



PMI SCIENCE  
PHILIP MORRIS INTERNATIONAL

# Implementation of automated processes at Philip Morris International R&D using Pipeline Pilot

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(Part of Philip Morris International group of companies)

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[www.pmiscience.com](http://www.pmiscience.com)

# Pipeline Pilot use at PMI

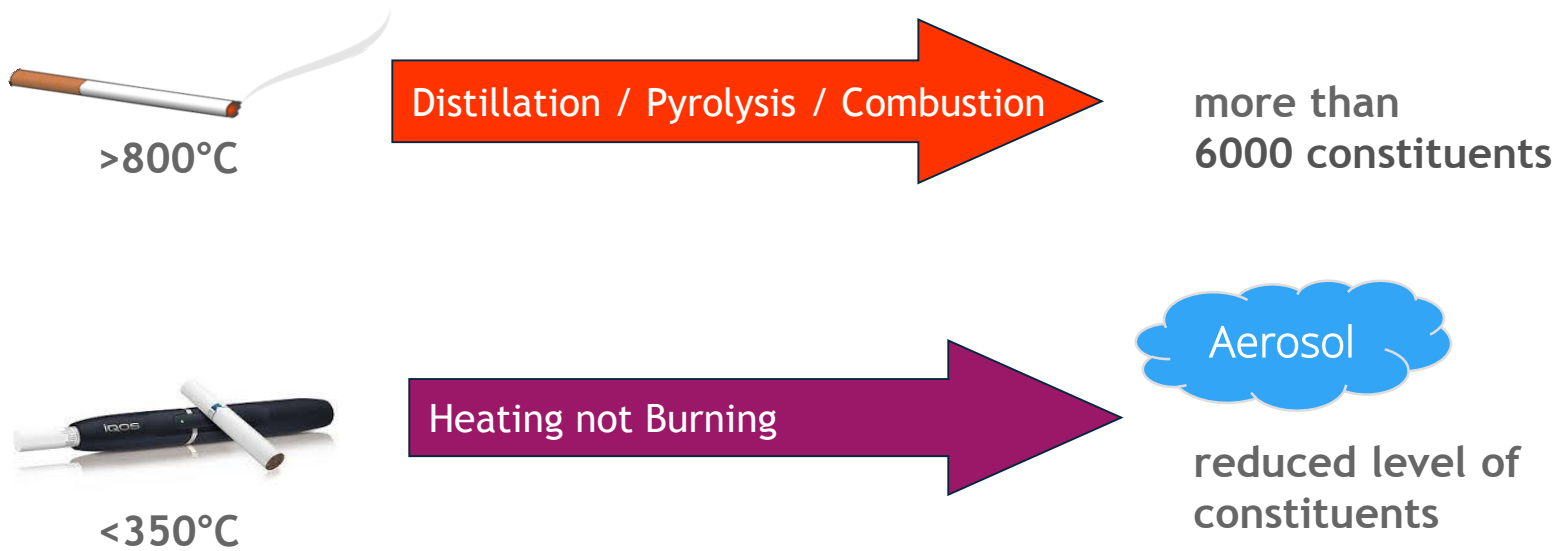
We develop PP protocols to

- improve collecting data from smoke or aerosol complex matrices
- handle and calculate chemical structures
- automate analytical processes

and we post them for users on Biovia Webport.



# Reduced-Risk Products



Some of these constituents are categorized as harmful and potentially harmful constituents (HPHCs)

Reduced-Risk Products (“RRPs”) is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. We have a range of RRP’s in various stages of development, scientific assessment and commercialization. Because our RRP’s do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

# Integrated Chemoinformatics Platforms



Aerosol

Smoking machines generate aerosols that are trapped and collected.



Analytical chemistry

Aerosols are analyzed for HPHCs.

Computational chemistry

Constituents are deposited in database, clustered and calculated.

Systems Toxicology, Clinics

Studies to advance scientific and medical knowledge are performed. Toxicological and Clinical assessments are done.

CASI

Structural Identification

UCSD

Chemical and Spectra Registry

REPORTING

PP used for:

# PMI Unique Compound & Spectra Database

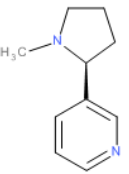
PMI Unique Compounds & Spectra Database Web Interface

Search Molecules Submit New Molecule Administration

Search Molecules > Molecules > Molecule Details

Back

PMI Mol Code: PMI0000249



Chemical classification

- A 5-membered and a 6-membered N-containing ring
- Pyrrolidine
- Pyridine

Physical Measurements

Ref. OR: Ref. BP: Ref. MP:

Calculated Mol. Properties

Mol. Formula: C10 H14 N2  
 Mol. Weight: 162.23155 g/mol  
 Isotopic Mass: 162.1157 g/mol  
 ACD/LogP: 0.6  
 Solubility (w): 5.87 mol/L  
 H. Bond Acceptors: 2  
 H. Bond Donor: 0  
 Drug-like: Yes  
 Lead-like: Yes

Predicted ADMET Properties

Hum. Intestinal Abs.: Good  
 Blood Brain Bar. Penetr.: Medium  
 Plasma Protein Binding: Non binder  
 CYP2D6 Inhibitor: No  
 Hepatotoxicity: Non toxic

Literature Data

Rose JE, Turner JE, Murugesan T, Behm FM, Laugesen M. Pulmonary de characteristics. *Exp Clin Psychopharmacol.* 2010; 18: 385-94.

Generated Names / Structure Codes

Smiles: CN1CCCC1c2cccnc2

InChI: InChI=1S/C10H14N2/c1-12-7-3-5-10(12)9-4-2-6-11-8-9/h2,4,6,8,10H,3,5,7H2,1H3/t10-/m0/s1

IUPAC: 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine

Alternatf Identifiers

Common Name
(-)-nicotine
(S)(-)-nicotine
NICOTINE
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-, sulfate
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-, sulfate (2:1)
l-nicotine
nicotine
nicotine pyruvate

Batch List

Each level of this list corresponds to one entity:

- molecule (neutral compound, e.g. PMI0000001)
- substance (molecule + counter ion, hydrate e.g. PMI0000001-A)
- batches (physical or literature substances, e.g. BC0000014)

Click on a batch code to see its details.  
 Batches matched by the search query are marked with a \*

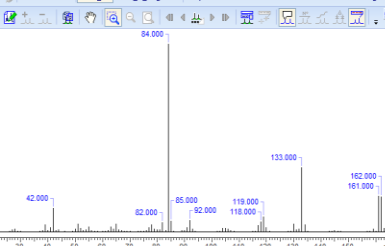
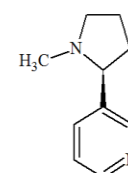
- PMI0000249
  - PMI0000249-A
    - BC000000352
    - BC000000353
    - BC000002437
    - BC000009622
    - BC000007086
    - BC000009236
    - BC000010292 (SPR000000192)
    - BC000010418 (SPR000000320)
    - BC000011160 (SPR000000704)
    - BC000011859
    - BC000012674 (SPR000000133)

ACD/Spectrus DB Enterprise: Database Window - [emartini is now connected to CHEMBOOK\_S... on rd-acid-chemfolder.app.pmi - Defaults]

Database View Record Search Lists Tables Options @CD/Labs Help

LOCAL REMOTE

File Table CFE\_U CFE\_U\_Register Export to NIST From Server Archive Calculate Missing Masses Export to CDX Import Update

Submitter: emartini

Scientist: Peter Calame Josée

Project: ZHM Product Assessment (J-100CP04019/0001/0001)

