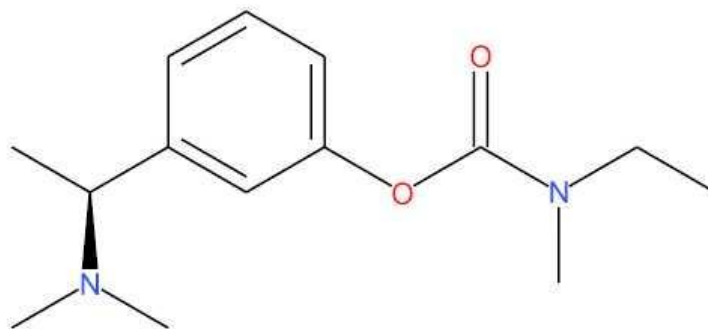




MetaDrug™ Analysis Report

Rivastigmine



Overview of MetaDrug™ Analysis Methodology

MetaDrug combines a suite of chemical structural analysis tools (metabolite prediction, QSAR, structural similarity searching), a comprehensive structure-activity database, and a systems biology database of molecular interactions (protein-protein, compound-protein, protein-enzymatic reaction, compound-enzymatic reaction), canonical signaling and metabolic pathways, and gene-biological property associations (gene-function, gene-disease, gene-toxicity, etc.).

The MetaDrug analysis starts with uploading a chemical structure (Fig. 1). Potential metabolites for the query compound are predicted and separated into major and minor phase 1 and phase 2 metabolites. A suite of pre-defined QSAR models is used to predict possible indications, toxicity issues and ADME properties of the molecule (and, optionally, its metabolites).

MetaDrug uses 3 basic methods to associate compounds to protein targets. **First**, compound's known targets are retrieved from the database (if any of them are described in literature). **Second**, input compound is subjected to similarity search and targets of similar compounds can be ascribed as possible targets of the input molecule. **Third**, QSAR predictions of protein target affinity from the included models or custom derived models define a limited number of potential targets. All 3 methods are available for predicted metabolites if specified in settings.

Possible targets can be then subjected to functional analysis to identify pathways and processes that may be affected by the input molecule. Experimental data, for example, expression data associated with compound treatment can be uploaded and overlaid to pathway maps and networks to cross-validate hypothesis about compound's mechanism of action.

To produce this report, the input molecule was run through therapeutic QSAR models. No other algorithms were used.

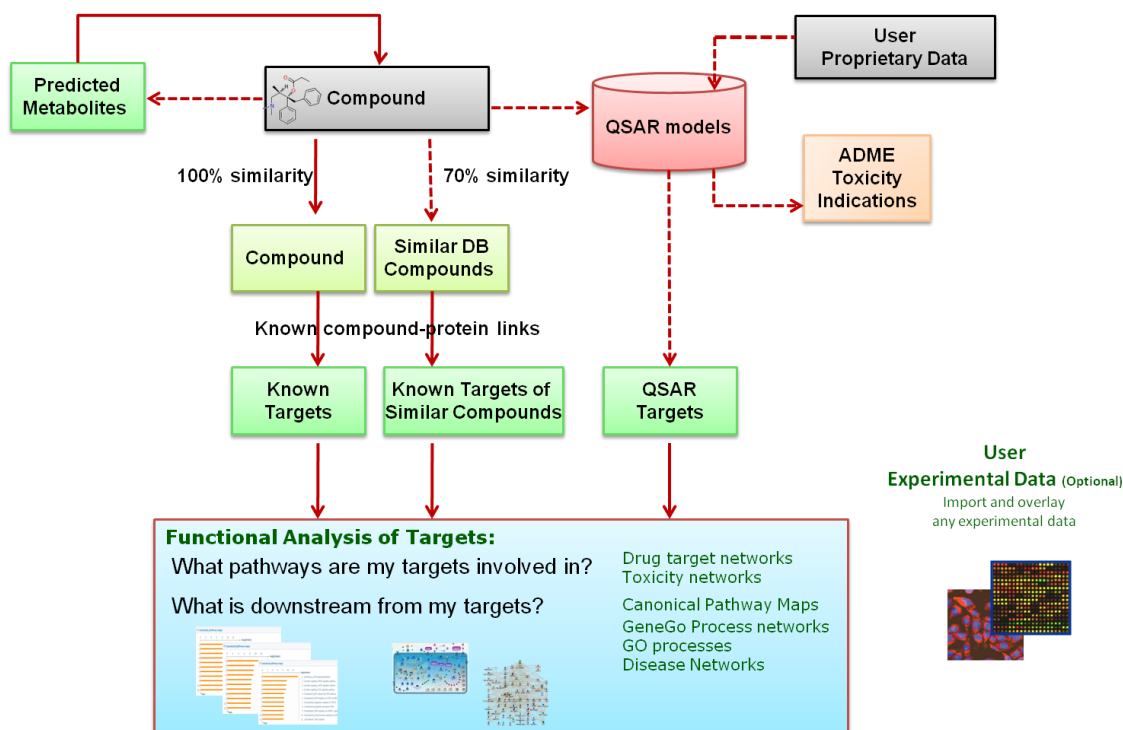





Fig. 1. MetaDrug compound analysis schema.

Possible Indications

To predict possible indications by QSAR method, MetaDrug incorporates ChemTree® 5.1 (Golden Helix, Bozeman, MT) technology applying recursive partitioning algorithm. Every model calculates a value from 0 to 1 showing the probability for a compound to be active for a given indication (**Table 1**). Reliability of the predictions are expressed through Tanimoto prioritization (TP), a percentage, representing the structural similarity of the input molecule to the most similar structure in the model's training set, which is displayed in parentheses.

