Tutorial of Simple QSAR calculation by MolAICal

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1. Introduction

The quantitative structure-activity relationship (QSAR) models are regression or classification models used in drug design. In this tutorial, the simple regression model of QSAR is introduced based on the ligands of signal transducer and activator of transcription 3 (STAT3) protein which is considered as a potential drug target of cancer. Here, the MolAICal soft package (https://doi.org/10.1093/bib/bbaa161) is employed for this tutorial.

2. Materials

2.1. Software requirement

1) MolAICal: https://molaical.github.io

2) DRAGON: http://www.talete.mi.it/index.htm

Note: You can use any molecular descriptor calculator besides DRAGON software for this tutorial.

2.2. Example files

1) All the necessary tutorial files are downloaded from:
https://github.com/MolAICal/tutorials/tree/master/006-QSAR

3. Procedure

3.1. Calculate molecular descriptor

1) Open DRAGON and load ligands in folder "006-QSAR/ligands" (see Figure 1). The .hin format of ligands is optimized and saved by HyperChem software. You can optimize the ligand structures and save them with Sybyl mol2, etc for calculation.

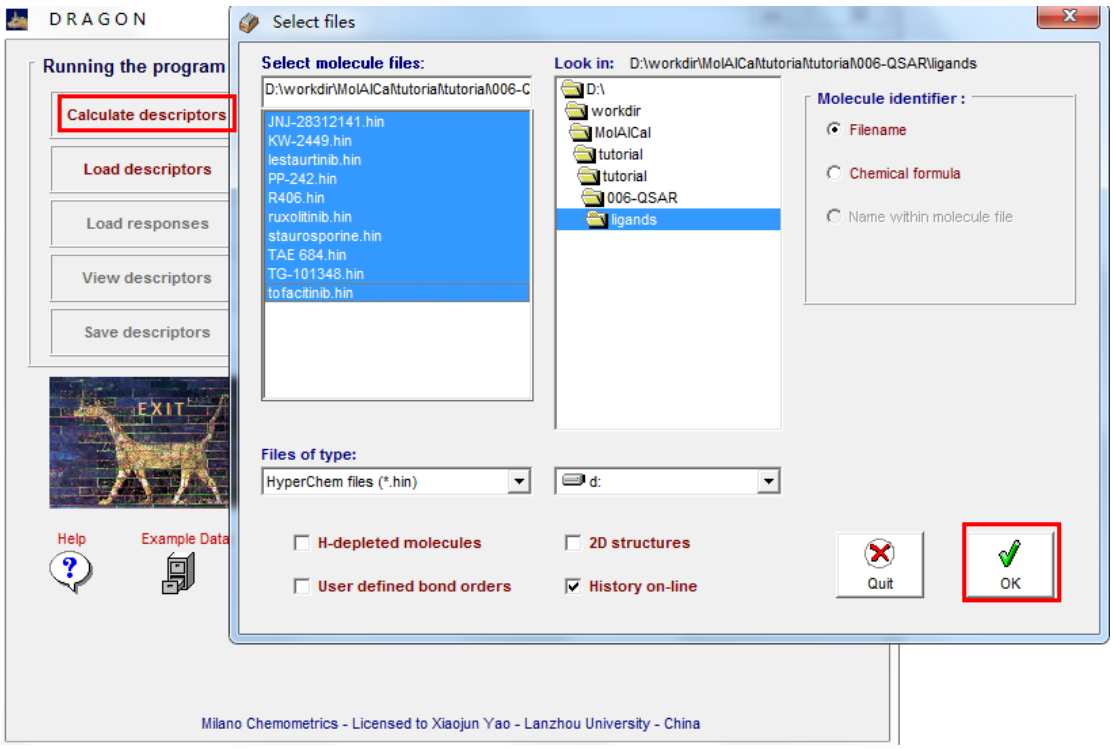


Figure 1. Molecular descriptor calculation by DRAGON

Note: You can retrieve the ligands of protein target on website: www.guidetopharmacology.org, etc.

2) Save the molecular descriptor named "QSARMolDes.txt" in TXT format file (see Figure 2).

