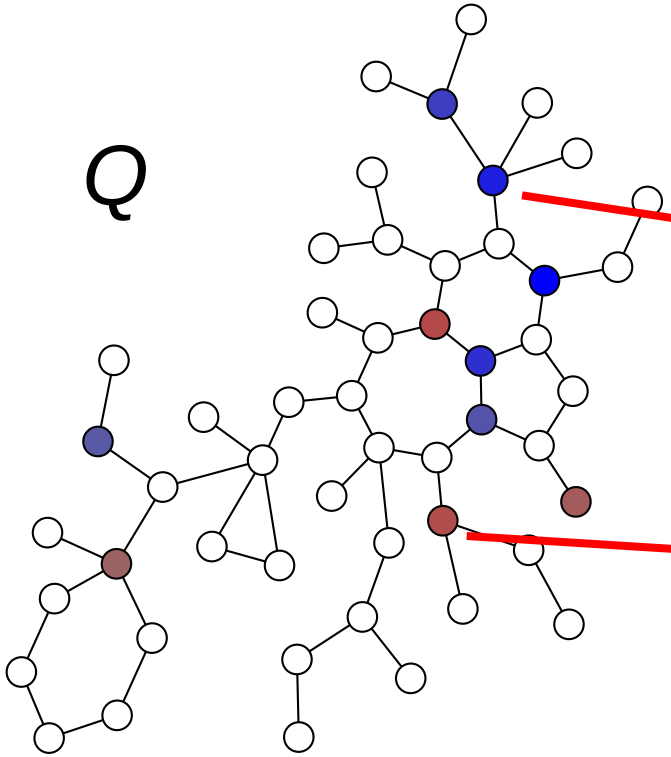
Activity: log (1/IC_{50})

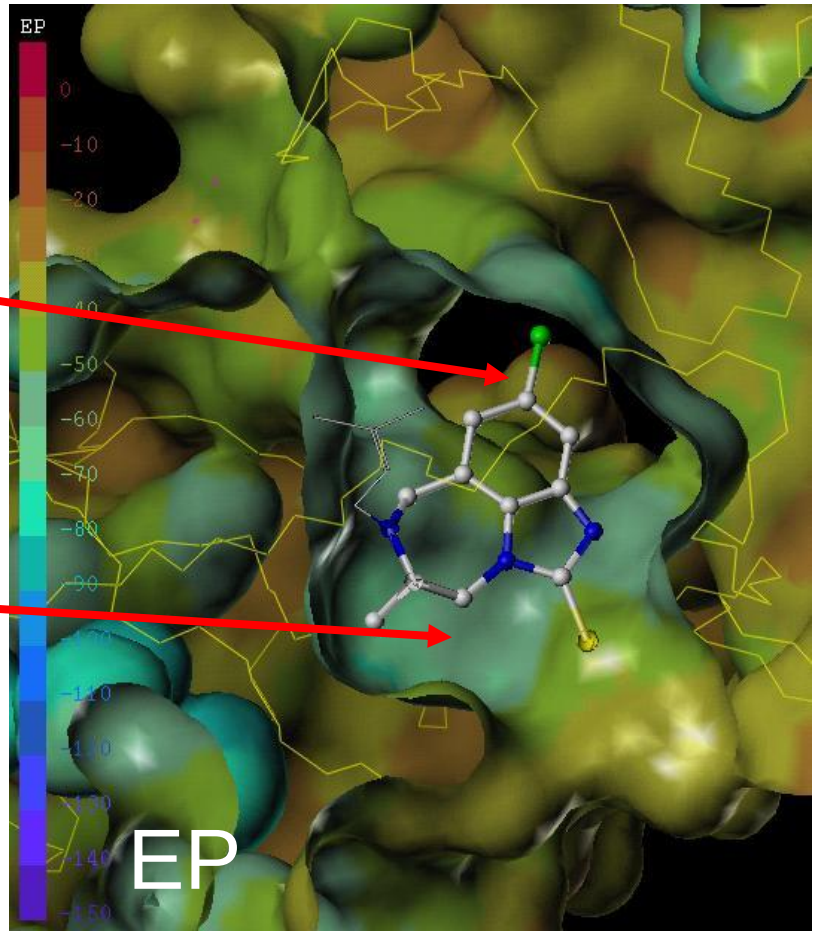
6 MFTA models for different local descriptors

Descriptor set	F	R	Q^2
Q	5	0.927	0.597
R	6	0.925	0.695
$Q\ R$	5	0.932	0.626
$Q\ R\ L_g$	**5**	**0.942**	**0.686**
$Q\ R\ H_d\ H_a$	6	0.943	0.672
$Q\ R\ H_d\ H_a\ L_g$	6	0.951	0.626

Anti-HIV Activity of TIBO Derivatives (Reverse Transcriptase Inhibition)

Complementarity of MFTA descriptor contributions and biotarget properties: 1tvr + 9-Cl-TIBO





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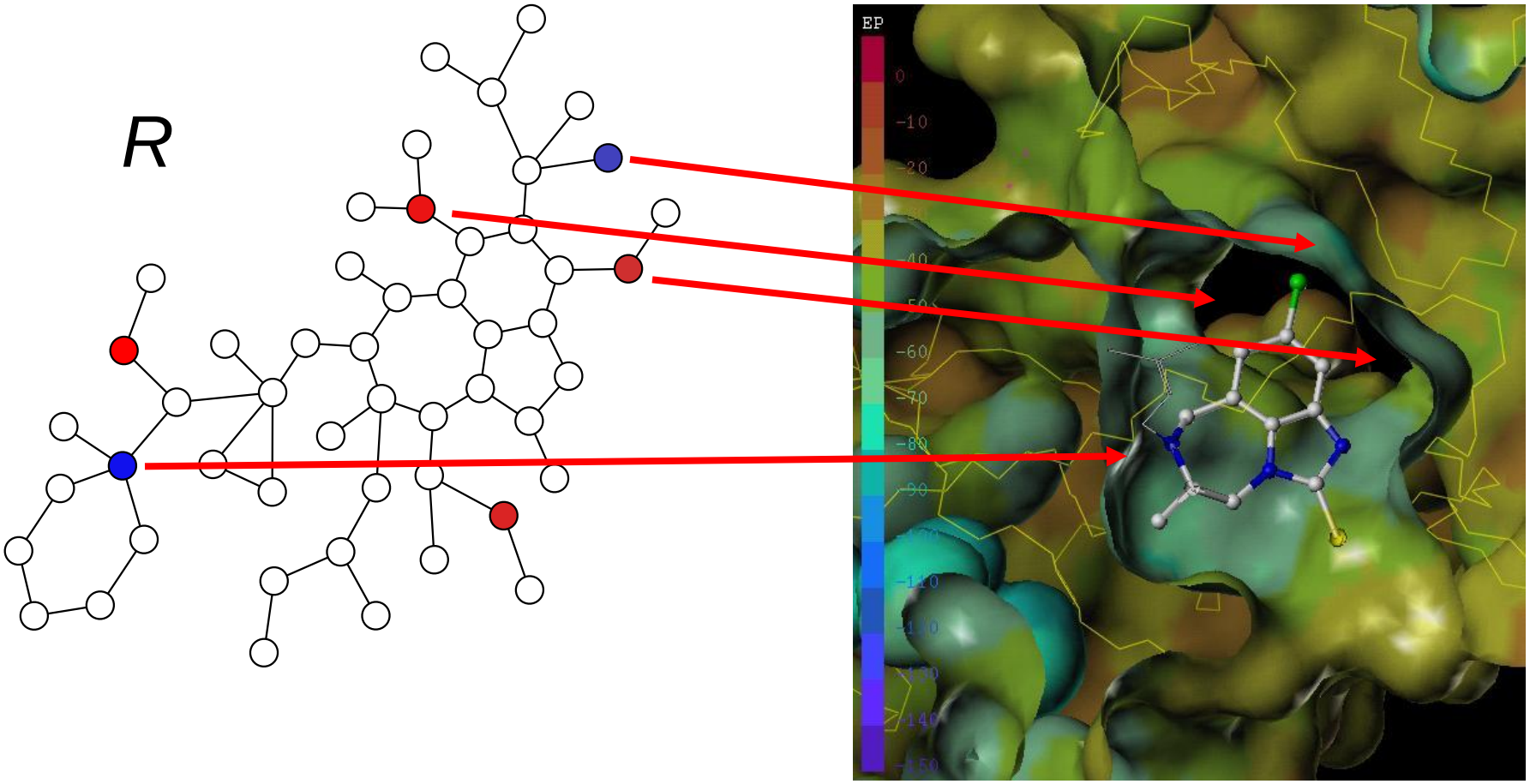

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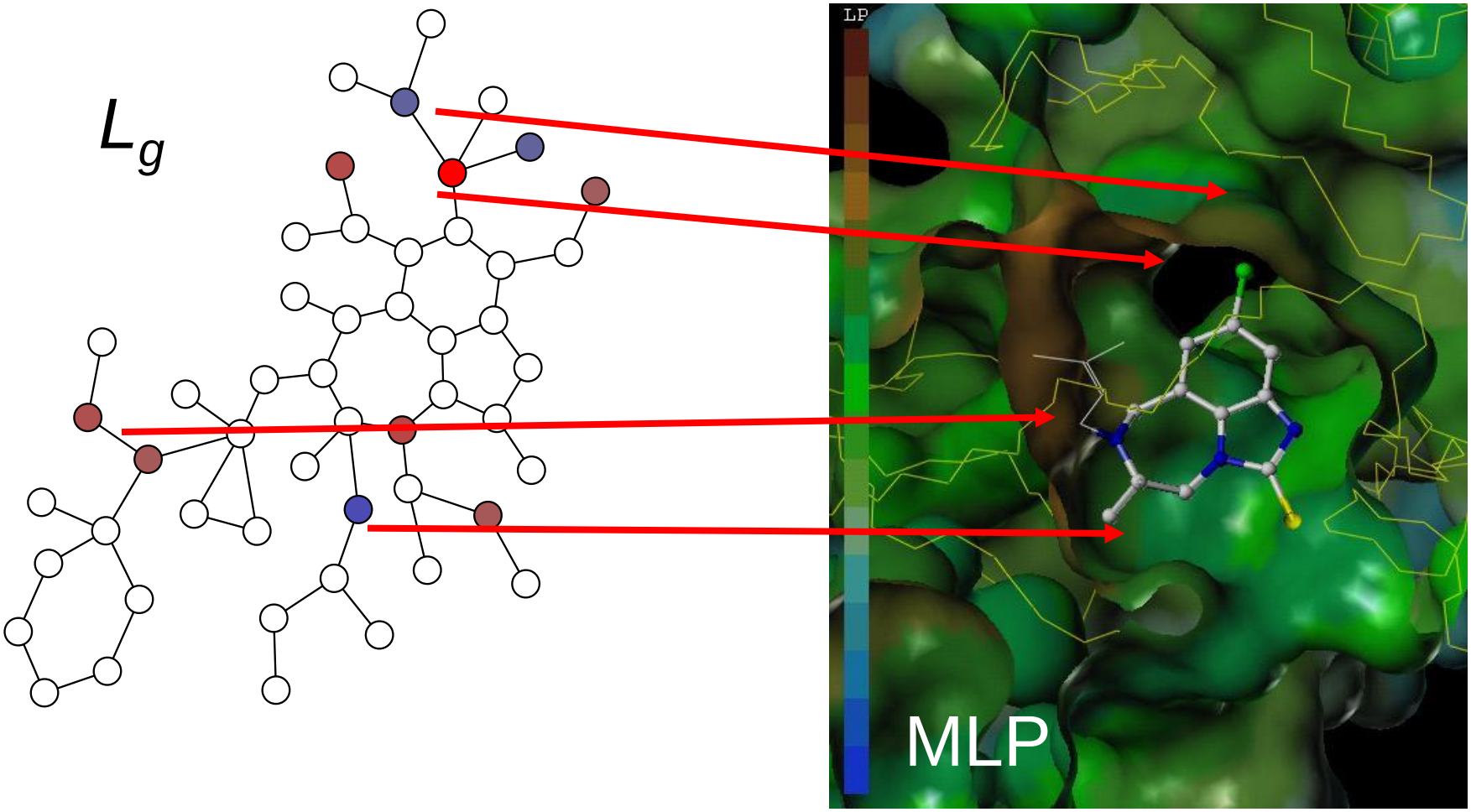
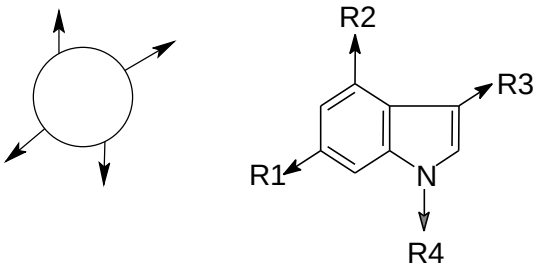


