# 5th Annual Global TechMining Conference

## Methodology for Identifying Pharmaceutical Key Molecules Using Technology Foresight of Patent Documents

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16/09/2015

# Introduction – Some data of Pharmaceutical Industry

- Global pharmaceutical sales reached an all-time high of approximately $980 billion in 2013
  - However, the rate of growth declined in 2013 compared to 2012 due to the expiration of patent protection on a number of blockbuster drugs in markets dominated by generic equivalent

- The number of New Molecular Entities (NMEs) launched in 2013 was the third-highest in the last decade

- Pharmaceutical R&D is a difficult and expensive process in an industry with high expectations

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# Introduction

- Technology race
  - R&D of new process of synthesis and formulations related to drugs/medicines

- Analysis of synthesis process using patent documents to identify key substances
  - Substances (intermediate) structurally similar to the drug of interest
  - Critical precursors for the preparation of the final product
  - Compound that is converted to the final product through simple / common synthetic routes

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# Document Patents

The pharmaceutical sector is one of the sectors that most protects its inventions using document patents

high costs incurred in the R&D of new products

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# Typical Claims of Patents Relating to Pharmaceutical Inventions

- Product (API)
- Processes
- Formulations and compositions
- Combinations
- Dosage/Dose
- Salts, Ethers and esters
- Polymorphs
- Markush Claims
- Method of treatment
- Use claims (including second use)

Fonte: WHO-ICTSD-UNCTAD, 2007

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# Technology Assessment based on Document Patent

- Contains descriptions of scientific and technical concepts as well as practical details of processes
- Conveys the most recent information
- Has a fairly uniform structure
- Contains information which is not divulged in any other form of literature
- Covers most of what is new and most of what is worthwhile knowing about technological development

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# Methodology for Identifying Pharmaceutical Key Substances

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# The Methodology – 6 STEPS

1. Searches for the process patents
2. Selects the process patents that explains the synthesis route
3. Identifies all the reagents and intermediates present in the routes patented
4. Selects the most frequently substances present in the routes patented
5. Compares the chemical structures of the most frequently cited substances with the API (drug)
   - Select the similar
6. Seeks producers/suppliers of the substances that are most structurally similar to the API (drug)
   - Selects the ones that have producers/suppliers

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# Exemplyfing the Methodology

Case Study

AIDS/HIV/ARVs

Zidovudine – first ARV

# Case Study - Zidovudine

- AIDS
  - First diagnosed in 1981 in the USA
  - Disease that affects about 35 million people worldwide (2012)

- Caused by infection with the human immunodeficiency virus (HIV)
  - There is currently no cure or effective HIV vaccine
- Treatment consists of highly active antiretroviral therapy

- There are 25 ARVs used in AIDS treatment in world
  - 88 drugs in developing phase
    - Searches for more effective drugs
    - Improved tolerability
    - Reducing side effects
    - Dosing simplification

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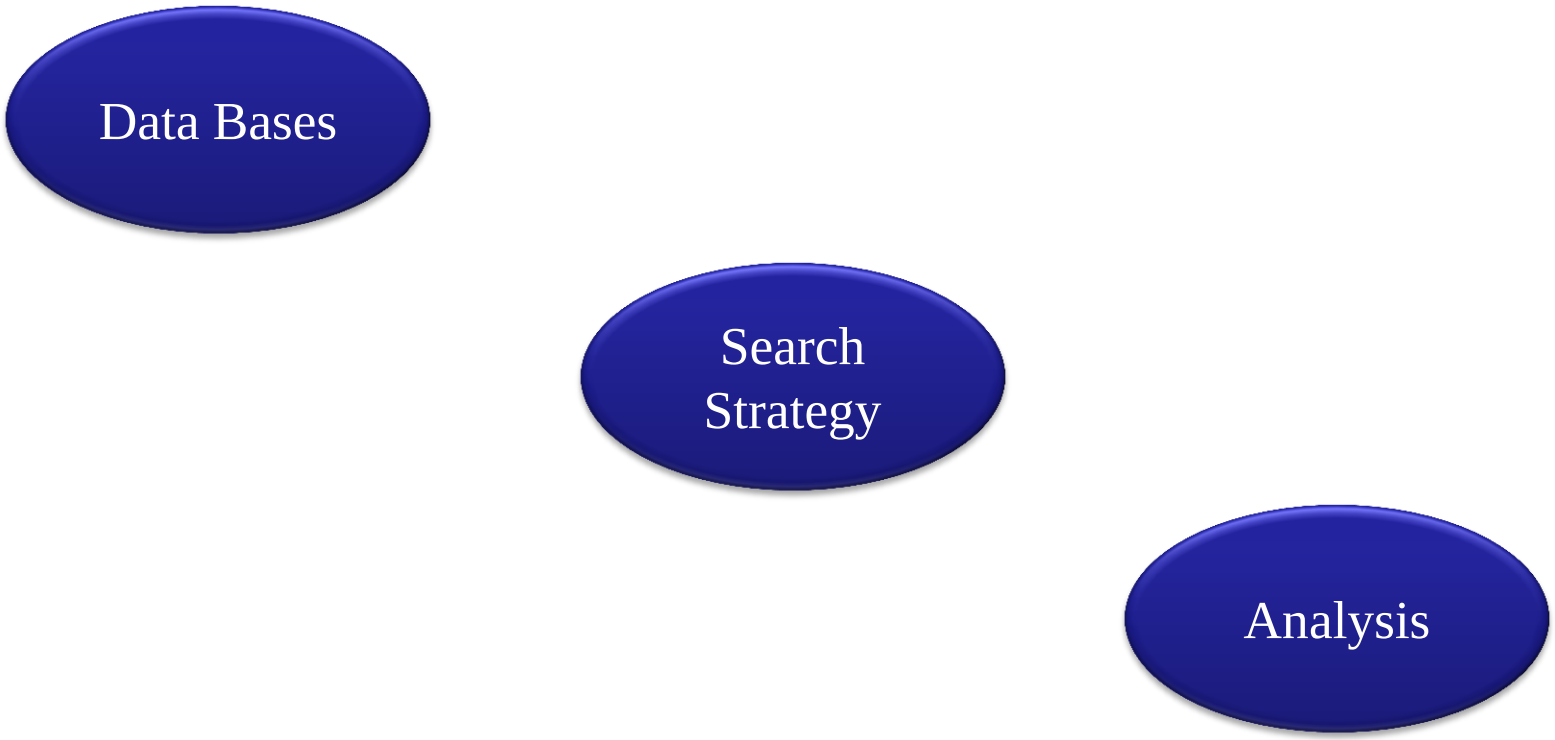
# Technology Assessment based on Document Patent

- Main steps of the technology assessment

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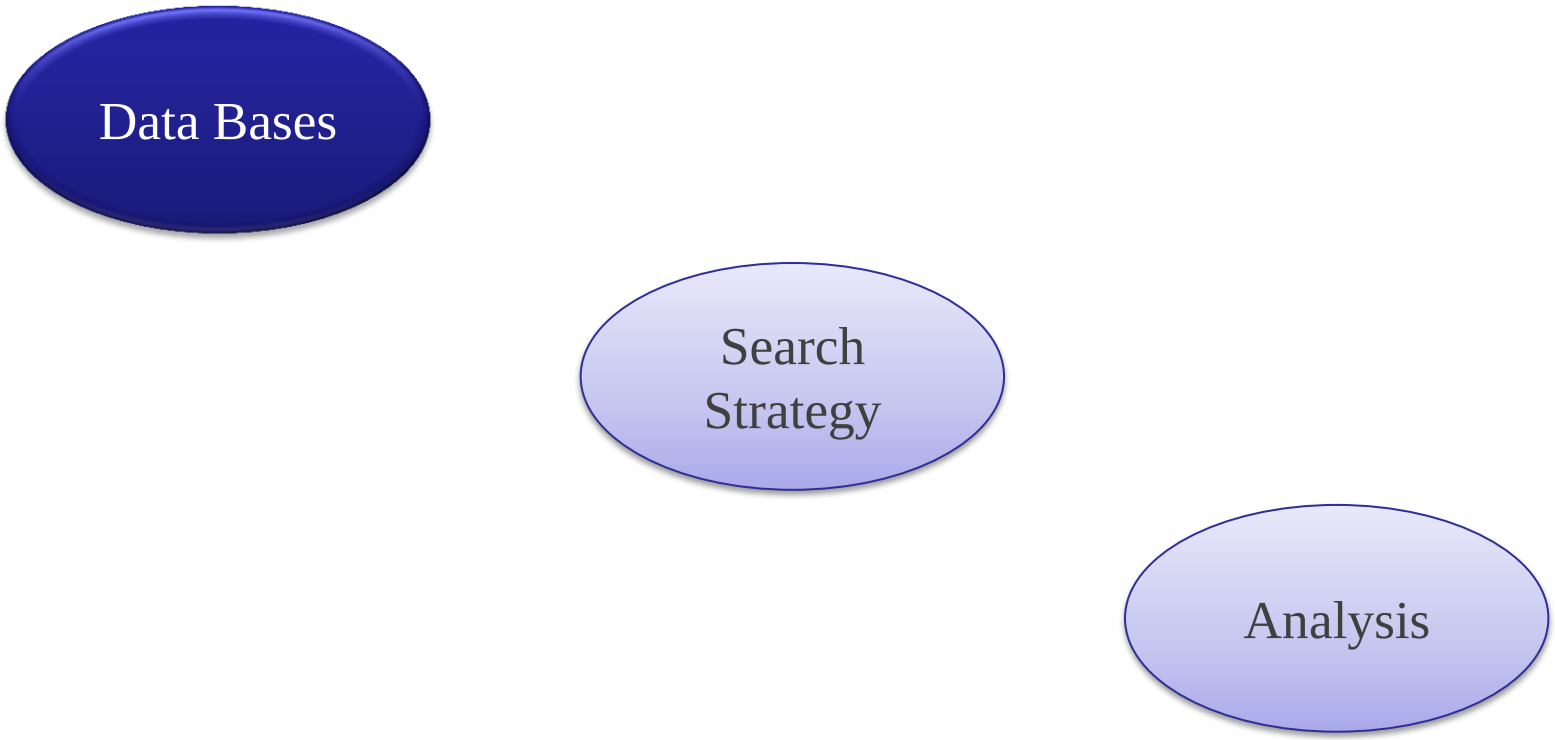
# Technology Assessment based on Document Patent

