Europäisches Patentamt
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Search Strategy in Medicinal Chemistry

(with Examples on Polymorphic Forms)

Overview

Search and retrieval of prior art for patents

1. How do EPO examiners work?
2. External database (STN)
3. Internal database (EPODOC / ESPACENET)
4. Other external databases (Reaxys, Integrity)
5. Classification

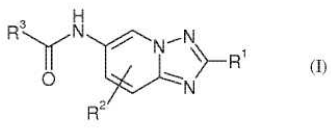
Basic search principles

- Search should be broad enough so that no relevant information is missing
- Search effort must stay within reasonable bounds in terms of time and resources
- Search is a dynamic process: adapt the strategy to the current case, the current needs and the current results

Search specificity of pharmaceutical applications

- Specificity of chemical/pharmaceutical applications:
  - Chemical formula (vs. keywords)
  - Classification system

The invention is concerned with triazolopyridine compounds of formula (I) wherein R1, R2 and R3 are as defined in the description and in the claims, as well as physiologically acceptable salts thereof. These compounds inhibit PDE10A and can be used as medicaments.



(I)

Structural Search in an external database (Reaxys):
64 compounds in 7 citations
(6 patents + 1 NPL)

[SS 1] ..fi epodoc

Database: EPODOC

[EPODOC: SS 1] /c c07d471/04

Results in EPODOC **101.109**

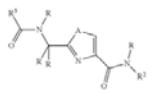
Search specificity of pharmaceutical applications

CLAIMS (22)

We claim:

1. A compound of Formula III

III



wherein, independently for each occurrence,

R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

A is —O—, —S—, or —NR—;

R is —H, or alkyl; and

R^5 is substituted or unsubstituted heteroaryl.

1 structural search

vs.

(at least) 3 classes

C07D403/12
C07D413/12
C07D417/12

Successful search strategy

- Stage 1: **Coarse filter**
  Develop search statements and screen the databases to select a subset of documents most likely to be relevant
- Stage 2: **Fine filter**
  Read the original documents to identify the most relevant and discard the others. Compare the invention with the documents
- Further searching necessary?

Stage 1: Coarse filter

1. Harvest information from the application and identify key search concepts
2. Analyse the key search concepts and identify synonyms, classes, etc.
3. Formulate search statements, query relevant databases
4. Collect documents which might be relevant

For which purpose?

- First medical use of novel active pharmaceutical ingredients; novel polymorphic forms

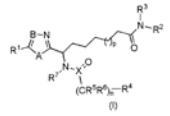
Claims

1. A polymorphic form C of Efavirenz **characterized by** an X-ray powder diffraction pattern which comprises characteristic 2θ values at: 7.1, 7.3, 11.0, 13.8, 14.2, 14.6, 19.1, 20.9, 21.2, 24.5 and 24.9 ± 0.2 degrees 2θ.

- Second (and further) medical use of a known active pharmaceutical ingredients

CLAIMS

1. A compound of general formula (I):

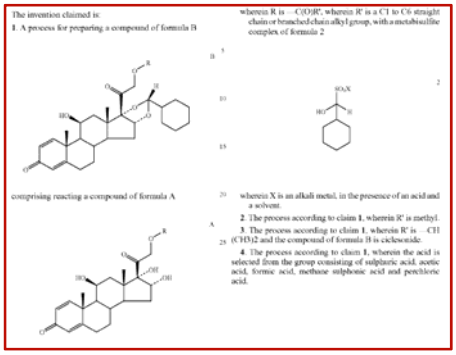


(I)

wherein:
X is C or S=O;
[...]
and pharmaceutically acceptable salts, tautomers, stereoisomers thereof, for use in the treatment of parasitic diseases.

For which purpose?

- Chemical process (alternative or improved process of a process for the preparation of a known compound)



The invention claimed is:

1. A process for preparing a compound of formula B

wherein R is —C(O)R', wherein R' is a C1 to C6 straight chain or branched chain alkyl group, with a metabisulfite complex of formula 2

comprising reacting a compound of formula A

wherein X is an alkali metal, in the presence of an acid and a solvent.

