DECEMBER 2014

REAXYS R203

ADVANCED REACTION QUERIES

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NOTES ON REAXYS R203

REAXYS R203

- Outlines:
  - How to search for preparations of single substances or groups of substances
  - How to *narrow* reactions by marking bonds and matching atoms involved in the reactions
  - How to *expand* your answers through finding similar reactions and through Similarity search (reactions)
  - How to develop Synthesis Plans
- For an outline of further presentations in this series, go here

NOTES

- Reaxys R104 gives an *introduction* to searching for chemical reactions, e.g. :
  - Outlines how to search for chemical reaction information through:
    - **AskReaxys**
    - **ReaxysTree**
    - Search Forms
  - Introduces the concept of searching for reactions by structure queries
  - Illustrates some of the post-processing options that may be applied to reaction answers

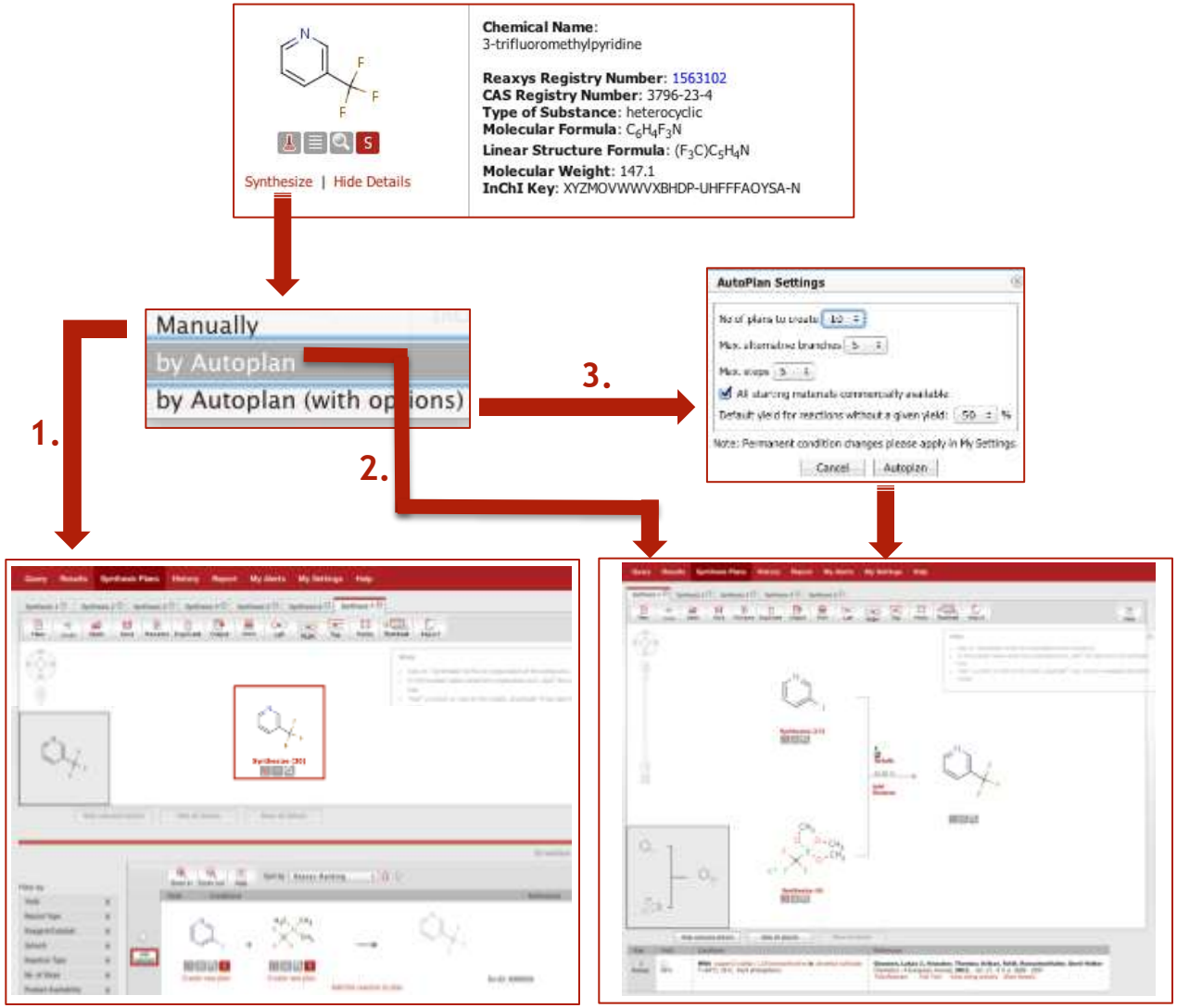
CONTENTS

THE "SYNTHESIZE" LINK

A SIMPLE OPTION TO PLAN SYNTHETIC ROUTES TO A SINGLE SUBSTANCE

Synthesize

- Below substances are links: Synthesize
- Click this when you want to find preparations of a single substance
- This link opens up a menu with 3 options:
  1. **Manually** opens a screen that shows the substance and a number of synthetic routes
     - The routes are shown underneath the screen - click those of interest, and then click Add
     - You then build your own synthetic routes to the substance
  2. **by Autoplan** opens up a number of plans:
     - You scroll through the different tabs and develop your own synthesis tree
  3. **by Autoplan (with options)** allows you to choose options for how many plans you wish to see, and your requirements for the plans
- Synthesize offers a simple and straight forward way to help you choose the syntheses of interest, and then to explore details further
  - For example, you may then create a Report, e.g., to share with colleagues