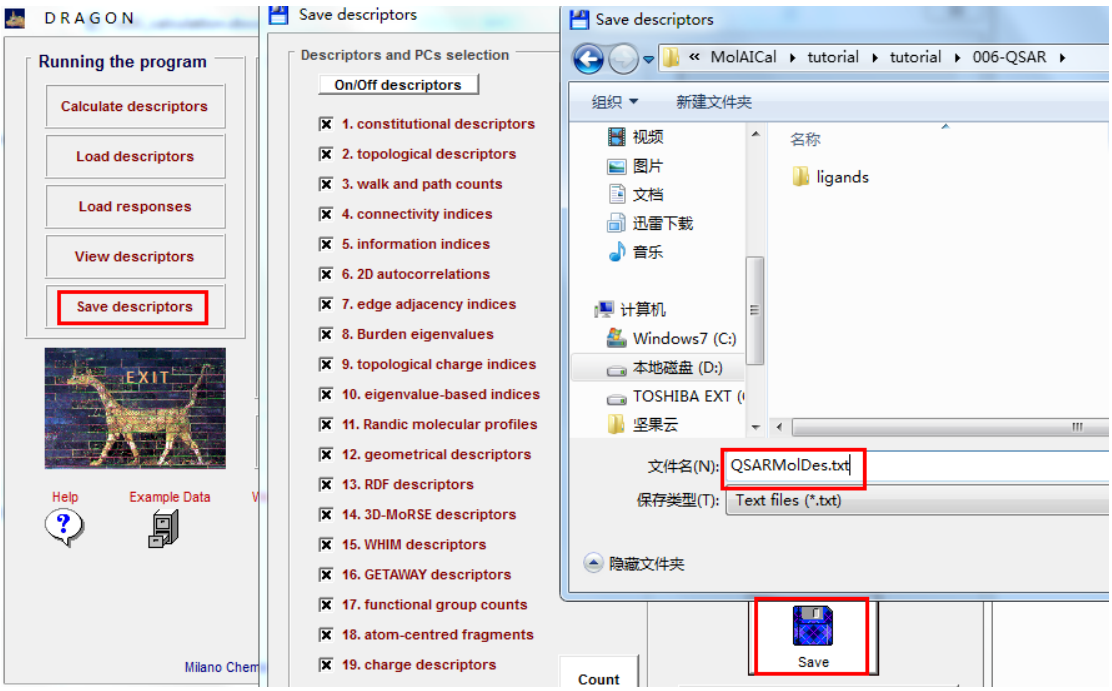
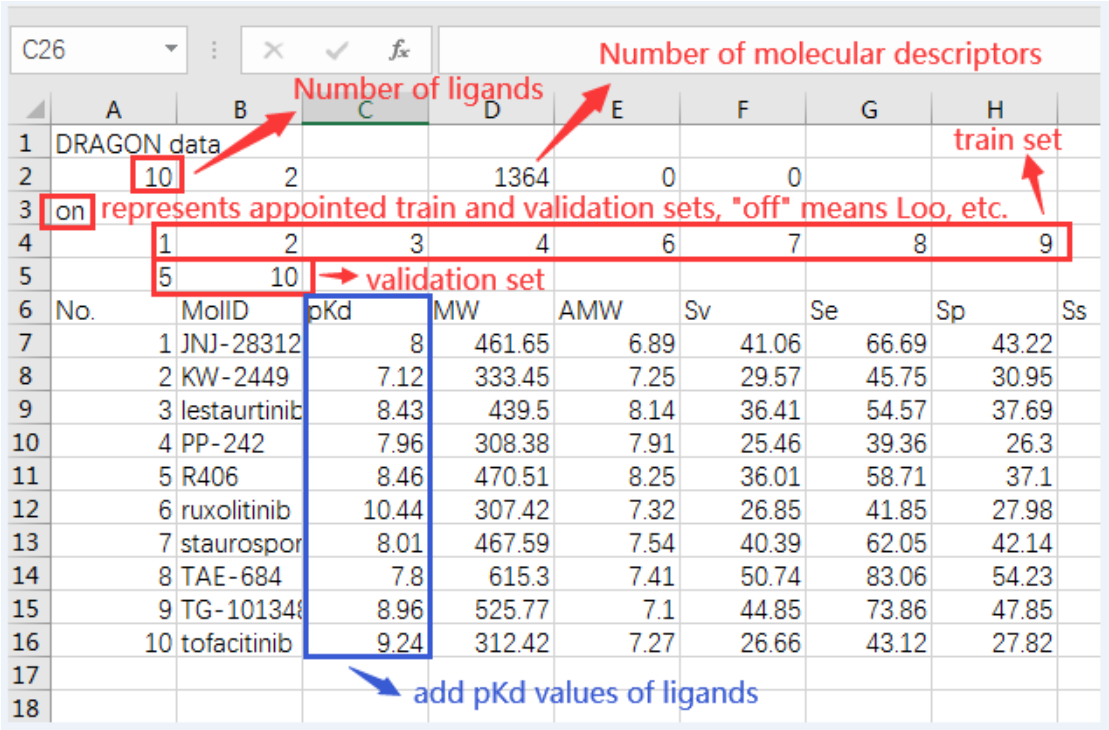


