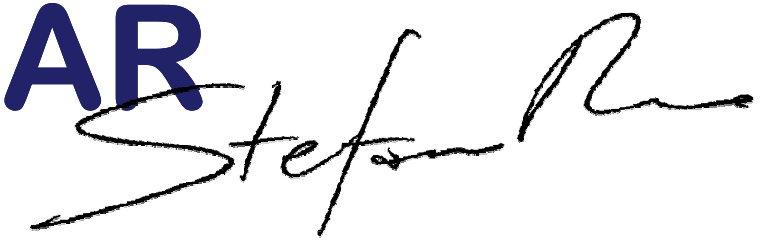
Computational Toxicology and QSAR



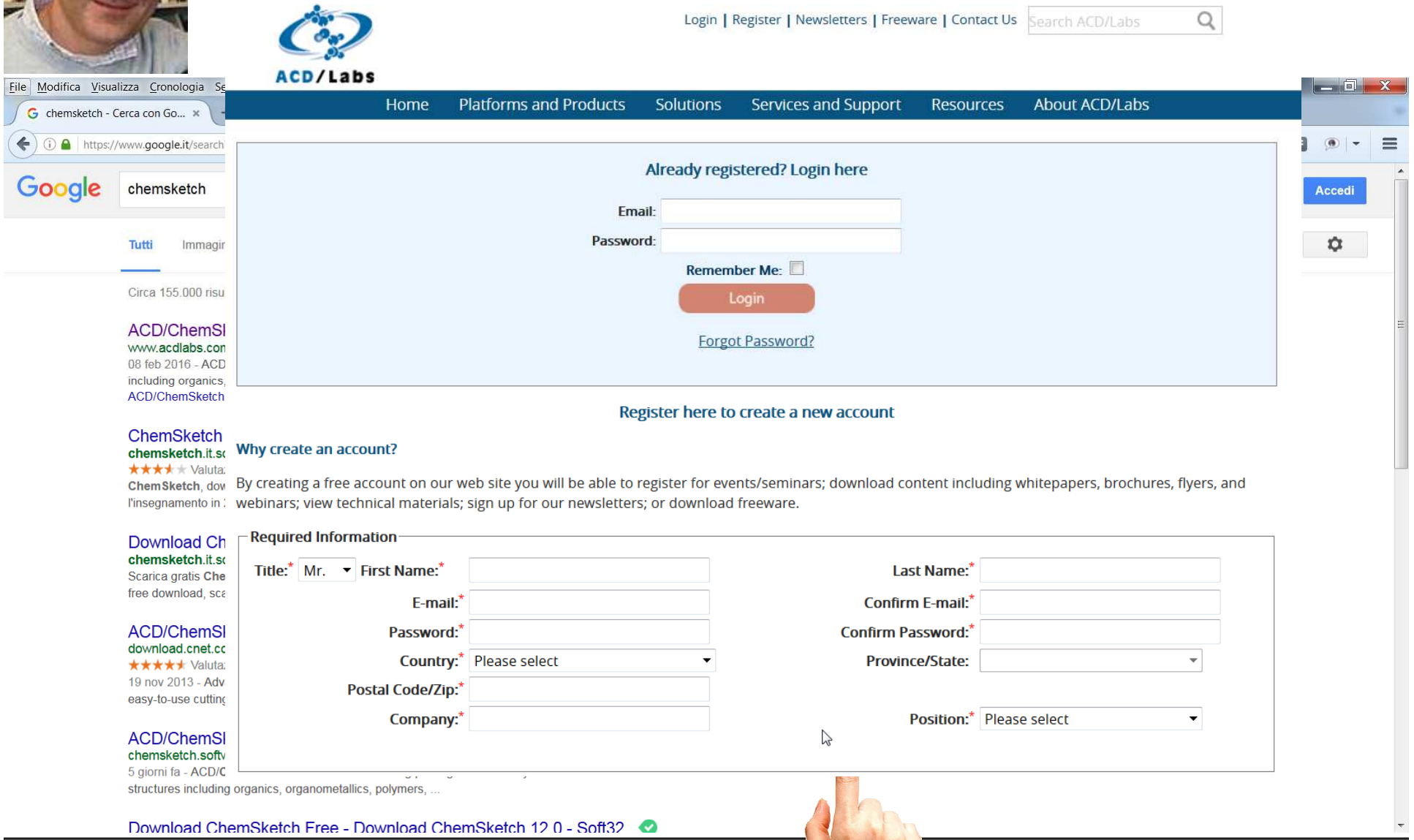
by **Stefano Moro**

Molecular Modeling Section (MMS)