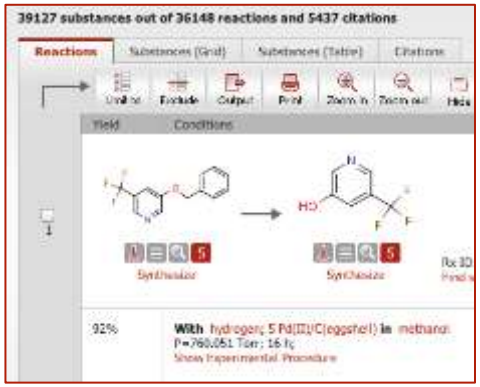


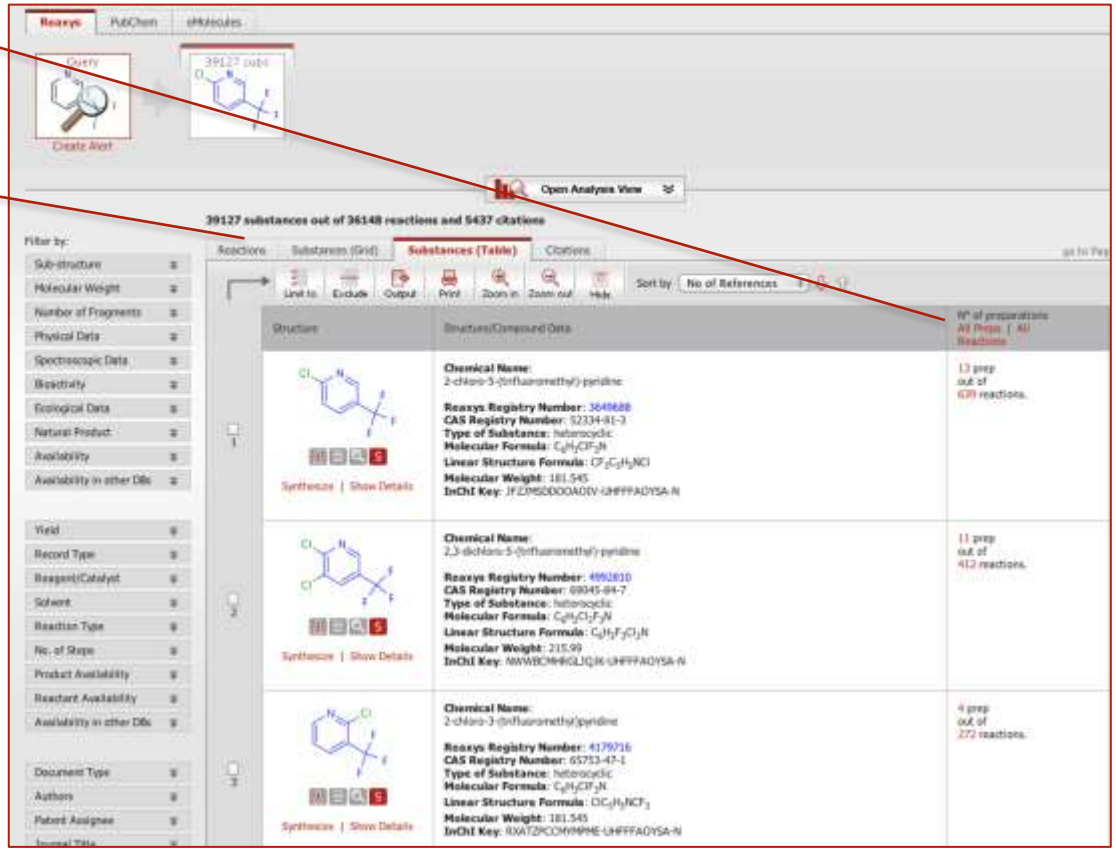
PREPARATION OF SUBSTANCES

STRUCTURE SEARCH IN THE SEARCH SUBSTANCES CONTEXT; CLICK LINKS TO PREPARATIONS AND REACTIONS

STRUCTURE SEARCH FOR SUBSTANCES

- To find preparations for a group of substances related by structure, you may:
  1. Perform a (sub)structure search under the Substances Icon (i.e., in the Search Substances Context)
  2. Click links to preparations in the column: Nº of preparations
- You may also click the **Reactions Tab** to view reaction information directly





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PREPARATION OF SUBSTANCES

STRUCTURE SEARCH IN THE SEARCH REACTIONS CONTEXT

SUBSTRUCTURE SEARCH FOR REACTIONS

- To find preparations for a group of substances related by structure, you may also search in the Search Reactions Context:

  1. Click the Reactions Icon
  2. Draw the structure and transfer it to the reaction query screen
  3. Click 

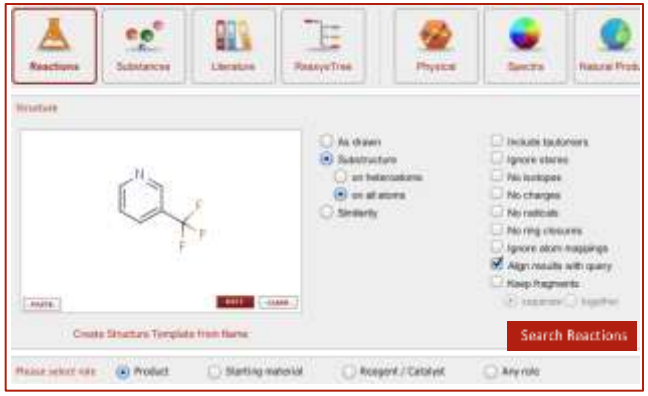
  4. Click 

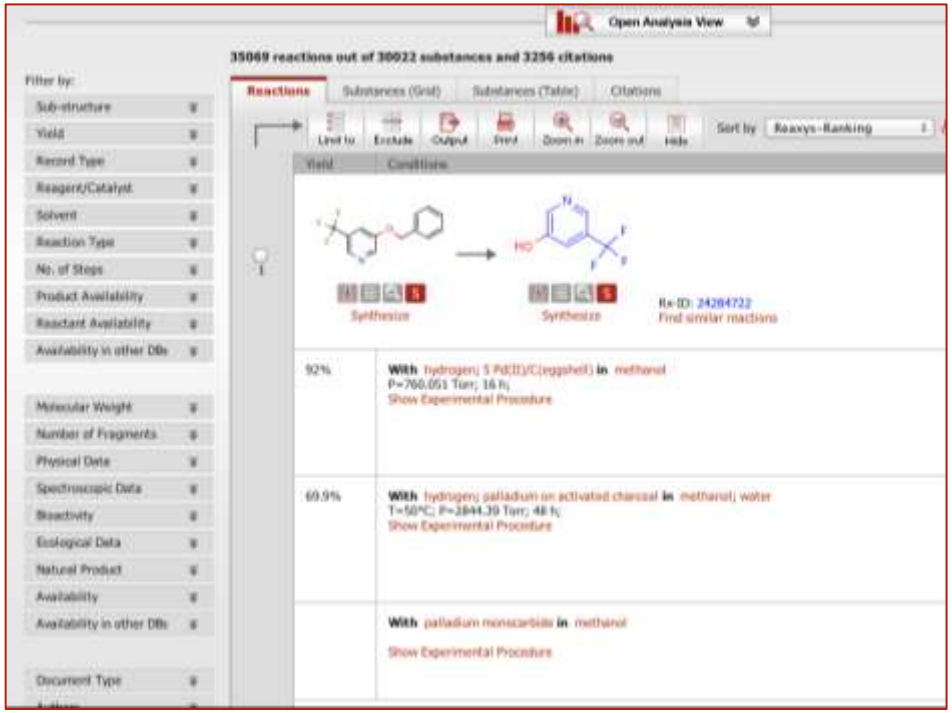
  Reaxys displays reactions. Remember each reaction is displayed separately (with different conditions and references under each reaction)

- Depending on the reaction query, you may get a large number of substances, which you may narrow through **Filter by:** (e.g., by substance or reaction filters) and/or **Analysis View**

- This process (and the process described in the previous slide) give answer sets for the preparations of substances, but it does not specify starting materials or the type of reaction involved

- Suggestions on how to search for specific conversions are shown on the next slides