Structure generation

Central fragment

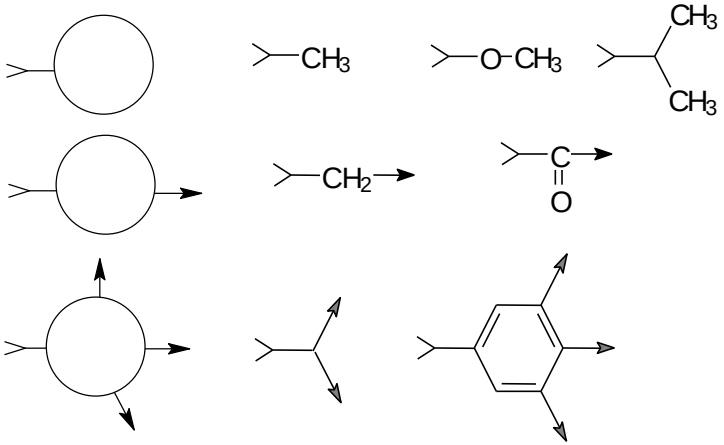


Tree-structured substituents constructed from three types of micro fragments:

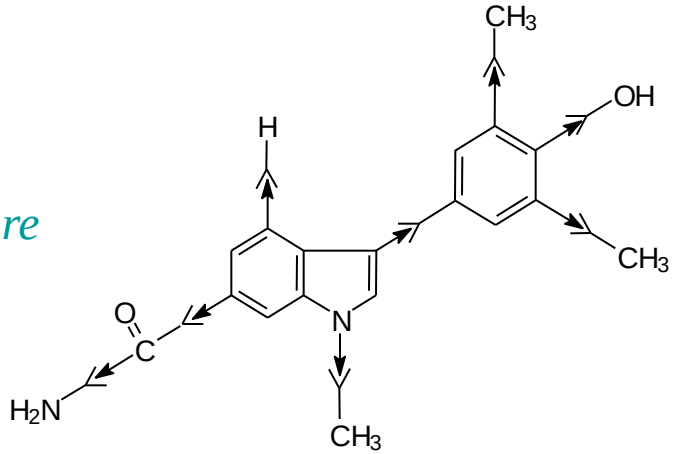
Terminal

Linear

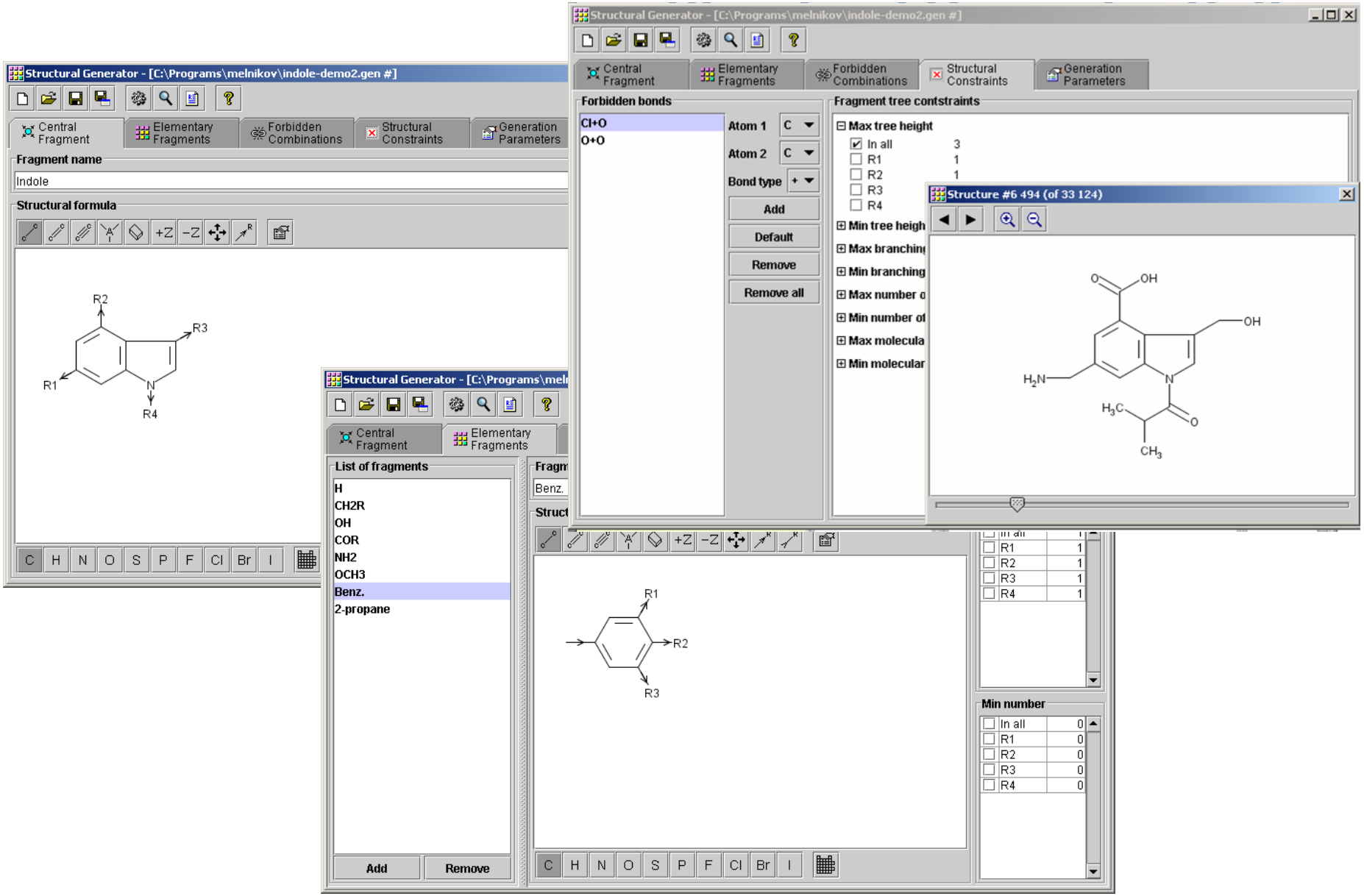
Branched



Example of a generated structure



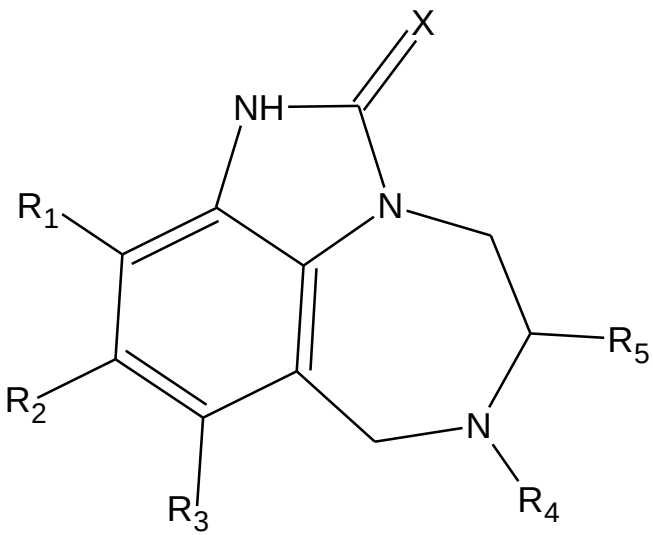
Structural Generator



Anti-HIV Activity of TIBO Derivatives (Reverse Transcriptase Inhibition)