2. The process according to claim 1, wherein R' is methyl.

3. The process according to claim 1, wherein R' is —CH(CH3)2 and the compound of formula B is ciclesonide.

4. The process according to claim 1, wherein the acid is selected from the group consisting of sulphuric acid, acetic acid, formic acid, methane sulphonic acid and perchloric acid.

- Novelty
- Inventive step

Crystalline forms of rifaximin (description)

CLAIMS

1. A crystalline form κ of Rifaximin, characterised by a powder XRD spectrum with peaks at values of the angle 2θ of 5.3°, 6.8°, 7.8°, 8.5°, 9.3°, 10.1°, 10.3°, 12.1°, 12.7°, 1
20.3° an

Patent application EP 1557421 A1 describes three polymorphs of Rifaximin. The first form, designated α, has a powder X-ray diffraction (XRD) spectrum which presents peaks at the values of angle 2θ of 6.6°, 7.4°, 7.9°, 8.8°, 10.5°, 11.1°, 11.8°, 12.9°, 17.6°, 18.5°, 19.7°, 21.0°, 21.4° and 22.1°. The second form, designated β, has a powder X-ray diffraction (XRD) spectrum with peaks at the values of angle 2θ of 5.4°, 6.4°, 7.0°, 7.8°, 9.0°, 10.4°, 13.1°, 14.4°, 17.1°, 17.9°, 18.3° and 20.9°. Finally, the third polymorphic form cited in this application, designated γ, has a lesser degree of crystallinity and has a powder X-ray diffraction (XRD) spectrum with peaks at the values of angle 2θ of 5.0°, 7.1° and 8.4°.

Patent application WO 2006/094662 A1 describes two polymorphic forms of Rifaximin, designated δ and ε, respectively; the first has a water content within the range from 2.5 to 6% by weight (preferably from 3 to 4.5%), and a powder XRD

2

Crystalline forms of rifaximin (STN)

CLAIMS

1. A crystalline form κ of Rifaximin, characterised by a powder XRD spectrum with peaks at values of the angle 2θ of 5.3°, 6.8°, 7.8°, 8.5°, 9.3°, 10.1°, 10.3°, 12.1°, 12.7°, 13.4°, 13.7°, 14.6°, 15.3°, 15.8°, 16.4°, 16.9°, 17.7°, 18.0°, 18.8°, 19.2°, 19.7°, 20.3° and 22.1°.

```
? rifaximin/CN
L1            1 RIFAXIMIN/CN
```

```
? 80621-81-4/rn
L1            1 80621-81-4/RN
```


Crystalline forms of rifaximin (STN)

```
? ..fi caplus
WARNING :On STN ,your queries are not renumbered at file switch
```

```
? l1 and (polymorph+ or cryst+ or recryst+)
          484 L1
       342134 POLYMORPH?
      2811351 CRYST?
       147977 RECRYST?
L2          35 L1 AND (POLYMORPH? OR CRYST? OR RECRYST?)
```

(amorph+)

(L) operator

```
? E polymorphism/CT
E#   FREQUENCY   AT    TERM
E1           0    1    POLYMORPHICA/CT
E2           0    1    POLYMORPHINOIDES/CT
E3        2289    3 --> POLYMORPHISM/CT
E4        5261    2    POLYMORPHISM (CRYSTAL)/CT
E5           0    3    POLYMORPHISM (CRYSTAL) (L) ALLOTROPY/CT
E6           0    2    POLYMORPHISM (CRYSTAL) (L) DIMORPHISM/CT
E7           0    2    POLYMORPHISM (CRYSTAL) (L) ENANTIOTROPY/CT
E8           0    2    POLYMORPHISM (CRYSTAL) (L) MONOTROPY/CT
E9           0    2    POLYMORPHISM (CRYSTAL) (L) PSEUDOPOLYMORPHISM/CT
E10         11         POLYMORPHISM (CRYSTAL), ALLOTROPY/CT
E11          7         POLYMORPHISM (CRYSTAL), DIMORPHISM/CT
E12          0    2    POLYMORPHISM (L) DIMORPHISM/CT
```