Figure 2. Storing file named "QSARMolDes.txt"

3) Open "QSARMolDes.txt" with Excel and set parameters (see Figure 3).



	A	B	C	D	E	F	G	H	
1	DRAGON data								
2		10	2	1364	0	0			
3	on								
4		1	2	3	4	6	7	8	9
5		5	10						
6	No.	MolID	pKd	MW	AMW	Sv	Se	Sp	Ss
7	1	JNJ-28312	8	461.65	6.89	41.06	66.69	43.22	
8	2	KW-2449	7.12	333.45	7.25	29.57	45.75	30.95	
9	3	lestaurtinib	8.43	439.5	8.14	36.41	54.57	37.69	
10	4	PP-242	7.96	308.38	7.91	25.46	39.36	26.3	
11	5	R406	8.46	470.51	8.25	36.01	58.71	37.1	
12	6	ruxolitinib	10.44	307.42	7.32	26.85	41.85	27.98	
13	7	staurospor	8.01	467.59	7.54	40.39	62.05	42.14	
14	8	TAE-684	7.8	615.3	7.41	50.74	83.06	54.23	
15	9	TG-10134	8.96	525.77	7.1	44.85	73.86	47.85	
16	10	tofacitinib	9.24	312.42	7.27	26.66	43.12	27.82	
17									
18									

Figure 3. Set parameter for QSAR

You must set the parameters in the "QSARMolDes.txt" strictly. You can use any title or default title in the first line. The first number in the second line must be the number of ligands for QSAR. The third number in the second line must be the number of molecular descriptors. The other numbers in

the second line can be the default numbers or arbitrary numbers. The character "on" in the third line means train and validation sets are appointed. The numbers in the fourth line are the sequence numbers of train set from the below No. of ligands. The numbers in the fifth line are the sequence numbers of validation set from the below No. of ligands (see Figure 3). If "off" is chosen, it means leave-one-out (LOO) cross-validation is used for QSAR calculation, in this case, the fourth and fifth lines for train and validation sets can be omitted (See file "QSARMolDes_LOO.txt"). In addition, the experimental values such as pKd should be added in the third column (see Figure 3).

3.2. QSAR calculations

Running command as below:

#> molaical.exe -qsar GA -i QSARMolDes.txt

Or

#> molaical.exe -qsar GA -i QSARMolDes_LOO.txt

If you want to know more parameters for QSAR, please check the manual of MolAICal. This tutorial just contains 10 ligands. When Q2 is enough for your research, you can stop the QSAR running by keyboard shortcut "Ctrl + C". The results are stored in file "QSAROutFile.dat". Open "QSAROutFile.dat" and the information is as below

```
****** The 1th model ******
The Q^2-LOO is: 0.8542
R^2 fitting is: 0.9473
R^2 adjusted is: 0.9210
RSS is: 0.4042
The formula is: y = 0.68376 + (1.12498) * H0p + (2.45137) * Mor26e + (0.79399) * ESpm06d
The standard errors of b0 to b3 corresponding to formula is: 1.83351, 2.17332, 0.25011, 0.23398
The standard error of the regression (sigma) is: 0.2595
The experiment values, predicted values, calculated values by LOO validation and residuals:
8.0      8.1138      8.1743      -0.1138
7.12      7.2904      7.4440      -0.1704
8.43      8.5246      8.5705      -0.0946
7.96      7.7950      7.6441      0.1650
8.46      8.7477      8.8000      -0.2877
10.44      10.5084      10.7288      -0.0684
8.01      7.8877      7.8584      0.1223
7.8      7.9168      8.3305      -0.1168
8.96      8.5185      8.3828      0.4415
9.24      9.1171      9.0764      0.1229
```