Table 1. Possible indications for studied compound.

#	Property 	Model description 	Value/(TP) 
1	Alzheimer	Potential activity against Alzheimer's disease. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=261, Test set N=44, Sensitivity=0.91, Specificity=0.82, Accuracy=0.86, MCC=0.73. Click here for details.	0.92 (100.00)
2	Depression	Potential antidepressant activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=335, Test set N=62, Sensitivity= 0.93, Specificity=0.82, Accuracy=0.87, MCC=0.75. Click here for details.	0.80 (57.69)
3	Pain	Potential analgetic activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=525, Test set N=84, Sensitivity= 0.92, Specificity=0.67, Accuracy=0.79, MCC=0.60. Click here for details.	0.79 (59.60)
4	Schizophrenia	Potential activity against schizophrenia. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=616, Test set N=93, Sensitivity=0.89, Specificity=0.91, Accuracy=0.90, MCC=0.80. Click here for details.	0.72 (100.00)
5	Thrombosis	Potential antithrombotic activity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=453, Test set N=80, Sensitivity= 0.98, Specificity=0.95, Accuracy=0.97, MCC=0.93. Click here for details.	0.63 (49.46)
6	Parkinson	Potential activity against Parkinson's disease. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=298, Test set N=49, Sensitivity=0.96, Specificity=0.96, Accuracy=0.96, MCC=0.92. Click here for details.	0.60 (100.00)
7	Hypertension	Potential antihypertensive activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=554, Test set N=111, Sensitivity= 0.89,	0.50 (52.94)

		Specificity=0.81, Accuracy=0.85, MCC=0.70. Click here for details.	
8	Obesity	Potential activity against obesity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGO data. Model description: Training set N=472, Test set N=75, Sensitivity= 0.89, Specificity=0.97, Accuracy=0.93, MCC=0.87. Click here for details.	0.50 (50.00)
9	Mycosis	Potential antifungal activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=172, Test set N=47, Sensitivity= 0.90, Specificity=0.88, Accuracy=0.89, MCC=0.79. Click here for details.	0.46 (50.45)
10	Viral	Potential antiviral activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=206, Test set N=35, Sensitivity= 0.92, Specificity=0.95, Accuracy=0.94, MCC=0.88. Click here for details.	0.45 (48.11)
11	Psoriasis	Potential antipsoriasis activity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=199, Test set N=32, Sensitivity= 0.93, Specificity=0.82, Accuracy=0.89, MCC=0.74. Click here for details.	0.44 (48.25)
12	Allergy	Potential antiallergic activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=258, Test set N=47, Sensitivity= 0.87, Specificity=0.88, Accuracy=0.87, MCC=0.74. Click here for details.	0.38 (56.79)
13	Arthritis	Potential activity against arthritis. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGO data. Model description: Training set N=460, Test set N=77, Sensitivity= 0.98, Specificity=0.94, Accuracy=0.96, MCC=0.92. Click here for details.	0.37 (50.00)
14	Heart Failure	Potential activity against heart failure. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=204, Test set N=33, Sensitivity= 0.78, Specificity=0.87, Accuracy=0.82, MCC=0.64. Click here for details.	0.37 (46.88)
15	Bacterial	Potential antibacterial activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=530, Test set N=97, Sensitivity= 0.87, Specificity=0.90, Accuracy=0.89, MCC=0.77. Click here for details.	0.34 (53.64)
16	Inflammation	Potential antiinflammatory activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=598, Test set N=93, Sensitivity= 0.86, Specificity=0.84, Accuracy=0.85, MCC=0.69. Click here for details.	0.33 (50.48)
17	Osteoporosis	Potential anti-osteoporosis activity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=595, Test set N=86, Sensitivity= 0.84, Specificity=0.85, Accuracy=0.85, MCC=0.70. Click here for details.	0.32 (50.00)

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18	Angina	Potential antianginal activity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=546, Test set N=95, Sensitivity= 0.90, Specificity=0.93, Accuracy=0.92, MCC=0.83. Click here for details.	0.26 (50.89)
19	Migraine	Potential anti-migraine activity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=515, Test set N=98, Sensitivity= 0.81, Specificity=0.84, Accuracy=0.83, MCC=0.65. Click here for details.	0.25 (64.58)
20	Asthma	Potential activity against asthma. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=366, Test set N=63, Sensitivity= 0.92, Specificity=0.86, Accuracy=0.89, MCC=0.78. Click here for details.	0.25 (55.21)
21	Diabetes	Potential antidiabetic activity. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=195, Test set N=34, Sensitivity= 0.85, Specificity=0.93, Accuracy=0.88, MCC=0.77. Click here for details.	0.23 (56.96)
22	HIV	Potential activity against HIV. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=491, Test set N=80, Sensitivity= 0.80, Specificity=0.86, Accuracy=0.84, MCC=0.67. Click here for details.	0.22 (64.58)
23	Cancer	Potential anticancer activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=886, Test set N=167, Sensitivity= 0.89, Specificity=0.83, Accuracy=0.86, MCC=0.72. Click here for details.	0.20 (64.58)
24	Skin Diseases	Potential activity against skin diseases. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=255, Test set N=36, Sensitivity= 1.00, Specificity=0.76, Accuracy=0.86, MCC=0.76. Click here for details.	0.20 (46.28)
25	Hyperlipidemia	Potential antihyperlipidemic activity. Training set consists of approved drugs. Cutoff is 0.5. The values higher than 0.5 indicate potentially active compounds. Reference: GeneGo data. Model description: Training set N=185, Test set N=24, Sensitivity= 0.75, Specificity=0.92, Accuracy=0.83, MCC=0.68. Click here for details.	0.11 (50.00)