Crystalline forms of rifaximin (STN)

tetracyanoethanesulfonic acid in the form of a light yellow powder, M. P. 197–198° C. A sample is recrystallized from water to give white needles, M. P. 198–199° C. *Analysis.*—Calcd. for $C_{25}H_{32}N_6SO_3$: C, 61.39; H, 6.34; N, 16.52; S, 6.30. Found: C, 61.18; H, 6.49; N, 16.52, 16.40; S, 6.41, 6.22.

```
  ?  L1
L2          685 L1
  ?  L1/prep/form
            685 L1
        6095157 PREP/RL
             26 L1/PREP
                   (L1 (L) PREP/RL)
            685 L1
        1038062 FORM/RL
              1 L1/FORM
                   (L1 (L) FORM/RL)
L3           27 L1/PREP OR L1/FORM
  ?
```


Crystalline forms of rifaximin (STN)

FILE 'REGISTRY'

L1 1 80621-81-4/RN

FILE 'CAPLUS'

L4 681 L1

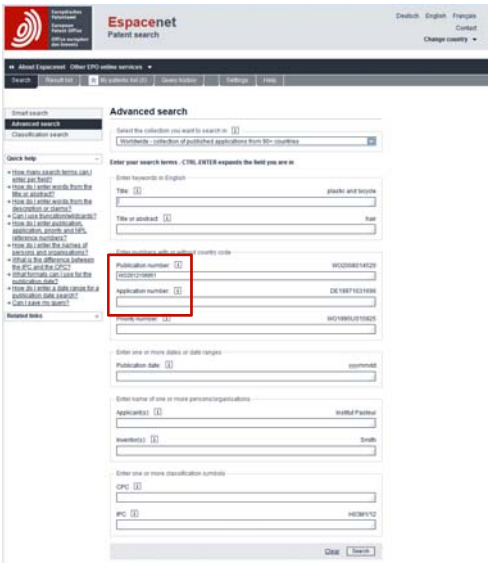
L5 61 L4 AND (POLYMORPH? OR CRYSTAL? OR RECRYSTAL?) ←

L9 34 L4 (L) (POLYMORPH? OR CRYSTAL? OR RECRYSTAL?)

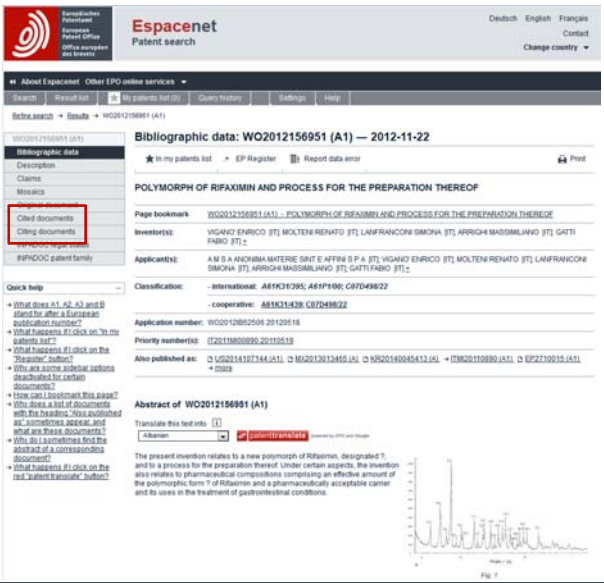
L7 4 L4 AND (E3 OR E4)

L8 26 L1/PREP ←

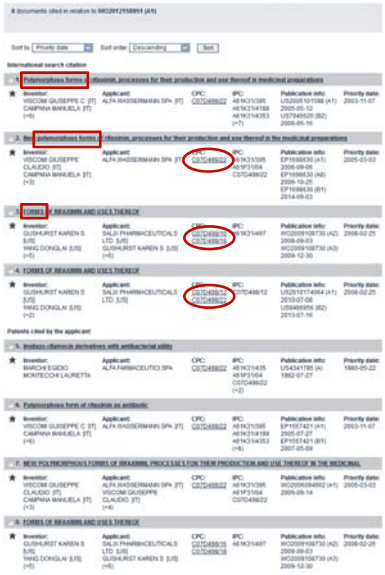
Crystalline forms of rifaximin (Espacenet / Epodoc)



Crystalline forms of rifaximin (Espacenet / Epodoc)