Design of more potent structures

Structure generation



X = S

R_1-R_3 = H, CH_3, OH, NH_2, Cl, OCH_3, $N(CH_3)_2$, $CONH_2$

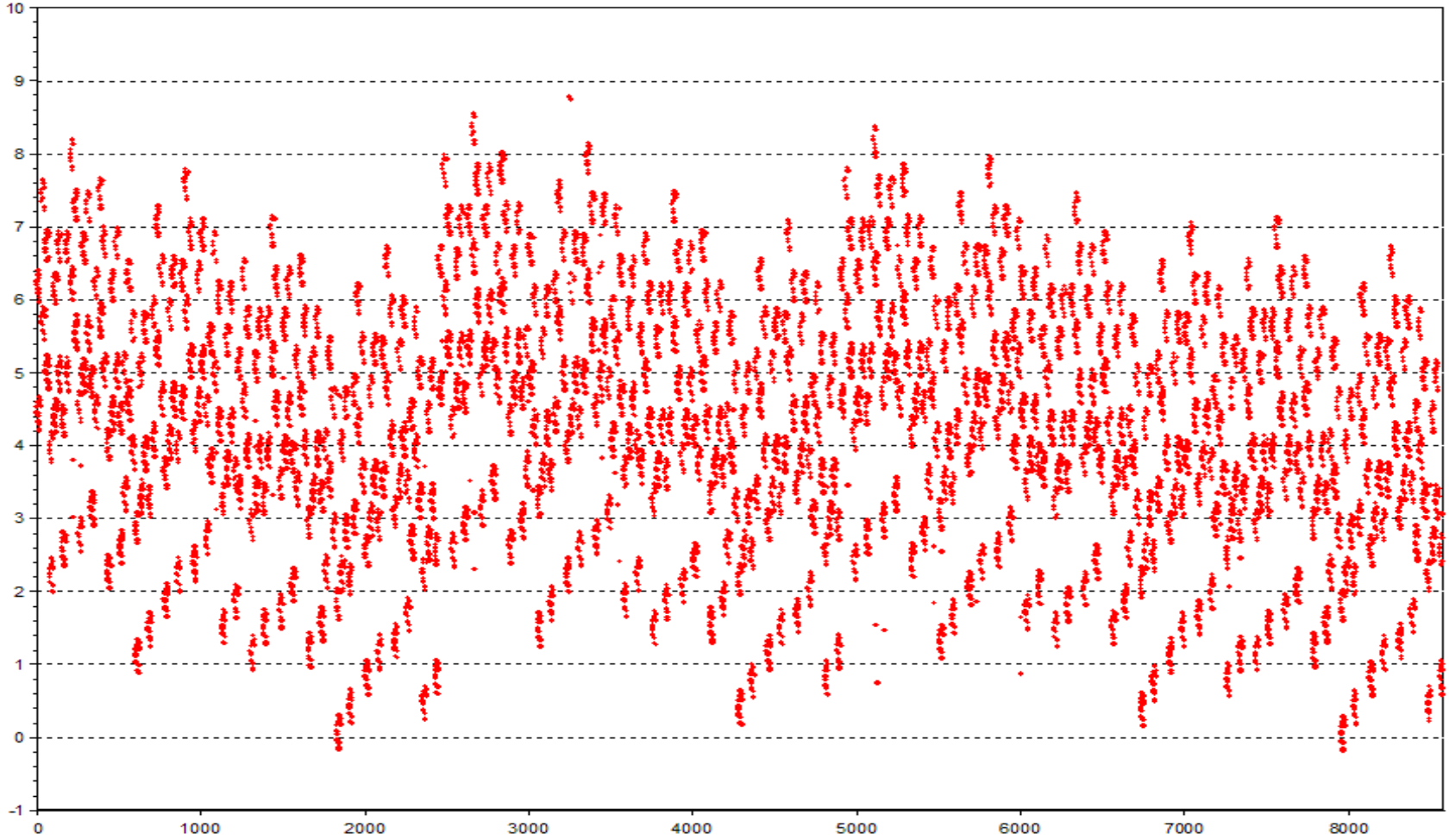
R_4-R_5 = H, CH_3, Et, Pr, ^{i}Pr

Total number of generated structures: 8575

Anti-HIV Activity of TIBO Derivatives (Reverse Transcriptase Inhibition)

Design of more potent structures

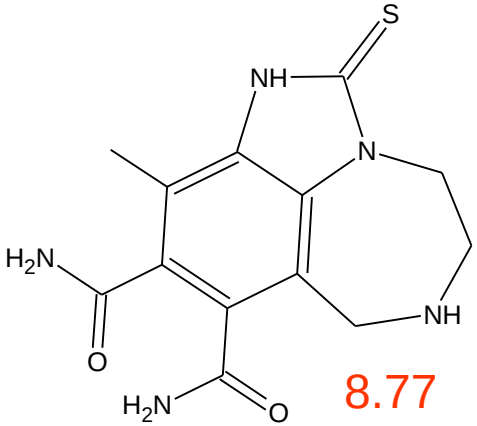
Prediction of activity using MFTA model



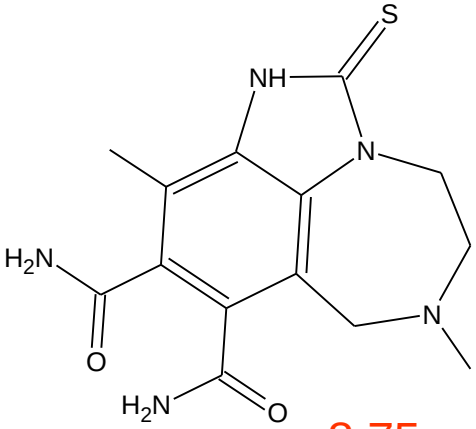
Anti-HIV Activity of TIBO Derivatives (Reverse Transcriptase Inhibition)

Design of more potent structures

5 best predicted structures



8.77



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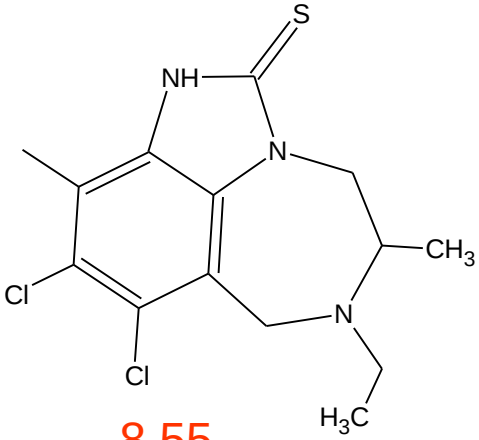

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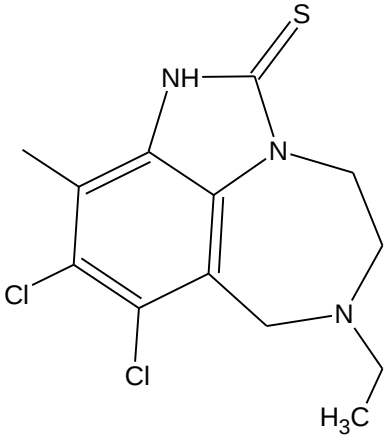

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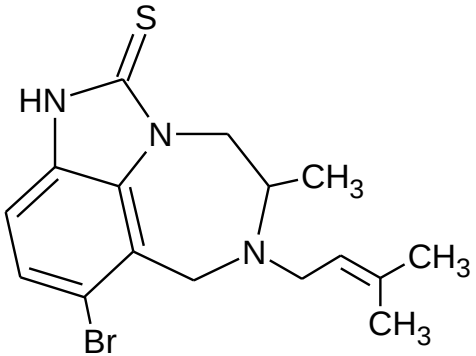
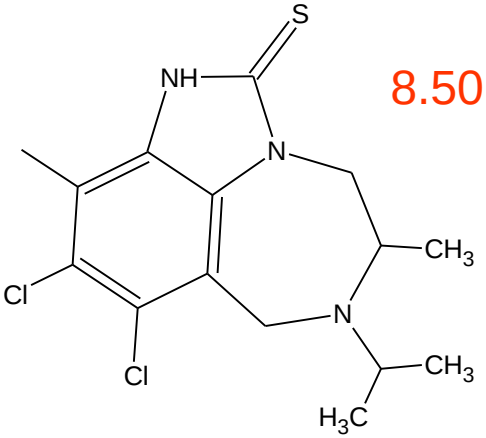


Best experimental
8.52

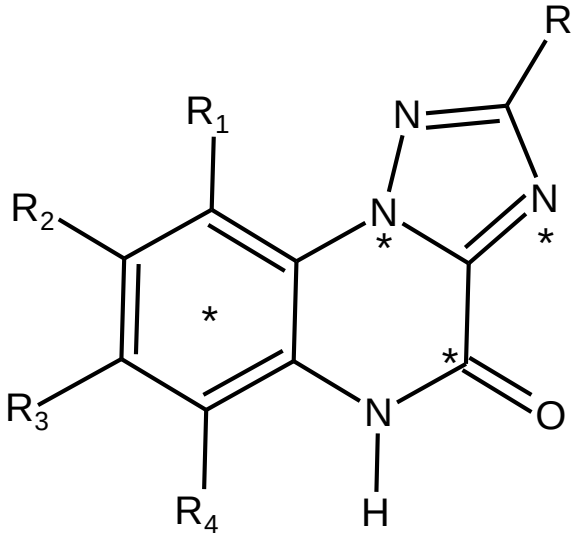


8.50

Ligand Selectivity

MFTA Study of the AMPA and Glycine/NMDA Receptor Antagonists

The difference between -logK_i for AMPA and glycine/NMDA was used as a target property in CoMFA for selectivity modelling.



-logK_i(AMPA) + logK_i(glycine/NMDA)

⇓

MFTA

⇓

SELECTIVITY MAPS

MFTA Study of the Antagonists of AMPA and glycine/NMDA Receptors: Modelling the Selectivity

$A_1=\log(1/K_i(\text{AMPA}))$

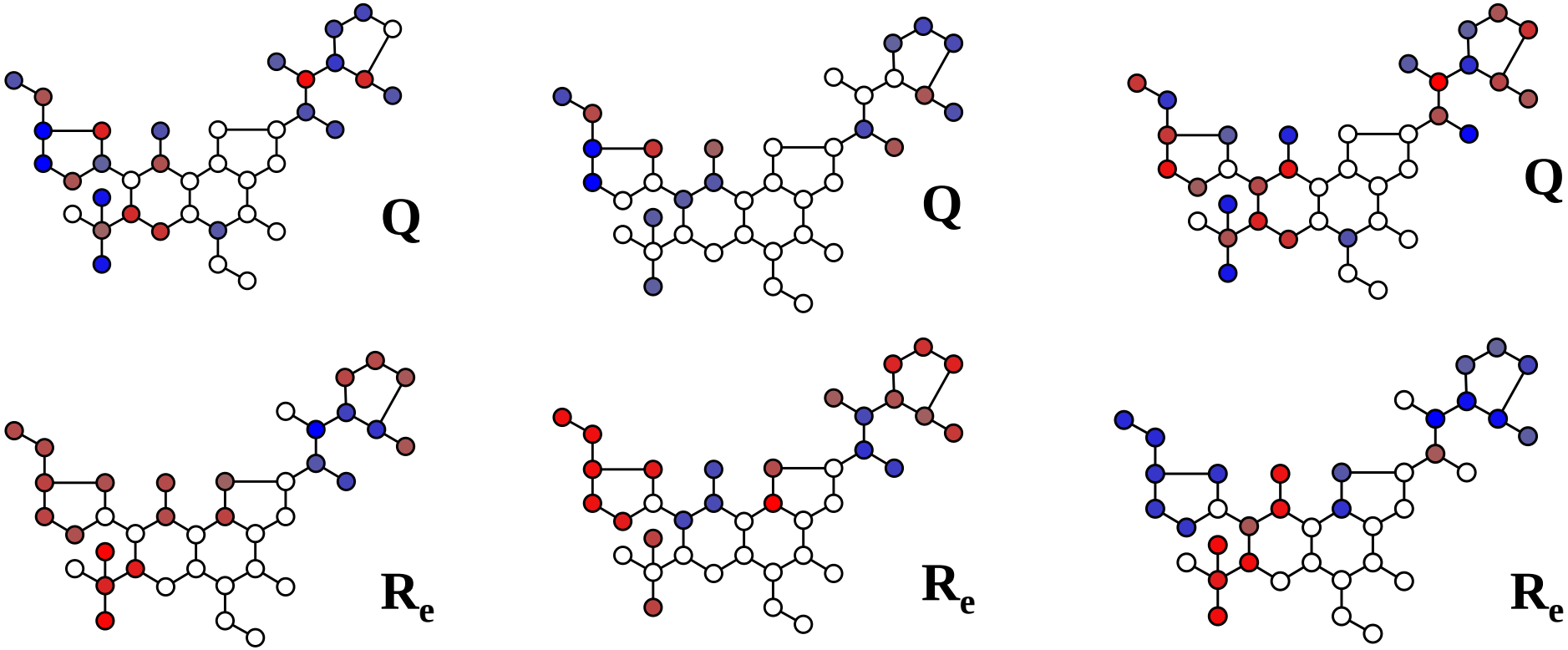
Training set: N=50, N_F=2, R^2=0.71, RMSE=0.38, Q^2=0.53, $RMSE_{cv}$=0.49

Selectivity $S=A_1-A_2$

Training set, N=50, N_F=2, R^2=0.69, RMSE=0.49, Q^2=0.45, $RMSE_{cv}$=0.66

$A_2=\log(1/K_i(\text{glycine/NMDA}))$

Training set, N=50, N_F=2, R^2=0.55, RMSE=0.54, Q^2=0.30, $RMSE_{cv}$=0.69



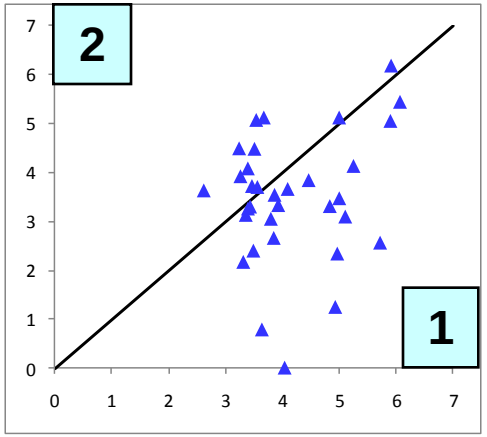
Red circles mean that the increase of a local descriptor value corresponds to the increase in activity, blue circles mean the opposite.