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SPECIFYING REACTING CENTERS

REACTING CENTERS => MARK BONDS

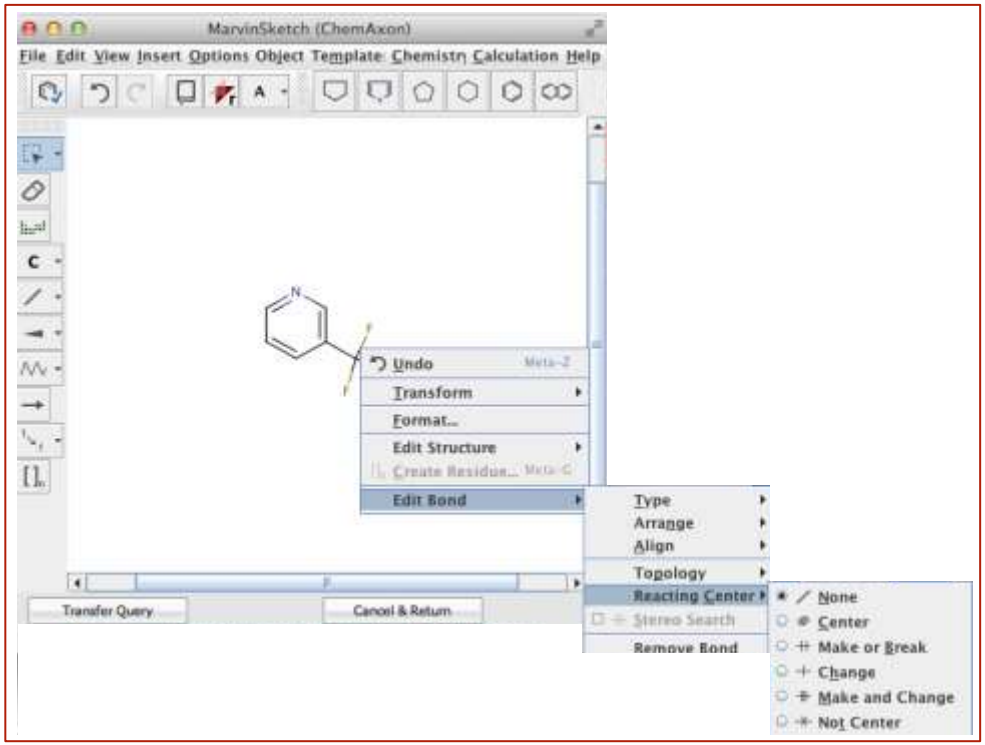
- The reaction query on the previous slide may be modified to require that specific bonds take part in the reaction

- A simple way to do this is to “right click” on the bond of interest, then choose **Edit Bond** => **Reacting Center**
- The default is None, but this may be overridden by any one of the 5 options shown
- The most general option is # Center and if this is chosen then that bond will be involved in the reaction; the query structure (A) has cross lines at an *angle* to the bond. If # Make or Break is chosen, the query structure (B) has cross lines at *right angles* to the bond

(A)

(B)

- In many cases very similar answer sets are obtained from queries (A)/(B)

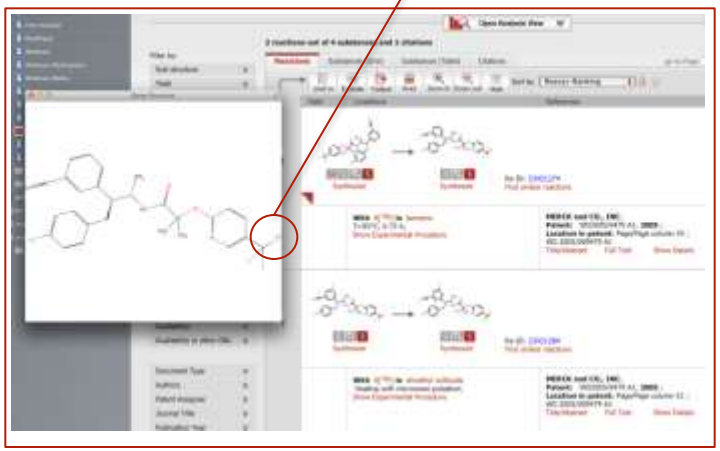


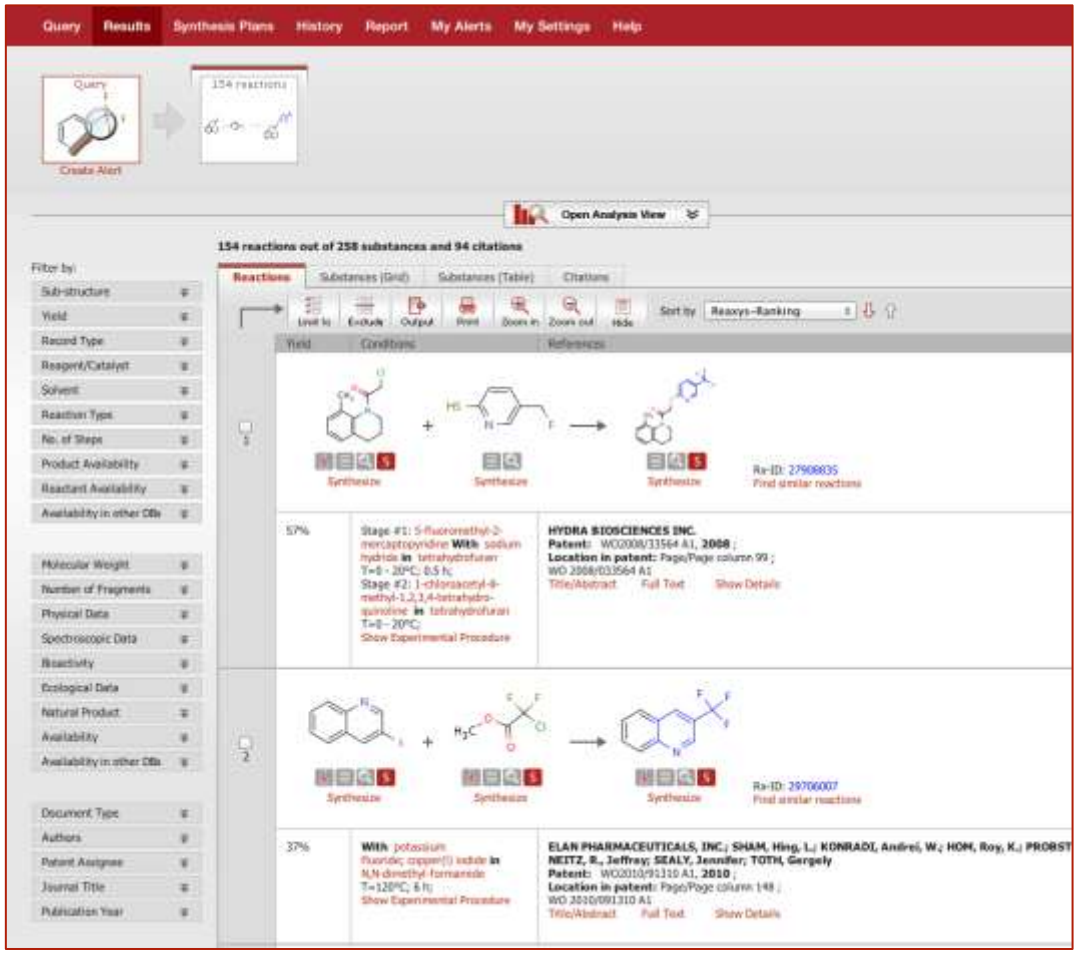
SPECIFYING REACTING CENTERS

○ # Center versus ○ ⋕ Make or Break

- The different options to specify reacting centers may give different answer sets, and the differences depend on the query involved

- The approach, if you are not getting the types of answers expected, is simply to try a few different options
- In the case of queries (A) and (B) (previous slide), query (A) gives two additional answers that involve the replacement of ^{19}F with ^{18}F