Crystalline forms of rifaximin (Espacenet / Epodoc)



Crystalline forms of rifaximin (Espacenet / Epodoc)

[SS 1] ..fi epodoc

Database: EPODOC

[EPODOC: SS 1] RIFAXIMIN

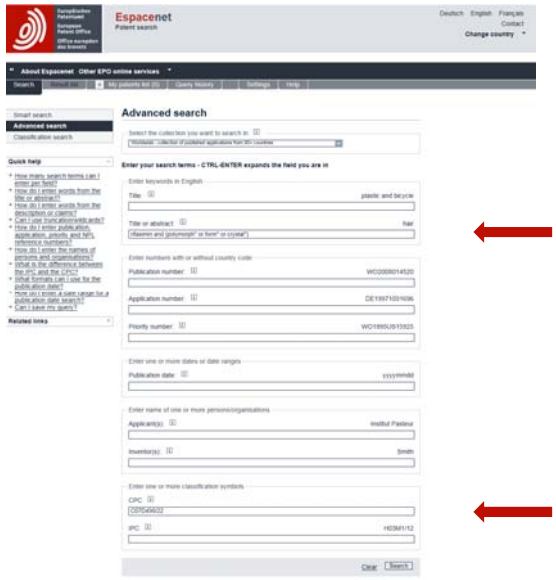
Results in EPODOC **425**

[SS 2] ..stat c

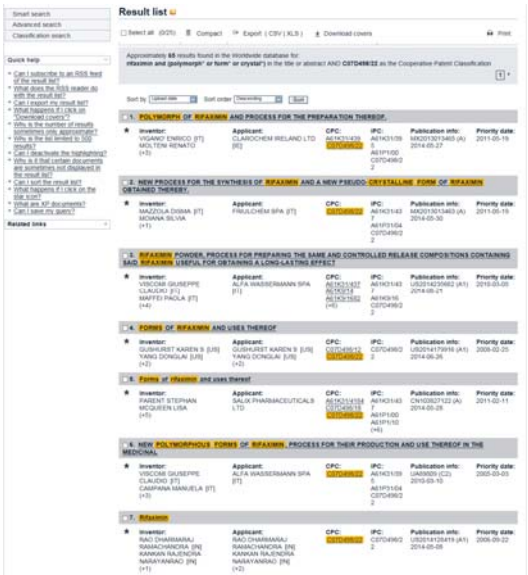
..STAT C

#	FREQ	/CCA /CCI /CQA /CQI /CUA /CUI	DESCRIPTION
1	185	**C07D498/22**	C07D498/22 in which the condensed system contains four or more hetero rings
2	144	**A61K31/437**	A61K31/437 ..... the heterocyclic ring system containing a five-membered ring having nitrogen as a ring hetero atom, e.g. indolizine, beta-carboline
3	67	**A61K31/44**	A61K31/44 .... Non condensed pyridines; Hydrogenated derivatives thereof
4	55	**A61K9/2054**	A61K9/2054 ..... {Cellulose; Cellulose derivatives, e.g. hydroxypropyl methylcellulose}
5	45	**A61K9/1652**	A61K9/1652 ..... {Polysaccharides, e.g. alginate, cellulose derivatives; Cyclodextrin }
6	40	**A61K9/5026**	A61K9/5026 ..... {obtained by reactions only involving carbon-to-carbon unsaturated bonds, e.g. polyvinyl pyrrolidone, polyacrylates}
7	34	**A61K31/395**	A61K31/395 .. having nitrogen as a ring hetero atom, e.g. guanethidine, rifamycins
8	34	**A61K45/06**	A61K45/06 . Mixtures of active ingredients without chemical characterisation, e.g. antiphlogistics and cardiaca
9	31	**A61K9/1635**	A61K9/1635 ..... {obtained by reactions only involving carbon-to-carbon unsaturated bonds, e.g. polyvinyl pyrrolidone, polyacrylates}
10	31	**A61K9/2027**	A61K9/2027 ..... {obtained by reactions only involving carbon-to-carbon unsaturated bonds, e.g. polyvinyl pyrrolidone, polyacrylates}
11	30	**A61K9/2866**	A61K9/2866 ..... {Cellulose; Cellulose derivatives, e.g. hydroxypropyl methylcellulose}
12	30	**C07D498/18**	C07D498/18 .. Bridged systems
13	26	**A61K47/10**	A61K47/10 ... Alcohols; Phenols; Salts thereof,{e.g. glycerol; Polyethylene glycol ; Poloxamers; PEG/POE alkyl ethers