Multi-Target Selectivity: Options

Separate activity models

– selectivity calculated based on predicted activities

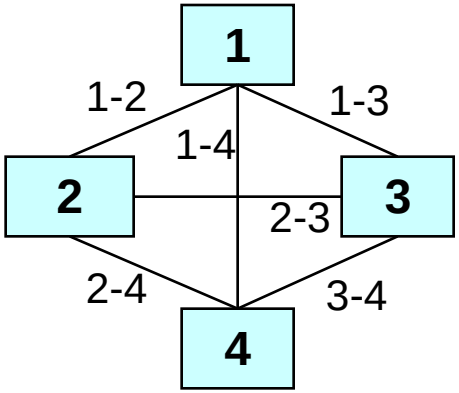
– factors controlling selectivity are difficult to identify



Models of pairwise selectivity (selectivity fields/maps in CoMFA/MFTA)

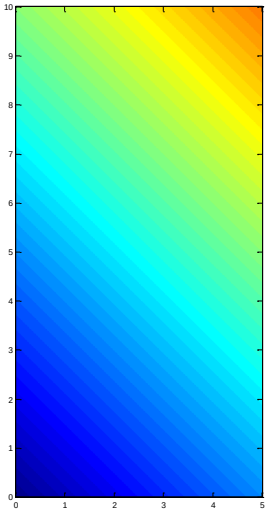
– more focused picture of factors controlling it

– rapidly increasing number of parameters
e.g. 4 activities → 6 selectivities → 10 endpoints total



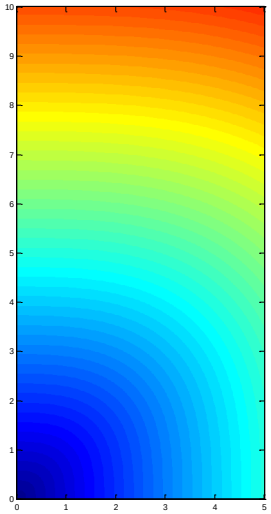
Multi-Target Activity.
Integral Activity Measures: Generalized Means.
Numerical Simulation

Arithmetic mean (M_1) (balances large and small values)



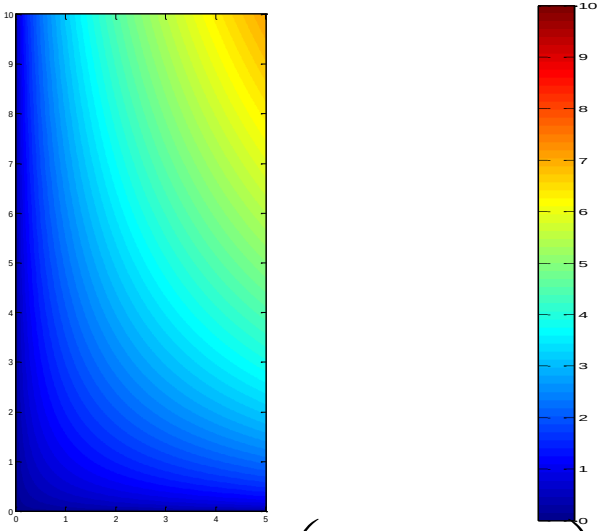
$$M_1 = \frac{1}{n}\sum_i x_i$$

Cubic mean (M_3) (dominated by larger values)



$$M_3 = \left(\frac{1}{n}\sum_i x_i^3\right)^{1/3}$$

Geometric mean (M_G) (simultaneous effect)

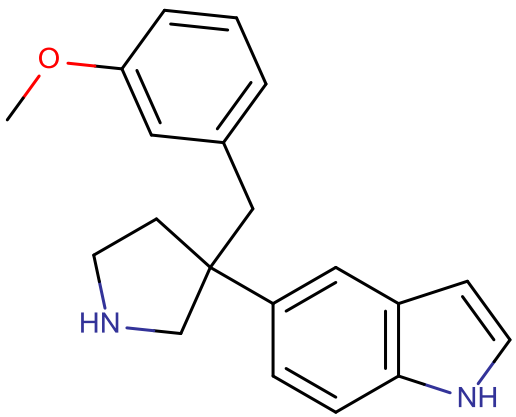


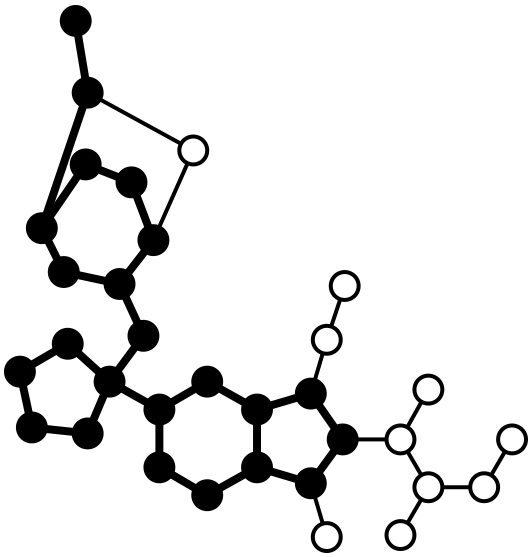
$$M_G = \sqrt[n]{\prod_i x_i} = \exp\left(\frac{1}{n}\sum_i \log x_i\right)$$

Triple Reuptake Inhibitors (TRI)

Inhibitors of serotonin transporter (SERT), norepinephrine (noradrenaline) transporter (NET) and dopamine transporter (DAT) as potential antidepressants

3,3-Disubstituted pyrrolidines





Bannwart L.M. et al., Novel 3,3-disubstituted pyrrolidines as selective triple serotonin / norepinephrine / dopamine reuptake inhibitors, *Bioorg. Med. Chem. Lett.*, 2008, 18 (23), 6062-6066

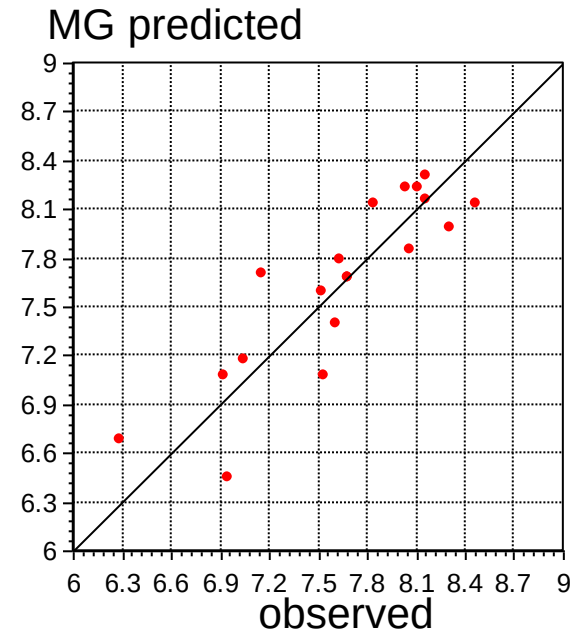
Triple Reuptake Inhibitors: MFTA

pKi SERT (Descriptors: Q, Re)
N = 19 N_F = 5 R^2 = 0.979 RMSE = 0.106 **Q^2 = 0.806** RMSEcv = 0.314

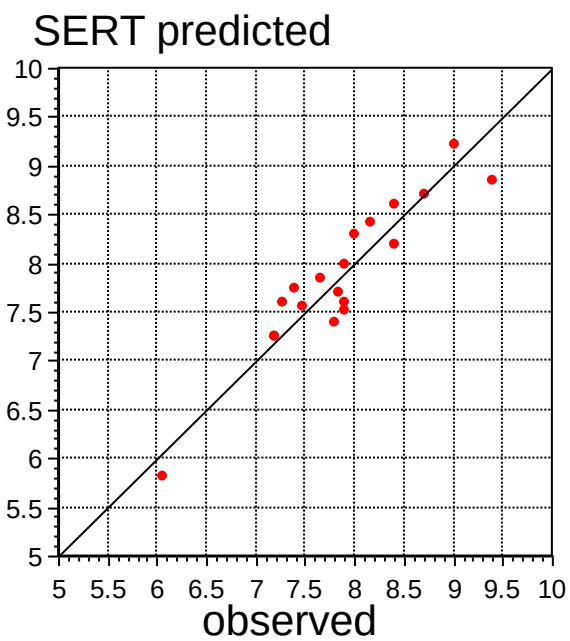
pKi NET (Descriptors: Q, Re)
N = 19 N_F = 3 R^2 = 0.827 RMSE = 0.274 **Q^2 = 0.643** RMSEcv = 0.392

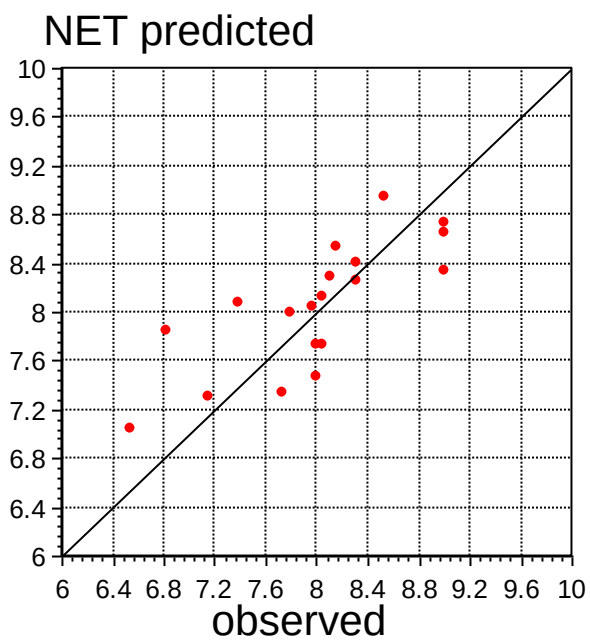
pKi DAT (Descriptors: Q, Re)
N = 19 N_F = 3 R^2 = 0.816 RMSE = 0.245 **Q^2 = 0.478** RMSEcv = 0.411