For a comment on Answer #1, go here

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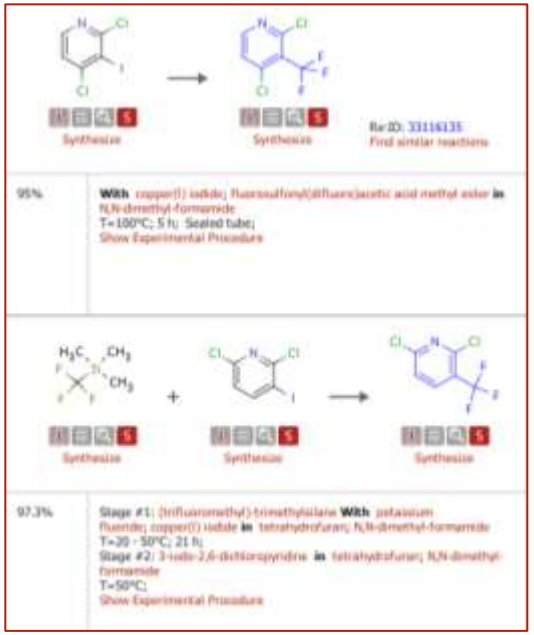
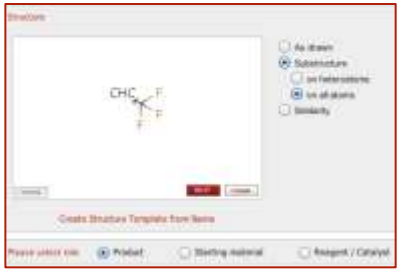
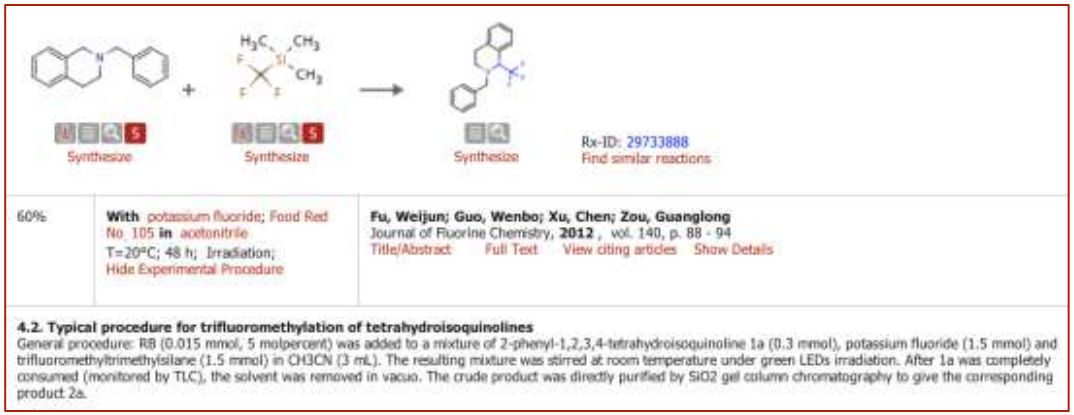
RETROSYNTHETIC ANALYSIS THROUGH SPECIFYING REACTING CENTERS

RETROSYNTHETIC ANALYSIS

- If a substance is known then the first steps are to find whether the substance is commercially available or whether there is a known, efficient synthesis
- Reaxys provides information on both of these and most easily through the links and Synthesize respectively
- If the substance is not known, or if alternative synthetic methods are required, then the synthetic chemist may undertake a retrosynthetic analysis
- One way to do this is to use the functions in Reacting Centers, and in particular through marking bonds to be formed
- For example the query (right) does a “retrosynthetic analysis” of starting materials where the bond indicated is formed
- An even more general query is shown below (CHC = any heterocyclic ring)
  - This search gives > 4,000 answers, and one is shown







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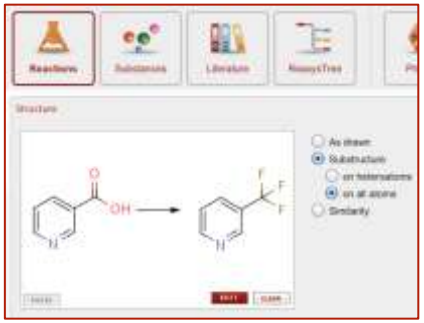
ATOM MAPPING

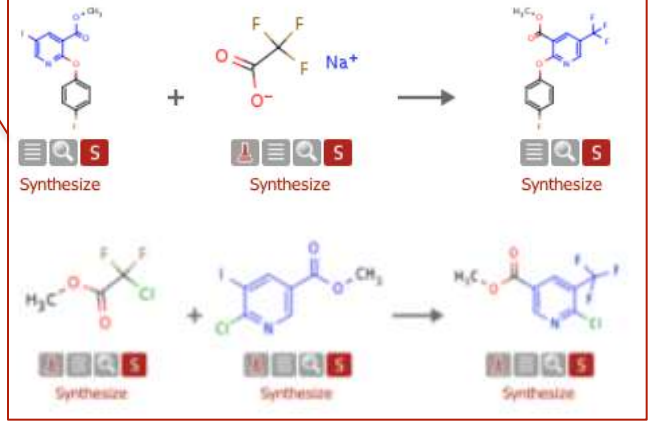
STARTING MATERIALS => PRODUCTS

- When a reaction query involves the conversion of specific reactants to products, e.g., the query on the right, then Reaxys performs a substructure search of the reactants and of the products, and retrieves reactions in which respective substructures are present
- However, if the intent of the query was to convert nicotinic acid derivatives to 3-trifluoromethylpyridines then some of the answers, e.g. those shown on the right, would not necessarily be of interest
- The solution is to map atoms in the reactants and products, and in MarvinSketch this may be done either through the Manual Atom Map icon in the left panel (A), or through the Chemistry drop-down menu (B)
- Having clicked either of these, you simply click on the atom in the reactant, drag to the required atom in the product, and then release
- The process, and outcomes (2 sample answers), are shown below



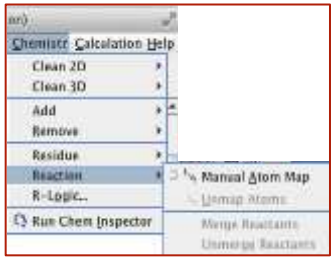
SOME OF THE ANSWERS

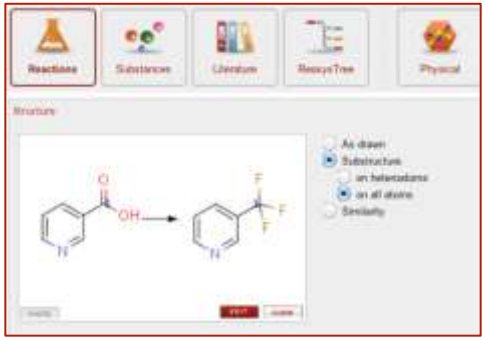
ONE OF THE REACTANTS HAS THE NICOTINIC ACID PART STRUCTURE AND THE PRODUCT HAS THE 3-TRIFLUOROMETHYLPYRIDINE PART STRUCTURE

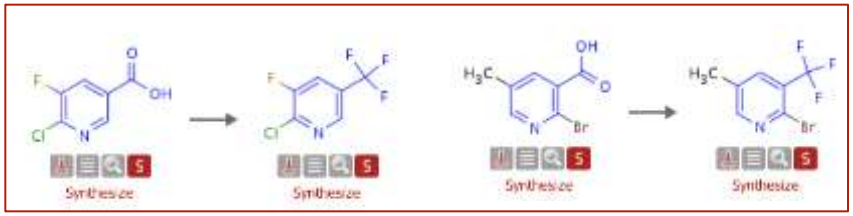


(A)

(B)







