GUSAR Models

Additionally to the GUSAR program, we provide ready-trained GUSAR models to predict certain biological activities. These are SAR bases that can be used with the GUSAR software for predictions on acute rat toxicity or antitargets (off-targets).

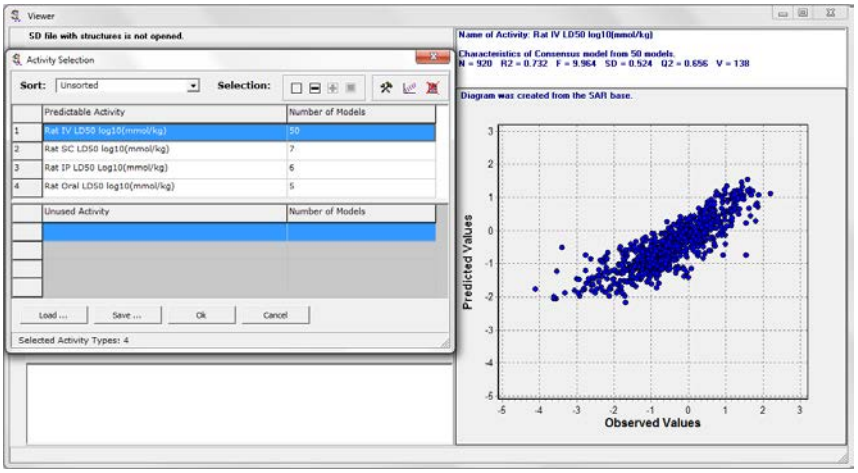
The acute rat toxicity SAR base can be used for in silico prediction of LD50 values for rats with four types of administration. The training sets were created on the basis of the SYMYX MDL Toxicity Database and data from RTECS and ChemIDPlus.

A quantitative prediction of antitarget interaction for chemical compounds can be done with the other SAR base. The QSAR models for the set of 32 activities (using IC_{50}, K_i or K_{act} values) includes data on about 4,000 chemical compounds interacting with 18 antitarget proteins (13 receptors, 2 enzymes and 3 transporters).

If you want to use these models, please send an e-mail to info@genexplain.com with your name, specifying which model you would like to use.

Acute Rat Toxicity

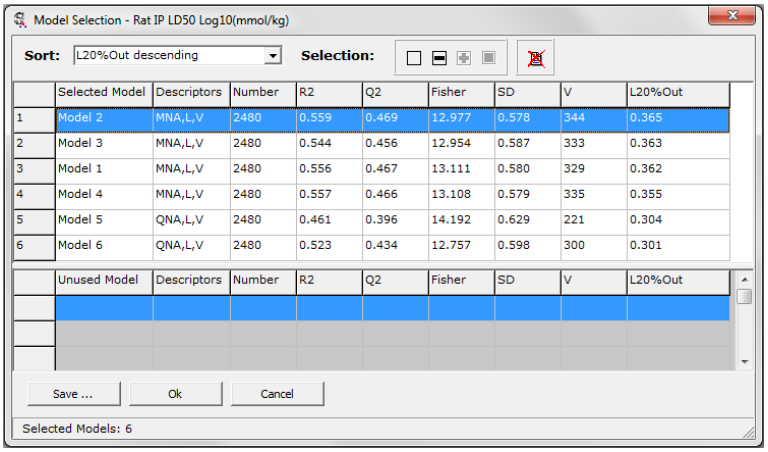
The SAR base on acute rat toxicity contains information about approximately 12,000 chemical structures with data on acute rat toxicity represented by LD50 (Lethal Dose, 50%) values for four types of administration:



- intravenous
- subcutaneous
- intraperitoneal
- oral

Characteristics of QSAR models for prediction of rat LD50 values (log10 (mmol/kg)) and their validation.
N_{train} - number of compounds in the training set; N_{test} - number of compounds in the test set; N_{models} – number of QNA/MNA models; R^2_{train} - average R^2 of the models calculated for the appropriate training set; Q^2_{train} - average Q^2 of the models calculated for the appropriate training set; Coverage - % compounds from the test set in Applicability Domain.

Administration	N_{train}	N_{test}	N_{models}		R^2_{train}	Q^2_{train}	R^2_{test}	$RMSE_{test}$	Coverage [%]
			QNA	MNA					
Oral	6280	2692	2	3	0.62	0.57	0.59	0.57	97.5
Intraperitoneal	2480	1065	2	4	0.63	0.54	0.57	0.57	96.1
Intravenous	920	394	10	40	0.73	0.66	0.63	0.62	99.2
Subcutaneous	759	325	2	5	0.69	0.59	0.50	0.69	92.0



With this SAR base, you can make predictions about what concentration of a substance in focus is required to lead to LD50 in rats. If the log10 of this concentration is below zero, the substance is considered as toxic using the given way of administration.