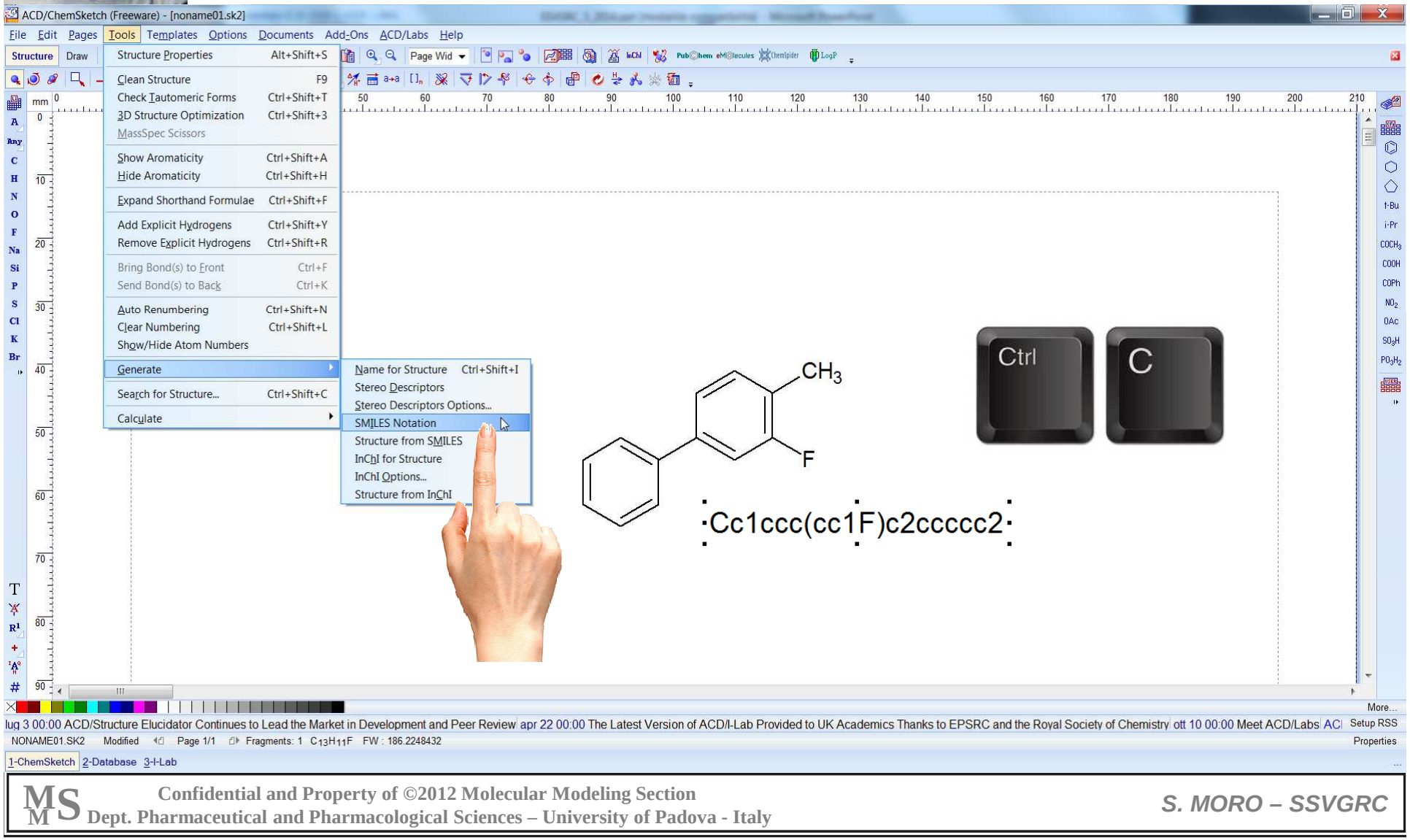
Department of Pharmaceutical and Pharmacological Sciences

University of Padova

First of all, draw your structure...