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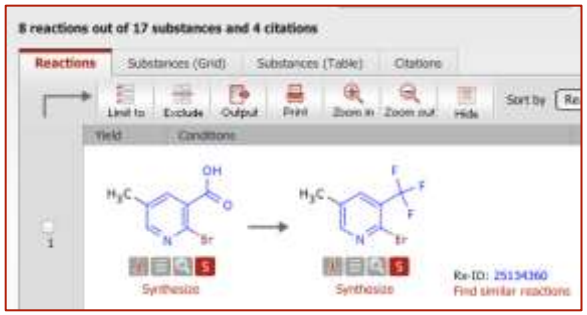
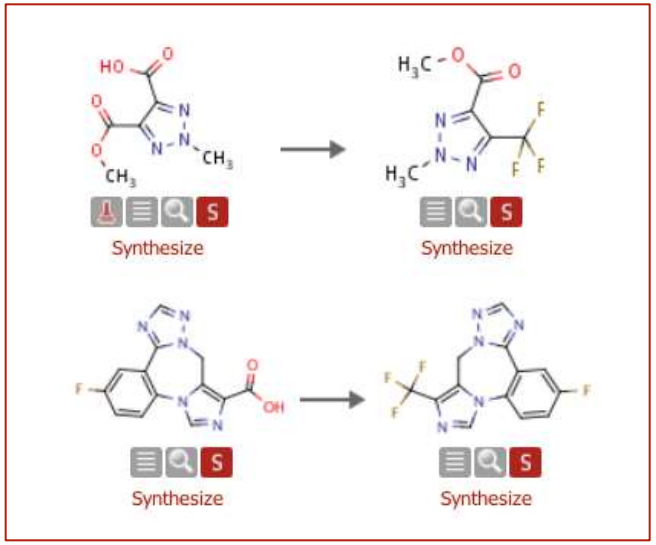
FIND SIMILAR REACTIONS

FIND SIMILAR REACTIONS

- Each different reaction in Reaxys is given a Reaction ID (Rx-ID), and all references to this reaction are given in a single display
- Underneath the Rx-ID is a link Find similar reactions
- When this is clicked, Reaxys considers the bonds formed/broken in the actual reaction, and then looks at the non-reacting atoms elsewhere in the structure(s)
  - i.e., Reaxys looks for the same conversion, but in different structure(s)
- The similarities of the non-reacting atoms are then specified as Tight, Near, Medium, Wide, and Widest; the usual process is to look at some of the categories in turn, and choose reactions of interest
- Further help on Find similar reactions is available at http://help.elsevier.com/app/answers/detail/a_id/3911/p/9459/kw/similar%20reactions





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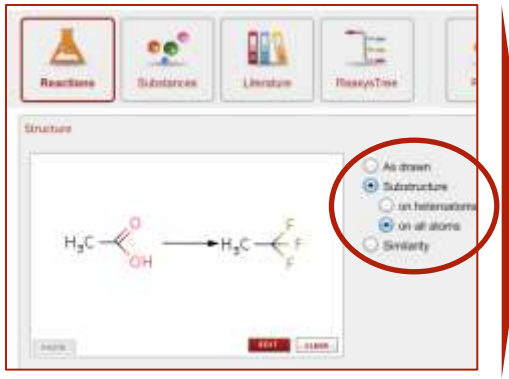
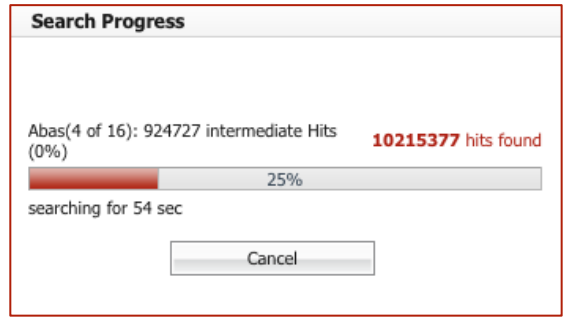
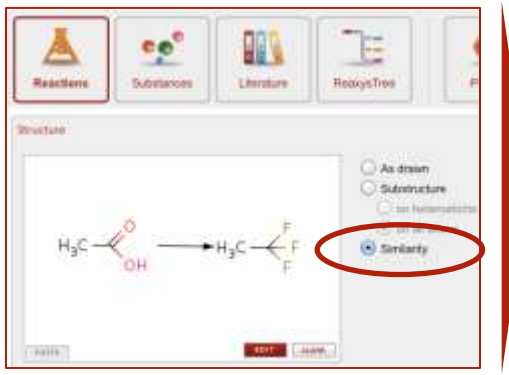
REACTION SEARCH: SIMILARITY

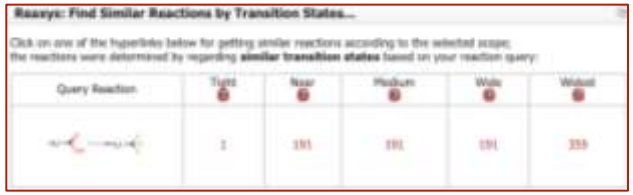
SIMILARITY SEARCH FOR REACTIONS

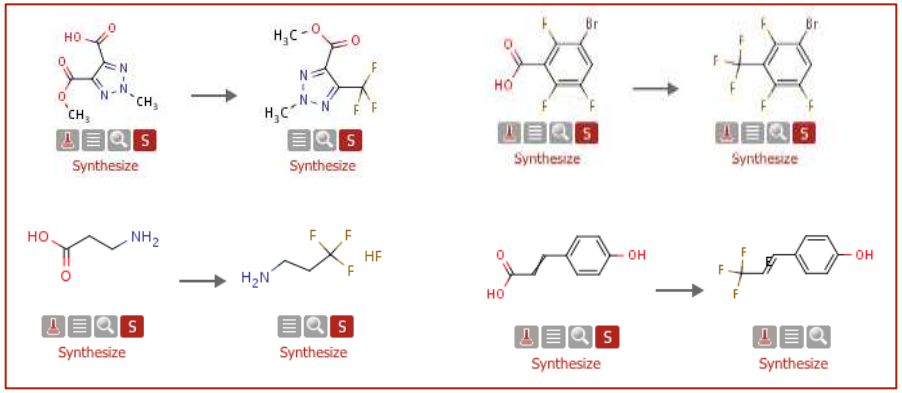
- There are three main choices for searching reactions by structure in the Reaction Query Context:
  - **As Drawn** - the precise reaction drawn is searched
  - **Substructure** – structure queries are searched as substructures, i.e. substituted at allowed positions
  - **Similarity** – the chemical transformation indicated is searched
- When very general reaction queries, e.g., the conversion of one functional group (COOH) to another (CF3) are searched by substructure, the structure search screening process may take several minutes
  - For example, the screening process for the reaction query (by substructure) on the top right is only 25% complete after almost 1 minute and millions of candidates have past the screening process; all these then will need to be matched atom-by-atom
- A solution is to use **Similarity**, and in this case similar reactions are identified in less than a second
  - (Some answers are shown)