Example: models for Rat IP LD_{50} Log10(mmol/kg).
L = topological length; V = volume of a molecule; R^2 = square of the regression coefficient; Q^2 = cross-validated R^2; Fisher = value of Fisher's statistics; SD = standard deviation; V = number of variables in the final regression equation; L10%Out = results of leave 10% out cross-validation.

As with SAR bases you created yourself, you can exclude whole activities and single QNA/MNA models that do not suit your needs with the "Selection" option. Thus, you are able to only use the most predictive models.

GUSAR can create a consensus model to predict one activity, or you can do batch predictions for all chosen activities at once.

Acute Mouse Toxicity

The descriptions given above for the rat toxicity model apply analogously to the mouse model. As for the detailed characteristics, please see table below.

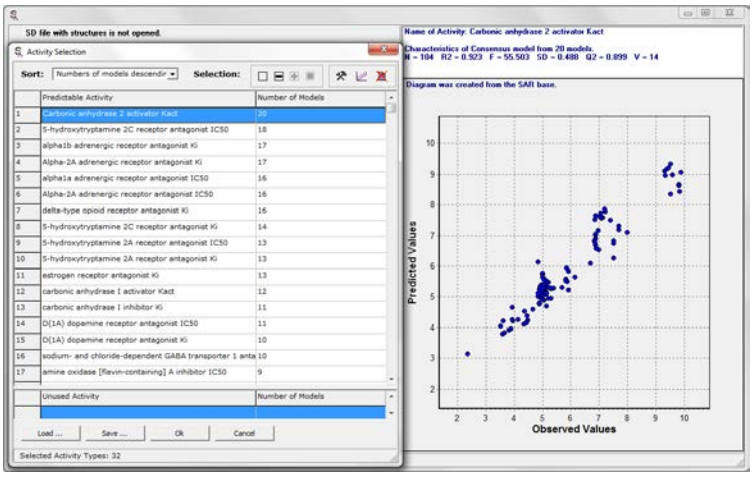
Characteristics of QSAR models for prediction of mouse LD50 values (log10 (mmol/kg)) and their validation.
$N_{train/test}$ - number of compounds in the training/test set; N_{models} – number of models; $R^2_{train/test}$ - average R^2 of the models calculated for the appropriate training/test set; Q^2_{train} - average Q^2 of the models calculated for the appropriate training set; $RMSE_{test}$ – root mean square error of the test set; Coverage - % compounds from the test set in Applicability Domain.

Administration	N_{train}	N_{test}	N_{models}		R^2_{train}	Q^2_{train}	R^2_{test}	$RMSE_{test}$	Coverage [%]
			QNA	MNA					
Oral	18188	2021	1	3	0.46	0.43	0.50	0.377	91.5
Intraperitoneal	25086	2787	1	5	0.45	0.43	0.53	0.397	91.6
Intravenous	9621	1069	1	10	0.54	0.50	0.50	0.401	94.5
Subcutaneous	3215	357	6	8	0.67	0.60	0.56	0.549	96.1

Antitargets (off-targets)

This is a SAR base on the affinity of substances to certain antitargets, containing 32 activities. The interactions of substances in focus with antitargets might be the cause of adverse or toxic effects.

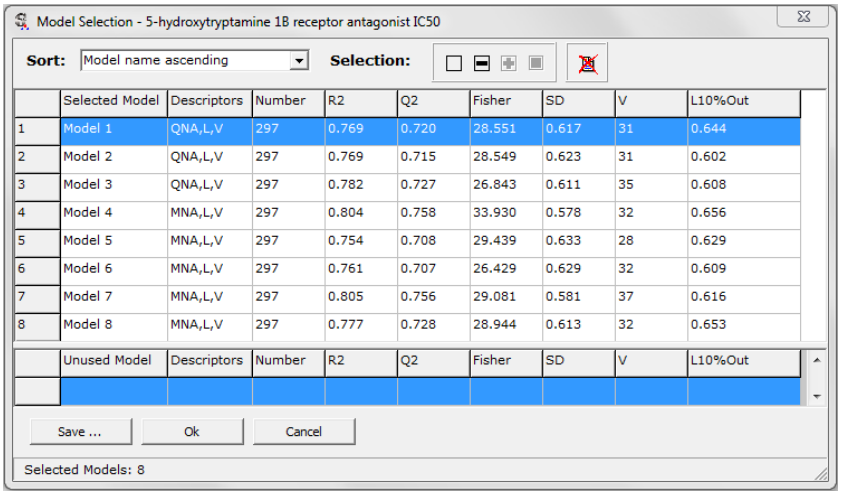
Activities are specified as IC_{50} (50% of the inhibitory concentration), K_i (inhibition constant), or K_{act} (activation constant).