First of all, draw your structure…



But you can do several other interesting things:

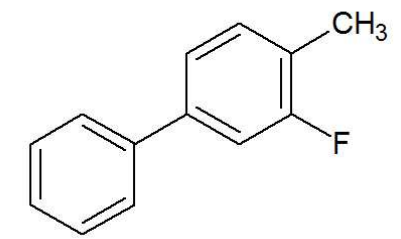
ACD/ChemSketch (Freeware) - [noname01.sk2]

File Edit Pages Tools Templates Options Documents Add-Ons ACD/Labs Help

Structure Draw

Structure Properties Alt+Shift+S
Clean Structure F9
Check Tautomeric Forms Ctrl+Shift+T
3D Structure Optimization Ctrl+Shift+3
MassSpec Scissors
Show Aromaticity Ctrl+Shift+A
Hide Aromaticity Ctrl+Shift+H
Expand Shorthand Formulae Ctrl+Shift+F
Add Explicit Hydrogens Ctrl+Shift+Y
Remove Explicit Hydrogens Ctrl+Shift+R
Bring Bond(s) to Front Ctrl+F
Send Bond(s) to Back Ctrl+K
Auto Renumbering Ctrl+Shift+N
Clear Numbering Ctrl+Shift+L
Show/Hide Atom Numbers
Generate
Search for Structure... Ctrl+Shift+C
Calculate

Molecular Formula
Formula Weight
Composition
Molar Refractivity
Molar Volume
Parachor
Index of Refraction
Surface Tension
Density
Dielectric Constant
Polarizability
RDBE
Monoisotopic Mass
Nominal Mass
Average Mass
M+
M-
[M+H]+
[M+H]-
[M-H]+
[M-H]-
All Properties



·Cc1ccc(cc1F)c2ccccc2·

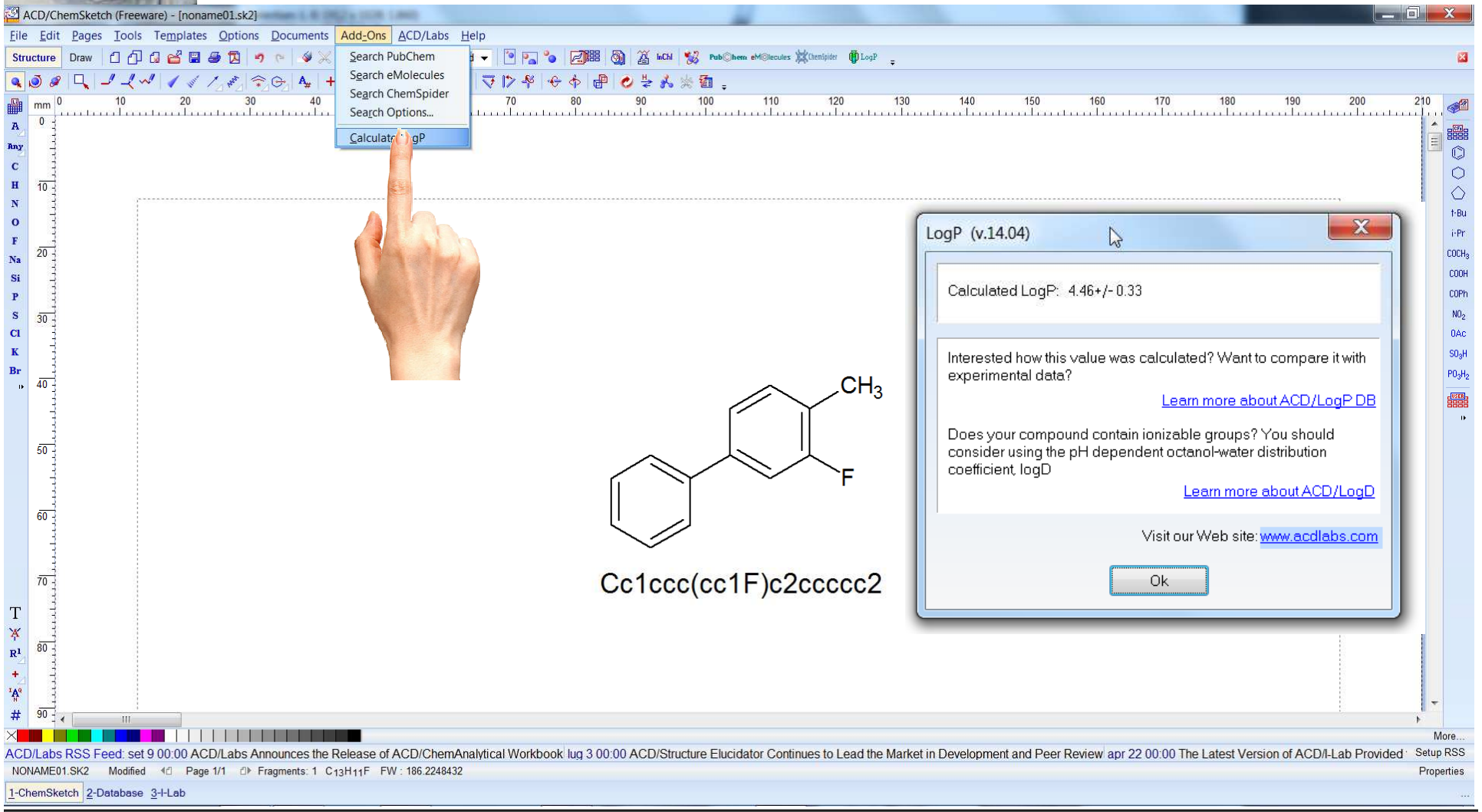
Molecular Formula:	$C_{13}H_{11}F$
Formula Weight:	186.2248432
Composition:	C(83.84%) H(5.95%) F(10.20%)
Molar Refractivity:	55.66 ± 0.3 cm^3
Molar Volume:	175.2 ± 3.0 cm^3
Parachor:	425.4 ± 4.0 cm^3
Index of Refraction:	1.548 ± 0.02
Surface Tension:	34.7 ± 3.0 dyne/cm
Density:	1.062 ± 0.06 g/cm^3
Dielectric Constant:	Not available
Polarizability:	22.06 ± 0.5 $10^{-24} cm^3$
RDBE:	8
Monoisotopic Mass:	186.084479 Da
Nominal Mass:	186 Da
Average Mass:	186.2248 Da
M+:	186.08393 Da
M-:	186.085027 Da
[M+H]+:	187.091755 Da
[M+H]-:	187.092852 Da
[M-H]+:	185.076105 Da
[M-H]-:	185.077202 Da