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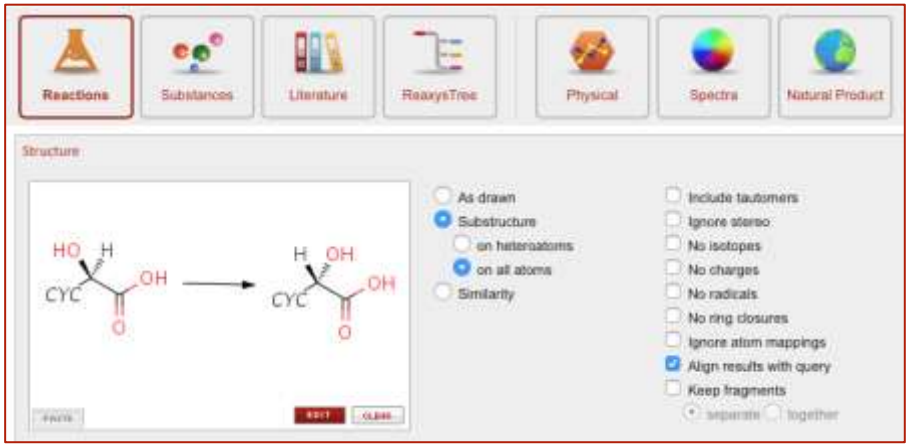
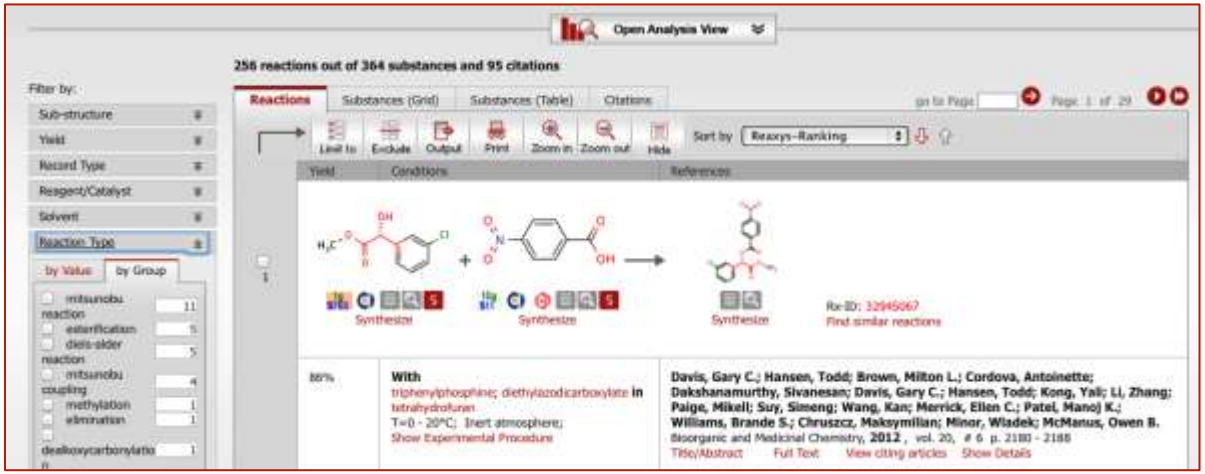
SEARCHING STEREOCHEMISTRY IN REACTION QUERIES

SEARCHING STEREOCHEMISTRY

- Stereochemical features may be built into reaction queries, and may be searched in Reaxys
- For example, if you wished to find reactions for α-hydroxycarboxylic acids (and derivatives) in which the stereochemistry was inverted at the α-C then you could build the reaction query on the left (below)
- One of the answers is shown
- If required, reactions may be narrowed through **Filter by: Reaction Type** gives further information about the types of reactions involved (note: mitsunobu reaction)
- You may also wish to search for Mitsunobu Reactions through **ReaxysTree**!





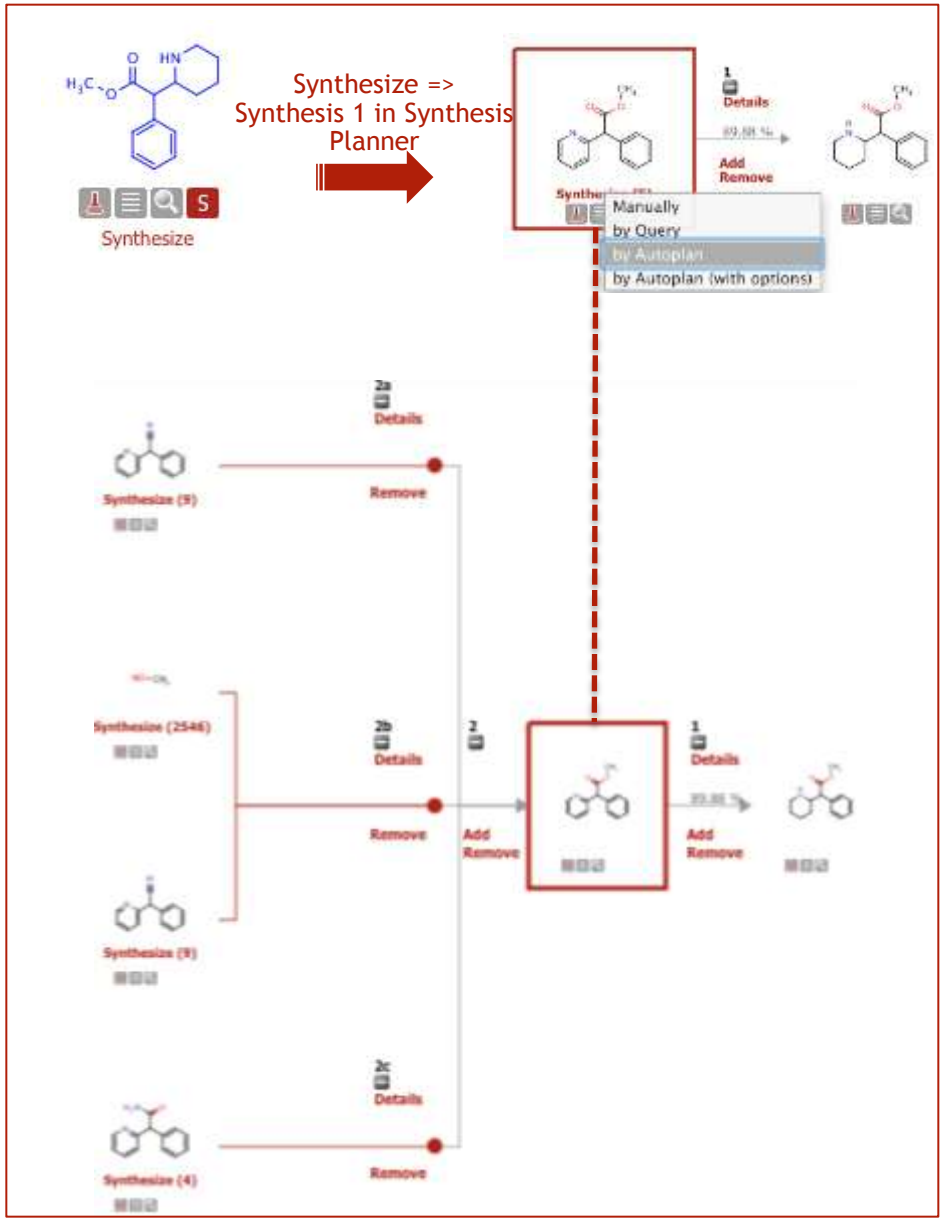
SYNTHESIS PLANNER

Synthesize opens SYNTHESIS PLANNER

- One way to open the Synthesis Planner is to click on the Synthesize link below the structure
- You choose the option required (e.g., **by Autoplan**) and the first (of a number of plans) is displayed
- If you need to go back further, simply click the Synthesize link under the starting material (e.g., on the pyridine precursor) and earlier steps are displayed
- Click Remove if you are not interested in a particular method
- Click Add to add another branch to the preparation of the compound
- Notes:
  - you may set your own Autoplan requirements through **My Settings**