SDMS\_ID

Study number: RLS-2012-VALD-108

Product/Sample

SpecID: SPR000000320

batchcode: BC000010418

Reference: PMI code: PMI0000249

Compound class: Machine type: PYRO\_PVR-GC-MS\_6336

IUPACNAME: 3[(2S)-1-methylpyrrolidin-2-yl]pyridine

Proposed element composition: common name: NICOTINE

Ionization type: Analyser type: single quad

Method name: E1

Retention Time 1D: 36.27

Retention Time 2D: PMI\_RD\_VN1\_000387\_Direct and indirect material analysis by Pyrolysis-GCMS

Relative retention time: Kovats index: 1374.181818

Theoretical monoisotopic mass: Theoretical monoisotopic mass of neutral molecule

Column name: Varian CP 5845 CP-SIL 6\_Lengeth 50m\_ID 0.25mm\_Flow 0.4micron

Method name: PMI\_RD\_VN1\_000387\_Direct and indirect material analysis by Pyrolysis-GCMS

Retention Time 1D: 36.27

Retention Time 2D: PMI\_RD\_VN1\_000387\_Direct and indirect material analysis by Pyrolysis-GCMS

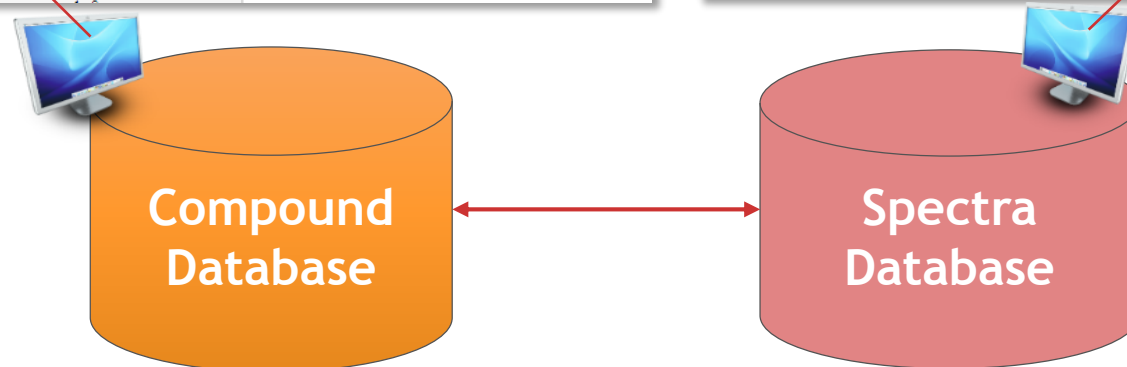
Relative retention time: Kovats index: 1374.181818

Confidence

Name	Value
CAS Name	NICOTINE
CAS Registry Num	54115
Count	90
Data Type	MASS SPECTRUM
Estimated Molecule	162.000
Molecular Formula	C10H14N2
Molecular Weight	162
Spectrum Title	PYRO_PASS entry 55
TIC	311.23
Total Signal	311.2

©: 182 A: 1820288 B: 5 Single DB Owners: CHEMFOLDER\_SCRIPT

1-ChemSketch 2-Database 3-Processor

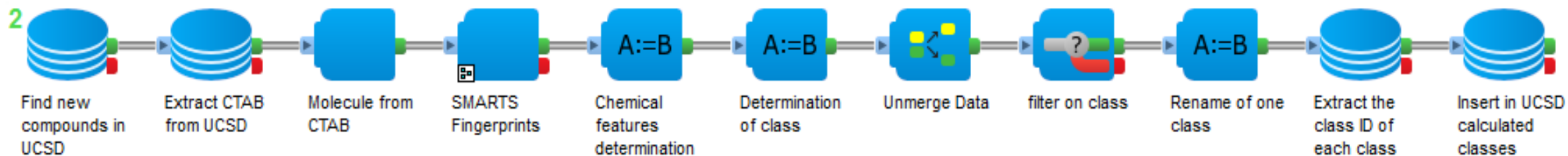


# Overnight protocols to fulfill UCSD

Protocol to determine to which chemical classes a compound belongs

The screenshot shows the PMI Unique Compounds & Spectra Database Web Interface. The main content area displays the chemical classification for a compound with PMI Mol Code: PMI0000. The classification is shown in a pop-up window titled "Chemical classification" with the following text: "A 5-membered and a 6-membered N-containing ring", "Pyrrolidine", and "Pyridine". Below the classification, there is a "Batch List" section with a tree view of batches. To the right, there is an "Alternatif Identifiers" table and a "Literature Data" section.

Common Name
(-)-nicotine
(S)-(-)-nicotine
NICOTINE
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-, sulfate
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-, sulfate (2:1)
l-nicotine
nicotine
nicotine pyruvate

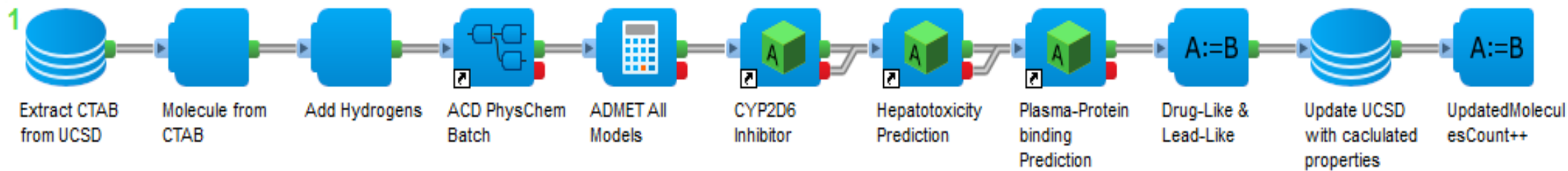




# Compute physicochemical properties

logP, water solubility, ADMET ...

The screenshot displays the PMI Unique Compounds & Spectra Database Web Interface. The main content area shows the chemical structure of a molecule (1-methyl-2-(pyridin-3-yl)pyrrolidine) with its SMILES string (CN1CCCC1c2ccncc2) and InChI string (CN1CCCC1c2ccncc2). The interface is divided into several panels: Chemical classification (A 5-membered and a 6-membered Nonaromatic ring), Physical Measurements (Ref. OR, Ref. BP, Ref. MP), Calculated Mol. Properties (Mol. Formula: C10 H14 N2, Mol. Weight: 182.23156 g/mol, Isotopic Mass: 182.1157 g/mol, ACD/LogP: 0.6, Solubility (w): 5.87 mol/L, H. Bond Acceptors: 2, H. Bond Donor: 0, Drug-like: Yes, Lead-like: Yes), Predicted ADMET Properties (Hum. Intestinal Abs.: Good, Blood Brain Bar. Penetr.: Medium, Plasma Protein Binding: Non binder, CYP2D6 Inhibitor: No, Hepatotoxicity: Non toxic), and a Batch List.