Crystalline forms of rifaximin (Espacenet / Epodoc)



Crystalline forms of rifaximin (Espacenet / Epodoc)



Crystalline forms of rifaximin (Espacenet / Epodoc)

- look for the recent applications from the same applicant, form the same inventor(s)
- look for applications having the same words in the title

Successful search strategy

- Stage 1: **Coarse filter**
  Develop search statements and screen the databases to select a subset of documents most likely to be relevant
- Stage 2: **Fine filter**
  Read the original documents to identify the most relevant and discard the others. Compare the invention with the documents
- Further searching necessary?

Stage 2: Fine filter

- Study documents in detail
- Do it methodically!

Successful search strategy

- Stage 1: **Coarse filter**
  Develop search statements and screen our databases to select a subset of documents most likely to be relevant.
- Stage 2: **Fine filter**
  Read the original documents to identify the most relevant and discard the others. Compare the invention with the documents.
- Further searching necessary?

Continue search yes/no?

- How successful already?
- How much time spent/left?
- How many databases tried?
- How many queries tried?
- How likely is future success?

Further searches

- Modify query
  - less restrictive queries
  - more restrictive queries
- Citation hopping

Modify query

CLAIMS

1. A crystalline form κ of Rifaximin, characterised by a powder XRD spectrum with peaks at values of the angle 2θ of 5.3°, 6.8°, 7.8°, 8.5°, 9.3°, 10.1°, 10.3°, 12.1°, 12.7°, 13.4°, 13.7°, 14.6°, 15.3°, 15.8°, 16.4°, 16.9°, 17.7°, 18.0°, 18.8°, 19.2°, 19.7°, 20.3° and 22.1°.

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?     80621-81-4/rn

L1          1 80621-81-4/RN
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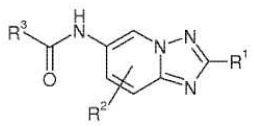
?     80621-81-4/crn