ACD/Labs RSS Feed: set 9 00:00 ACD/Labs Announces the Rele ... ok lug 3 00:00 ... tinues to Lead the Market in Development and Peer Review apr 22 00:00 The Latest Version of ACD/I-Lab Provided

NONAME01.SK2 Modified Page 1/1 Fragments: 1 $C_{13}H_{11}$

1-ChemSketch 2-Database 3-I-Lab

But you can do several other interesting things:



Now, we can download VEGA…

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To access the download area you are just requested to register, so that we can keep track of who is downloading the application and contact you when a new version is available. If you are not registered, please register now.

If you are interested in other chemoinformatics tools, you can find a collection of applications based on the VEGA core libraries at Kode Chemoinformatics website. A KNIME extension is also available.

How to INTERPRET RESULTS

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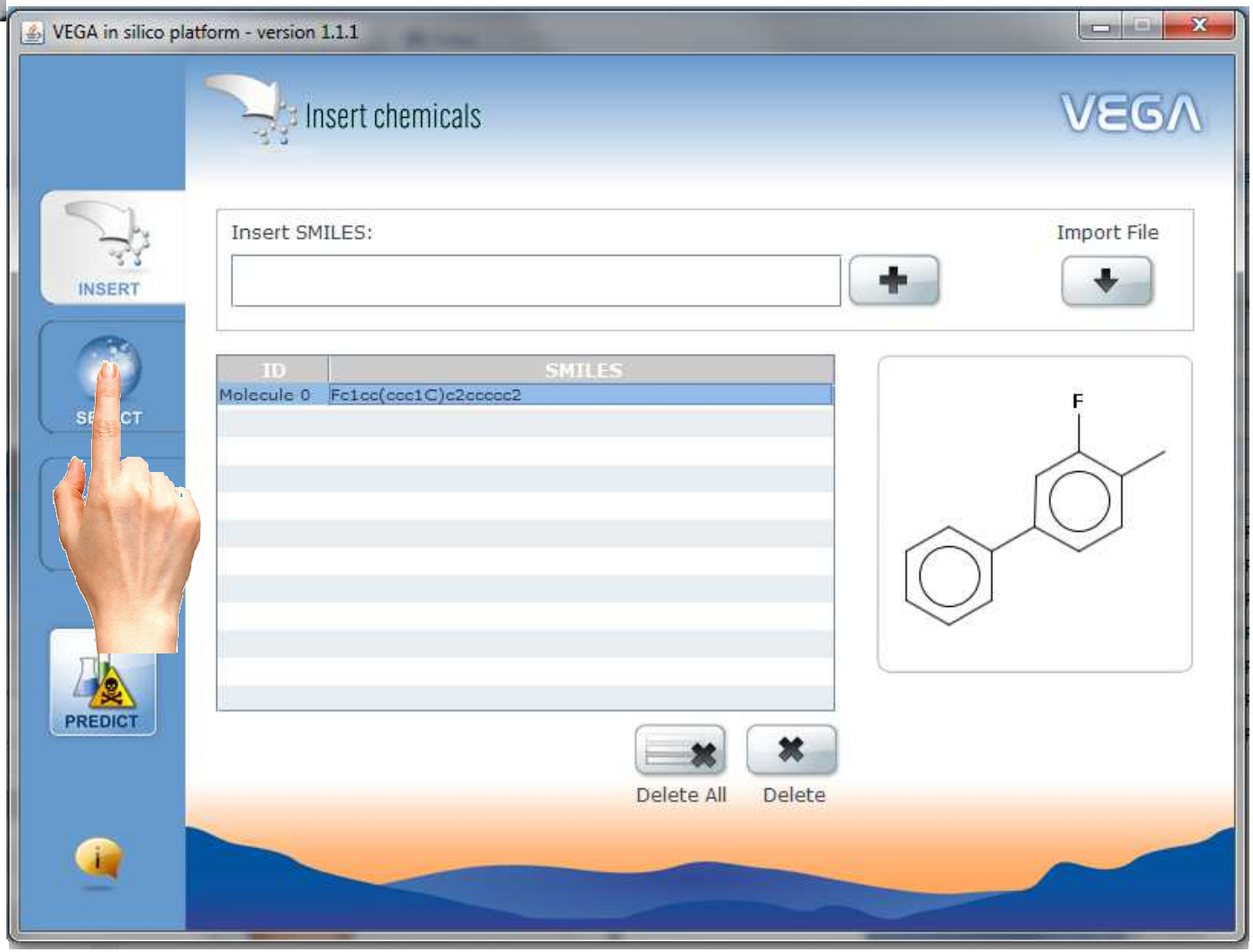
User (e-mail): stefano.moro@unipd.it