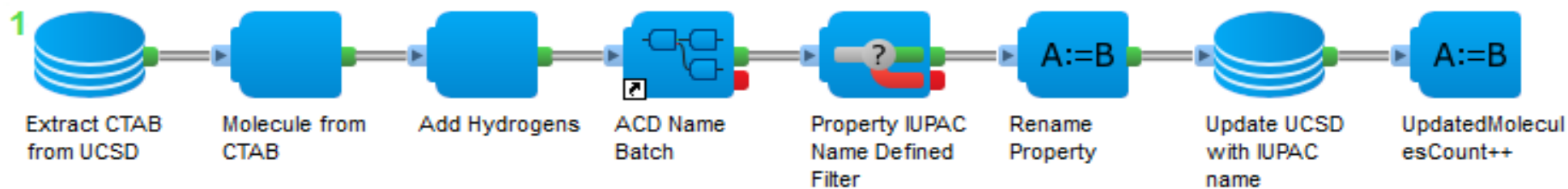


# Naming

IUPAC name

The screenshot displays the PMI Unique Compounds & Spectra Database Web Interface. The main page shows the molecule's details, including its chemical structure, chemical classification (A 5-membered and a 6-membered N-containing ring), and physical measurements. A pop-up window titled "Generated Names / Structure Codes" is overlaid on the page, showing the following information:

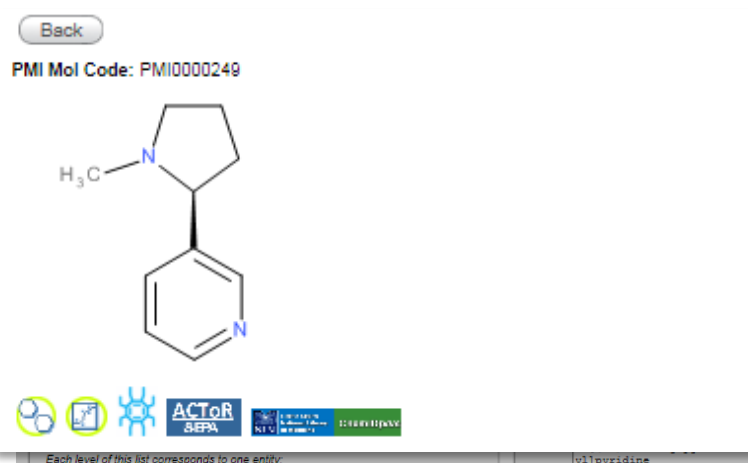
- Smiles: CN1CCC(C@H)1c2ccccc2
- InChI: InChI=1S/C10H14N2/c1-12-7-3-5-10(12)9-4-2-6-11-8-9/h2,4,6,8,10H,3,5,7H2,1H3/t10-m/s1
- IUPAC: 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine





# Links to other databases

## PubChem CID



Physical Measurements

Ref. OR:	Ref. BP:	Ref. MP:

Calculated Mol. Properties

Mol. Formula: C10 H14 N2  
Mol. Weight: 162.23166 g/mol  
Isotopic Mass: 162.1157 g/mol  
ACDLogP: 0.6  
Solubility (w): 5.87 mol/L  
H. Bond Acceptors: 2  
H. Bond Donor: 0  
Drug-like: Yes  
Lead-like: Yes

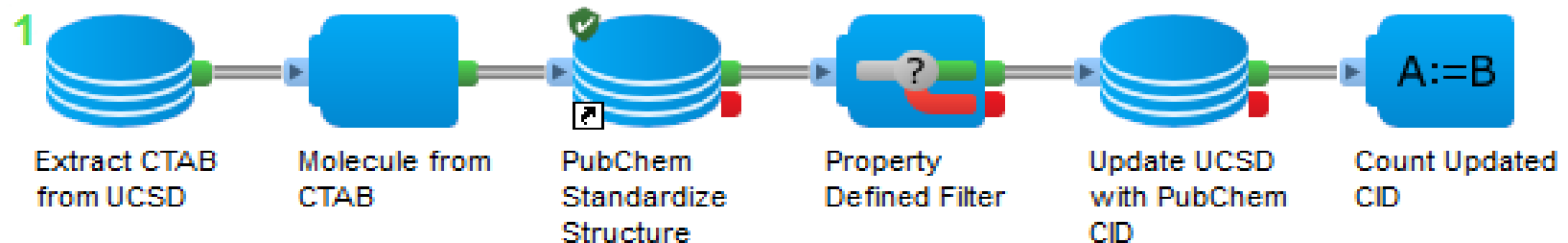
Predicted ADMET Properties

Hum. Intestinal Abs.: Good  
Blood Brain Bar. Penetr.: Medium  
Plasma Protein Binding: Non binder  
CYP2D6 Inhibitor: No  
Hepatotoxicity: Non toxic

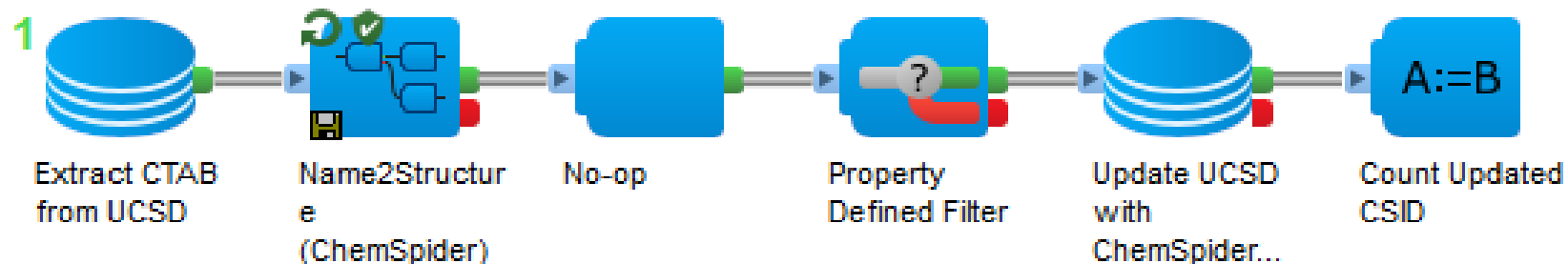
Literature Data

Bibliographical I

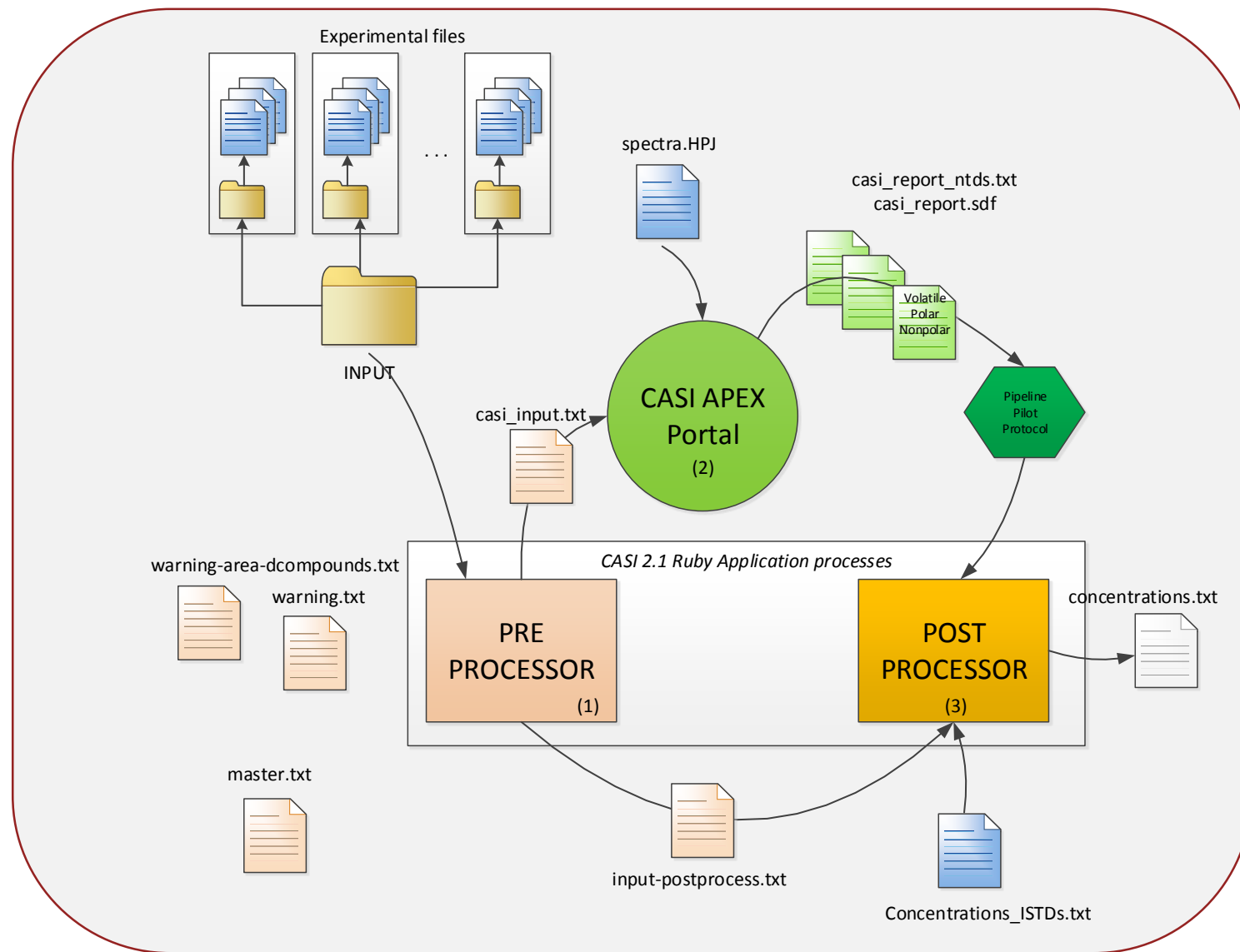
Rose JE, Turner JE, Murugesan T, Behm FM, Laugesen M. Pulmonary de  
characteristics. Exp Clin Psychopharmacol. 2010; 18: 335-64.