L2         21 80621-81-4/CRN
```

noise or further relevant documents?

Modify query

The invention is concerned with triazolopyridine compounds of formula (I) wherein R1, R2 and R3 are as defined in the description and in the claims, as well as physiologically acceptable salts thereof. These compounds inhibit PDE10A and can be used as medicaments.

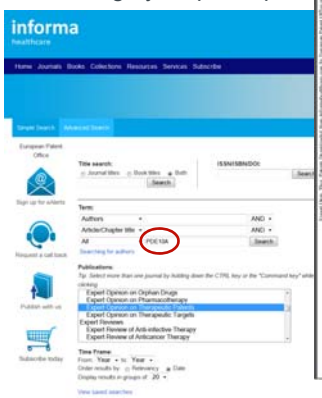


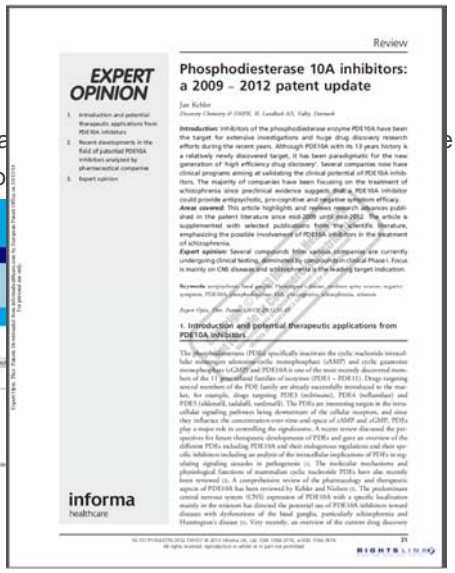
(I)

- Search a broader chemical structure in Registry to find documents potentially relevant not only for novelty but for inventive step as well
- Combine with keywords in Chemical Abstract (receptor, diseases)
- Or do the opposite approach: search a disease first and a structure within said set

Modify query

- Think of bioisosterism
- Look for reviews on a particula
  patent, integrity, Expert Opinio



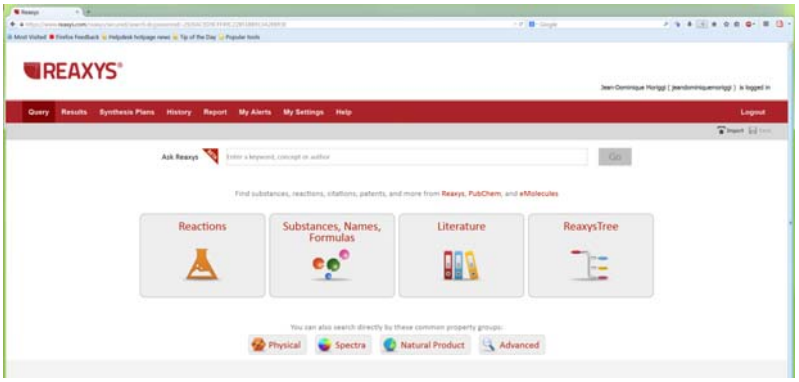


Citation hopping

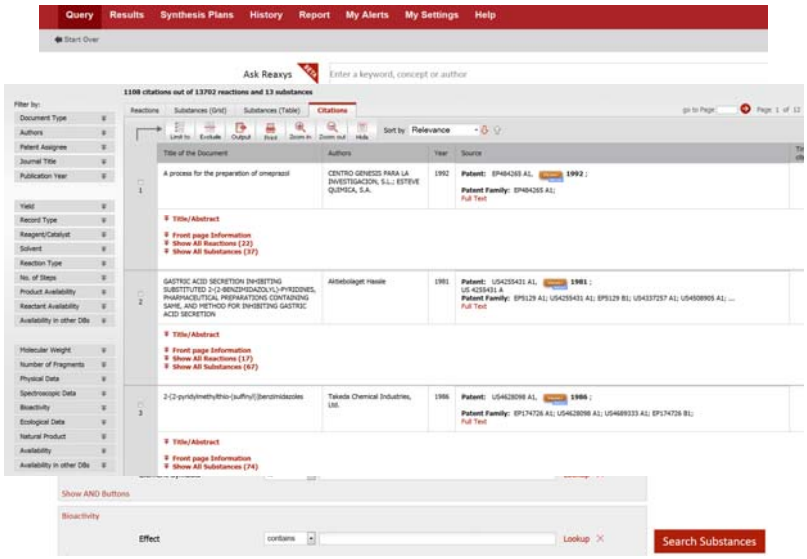
If possible, use regularly and iteratively until no further new or interesting documents turn up

Reaxys

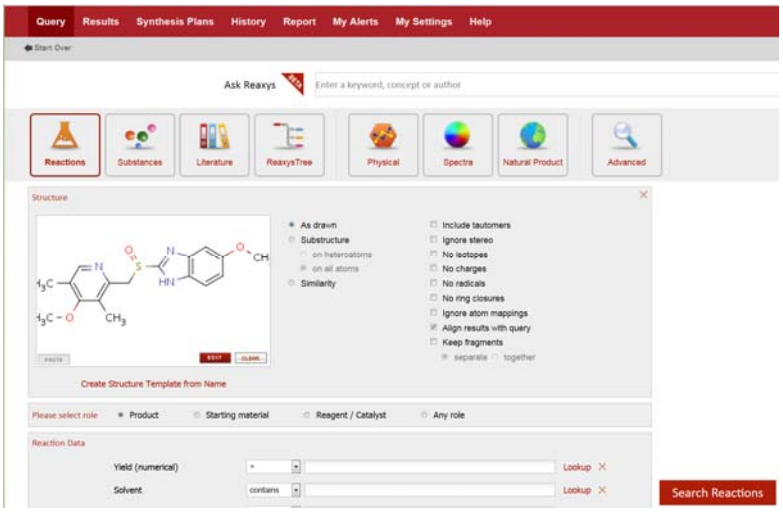