  - algorithms behind Autoplan choose highest yielding routes and …

    this is very convenient since when there are a large number of preparative options, Reaxys ranks displays in the Synthesis Planner so preferred methods are shown first



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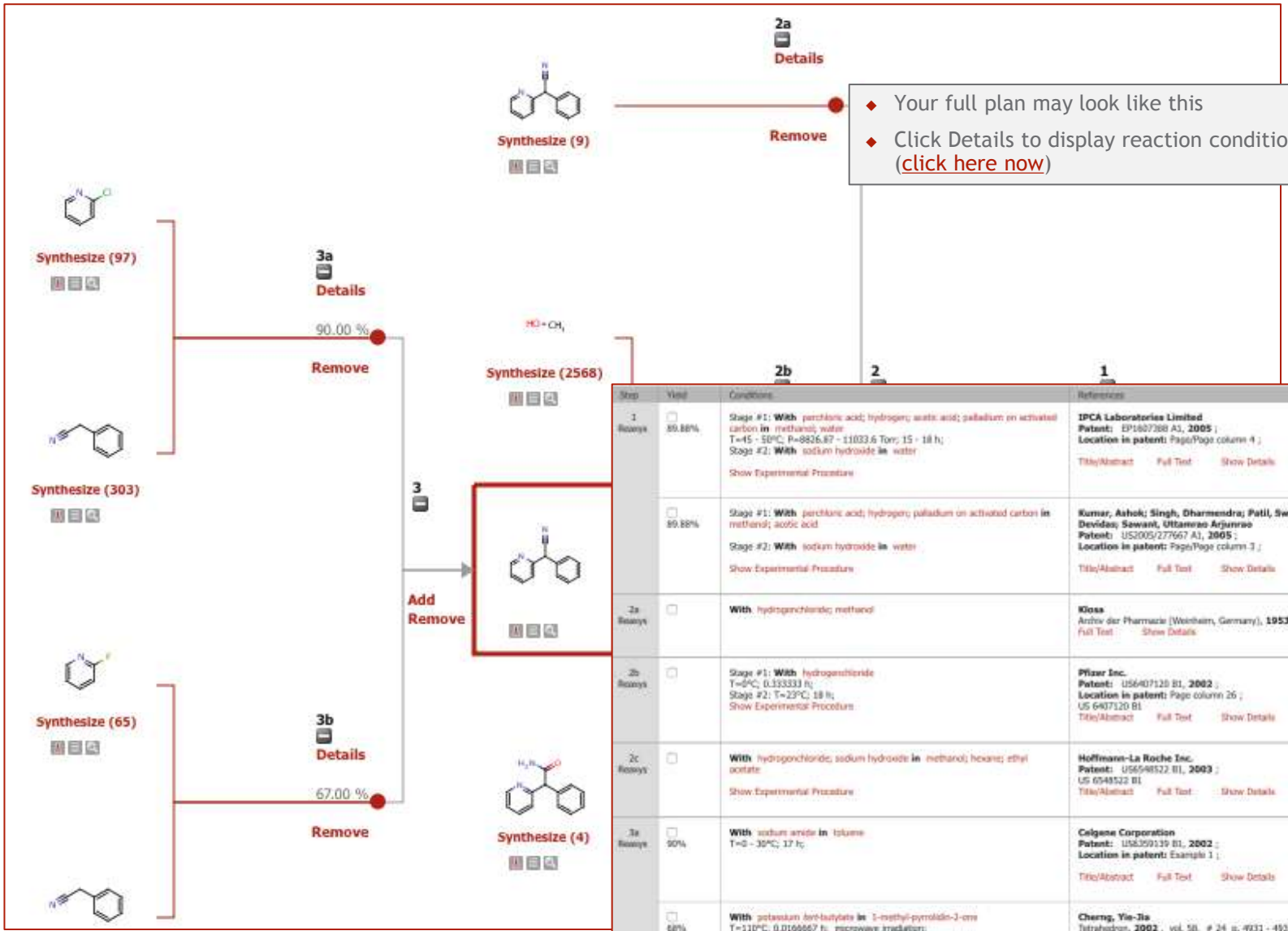
A FULL SYNTHESIS PLAN



- Your full plan may look like this
- Click Details to display reaction conditions (click here now)

Step	Yield	Conditions	References
1 Reaxys	89.88%	Stage #1: **With** perchloric acid; hydrogen; acetic acid; palladium on activated carbon **in** methanol; water T=45 - 50°C; P=8826.87 - 11033.6 Torr; 15 - 18 h; Stage #2: **With** sodium hydroxide **in** water Show Experimental Procedure	**IPCA Laboratories Limited** **Patent:** EP1607388 A1, **2005** ; **Location in patent:** Page/Page column 4 ; Title/Abstract Full Text Show Details
	89.88%	Stage #1: **With** perchloric acid; hydrogen; palladium on activated carbon **in** methanol; acetic acid Stage #2: **With** sodium hydroxide **in** water Show Experimental Procedure	**Kumar, Ashok; Singh, Dharmendra; Patil, Swapnali Hemant; Mahale, Devidas; Sawant, Uttamrao Arjunrao** **Patent:** US2005/277667 A1, **2005** ; **Location in patent:** Page/Page column 3 ; Title/Abstract Full Text Show Details
2a Reaxys		**With** hydrogenchloride; methanol	**Klosa** Archiv der Pharmazie (Weinheim, Germany), **1953** , vol. 286, p. 433,436 Full Text Show Details
2b Reaxys		Stage #1: **With** hydrogenchloride T=0°C; 0.333333 h; Stage #2: T=23°C; 18 h; Show Experimental Procedure	**Pfizer Inc.** **Patent:** US6407120 B1, **2002** ; **Location in patent:** Page column 26 ; US 6407120 B1 Title/Abstract Full Text Show Details
2c Reaxys		**With** hydrogenchloride; sodium hydroxide **in** methanol; hexane; ethyl acetate Show Experimental Procedure	**Hoffmann-La Roche Inc.** **Patent:** US6548522 B1, **2003** ; US 6548522 B1 Title/Abstract Full Text Show Details
3a Reaxys	90%	**With** sodium amide **in** toluene T=0 - 30°C; 17 h;	**Celgene Corporation** **Patent:** US8350139 B1, **2002** ; **Location in patent:** Example 1 ; Title/Abstract Full Text Show Details
	68%	**With** potassium tert-butylate **in** 1-methyl-pyrrolidin-2-one T=110°C; 0.0166667 h; microwave irradiation;	**Cherng, Yie-Jia** Tetrahedron, **2002** , vol. 58, # 24 p. 4931 - 4935 Title/Abstract Full Text View citing articles Show Details
		With sodium amide; toluene	**Panizzon** Helvetica Chimica Acta, **1944** , vol. 27, p. 1748,1753 Full Text Show Details **Klosa** Archiv der Pharmazie (Weinheim, Germany), **1953** , vol. 286, p. 433,436 Full Text Show Details