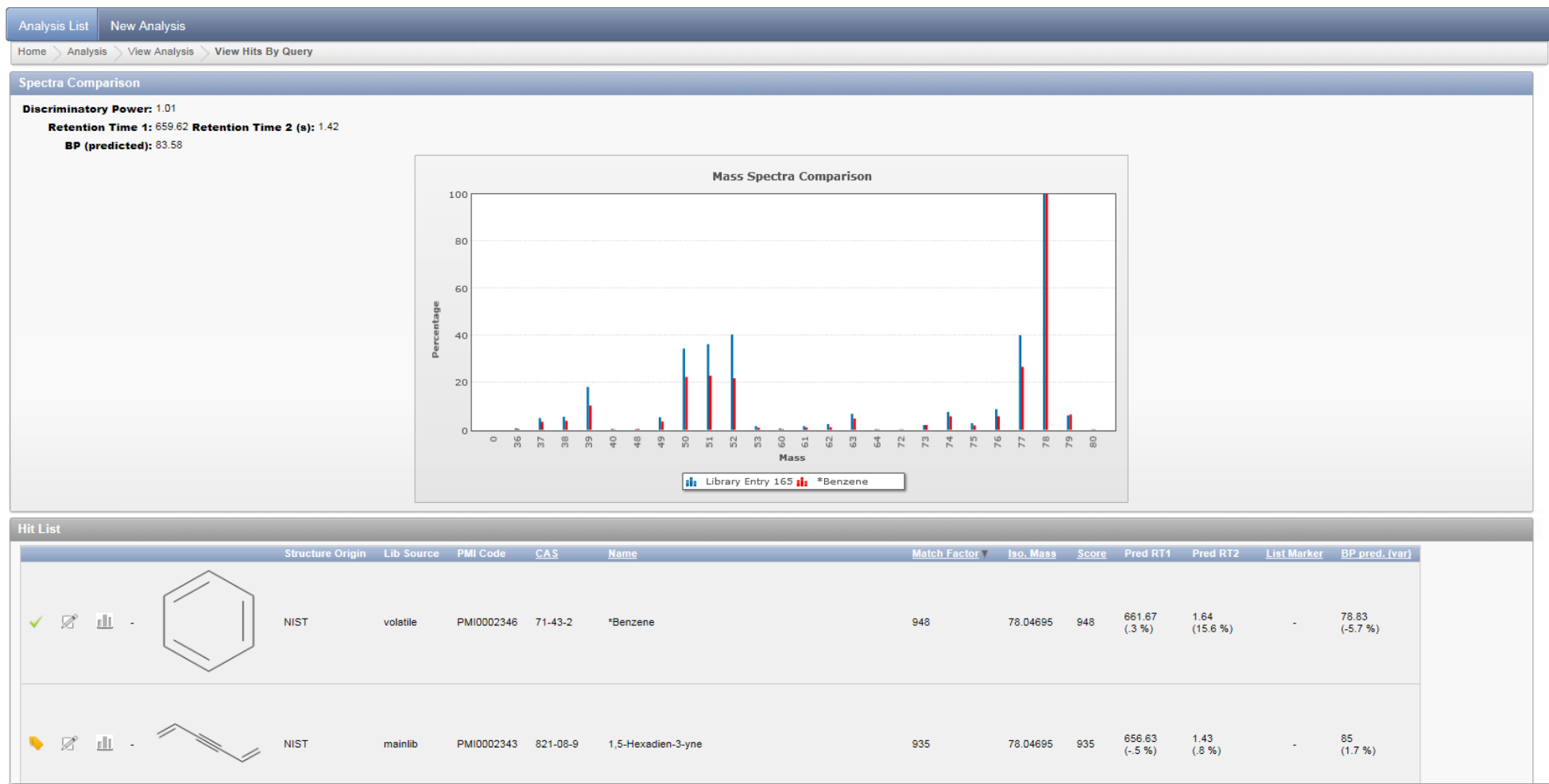
## ChemSpider CSID



# PMI Computer-Assisted Structure Identification Platform



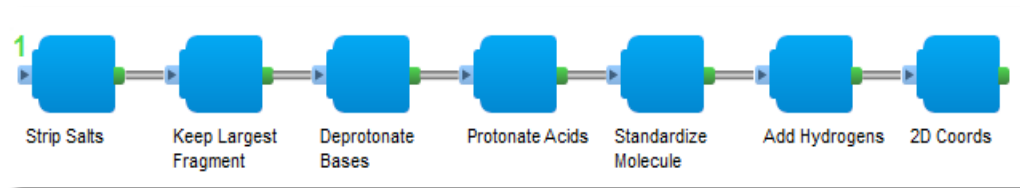
# PMI Computer-Assisted Structure Identification