- Main steps of the technology assessment

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# Technology Assessment based on Document Patent

- SciFinder Scholar®
  - Internationally recognized database
  - Facilitates the retrieval of patent application – by API
  - Contains filter that enable only document for the synthesis of the API
  - Allows to select the documents with detailed production route

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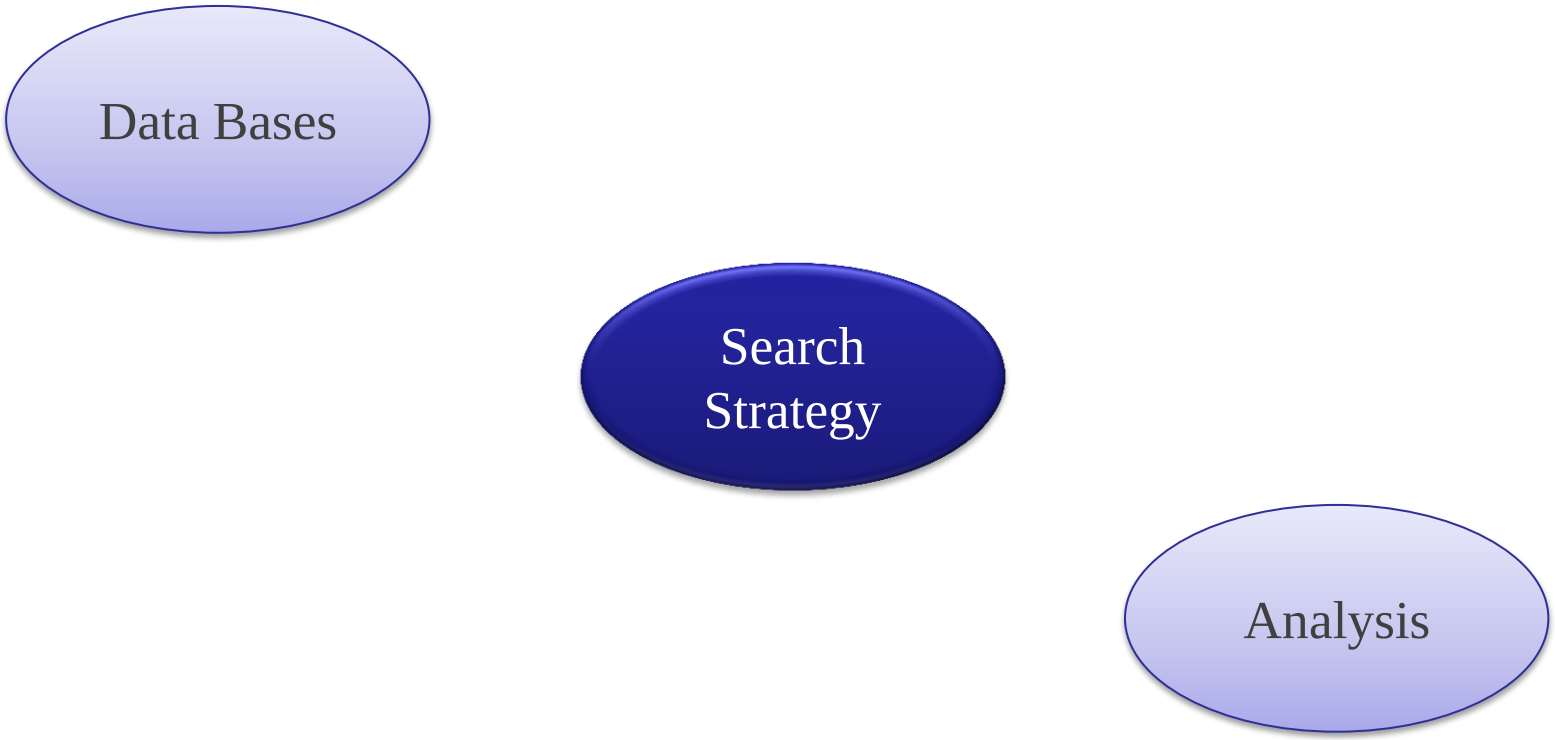
# Technology Assessment based on Document Patent

- Main steps of the technology assessment




**Steps 1 and 2 of the Methodology**

1. Search for the process patents
2. Select the process patents that explain the synthesis route

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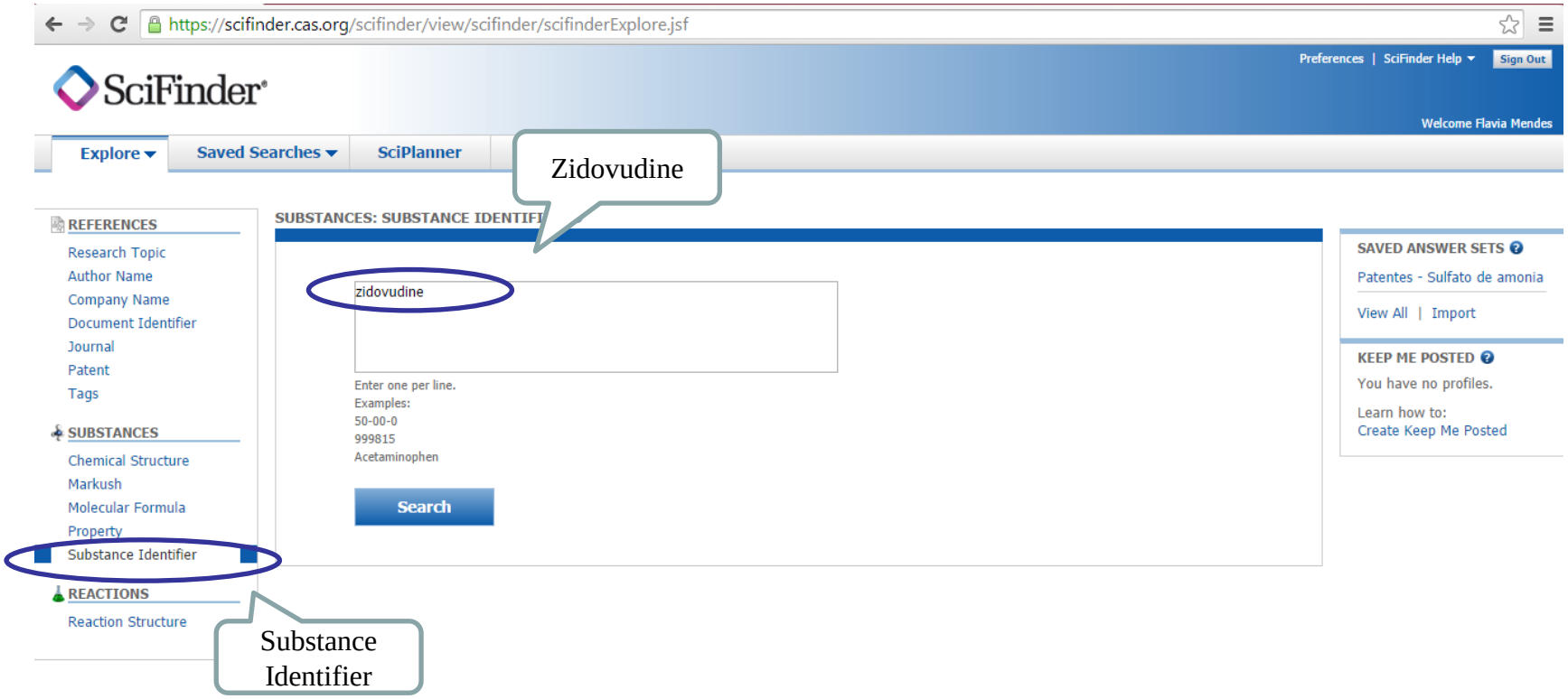
# Search for the process patents and Select the process patents that explain the synthesis route – STEPS 1 and 2