Password: ••••••••

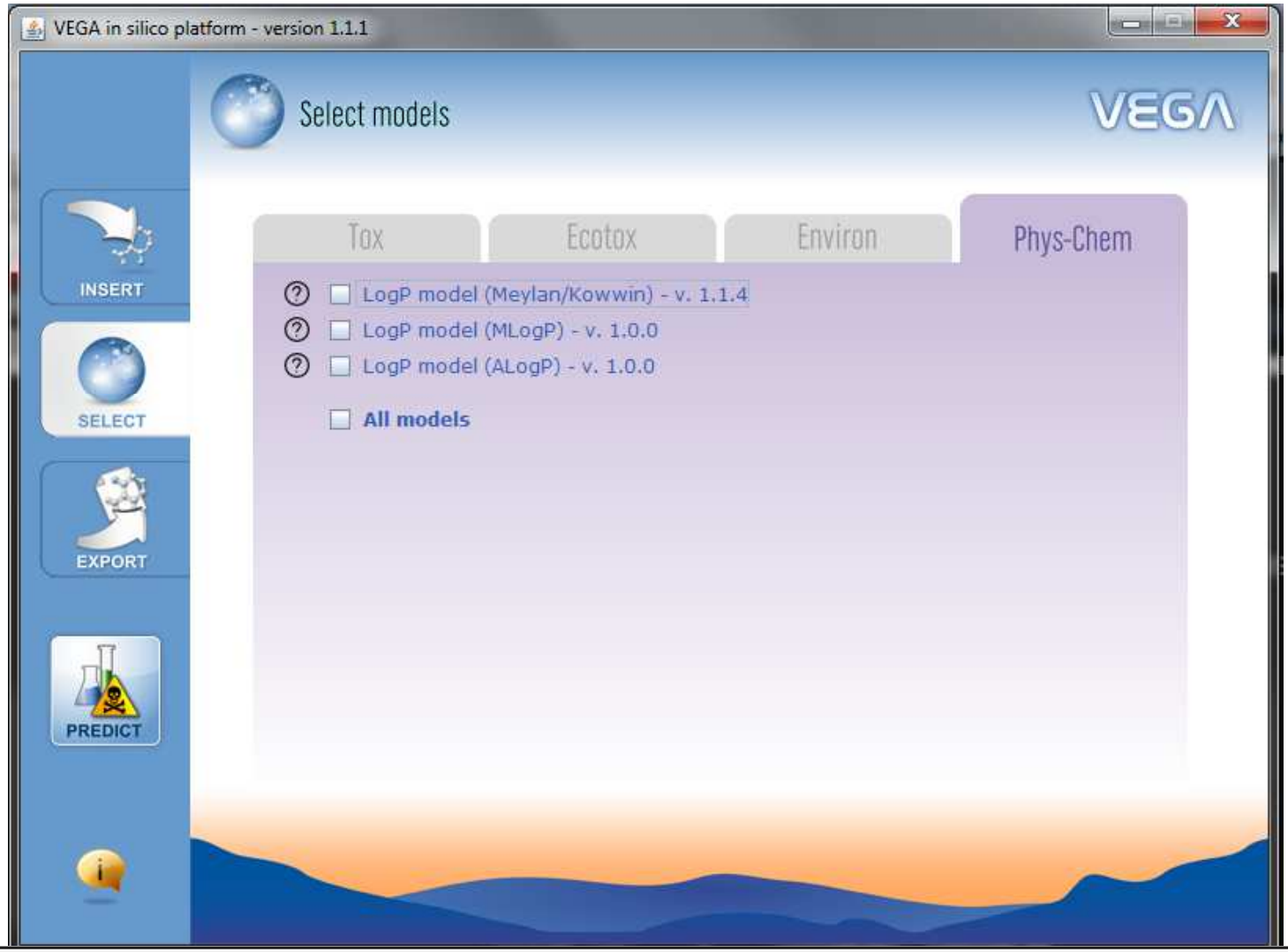
Login

Forgot your