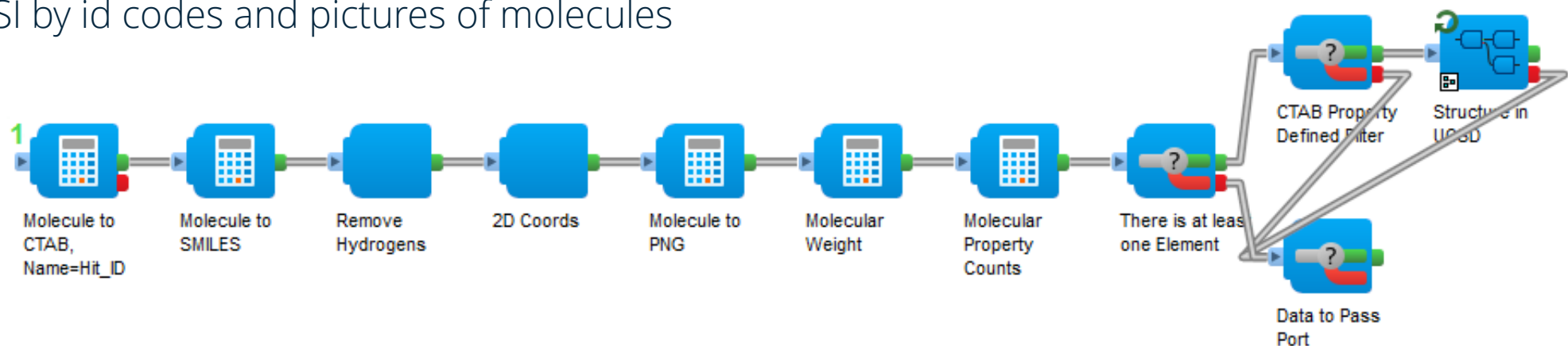
# Protocols used in CASI process

Structure Origin	Lib Source	PMI Code	CAS	Name	Match Factor	Iso. Mass	Score	Pred RT1	Pred RT2	List Marker	BP pred. (var)
NIST	volatile	PMI0002346	71-43-2	*Benzene	948	78.04695	948	661.67 (.3 %)	1.64 (15.6 %)	-	78.83 (-5.7 %)
NIST	mainlib	PMI0002343	821-08-9	1,5-Hexadien-3-yne	935	78.04695	935	656.63 (-.5 %)	1.43 (.8 %)	-	85 (1.7 %)