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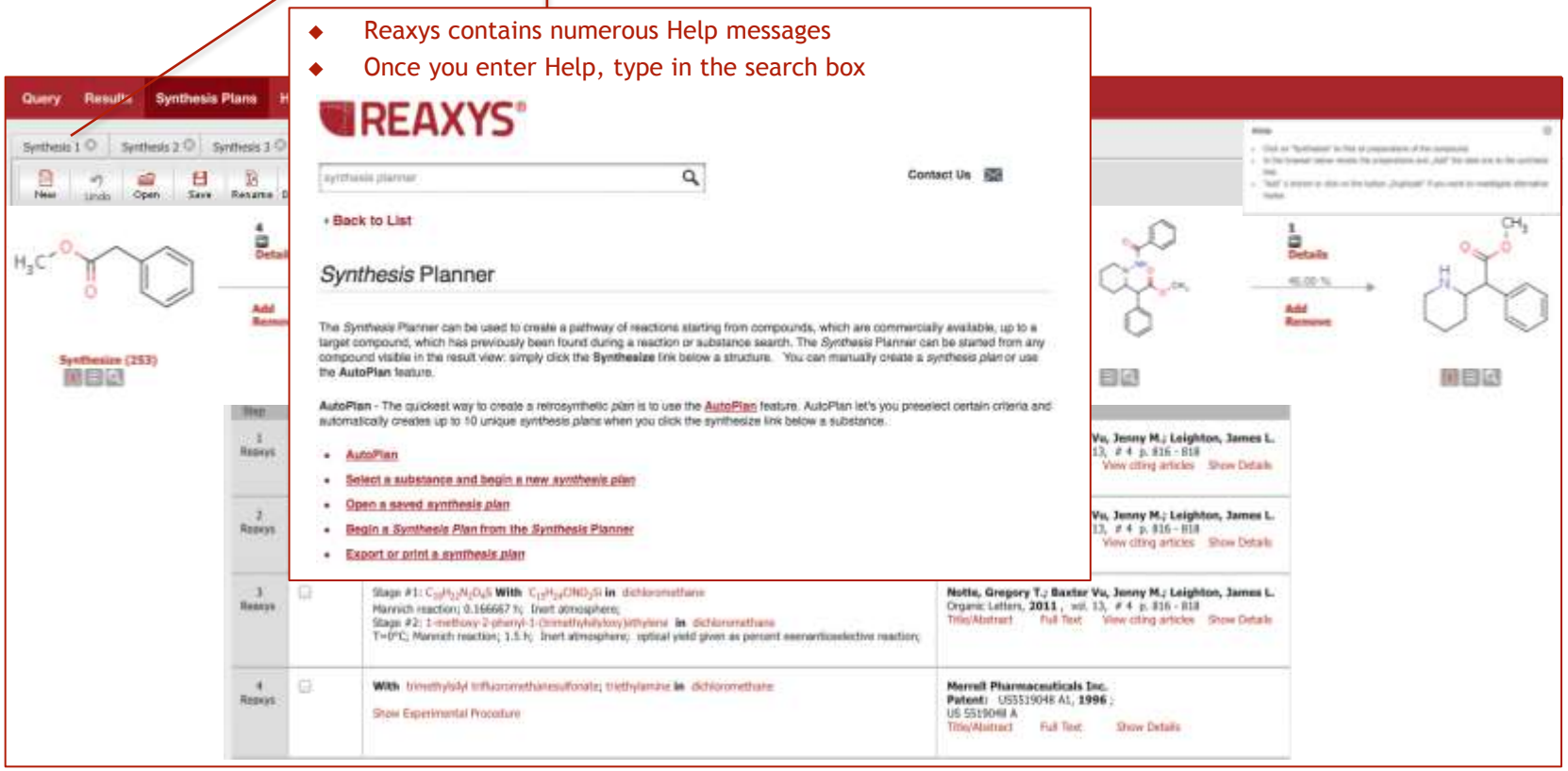
SYNTHESIS PLANNER

Other Syntheses of Ritalin

- The previous set of slides developed a plan from "Synthesis 1"
- However, Reaxys generated other plans, e.g. "Synthesis 6" (second tool bar)
- Note the various functions in the third tool bar: Save, Resize, Report…
- Note also you can click Help (click Help now)



- Reaxys contains numerous Help messages
- Once you enter Help, type in the search box

Supplementary Slides

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FURTHER PRESENTATIONS IN THIS SERIES

REAXYS R101

A QUICK GUIDE

An overview of the functions of Reaxys 2014

REAXYS R102

TIPS FOR LITERATURE SEARCHING

A quick guide to searching literature

REAXYS R103

BASIC SUBSTANCE QUERIES

A quick guide to searching for specific substances by name, formula and structure

REAXYS R104

BASIC REACTION QUERIES

A quick guide to searching for chemical reactions

REAXYS R105

SEARCHING PROPERTIES

A quick guide to searching for properties

REAXYS R201

ADVANCED STRUCTURE SEARCHING

Searching by substructure

REAXYS R202

ADVANCED NAME AND FORMULA SEARCHING

Searching for Substances by Names and Formulas

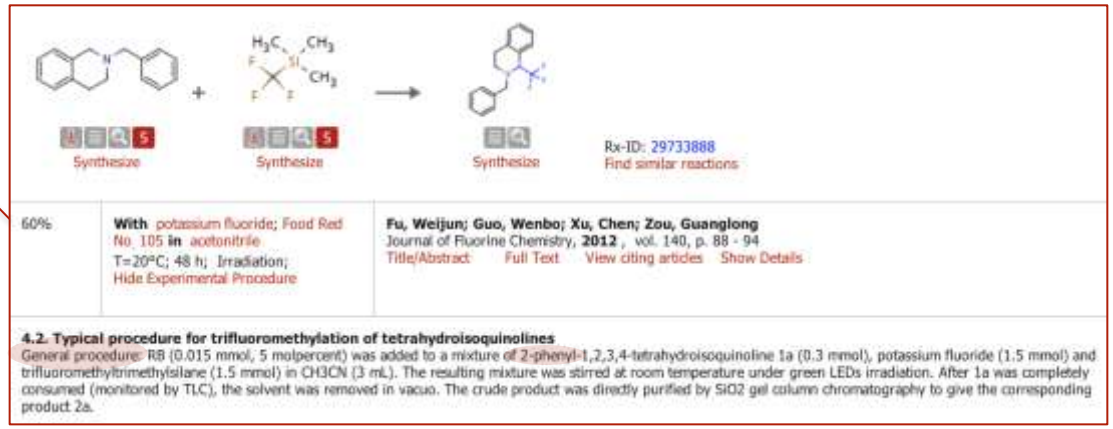
REAXYS R203

ADVANCED REACTION QUERIES

Additional ways to search for reactions

INCONSISTENT DATA?

- At times data may appear "inconsistent" and this may be because of a variety of reasons including apparent errors/inconsistencies:
  1. In the original documents
  2. In the input of data into the database
  3. In the way the search engine interprets the query and in the way the data is presented in answers
- For example:
  - the answer on the right (above) mentions the reactant 5-fluoromethyl-2-mercaptopyridine in the Experimental Procedure and shows this substance in the reaction diagram but the starting material should be 5-trifluoromethy-2-mercaptopyridine
  - the answer on the right (below) describes a phenyl tetrahydroisoquinoline whereas the diagram shows the reaction of the benzyl derivative (in this case the issue is the reporting of a general procedure, whereas the actual reaction describes a specific example)
- The addition of millions of records annually is challenging, and databases endeavour to maintain data quality
- However "inconsistencies" arise and, when detected, users are encouraged to report them to the database producer
- Additionally, authors and referees (unfortunately data in patents is not refereed) need to be vigilant to ensure the quality of the original data



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Back to referring slide