password? Retrieve it here.

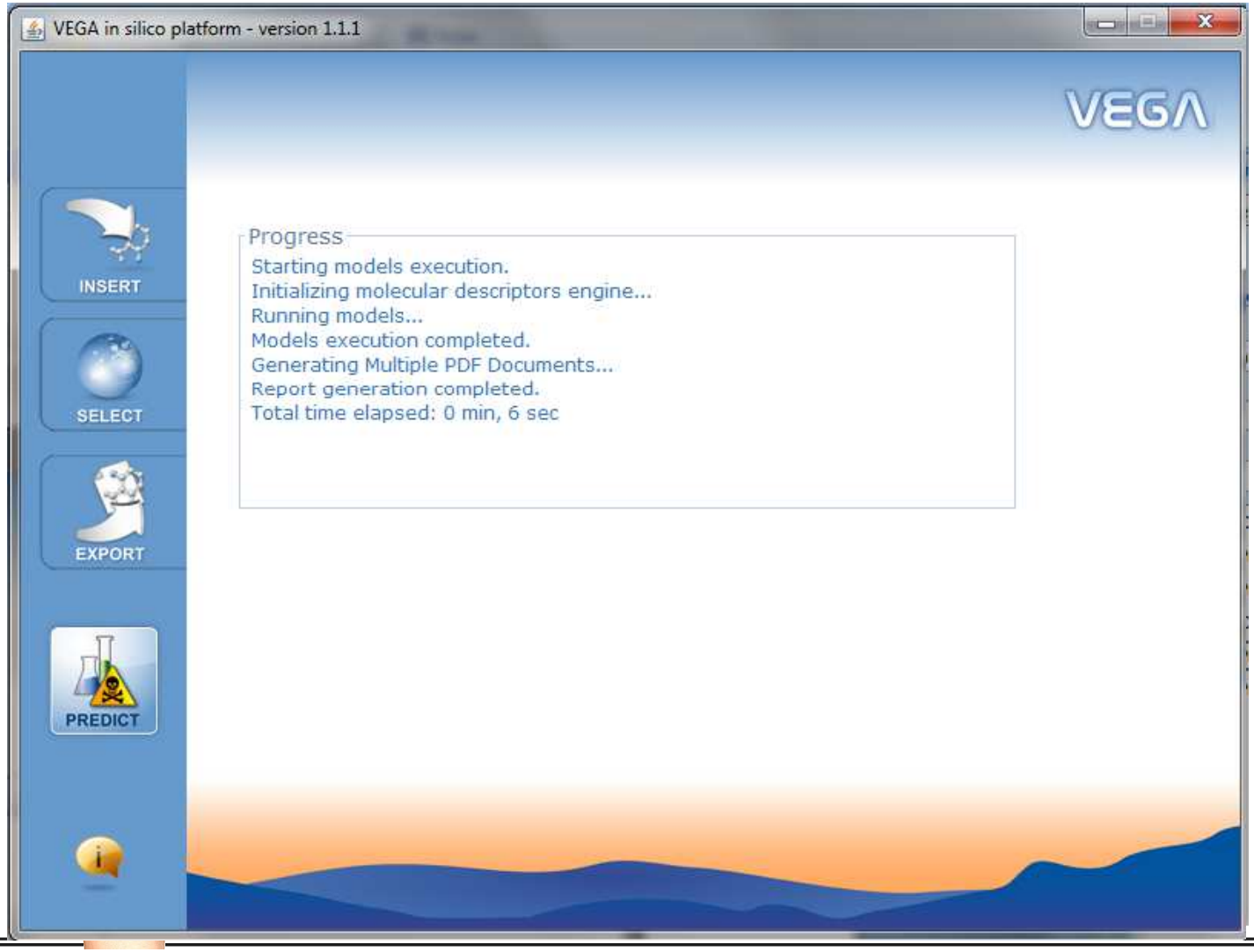
Here is VEGA!