## 2D standardization of compounds

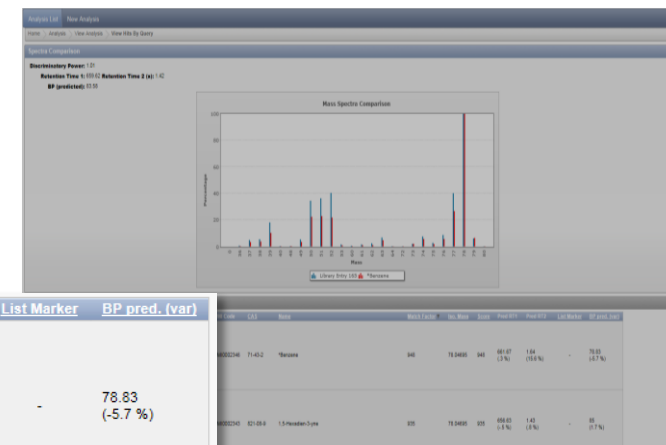


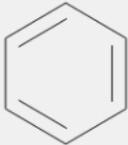

## Updating data in CASI by id codes and pictures of molecules

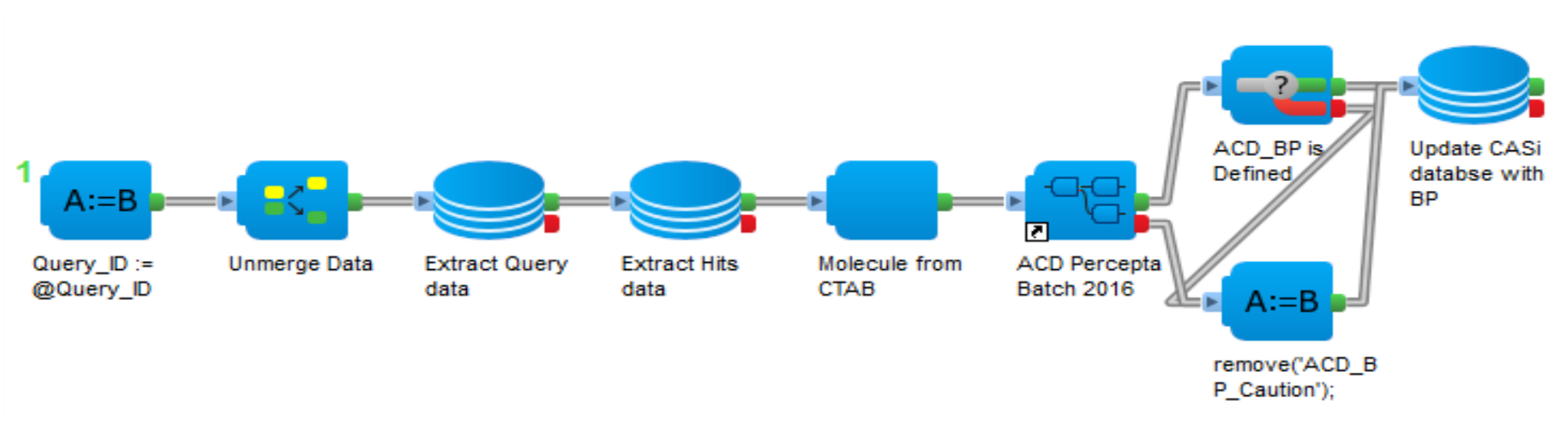


# Protocols used in CASi process

## Calculation of Boiling Point using PP and ACD/Labs

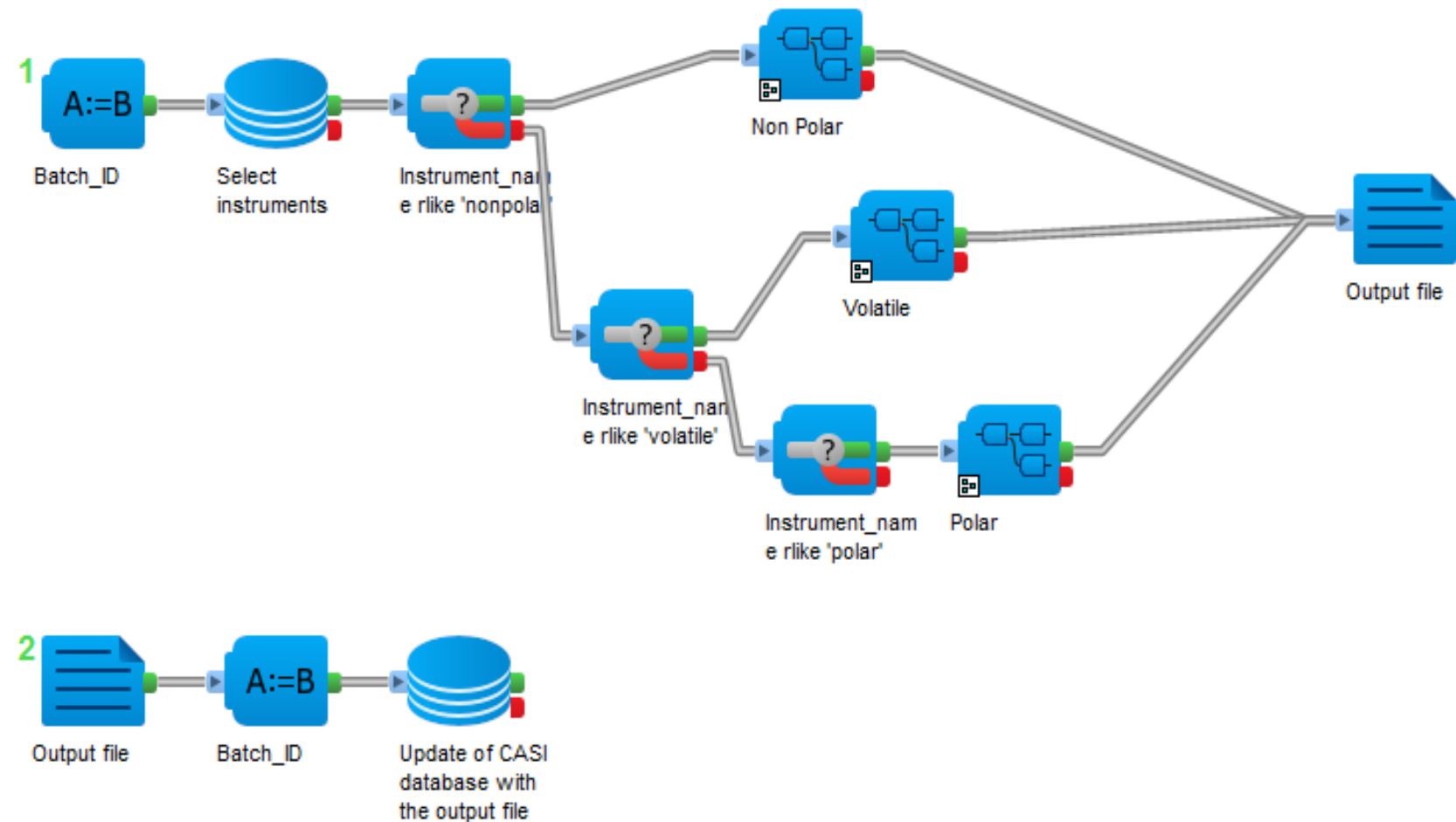


Structure Origin	Lib Source	PMI Code	CAS	Name	Match Factor	Iso. Mass	Score	Pred RT1	Pred RT2	List Marker	BP pred. (var)	
	NIST	volatile	PMI0002346	71-43-2	*Benzene	948	78.04695	948	661.67 (.3 %)	1.64 (15.6 %)	-	78.83 (-5.7 %)
	NIST	mainlib	PMI0002343	821-08-9	1,5-Hexadien-3-yne	935	78.04695	935	656.63 (-.5 %)	1.43 (.8 %)	-	85 (1.7 %)



# Protocols used in CASI process

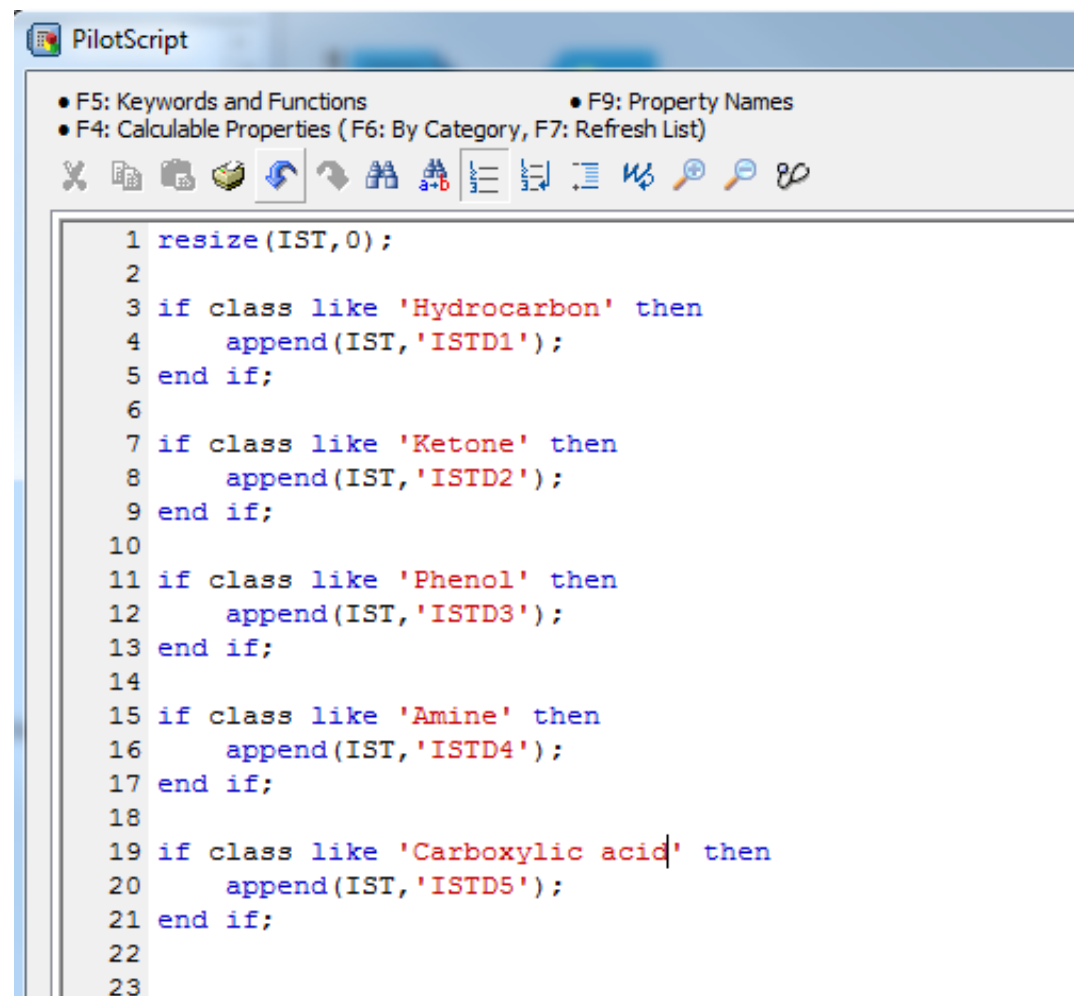
Determination of which internal standard to use to semi-quantify compounds concentrations