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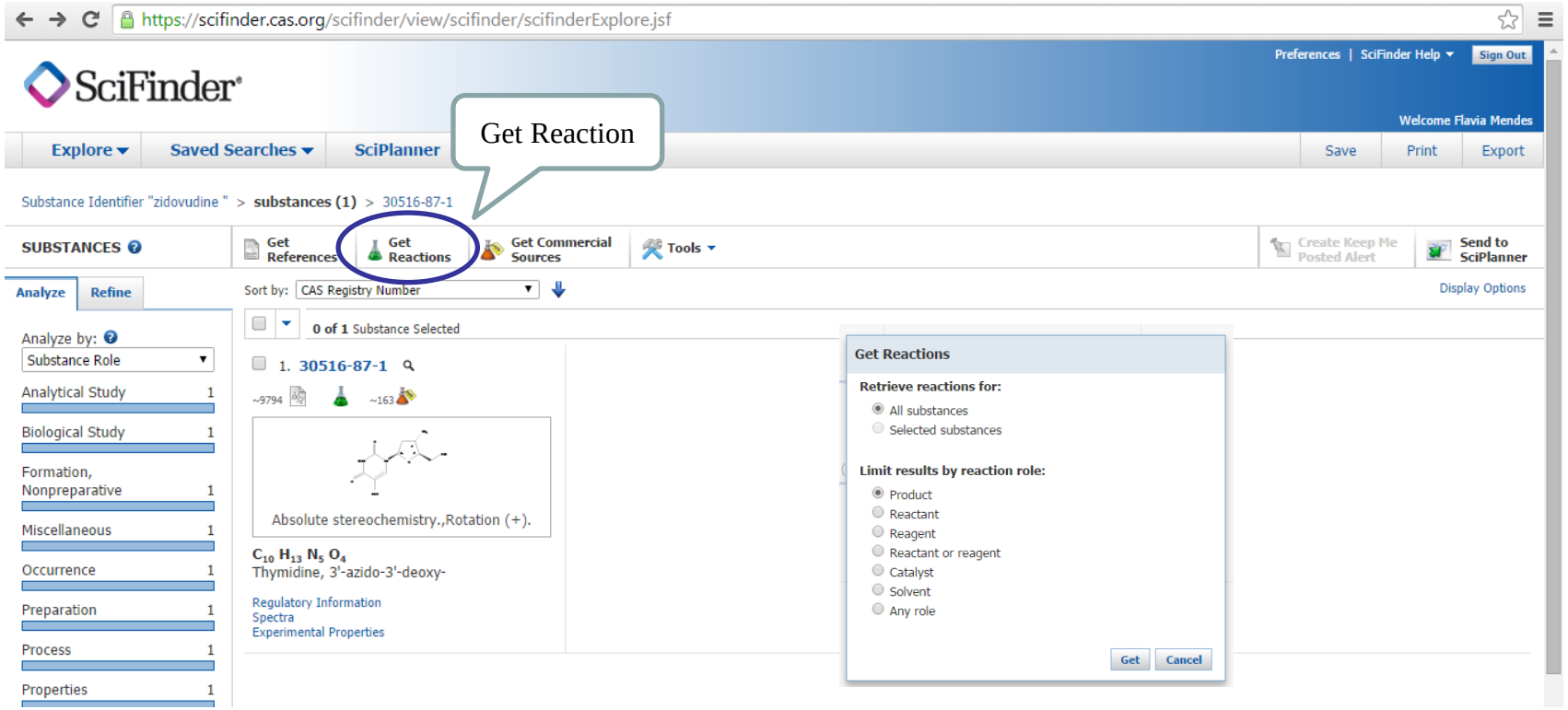
# Search for the process patents and Select the process patents that explain the synthesis route – STEPS 1 and 2

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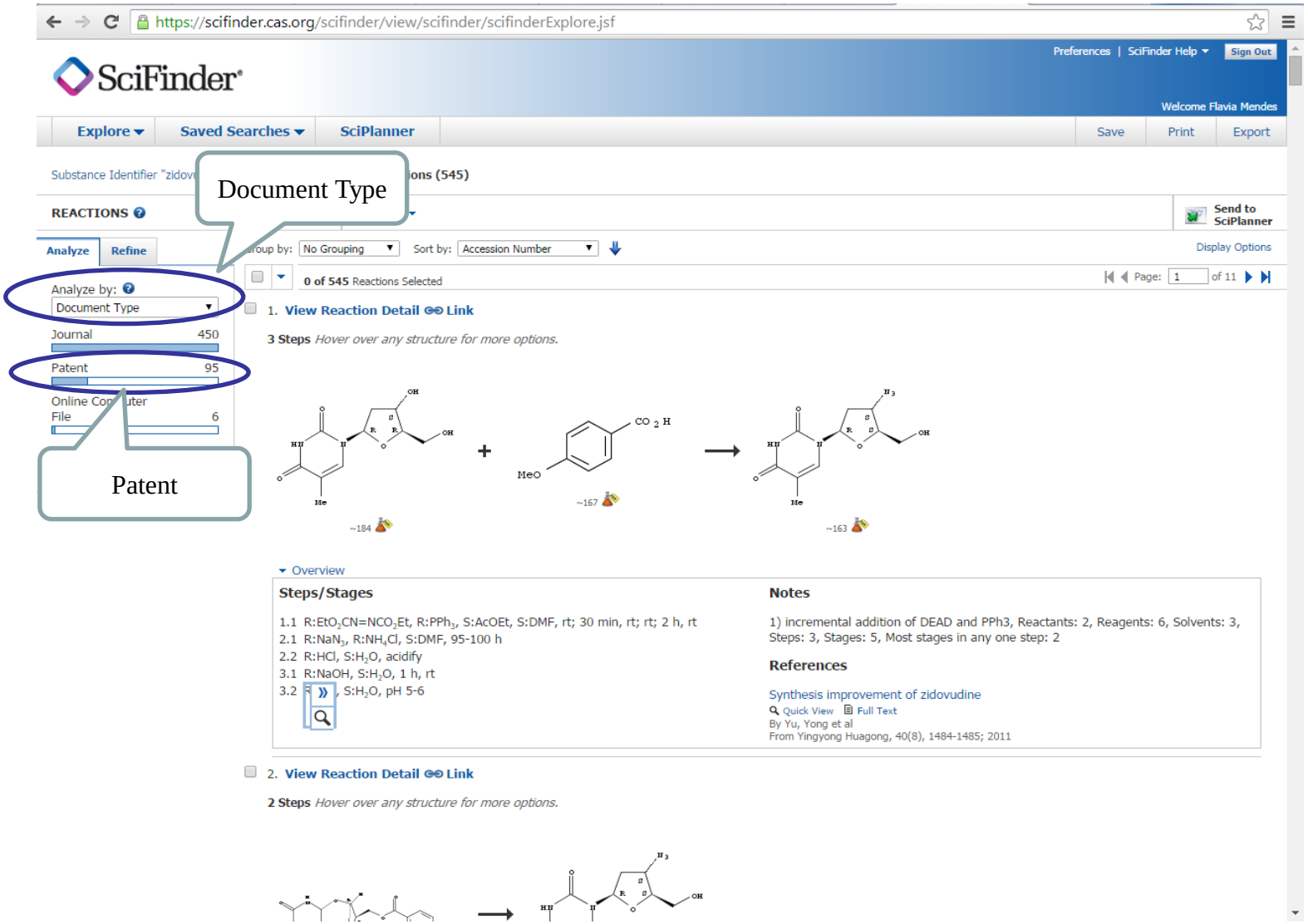
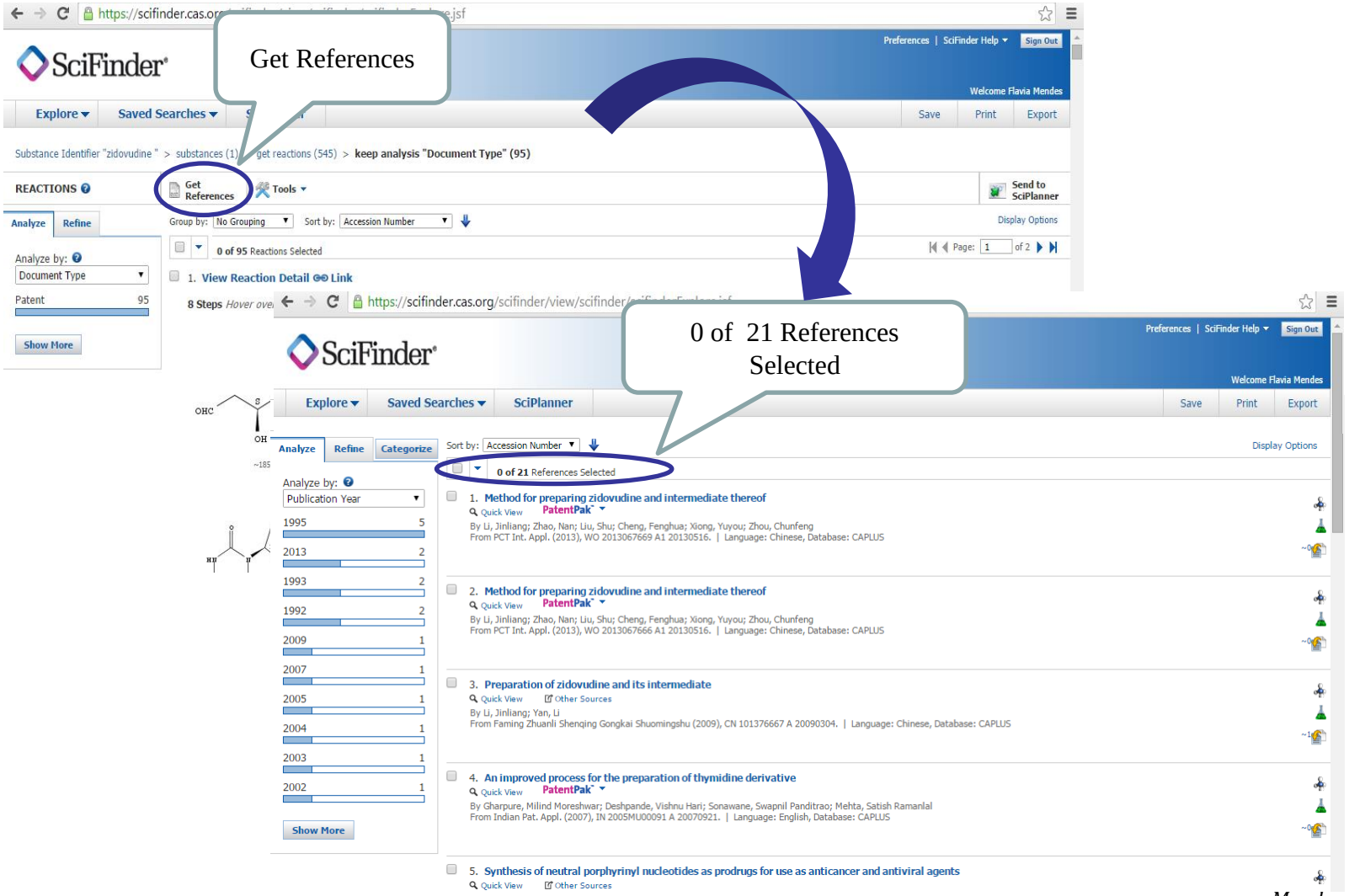
# Search for the process patents and Select the process patents that explain the synthesis route – STEPS 1 and 2