VEGA in silico platform - version 1.1.1
Insert chemicals
VEGA
INSERT
Insert SMILES:
Import File
ID
SMILES
Molecule 0
Fc1cc(ccc1C)c2ccccc2
F
PREDICT
Delete All
Delete

Here is VEGA!


VEGA in silico platform - version 1.1.1
Select models
VEGA
INSERT
SELECT
EXPORT
PREDICT
Tox
Ecotox
Environ
Phys-Chem
LogP model (Meylan/Kowwin) - v. 1.1.4
LogP model (MLogP) - v. 1.0.0
LogP model (ALogP) - v. 1.0.0
All models

Here is VEGA!

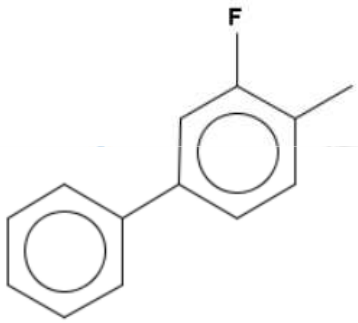

VEGA in silico platform - version 1.1.1
VEGA
INSERT
SELECT
EXPORT
PREDICT
Progress
Starting models execution.
Initializing molecular descriptors engine...
Running models...
Models execution completed.
Generating Multiple PDF Documents...
Report generation completed.
Total time elapsed: 0 min, 6 sec

and here our report…

VEGA Mutagenicity (Ames test) model (CAESAR) 2.1.13 page 1

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

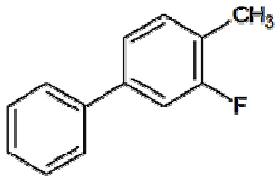
Prediction is Mutagenic, but the result shows some critical aspects, which require to be checked:
- similar molecules found in the training set have experimental values that disagree with the predicted value

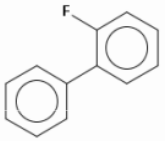
Compound: Molecule 0
Compound SMILES: Fc1cc(ccc1C)c2ccccc2
Experimental value: -
Predicted Mutagen activity: Mutagenic
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

and here our report...

3.1 Applicability Domain:

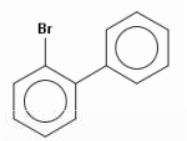
Similar Compounds, with Predicted and Experimental Values





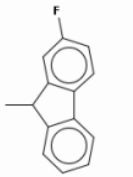
CAS: 321-60-8
Dataset id: 1502 (Test set)
SMILES: Fc1ccccc1c2ccccc2
Similarity: 0.936

Experimental value: NON-Mutagenic
Predicted value: NON-Mutagenic



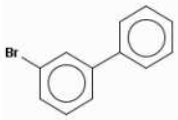
CAS: 2052-07-5
Dataset id: 577 (Training set)
SMILES: c1ccc(cc1)c2ccccc2Br
Similarity: 0.858

Experimental value: NON-Mutagenic
Predicted value: NON-Mutagenic



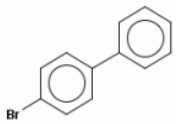
CAS: 96563-11-0
Dataset id: 405 (Test set)
SMILES: Fc2ccc3c1ccccc1C(c3(c2))C
Similarity: 0.868