# Protocols used in CASI process

Example of script used in  
Non Polar sub-protocol

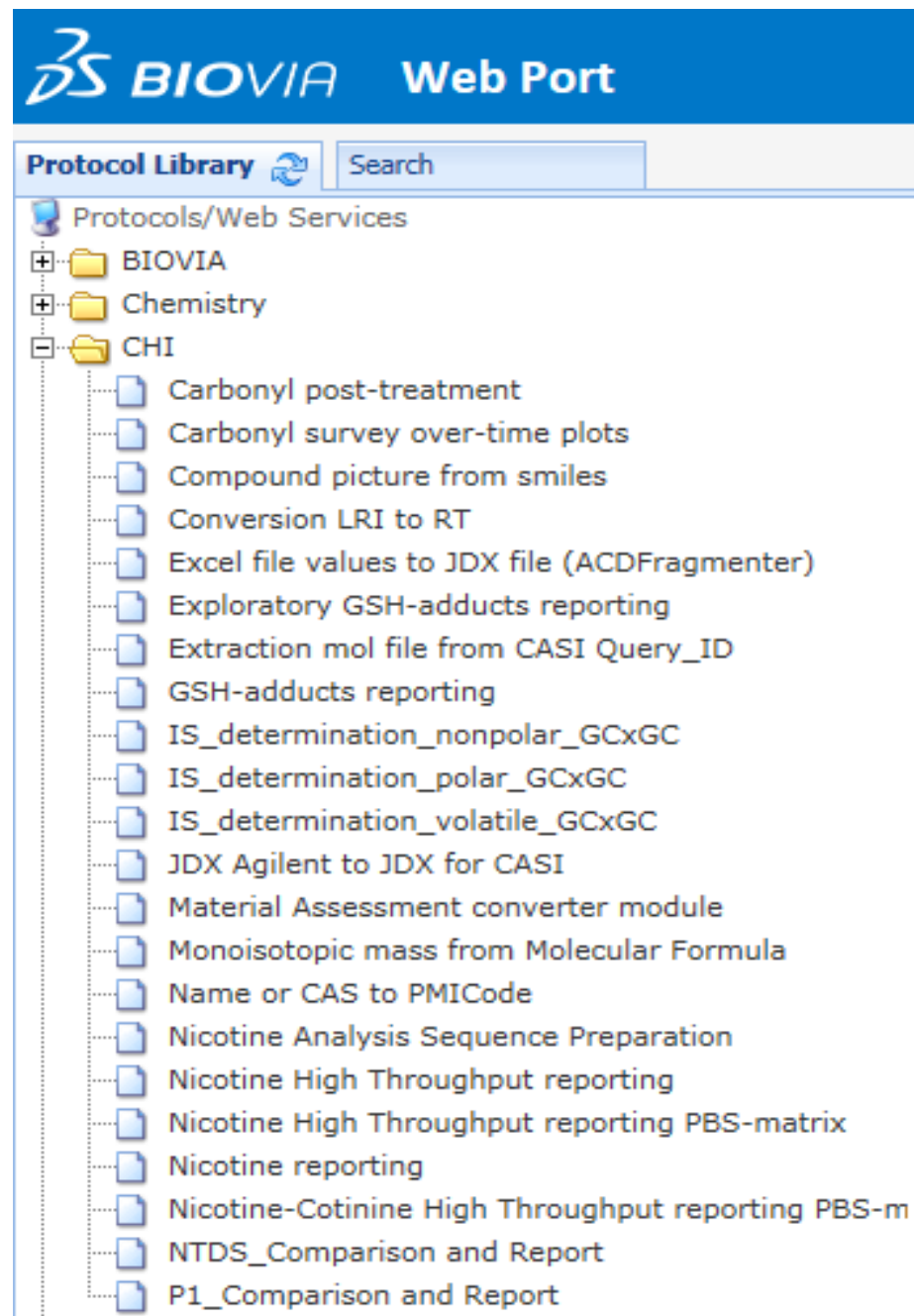


The screenshot shows the PilotScript software interface. At the top, there are two columns of keyboard shortcuts: F5: Keywords and Functions, F9: Property Names, and F4: Calculable Properties (F6: By Category, F7: Refresh List). Below the shortcuts is a toolbar with various icons. The main area contains a script with the following code:

```
1 resize(IST,0);
2
3 if class like 'Hydrocarbon' then
4     append(IST,'ISTD1');
5 end if;
6
7 if class like 'Ketone' then
8     append(IST,'ISTD2');
9 end if;
10
11 if class like 'Phenol' then
12     append(IST,'ISTD3');
13 end if;
14
15 if class like 'Amine' then
16     append(IST,'ISTD4');
17 end if;
18
19 if class like 'Carboxylic acid' then
20     append(IST,'ISTD5');
21 end if;
22
23
```

# Web Port applications

List of protocols used via webport



The screenshot displays the BIOVIA Web Port interface. At the top, there is a blue header with the BIOVIA logo and the text "Web Port". Below the header, there is a "Protocol Library" section with a search bar. The main content area shows a tree view of folders and files. The folders are "BIOVIA", "Chemistry", and "CHI". The "CHI" folder is expanded, showing a list of protocols, each represented by a document icon. The protocols listed are:

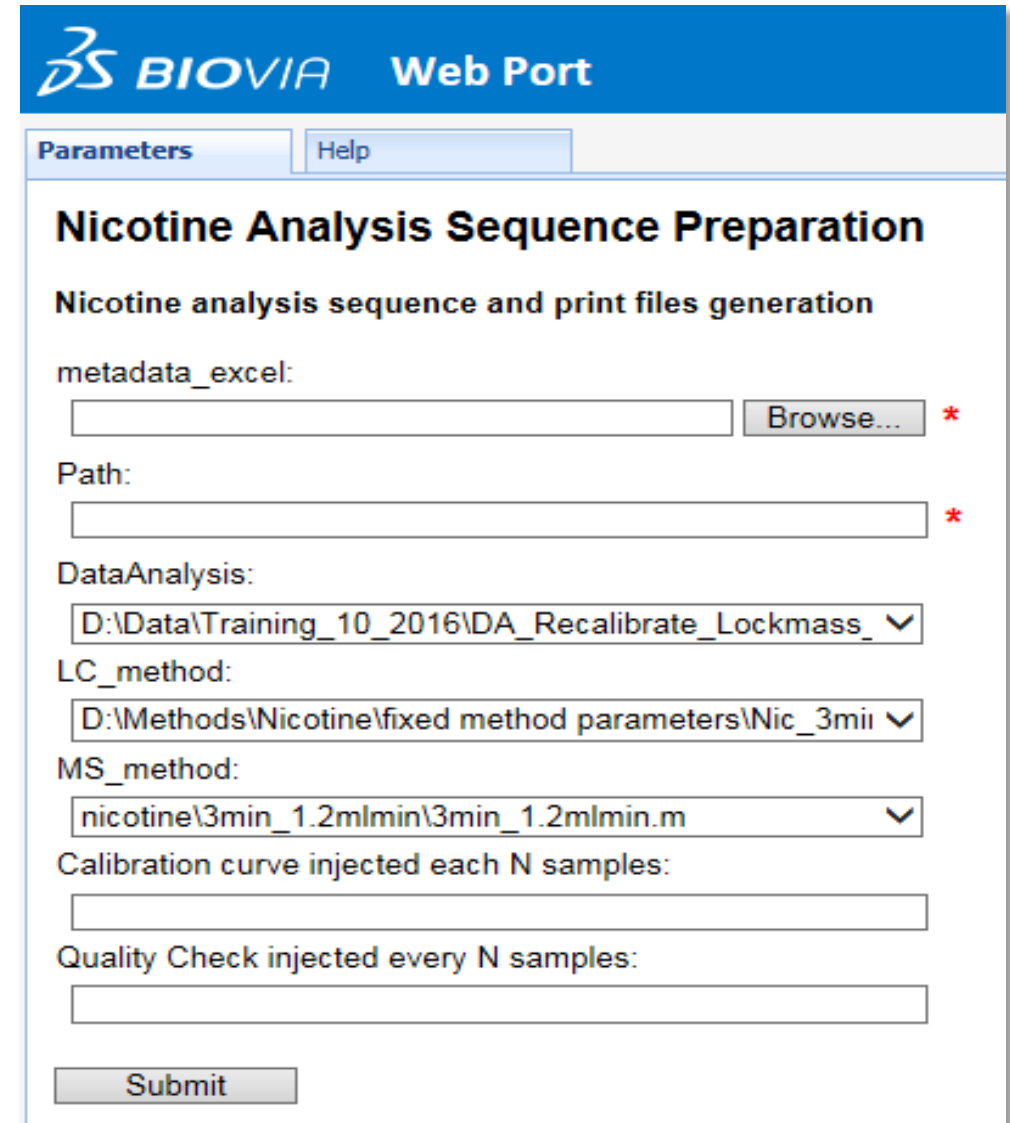
- Carbonyl post-treatment
- Carbonyl survey over-time plots
- Compound picture from smiles
- Conversion LRI to RT
- Excel file values to JDX file (ACDFragmenter)
- Exploratory GSH-adducts reporting
- Extraction mol file from CASI Query\_ID
- GSH-adducts reporting
- IS\_determination\_nonpolar\_GCxGC
- IS\_determination\_polar\_GCxGC
- IS\_determination\_volatile\_GCxGC
- JDX Agilent to JDX for CASI
- Material Assessment converter module
- Monoisotopic mass from Molecular Formula
- Name or CAS to PMICode
- Nicotine Analysis Sequence Preparation
- Nicotine High Throughput reporting
- Nicotine High Throughput reporting PBS-matrix
- Nicotine reporting
- Nicotine-Cotinine High Throughput reporting PBS-m
- NTDS\_Comparison and Report
- P1\_Comparison and Report