*Mendes e Antunes, 2015*

# Search for the process patents and Select the process patents that explain the synthesis route – STEPS 1 and 2

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# Results of STEPS 1 and 2

- 21 patent documents for the zidovudine production process

- 25 different synthesis route for zidovudine were identified
  - One patent may have more than one processes

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# Technology Assessment based on Document Patent

- Main steps of the technology assessment

**Steps 3 to 6 of the Methodology**

3. Identify all the reagents and intermediates present in the routes patented
4. Select the most frequently substances present in the routes patented
5. Compare the chemical structures of the most frequently cited substances with the API
6. Seek producers/suppliers of the substances that are most structurally similar to the API


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# Step 3
# Identifies all the reagents and intermediates present in the routes patented

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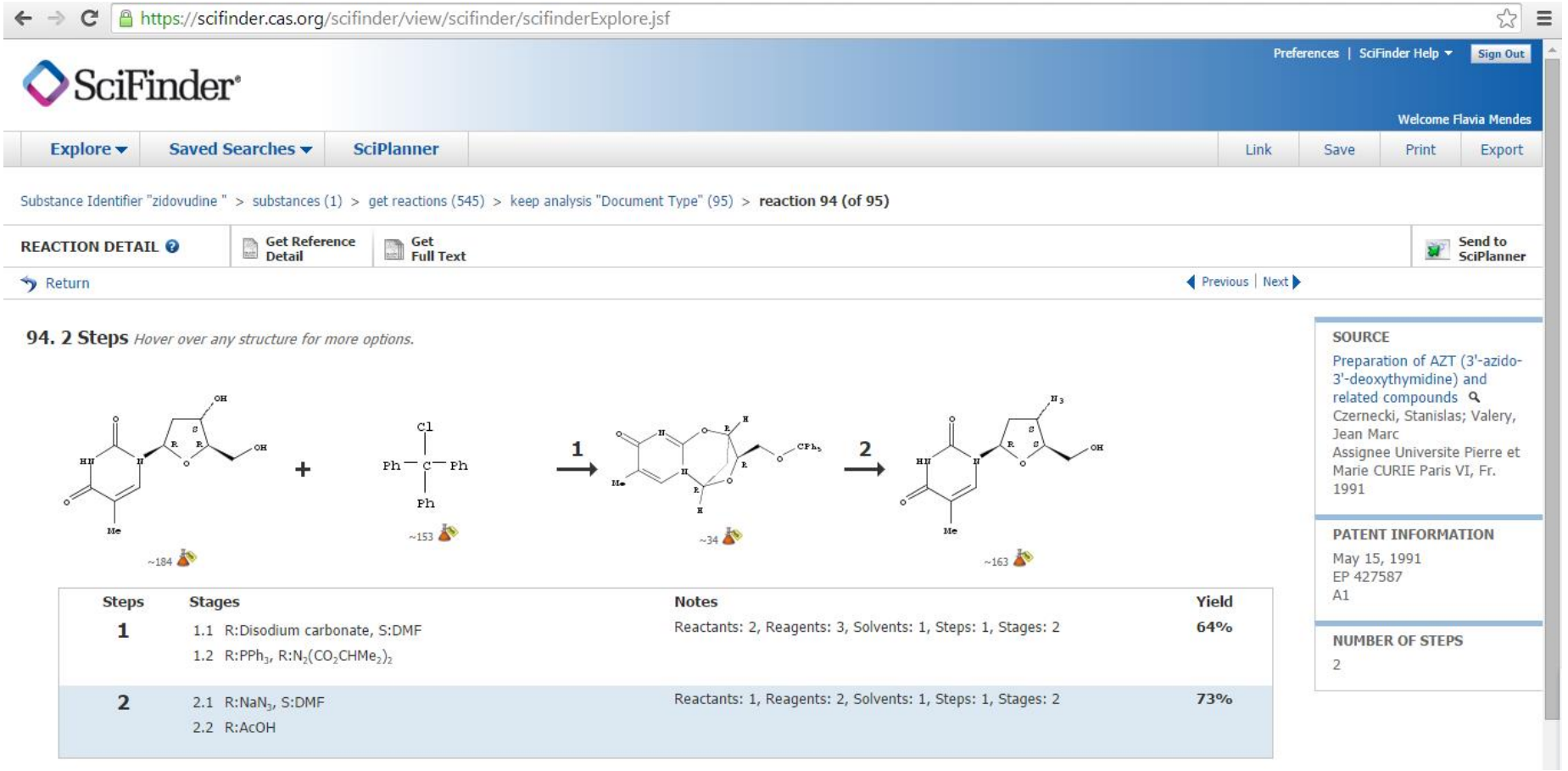
# Identifies all the Reagents and Intermediates – Zidovudine – STEP 3

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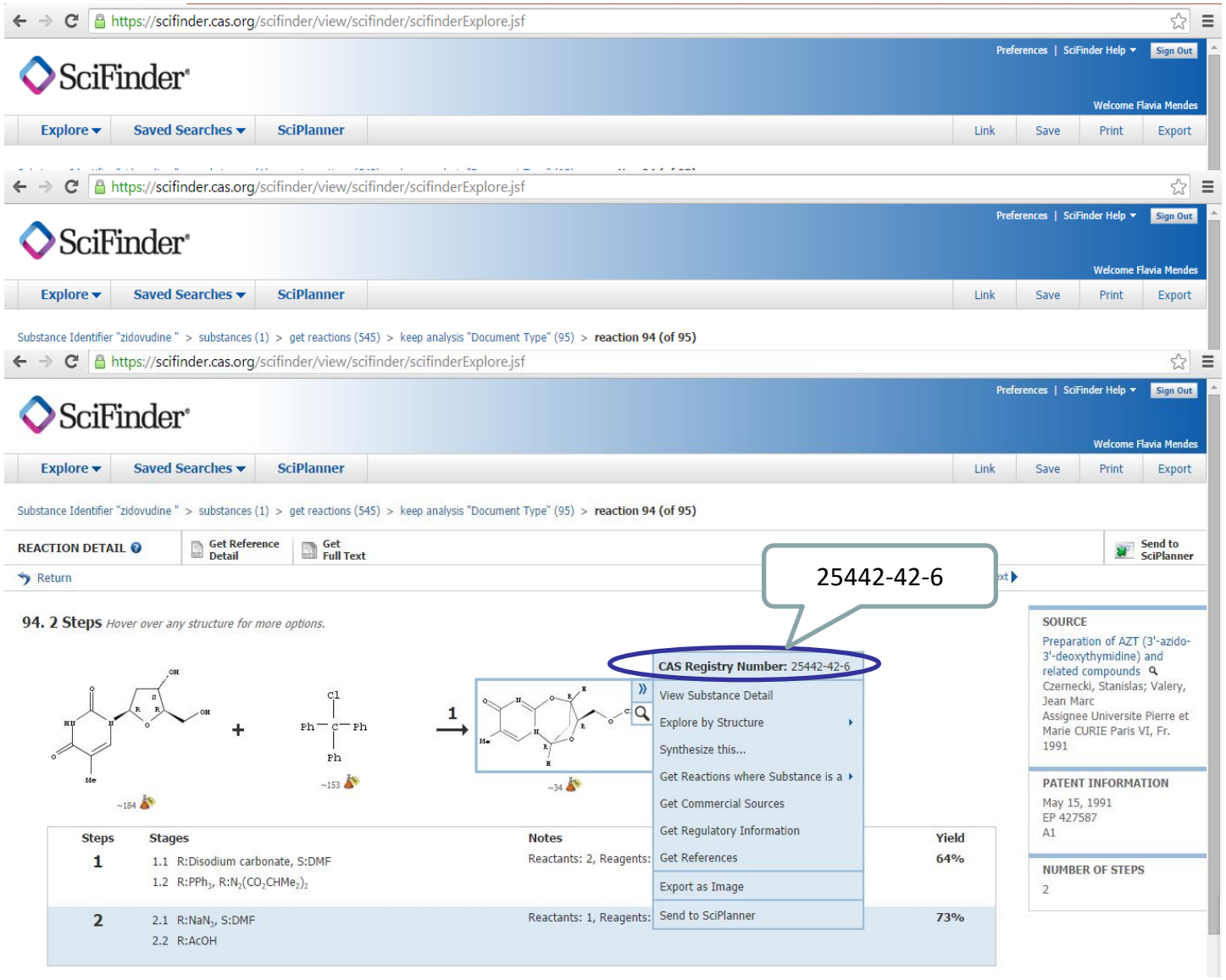
# Identifies all the Reagents and Intermediates – Zidovudine – STEP 3