Reaxys @ www.reaxys.com covers 400 journals and chemistry patents with the International Patent Classes C07, A61K, A01N and C09B



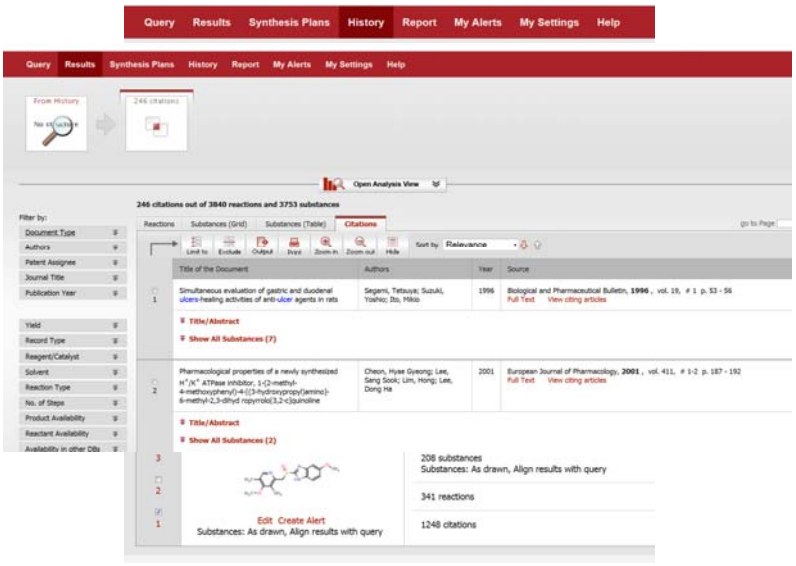
Reaxys - Compounds



Reaxys – Chemical process



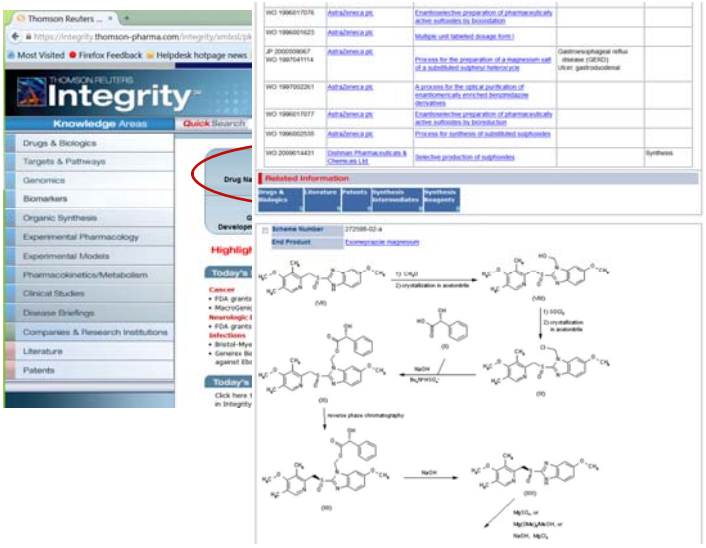
Reaxys – Biological activity



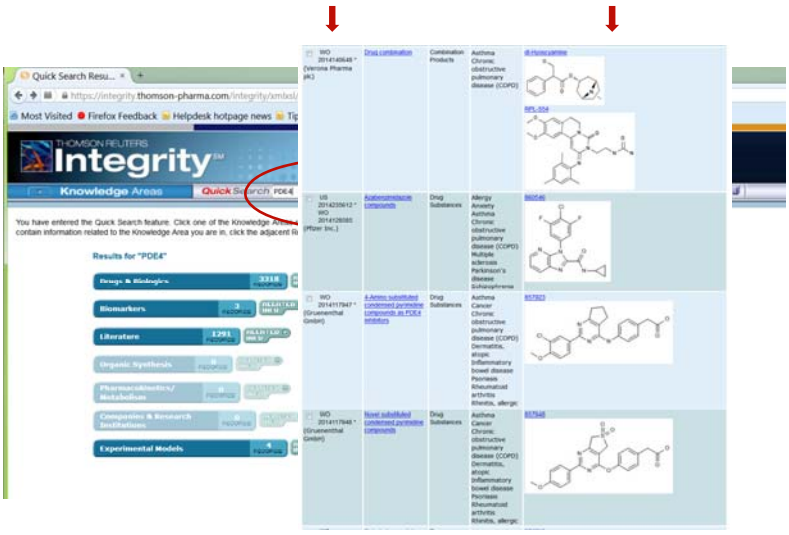
Integrity

- Integrity @ https://integrity.thomson-pharma.com encompasses essential information on over 380,000 bioactive compounds, 24,000 synthesis schemes, 8,000 companies and research institutions, etc.
- Patent offices covered include WO, EP, US, JP, CN, KR, and IN.

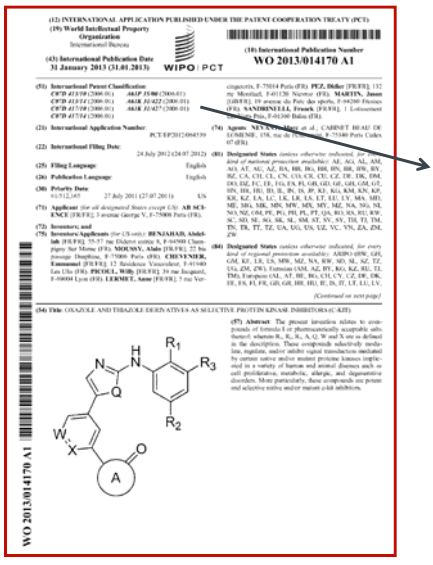
Integrity – Chemical process



Integrity – Biological activity



Classification



C07D: heterocyclic compounds

A61K31: medicinal preparations containing organic active ingredients

(**A61P:** specific therapeutic activity of chemical compounds or medical preparations)

Classification

- 1991: all documents classified via EC codes according to European Classification only. Additional indexing system of "In Computer Only" codes (ICO codes) was also developed