# Nicotine Analysis Sequence Preparation

This protocol is used to prepare a sequence of input to the analytical instrument

and

to create a file to automatically print labels on vials

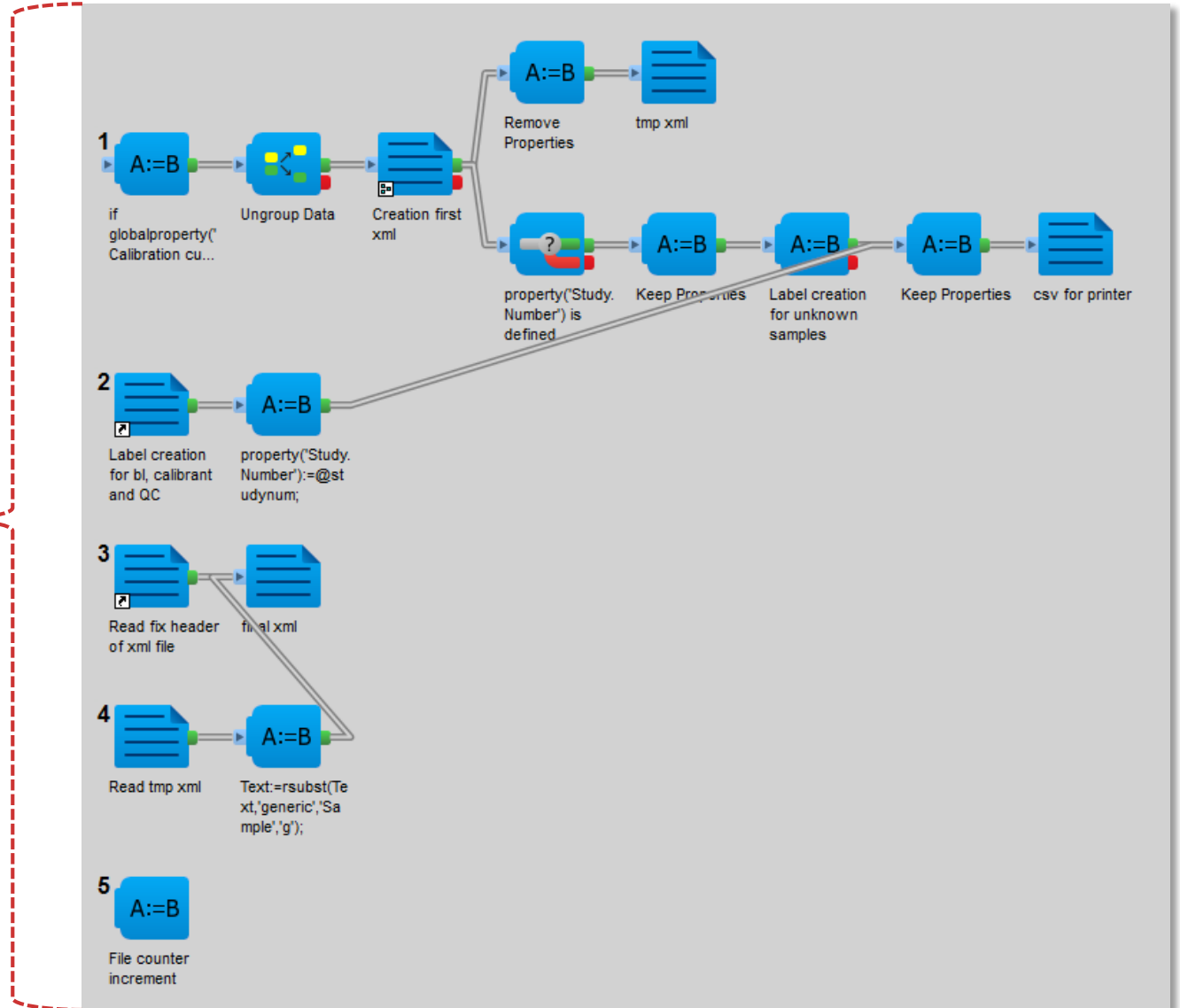
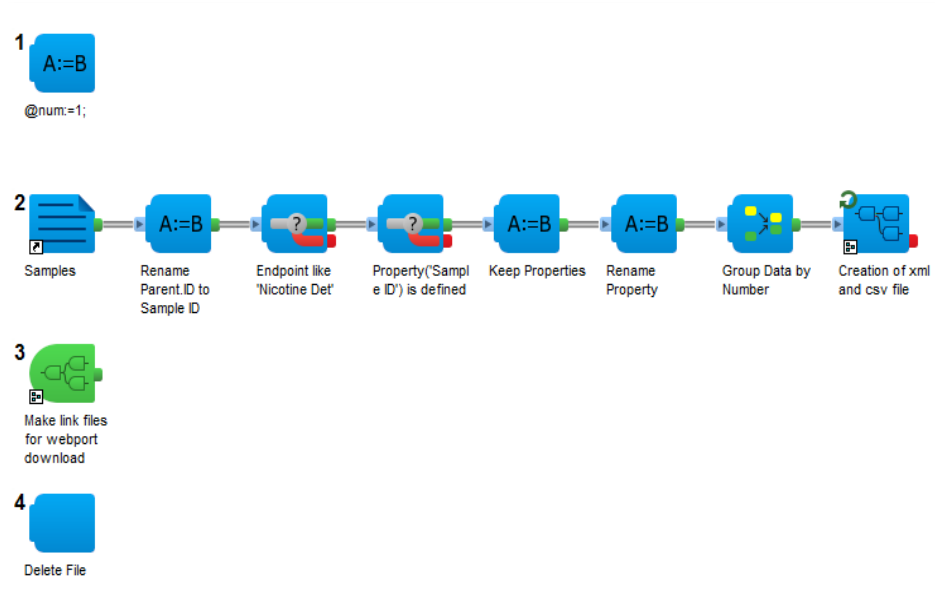


The screenshot shows the BIOVIA Web Port interface for the 'Nicotine Analysis Sequence Preparation' tool. The interface includes a header with the BIOVIA logo and 'Web Port' text. Below the header are two tabs: 'Parameters' (selected) and 'Help'. The main content area is titled 'Nicotine Analysis Sequence Preparation' and 'Nicotine analysis sequence and print files generation'. It contains several input fields and dropdown menus:

- metadata\_excel:** A text input field with a 'Browse...' button and a red asterisk.
- Path:** A text input field with a red asterisk.
- DataAnalysis:** A dropdown menu with the selected value 'D:\Data\Training\_10\_2016\DA\_Recalibrate\_Lockmass\_'.
- LC\_method:** A dropdown menu with the selected value 'D:\Methods\Nicotine\fixed method parameters\Nic\_3mi'.
- MS\_method:** A dropdown menu with the selected value 'nicotine\3min\_1.2mlmin\3min\_1.2mlmin.m'.
- Calibration curve injected each N samples:** A text input field.
- Quality Check injected every N samples:** A text input field.

A 'Submit' button is located at the bottom of the form.

# Nicotine Analysis Sequence Preparation



# Conclusion

At Philip Morris R&D we use Biovia Pipeline Pilot scripts to automate processes in analytical and computational chemistry.

We provide users with over 15 Webport scripts helping them sequence processing and reporting.

Thank you for your attention.

Questions?