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# Identifies all the Reagents and Intermediates – Zidovudine – STEP 3

- Organizes the data – Example

| API | Patent Number | Type of the Substance | Substances' CAS |
|---|---|---|---|
| **Zidovudine** | CN101376667 | Reagent | 67-56-1 |
| | CN101376667 | Reagent | 533-67-5 |
| | CN101376667 | Intermediates | 60134-26-1 |
| | CN101376667 | Reagent | 98-59-9 |
| | CN101376667 | Intermediates | 1133973-26-8 |
| | CN101376667 | Intermediates | 1133973-41-7 |
| | CN101376667 | Intermediates | 1133973-43-9 |
| | CN101376667 | Reagent | 7288-28-0 |
| | CN101376667 | Intermediates | 1133973-45-1 |
| | CN101376667 | Intermediates | 1133973-47-3 |
| | CN101376667 | Intermediates | 108441-90-3 |

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# Results of Step 3

- 111 different molecules identified in 25 processes

## Step 4
## Selects the most frequently substances present in the routes patented

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# Selects the Most Frequently Substances – STEP 4

- 14 were present in more than one route

| Substances' CAS | Number of times that it appears on the routes of synthesis |
|---|---|
| 124-63-0 Mesyl chloride | 7 |
| 50-89-5 Thymidine | 5 |
| 7288-28-0 | 4 |
| 76-83-5 | 4 |
| 29706-84-1 | 3 |
| 104218-44-2 | 3 |
| 4234-08-6 | 2 |
| 134623-19-1 | 2 |
| 75-15-0 | 2 |
| 134485-36-2 | 2 |
| 99018-98-1 | 2 |
| 142741-93-3 | 2 |
| 2417-90-5 | 2 |
| 1463-10-1 | 2 |

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# Step 5
# Compares the chemical structures of the 14 most frequently cited substances with the API

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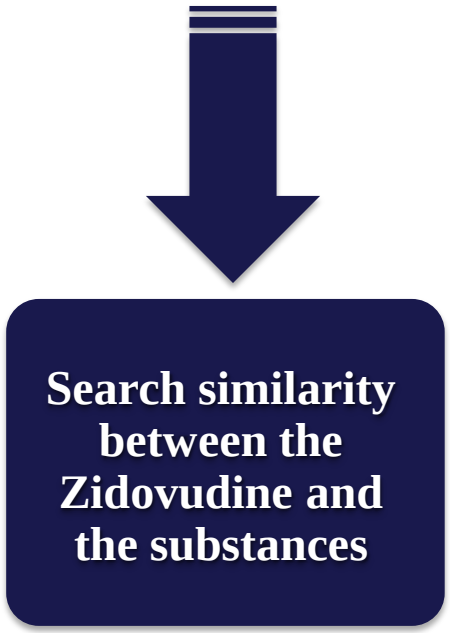
# Compares the Chemical Structures of the Zidovudine with the 14 Most Frequently Substances - STEP 5

- Comparison of the structures




8 substances selected

6 substances excluded

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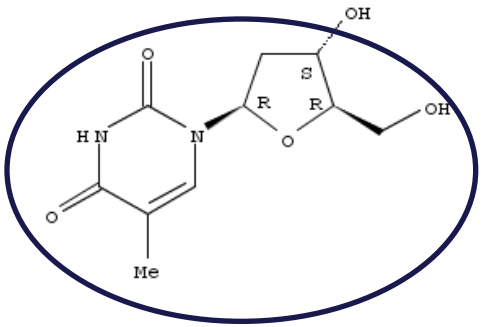
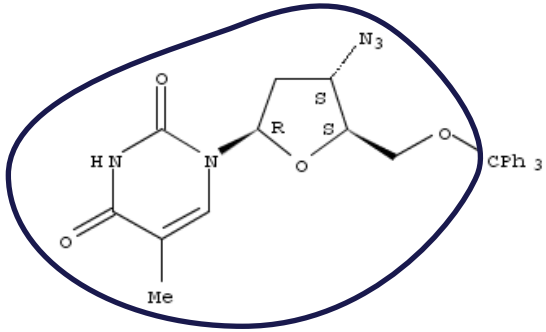
# Compares the Chemical Structures of the Zidovudine with the 14 Most Frequently Substances - STEP 5

- Substance with structure similarity - Selected

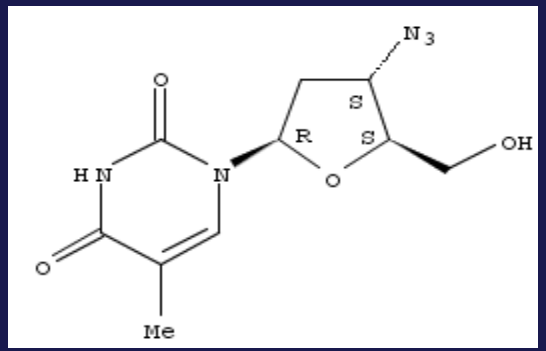
Thymidine
CAS: 50-89-5
N. of routes: 5



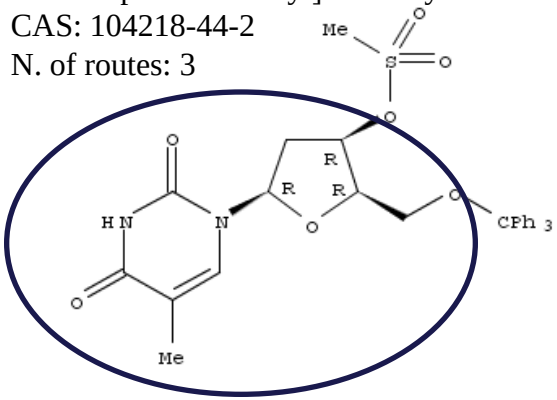
3'-azido-3'-deoxy-5'-O-(triphenylmethyl)- Thymidine
CAS: 29706-84-1
N. of routes : 3



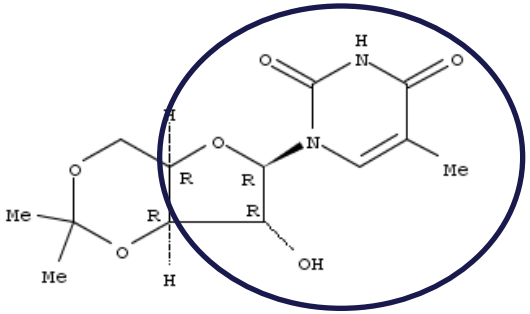
**ZIDOVUDINE**



2,4(1H,3H)-Pyrimidinedione, 1-[2-deoxy-3-O-(methylsulfonyl)-5-O-(triphenylmethyl)-β-D-threo-pentofuranosyl]-5-methyl-
CAS: 104218-44-2
N. of routes: 3



5-methyl-1-[3,5-O-(1-methylethylidene)-b-D-xylofuranosyl]-2,4(1H,3H)-Pyrimidinedione
CAS: 4234-08-6
N. of routes: 2



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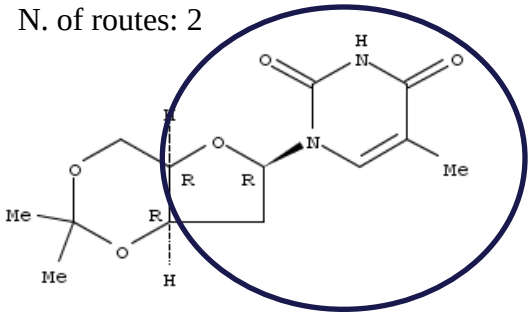
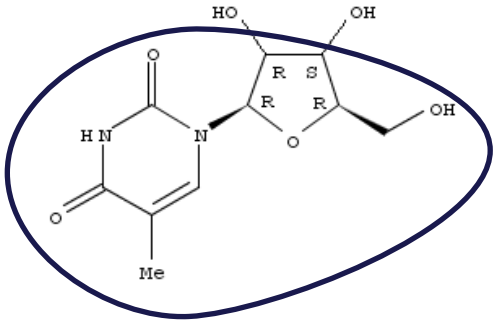
# Compares the Chemical Structures of the Zidovudine with the 14 Most Frequently Substances - STEP 5