Characteristics of QSAR models for antitarget sets.
N_{train} - number of compounds in the training set; N_{test} - number of compounds in the test set; N_{models} – number of QNA/MNA models; R^2_{train} - average R^2 of the models calculated for the appropriate training set; Q^2_{train} - average Q^2 of the models calculated for the appropriate training set; Coverage - % compounds from the test set in Applicability Domain.

Activity	N_{train}/N_{test}	N_{models}		R^2_{train}	Q^2_{train}	R^2_{test}	Coverage [%]
		QNA	MNA				
5-hydroxytryptamine 1B receptor antagonist IC_{50}	297/74	3	5	0.83	0.79	0.67	100.0
5-hydroxytryptamine 1B receptor antagonist K_i	266/66	3	4	0.73	0.66	0.72	100.0
5-hydroxytryptamine 2A receptor antagonist IC_{50}	555/143	6	7	0.83	0.78	0.71	98.6
5-hydroxytryptamine 2A receptor antagonist K_i	1010/252	3	10	0.72	0.65	0.59	99.6
5-hydroxytryptamine 2C receptor antagonist IC_{50}	128/32	3	15	0.77	0.73	0.58	100.0
5-hydroxytryptamine 2C receptor antagonist K_i	487/121	6	8	0.74	0.66	0.62	99.2
alpha1a adrenergic receptor antagonist IC_{50}	438/111	6	10	0.79	0.73	0.72	98.2
alpha1a adrenergic receptor antagonist K_i	1366/344	1	4	0.83	0.79	0.80	97.0
alpha1b adrenergic receptor antagonist K_i	410/102	5	12	0.73	0.66	0.63	100.0
alpha-2A adrenergic receptor antagonist IC_{50}	109/207	5	11	0.88	0.84	0.75	100.0
alpha-2A adrenergic receptor antagonist K_i	525/131	4	13	0.84	0.79	0.77	99.2
amine oxidase [flavin-containing] A inhibitor IC_{50}	186/71	4	5	0.80	0.75	0.72	100.0
amine oxidase [flavin-containing] A inhibitor K_i	60/15	2	3	0.73	0.62	0.64	100.0
androgen receptor antagonist IC_{50}	116/29	2	6	0.79	0.73	0.67	100.0
carbonic anhydrase I activator K_{act}	108/27	4	8	0.98	0.97	0.93	100.0

carbonic anhydrase I inhibitor K_i	935/234	4	7	0.91	0.86	0.86	98.3
carbonic anhydrase II activator K_{act}	104/26	6	14	0.92	0.90	0.91	100.0
carbonic anhydrase II inhibitor K_i	866/217	1	6	0.87	0.79	0.76	98.6
d(1A) dopamine receptor antagonist IC_{50}	126/31	2	9	0.76	0.72	0.80	100.0
d(1A) dopamine receptor antagonist K_i	291/73	4	6	0.72	0.66	0.57	100.0
d3 dopamine receptor antagonist K_i	822/206	3	6	0.73	0.66	0.62	98.0
delta-type opioid receptor antagonist K_i	1044/261	3	13	0.75	0.70	0.65	98.5
estrogen receptor antagonist IC_{50}	402/100	2	2	0.66	0.61	0.70	97.0
estrogen receptor antagonist K_i	255/68	2	11	0.76	0.71	0.70	100.0
kappa-type opioid receptor antagonist K_i	844/221	3	4	0.74	0.67	0.65	100.0
mu-type opioid receptor antagonist IC_{50}	545/136	2	5	0.67	0.61	0.70	97.8
mu-type opioid receptor antagonist K_i	1354/338	1	3	0.69	0.62	0.60	96.7
sodium- and chloride-dependent GABA transporter 1 antagonist IC_{50}	79/19	2	8	0.9	0.86	0.89	100.0
sodium-dependent dopamine transporter antagonist IC_{50}	920/230	3	2	0.7	0.65	0.67	98.3
sodium-dependent dopamine transporter antagonist K_i	655/164	3	4	0.77	0.69	0.64	100.0
sodium-dependent serotonin transporter antagonist IC_{50}	796/199	5	2	0.8	0.75	0.69	97.5
sodium-dependent serotonin transporter antagonist K_i	823/206	1	1	0.72	0.65	0.61	95.6



Example: models for 5-hydroxytryptamine 1B receptor antagonist IC_{50}. R^2 = square of the regression coefficient; Q^2 = cross-validated R^2; Fisher = value of Fisher's statistics; SD = standard deviation; V = number of variables in the final regression equation; L10%Out = results of leave 10% out cross-validation.

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