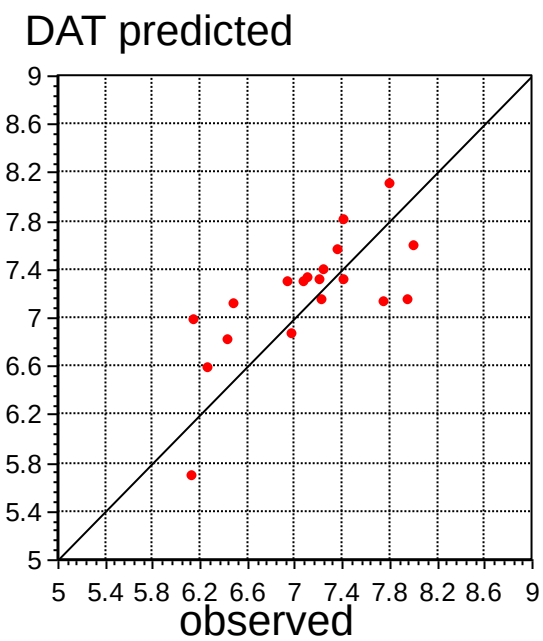
pKi MG (Descriptors: Q, Re)
N = 19 N_F = 5 R^2 = 0.985 RMSE = 0.067 **Q^2 = 0.766** RMSEcv = 0.263



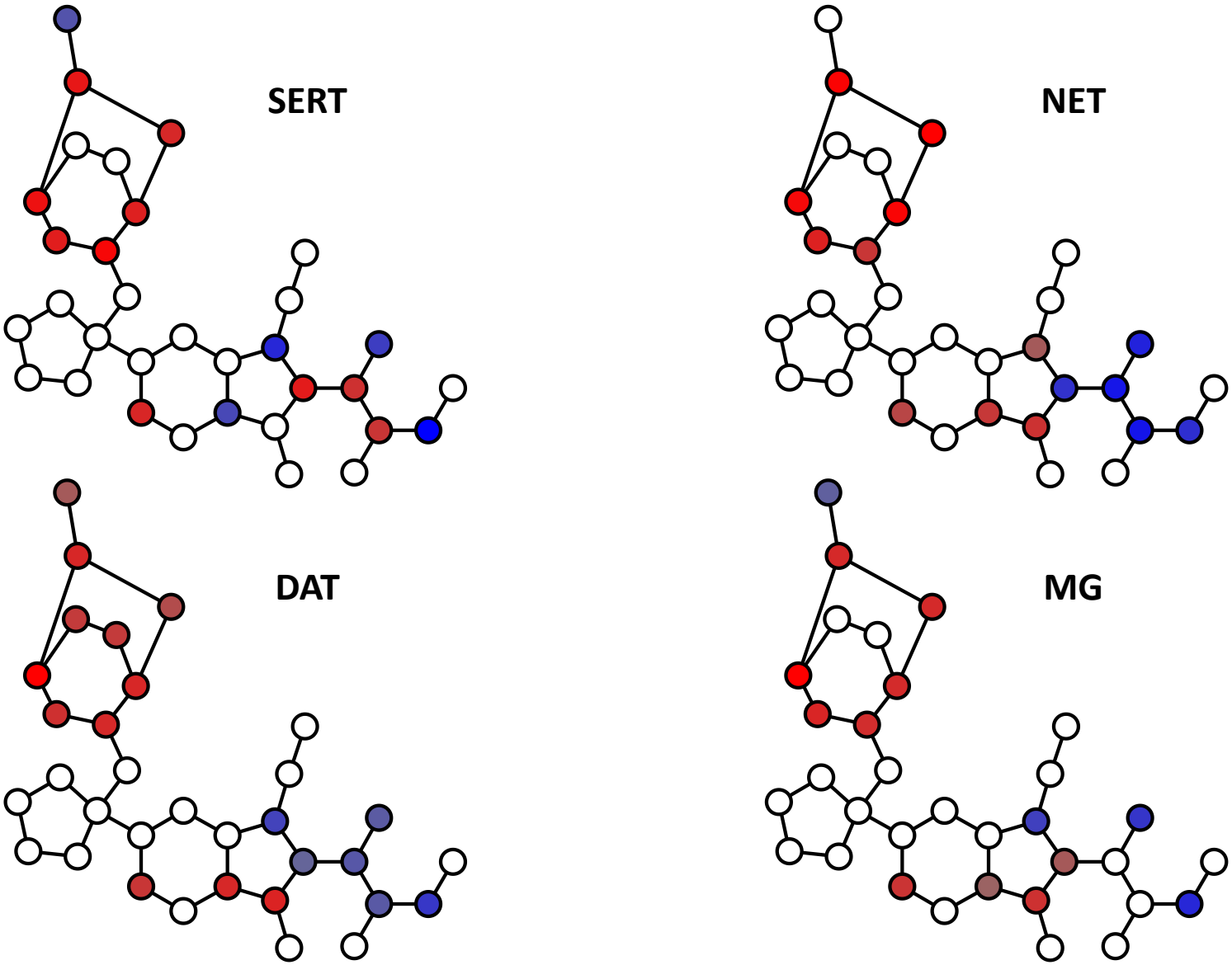
Plots of CV-predicted vs observed endpoints



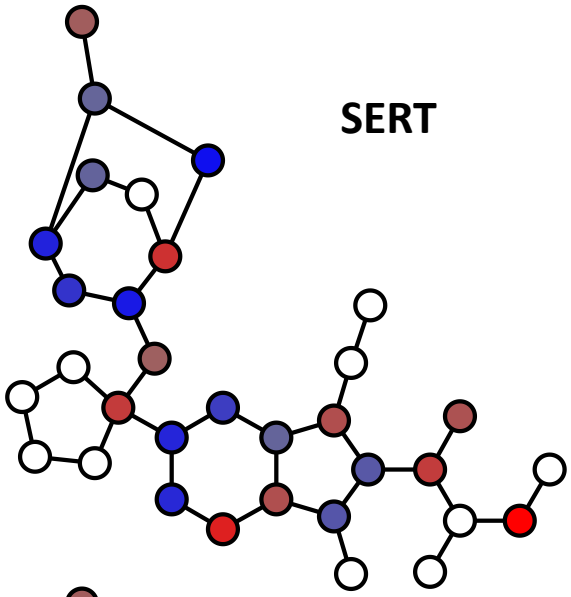


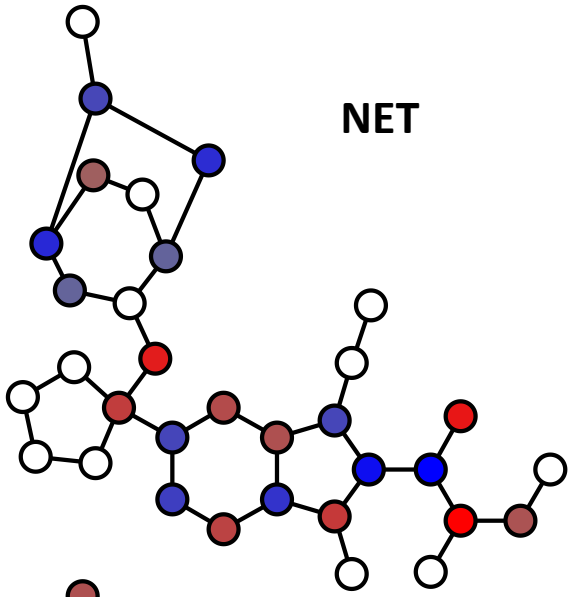


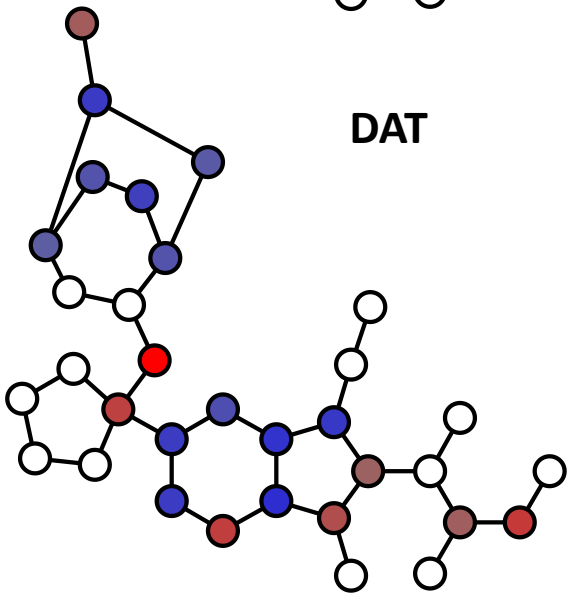
TRI Activity Maps: Steric Descriptors (Re)

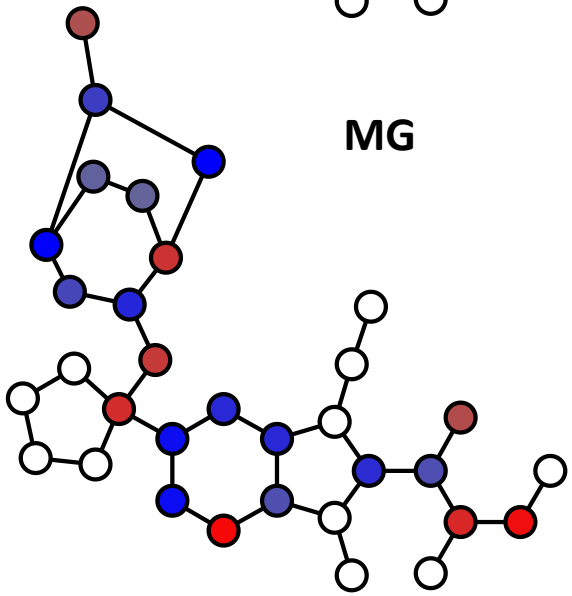


TRI Activity Maps: Partial Atomic Charges (Q)