- Substance with structure similarity - Selected

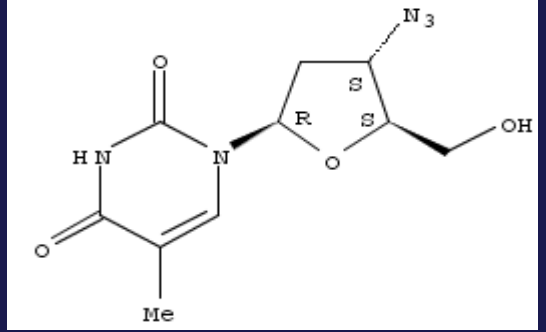
1-[2-deoxy-3,5-O-(1-methylethylidene)-b-D-threo-pentofuranosyl]-5-meth yl-2,4(1H,3H)-Pyrimidinedione
CAS: 99018-98-1
N. of routes: 2



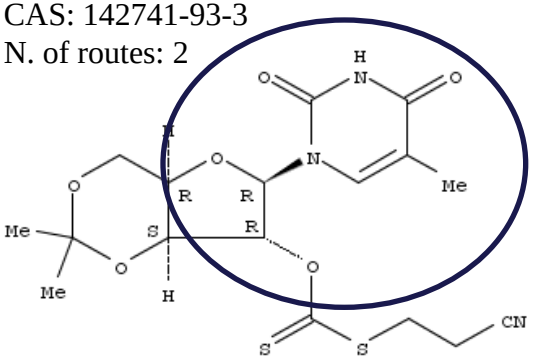
5-methyl- Uridine
CAS: 1463-10-1
N. of routes: 2



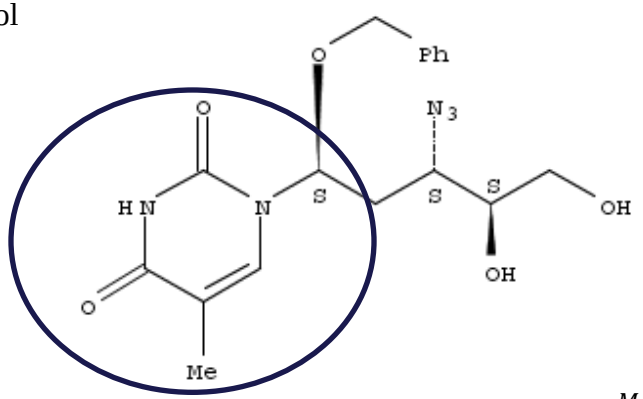
**ZIDOVUDINE**



1-[2-O-[[(2-cyanoethyl)thio]thioxomethyl]-3,5-O-(1-methylethylidene)-b-D-2,4(1H,3H)-Pyrimidinedione
CAS: 142741-93-3
N. of routes: 2



3-azido-2,3-dideoxy-1-C-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimi dinyl)-1-O-D-erythro-Pentitol
CAS: 134623-19-1
N. of routes: 2



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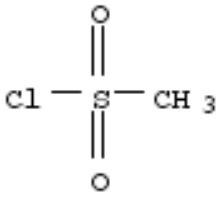
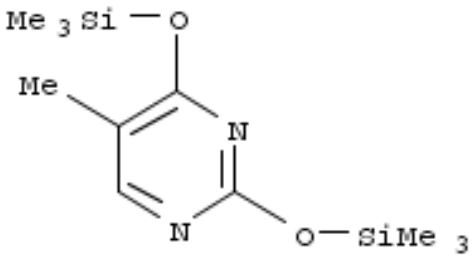
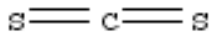
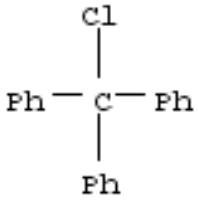
# Compares the Chemical Structures of the Zidovudine with the 14 Most Frequently Substances - STEP 5

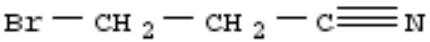
- Substance without structure similarity - Excluded

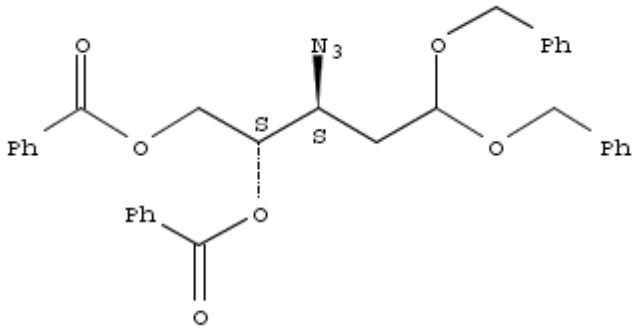




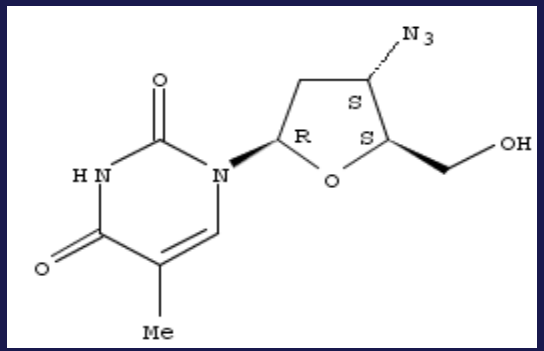








**ZIDOVUDINE**



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# Step 6
# Seeks producers/suppliers of the substances that are most structurally similar to the API

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# Seeks Producers/Suppliers - STEP 6

- The commercial availability of key molecules may facilitate the synthesis

- Databases Example
  - Directory of World Chemical Producers (DWCP) of Chemical Info
  - Directory of Chemical Producers - Products of SRI Consulting
  - American Chemical Society (ACS)
  - Chemistry Industry Association of Canada, a International Council of Chemical Associations (ICCA)
  - Chinese Chemical Society
  - Indian Speciality Chemical Manufacturers' Association
  - SciFinder Scholar®

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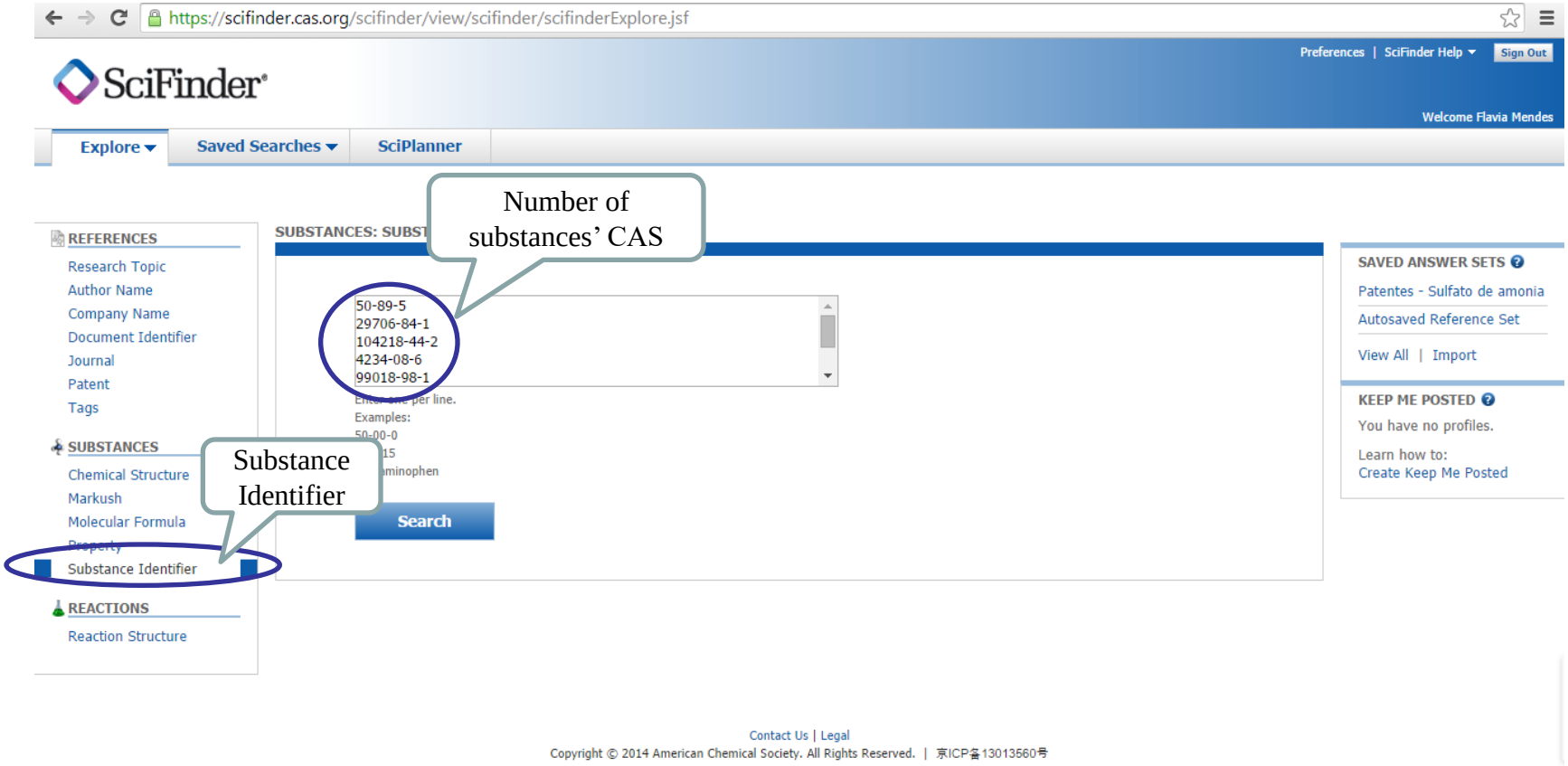
# Seeks Producers/Suppliers Using the SciFinder Scholar® - STEP 6