Experimental value: Mutagenic
Predicted value: Mutagenic



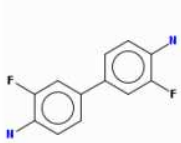
CAS: 2113-57-7
Dataset id: 2319 (Training set)
SMILES: c1ccc(cc1)c2cccc(c2)Br
Similarity: 0.858

Experimental value: NON-Mutagenic
Predicted value: NON-Mutagenic



CAS: 92-66-0
Dataset id: 845 (Training set)
SMILES: c1ccc(cc1)c2ccc(cc2)Br
Similarity: 0.86

Experimental value: NON-Mutagenic
Predicted value: NON-Mutagenic



CAS: 448-97-5
Dataset id: 2515 (Training set)
SMILES: Fc1cc(ccc1(N))c2ccc(N)c(F)c2
Similarity: 0.829

Experimental value: Mutagenic
Predicted value: Mutagenic

and here our report…

3.2 Applicability Domain:

Measured Applicability Domain Scores

Global AD Index
AD index = 0.709
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.883
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 0.325
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

…again:

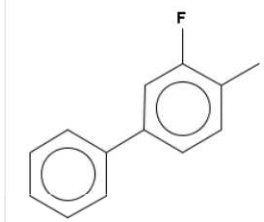

VEGA in silico platform - version 1.1.1
Select models
VEGA
INSERT
SELECT
EXPORT
PREDICT
Tox
Ecotox
Environ
Phys-Chem
Fish Acute (LC50) Toxicity classification (SarPy/IRFMN) - v. 1.0.2
Fish Acute (LC50) Toxicity model (KNN/Read-Across) - v. 1.0.0
Fathead Minnow LC50 96h (EPA) - v. 1.0.7
Daphnia Magna LC50 48h (EPA) - v. 1.0.7
Daphnia Magna LC50 48h (DEMETRA) - v. 1.0.4
All models

...again:

VEGA Fish Acute (LC50) Toxicity classification (SarPy/IRFMN) 1.0.2 page 1

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

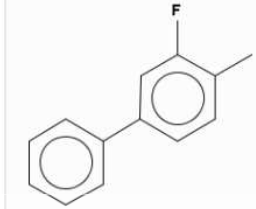
Prediction is Toxic-2 (between 1 and 10 mg/l), the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections. Anyway some issues could be not optimal:
- only moderately similar compounds with known experimental value in the training set have been found
The following relevant fragments have been found: Toxicity class 2 alert no. 16; Toxicity class 3 alert no. 4; Toxicity class 3 alert no. 24

Compound: Molecule 0
Compound SMILES: Fc1cc(ccc1C)c2ccccc2
Experimental value: -
Predicted toxicity class: Toxic-2 (between 1 and 10 mg/l)
Structural alerts: Toxicity class 2 alert no. 16; Toxicity class 3 alert no. 4; Toxicity class 3 alert no. 24
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

VEGA Fish Acute (LC50) Toxicity model (KNN/Read-Across) 1.0.0 page 1

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is 3.77 mg/L, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: Fc1cc(ccc1C)c2ccccc2
Experimental value [-log(mg/L)]: -
Predicted toxicity [-log(mg/L)]: -0.58
Predicted toxicity [mg/L]: 3.77
Molecules used for prediction: 4
Experimental value [mg/l]: -
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

Category: Acute I	**Acute toxicity**	
	96 hr LC_{50} (for fish)	≤1 mg/L and/or
	48 hr EC_{50} (for crustacea)	≤1 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/L.
Category: Acute I may be subdivided for some regulatory systems to include a lower band at $L(E)C_{50}$ ≤0.1 mg/L.		
Category: Acute II		
	96 hr LC_{50} (for fish)	>1 - ≤10 mg/L and/or
	48 hr EC_{50} (for crustacea)	>1 - ≤10 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	>1 - ≤10 mg/L.
Category: Acute III		
	96 hr LC_{50} (for fish)	>10 - ≤100 mg/L and/or
	48 hr EC_{50} (for crustacea)	>10 - ≤100 mg/L and/or
	72 or 96hr ErC_{50} (for algae or other aquatic plants)	>10 - ≤100 mg/L.
Some regulatory systems may extend this range beyond an $L(E)C_{50}$ of 100 mg/L through the introduction of another class.		

Enjoy your predictions… but *cum granum salis* !!!