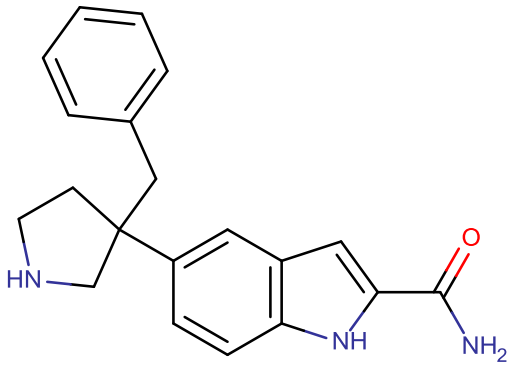


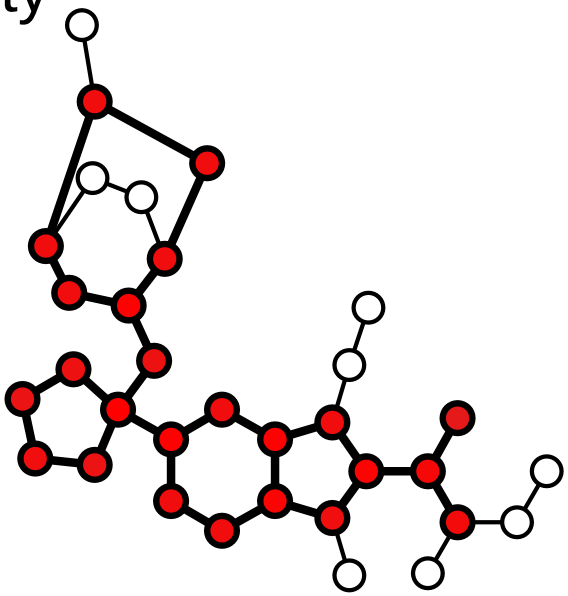


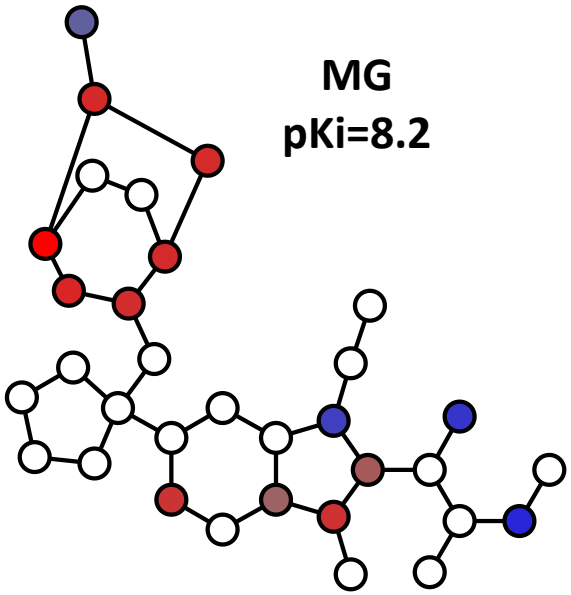


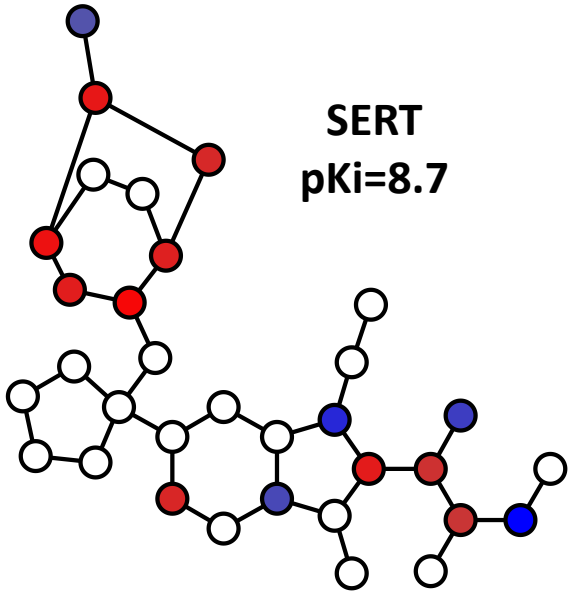
TRI Activity Maps: Steric Descriptors (Re)

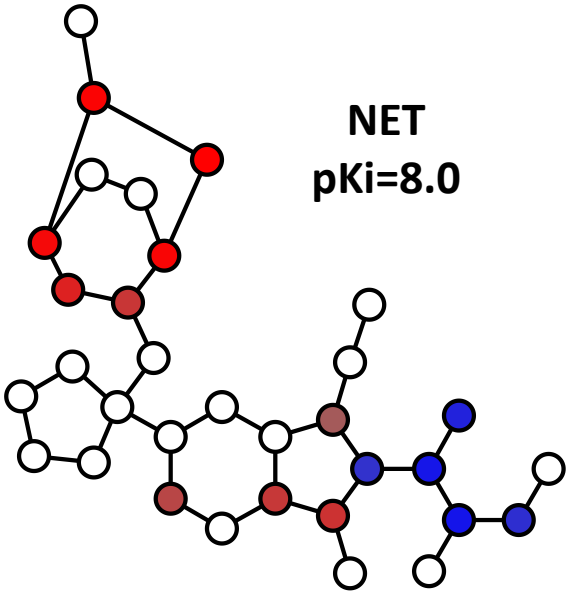
Balanced high TRI activity

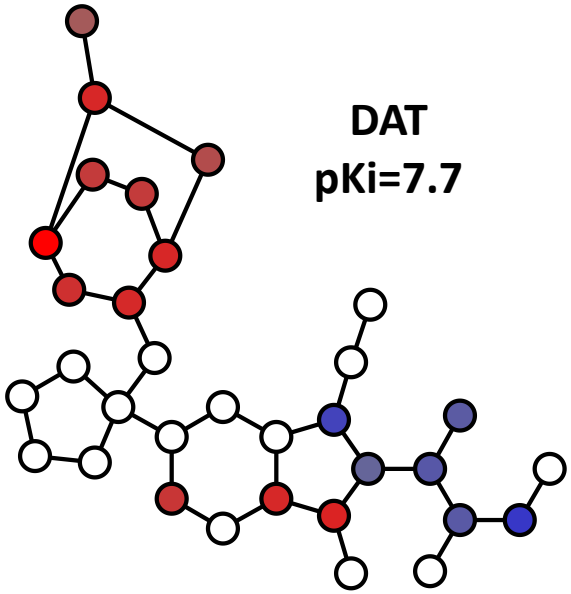






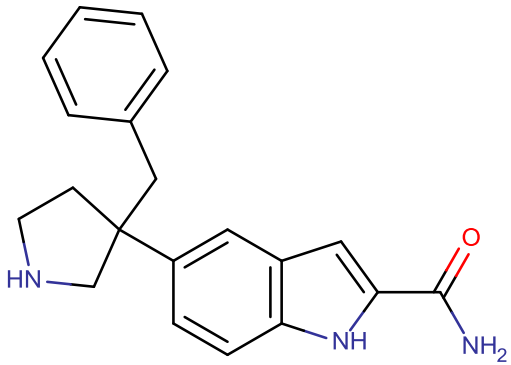


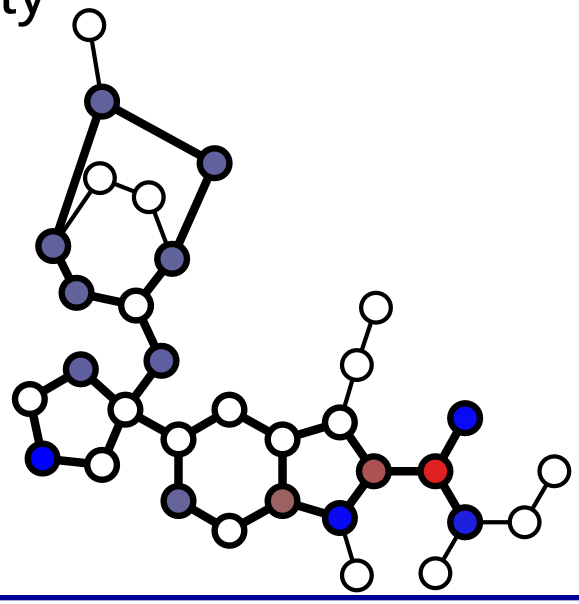


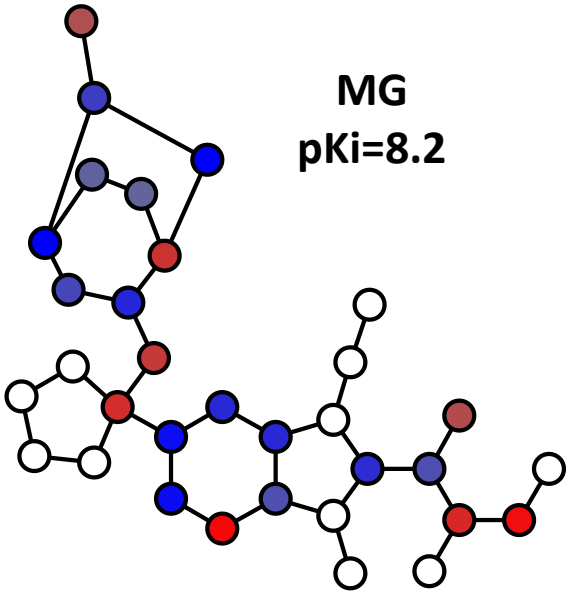


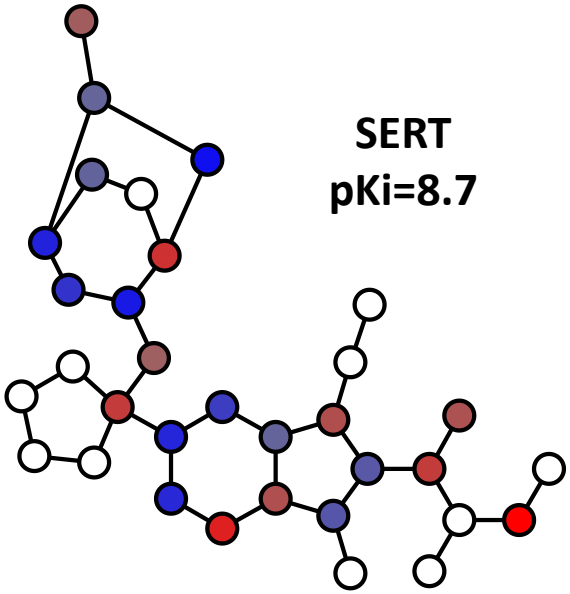
TRI Activity Maps: Partial Atomic Charges (Q)