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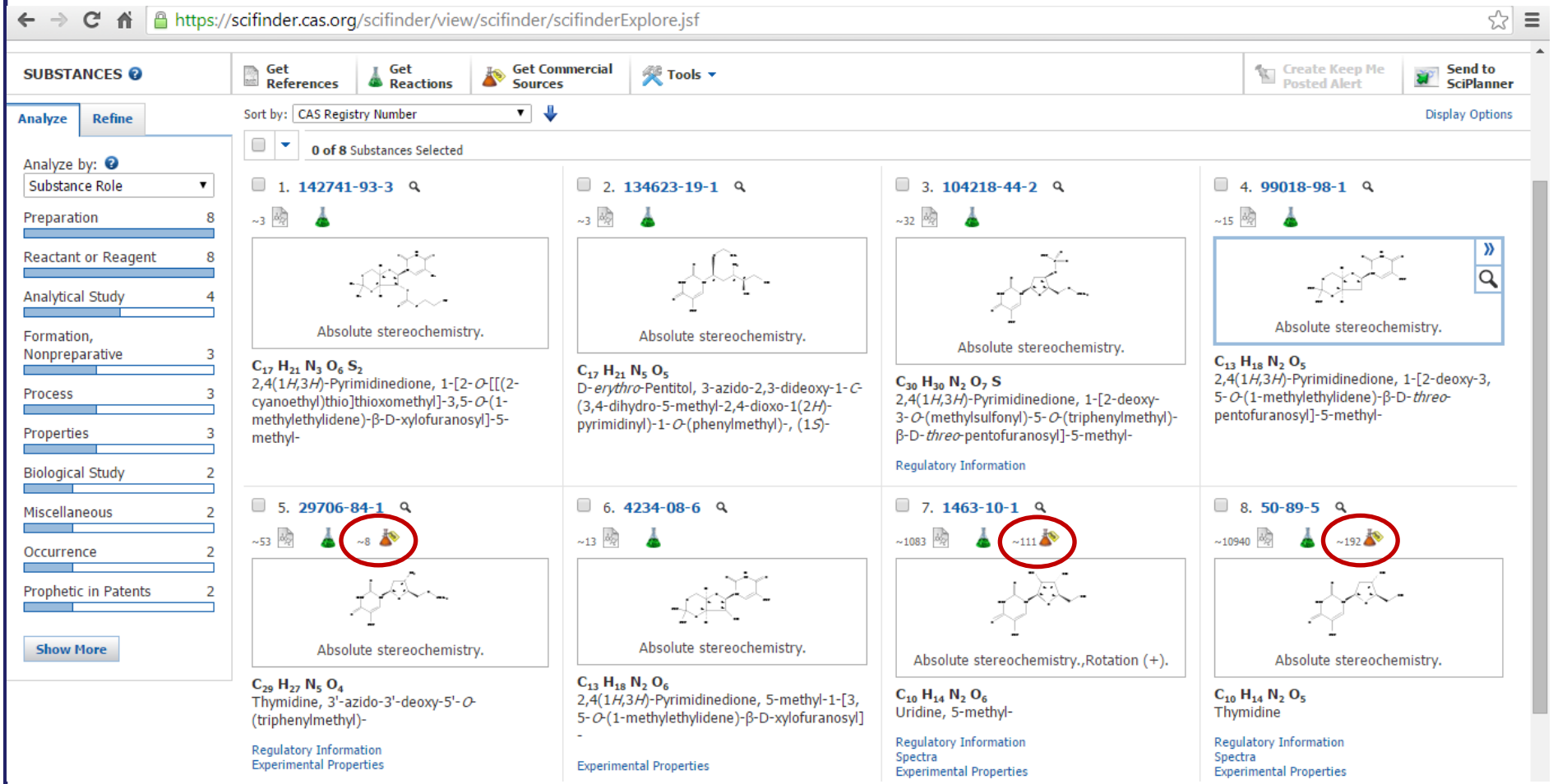
# Seeks Producers/Suppliers Using the SciFinder Scholar® - STEP 6

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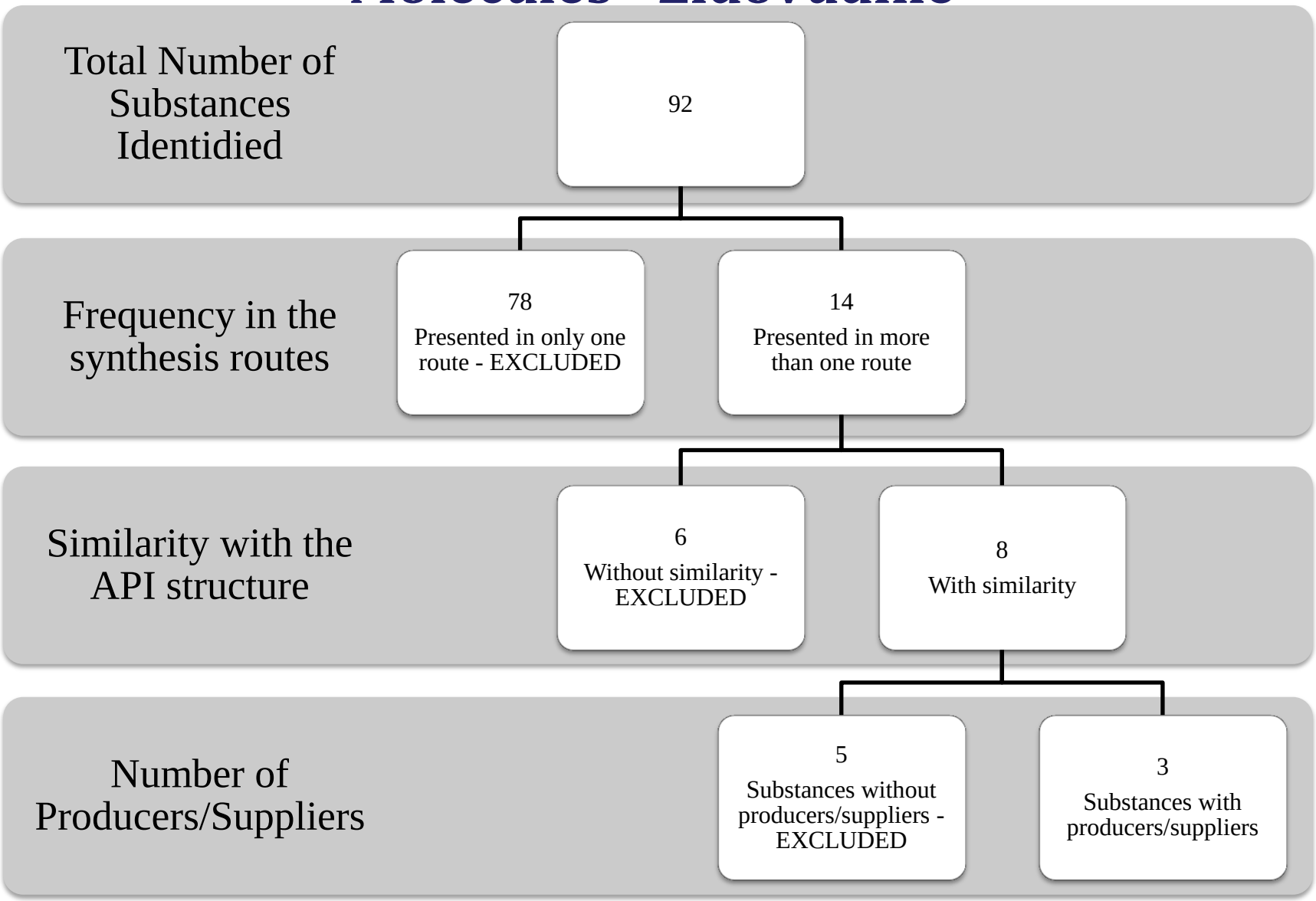
# Methodology for Identifying Pharmaceutical Key Molecules - Zidovudine

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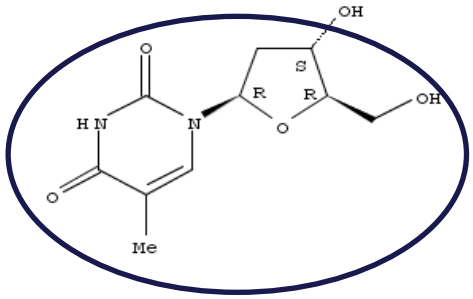
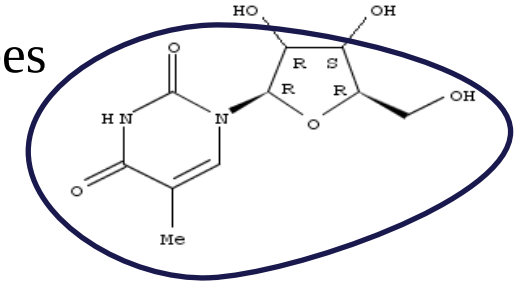
# Key Molecules of Zidovudine Using the Methodology