- 01 January 2013: EPO replaced EC and ICO by a joint classification system co-owned with USPTO and called the Cooperative Patent Classification (CPC)
- The structure of the CPC Scheme and Definitions is generally similar to that of the IPC
- Unless otherwise stated, CPC structure, rules and principles are identical to the IPC ones
- The general policy of CPC is to follow the current IPC and to progressively reduce any divergence between the two systems

Classification

- **CPC databa**

The text of CP

Examples

? ..fi CPC
? /cc A01B
? ..li
? /cch A01
? ..li

- **Internet**

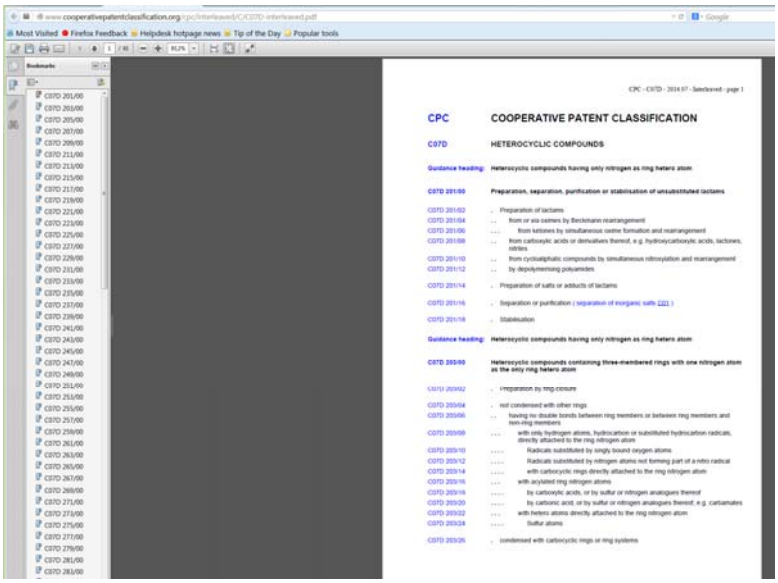
PDF versions of the CPC scheme and definitions are available on the official page of the CPC:

http://www.cooperativepatentclassification.org/cpcSchemeAndDefinitions/table.html

The CPC can also be searched and browsed on Espacenet:

http://worldwide.espacenet.com/classification

Classification



Köszönöm a figyelmet!

Van kérdés?

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