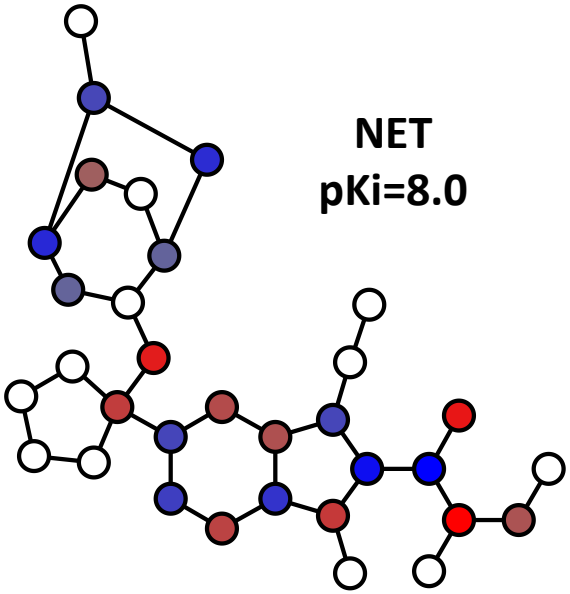
Balanced high TRI activity

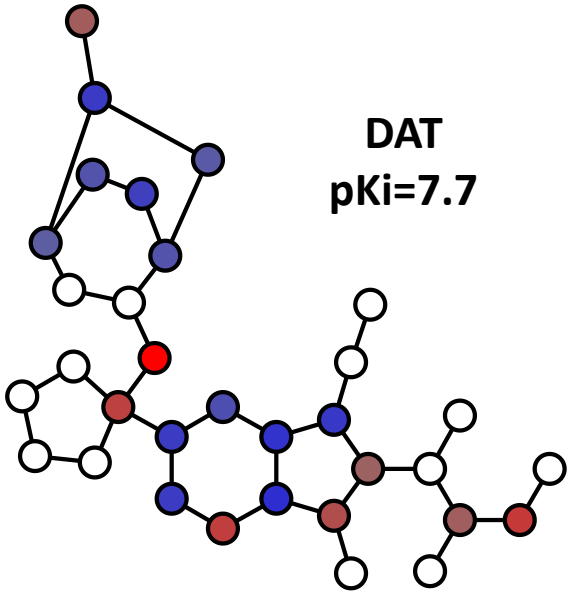






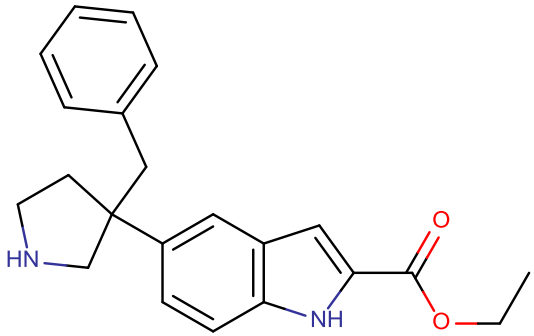


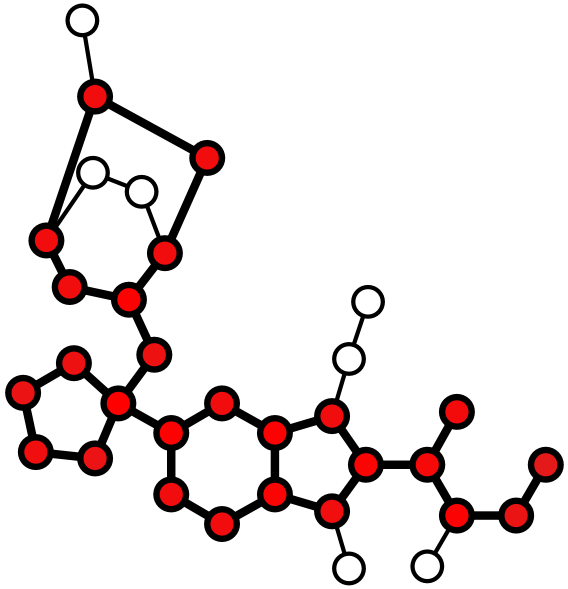


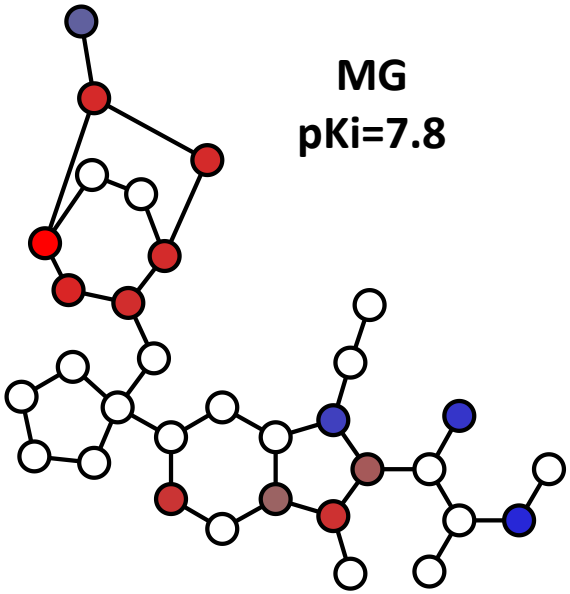


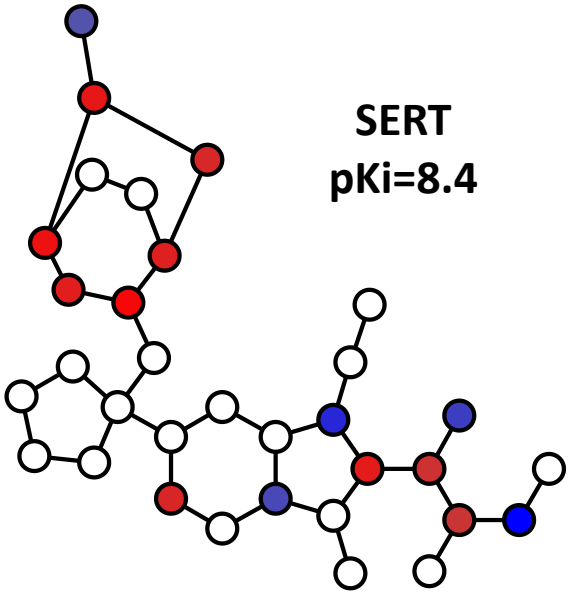
TRI Activity Maps: Steric Descriptors (Re)

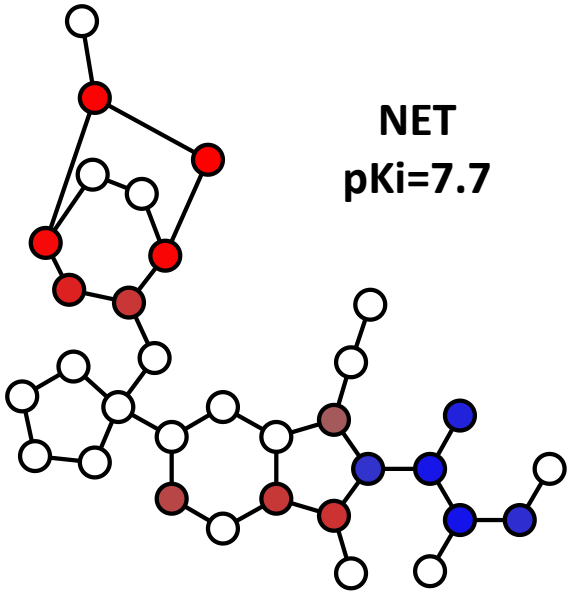
SERT-selective: SERT > NET > DAT

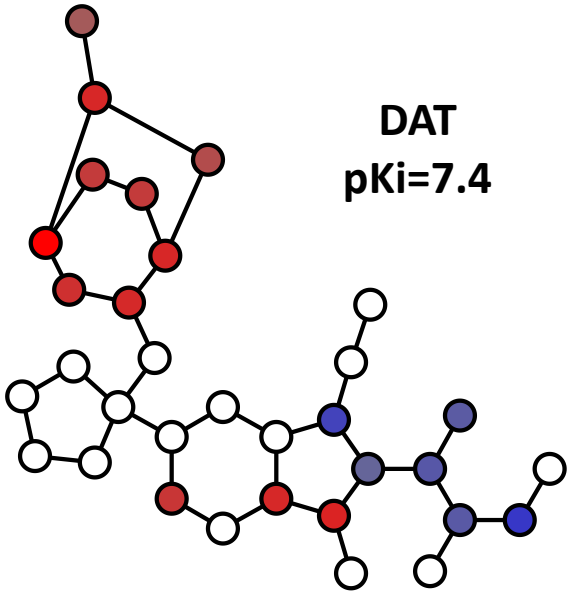






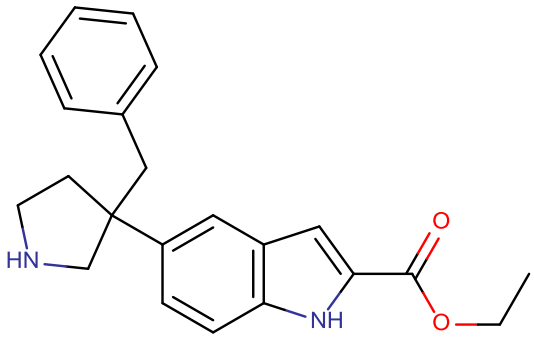


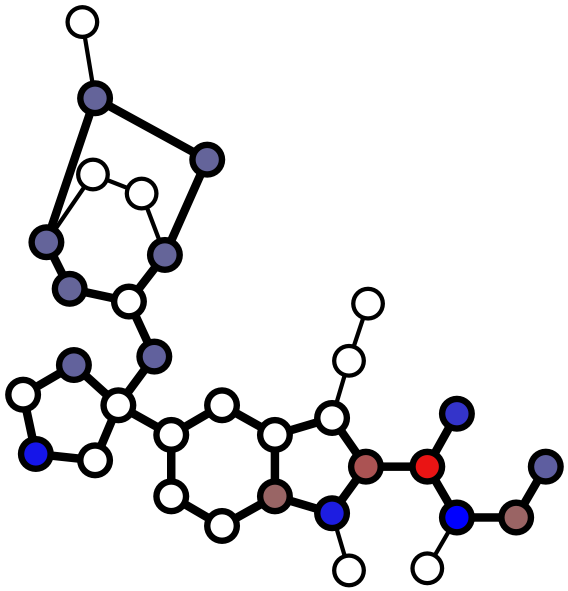


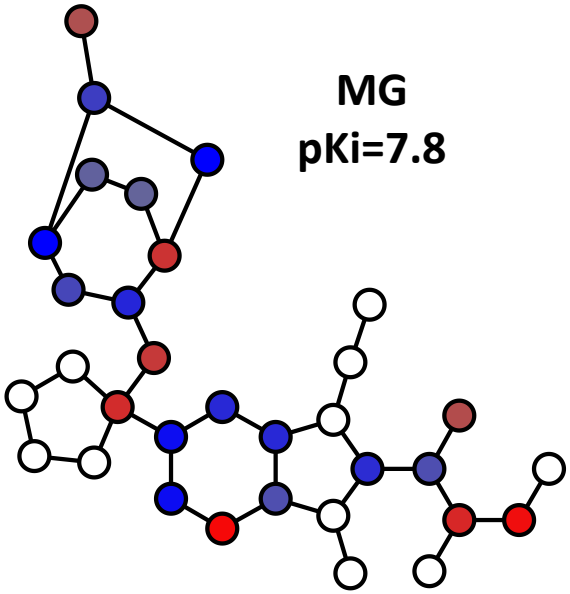


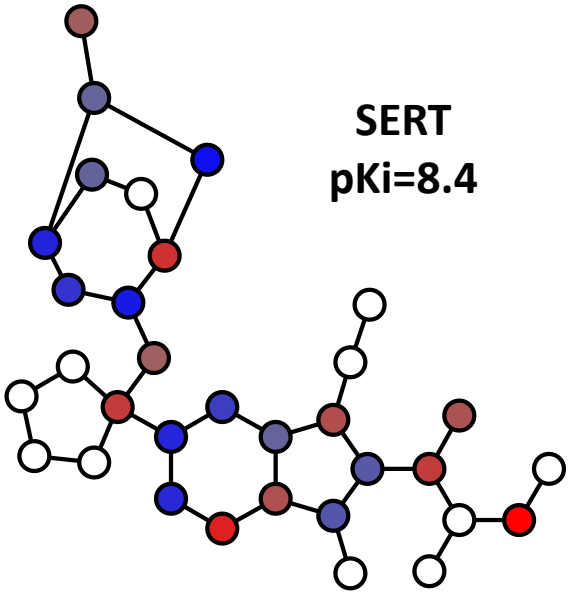
TRI Activity Maps: Partial Atomic Charges (Q)