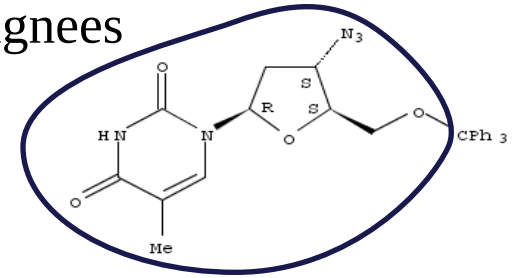
- Thymidine: 50-89-5
  - Present in 5 routes of synthesis – different assignees
  - First patent in 1958 (public domain)
  - 187 international producers/suppliers




- 5-Methyl-Uridine: 1463-10-1
  - Present in 2 routes of synthesis – different assignees
  - First patent in 1962 (public domain)
  - 111 international producers/suppliers




- 3'-azido-3'-deoxy-5'-O-(triphenylmethyl)-Thymidine: 29706-84-1
  - Present  in 3 routes of synthesis – different assignees
  - First patent in 1957 (public domain)
  - 8 international producers/suppliers

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# Conclusions

- Analysis of synthesis patents
  - All substances (reagents, intermediates products) can be identified
- The comparison between the molecular structure of the API and the substances that most appears in route of synthesis allows:
  - The selection of more complexity substances
- It is possible to use the methodology to identify key molecules in a group of API's
- Other analysis can be done:
  - Temporal evaluation of the patents
  - Identify the key assignees
  - Relation between the assignees and the substances

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# 5th Annual Global TechMining Conference

## Methodology for Identifying Pharmaceutical Key Molecules Using Technology Foresight of Patent Documents

**THANKS!!!**

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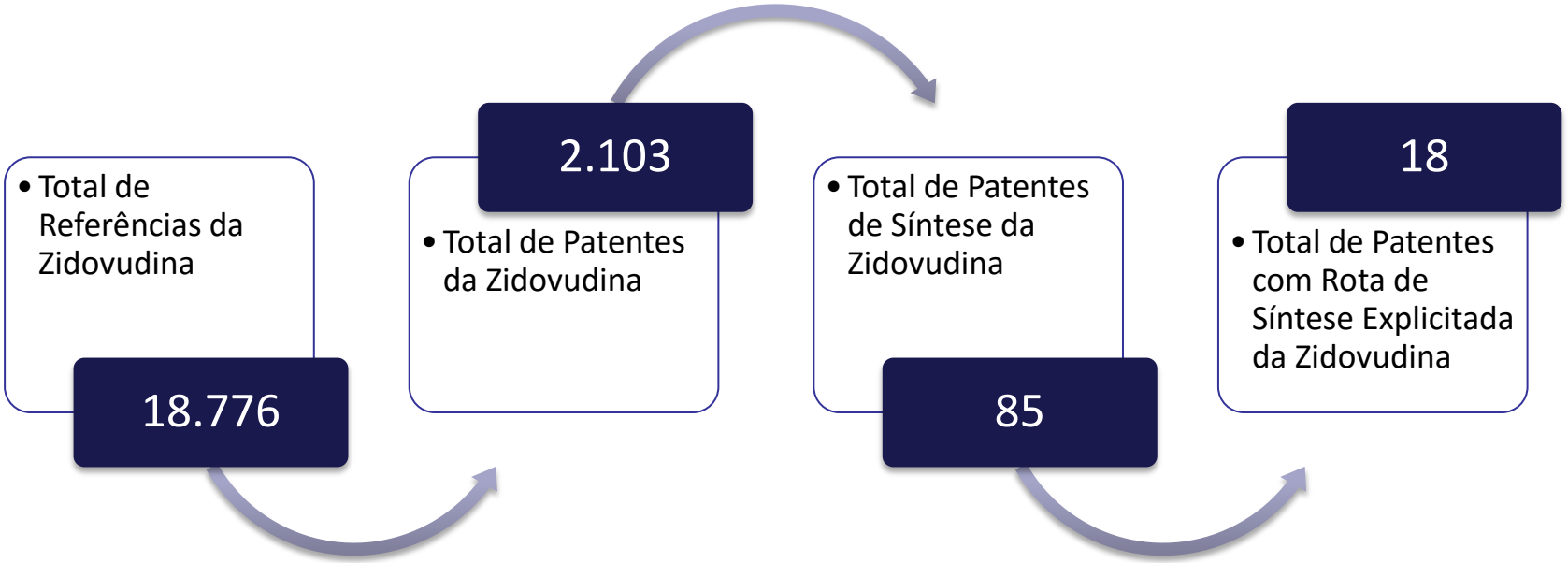
Adelaide Maria de Souza Antunes (INPI/UFRJ, Brazil)
16/09/2015

# Patentes Zidovudina

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- http://www.jstor.org/stable/2555803?seq=1#page_scan_tab_contents

# Patent Documents Analysis Allows

- knowledge about existing prospective industrial property rights in the country (validity, ownership, ...), particularly to avoid infringement actions;
- knowledge about the state-of-the-art in a specific technology;
- assessment of novelty and patentability of own developments with a view to applying for a domestic or foreign industrial property right;
- evaluation of a specific technology;
- identification of alternative technology and its sources;
- location of sources of know-how in a specific field in a given country;

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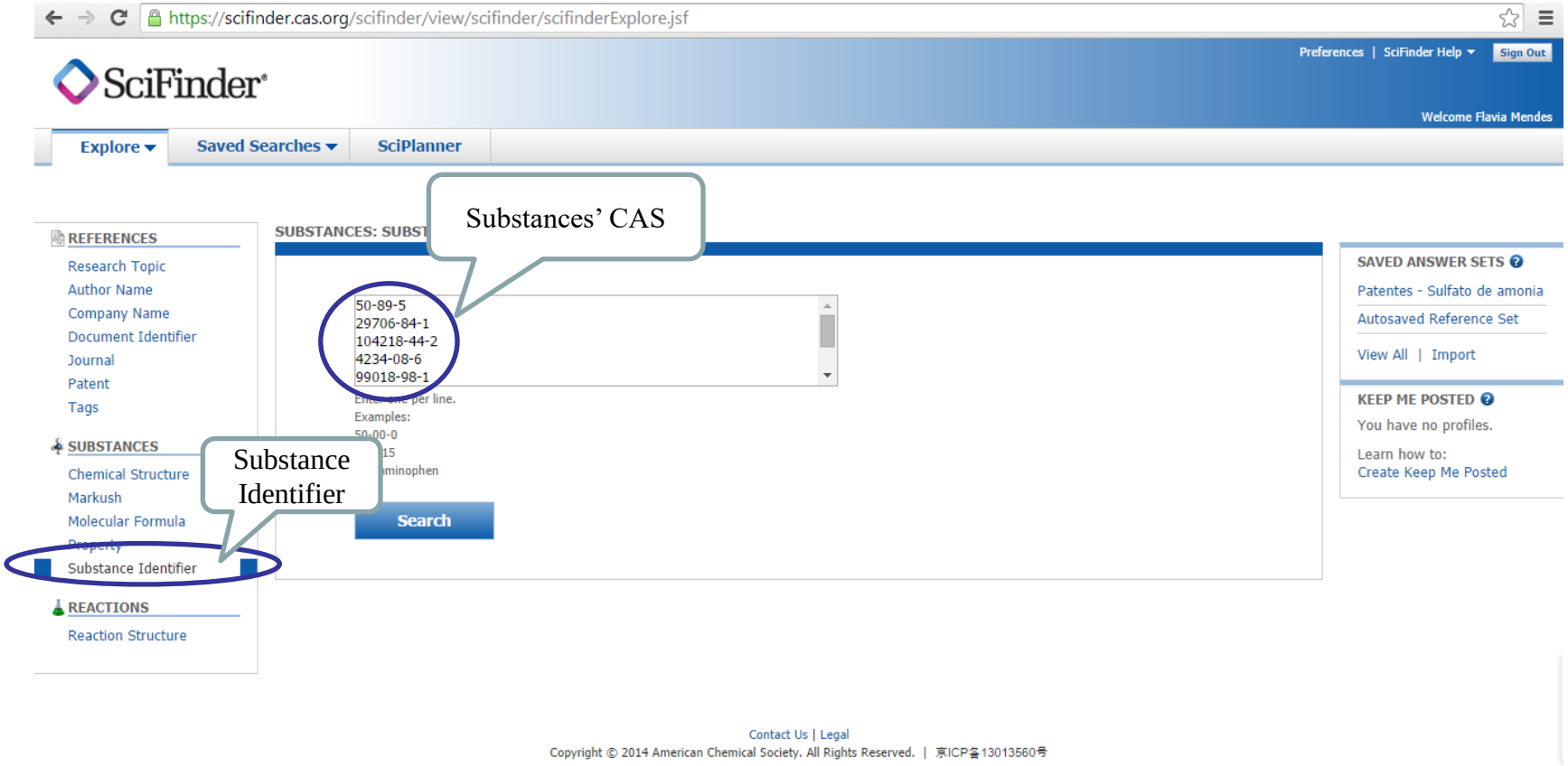
# Patent Documents Analysis Allows (cont.)

- improvement of an existing product or process;
- development of new products or processes;
- solution of a specific technical problem;
- assessment of a particular technical approach;
- monitoring of activities of competitors both within the country and abroad;
- survey of the market in order to identify a gap or to discover new trends at an early stage

*Mendes e Antunes, 2015*

# Compares the Chemical Structures of the Zidovudine with the 14 Most Frequently Substances - STEP 5

- Recovery of structures of selected substances – SciFinder Scholar®




*Mendes e Antunes, 2015*