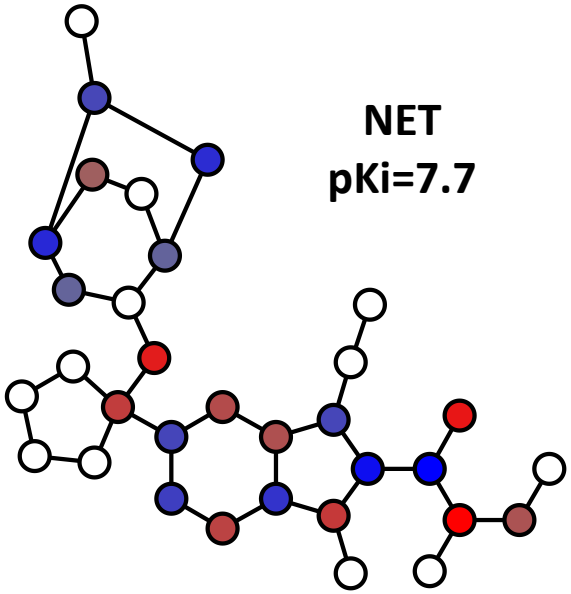
SERT-selective: SERT > NET > DAT

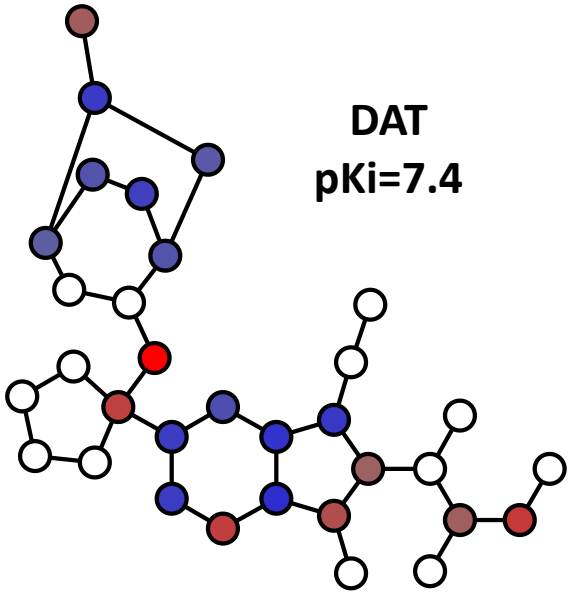












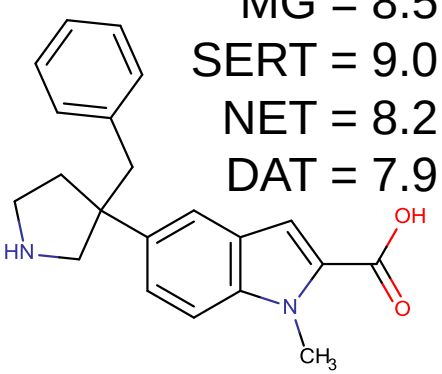
Triple Reuptake Inhibitors: Virtual Screening

- *Representative set of 5000 structures of the same class was generated from the MFTA supergraph in stochastic mode*

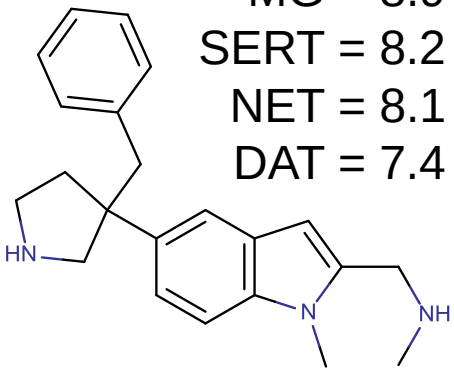
- *Endpoints were predicted using MFTA MG models and then individual models*

- *14 compounds have predicted pKiMG value > 8.5*

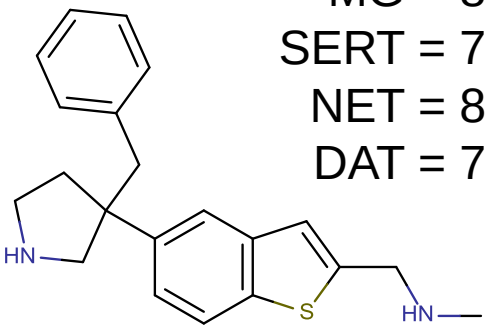
Pred pKi
MG = 8.5
SERT = 9.0
NET = 8.2
DAT = 7.9



Pred pKi
MG = 8.9
SERT = 8.2
NET = 8.1
DAT = 7.4



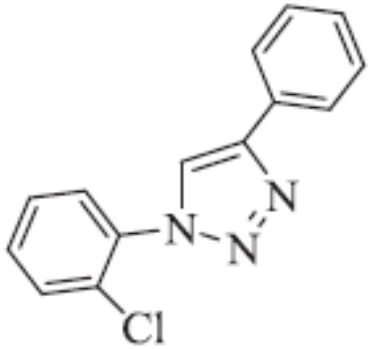
Pred pKi
MG = 8.7
SERT = 7.9
NET = 8.1
DAT = 7.6



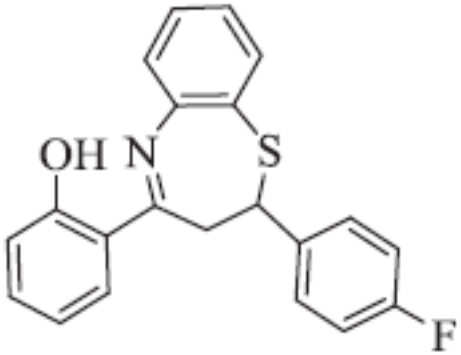
Dual inhibition of the α-glucosidase and butyrylcholinesterase

Common pharmacophore for large structurally diverse set of compounds

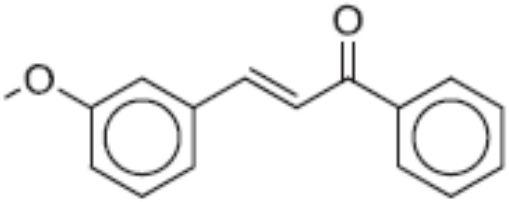
1,2,3-Triazoles



Benzothiazepines



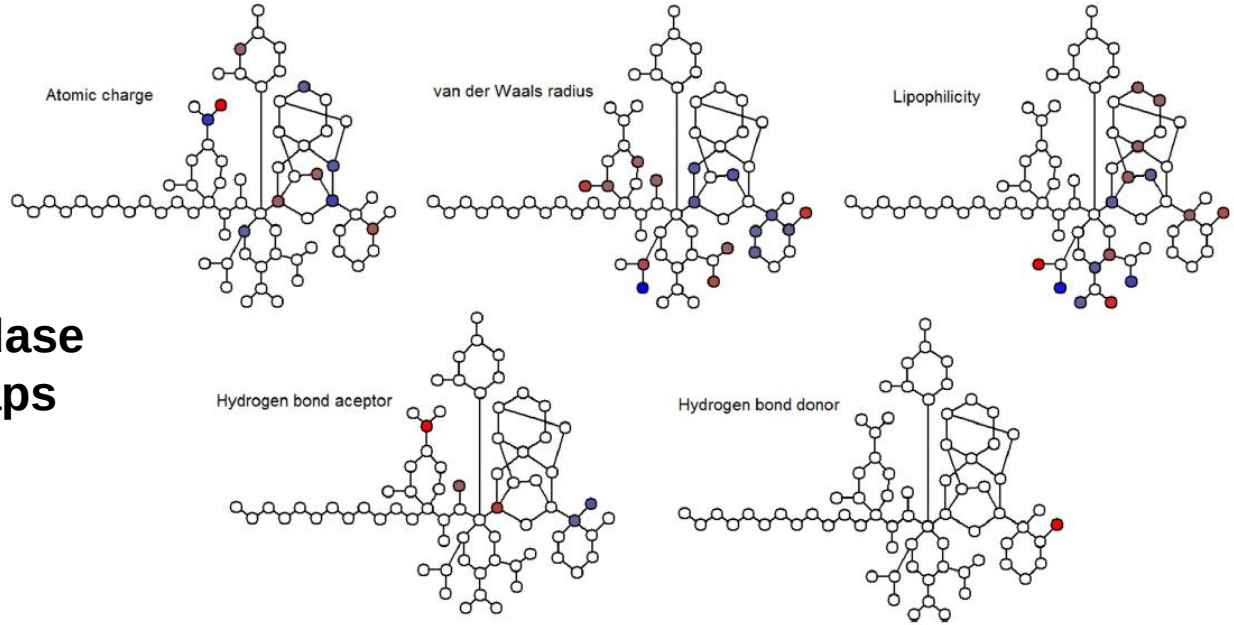
Chalcones



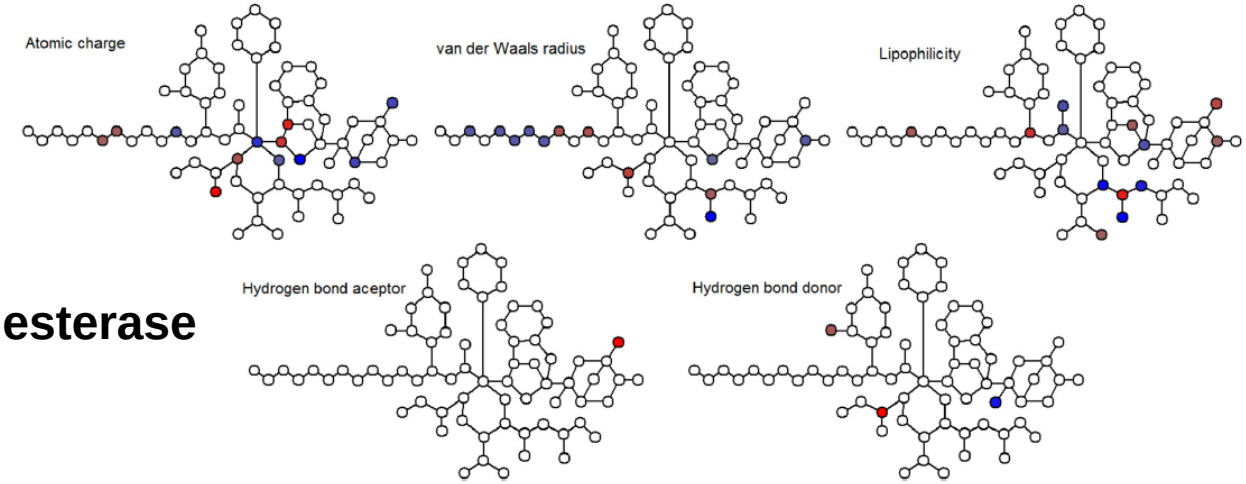
Jabeen F., Oliferenko P.V., Oliferenko A.A. et al., Dual inhibition of the α-glucosidase and butyrylcholinesterase studied by Molecular Field Topology Analysis, Eur. J. Med. Chem., 2014, 80, 228-242

Dual inhibition of the α-glucosidase and butyrylcholinesterase

α-Glucosidase activity maps



Butyrylcholinesterase activity maps



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THANK YOU

FOR YOUR ATTENTION!