



ADVANCED SEARCHING CHEMICAL STRUCTURES IN PATENTS

IP SOLUTIONS

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THOMSON REUTERS

OUTLINE

- WHAT IS A PATENT?
- WHAT IS A MARKUSH STRUCTURE?
- CASE STUDY; A TYPICAL PATENT SEARCH INVOLVING CHEMICAL STRUCTURES

WHAT IS A PATENT?

- A patent is an agreement between inventors and the government in which the inventor is given an exclusive, monopoly right to make use of and exploit their inventions for a limited period of time. The patent owner has the legal authority to exclude others from making, using, or selling the claimed invention in that country without their consent, for a fixed period of time.
 - This authority does not extend to any other country. A patent needs to be obtained in each country where protection is sought.
- In exchange for the privilege of monopoly, the owner of the invention agrees to disclose the complete details of the invention.

WHAT IS A PATENT? (contd.)

- When an inventor seeks patent protection, she must submit an application to the patent office of the country in question. The application must show the details of the invention that can be understood by anyone who is skilled in that particular technology. It must be written in order to allow the invention to be duplicated.



A PATENT IS BOTH A LEGAL DOCUMENT AND A SCIENTIFIC PAPER.

- It gives technical details describing the invention, including drawings, diagrams or chemical formulas, and is enforceable in court.



US006087380A

United States Patent [19] [11] **Patent Number:** 6,087,380
Huel et al. [45] **Date of Patent:** *Jul. 11, 2000

[54] DIS
HET
ANE
PHA

EXAMPLE 1

[75] Inven 3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid -N-phenyl-N-(2-ethoxycarbonyl)ethyl)-amide

[73] Assig a) Methyl 6-methylamino-5-nitro-nicotinate
1.6 g (7.4 mMol) of methyl 6-chloro-5-nitro-nicotinate (see Bernie et al. in J. Chem. Soc. 1951, 2590) were stirred in 20 ml of 40% aqueous methylamine solution at room temperature for 30 minutes. The reaction mixture was then diluted with ice water, the yellow precipitate formed was filtered off and dried. Yield: 1.2 g (80% of theory), R_f value: 0.66 (silica gel; ethyl acetate/ethanol/glacial acetic acid=90:5:5)

[21] Appl
[22] Filed
[60] Provi
[30] b) Methyl 5-amino-6-methylamino-nicotinate
To a solution of 3.1 g (15 mMol) of methyl 6-methylamino-5-nitro-nicotinate in 100 ml of ethanol/dichloromethane (3:1) was added 1 g of palladium on charcoal (10%) and the resulting suspension was hydrogenated at room temperature under 5 bar of hydrogen pressure for 1.5 hours. The catalyst was then filtered off and the solvent was distilled off in vacuo. The crude oily product obtained was further reacted directly. Yield: 2.4 g (92% of theory), R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia=90:10:1)

[51] Int.
[52] U.S.
[58] Filed
[56] c) Methyl 5-[2-(4-cyanophenyl)ethylcarbonylamino]-6-methylamino-nicotinate
A solution of 2.6 g (15 mMol) of 3-(4-cyanophenyl) propionic acid in 25 ml of absolute tetrahydrofuran was mixed with 2.4 g (15 mMol) of N,N'-carbonyldiimidazole

4,675,4
5,416,0

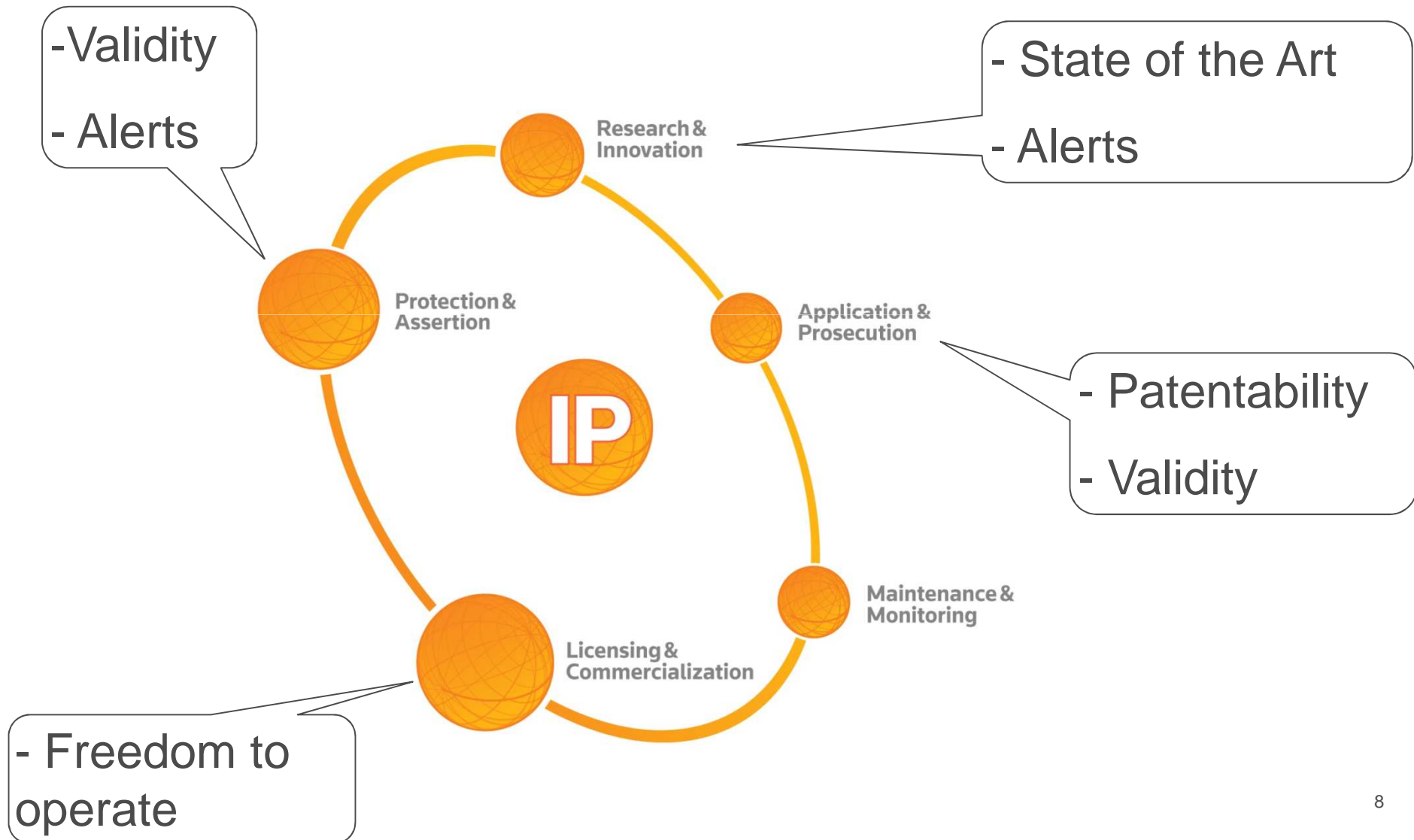
CATEGORIES OF INFORMATION IN A PATENT

- **MONOPOLY RIGHTS** the legal limits which define how close another invention may come to the patented one before the inventor's rights are infringed.
- **TECHNICAL INFORMATION** this may include the nature of a manufacturing process, the composition of a new drug, the design of new pieces of machinery, etc. Such information helps to stimulate further progress on new ideas. At the same time, its availability avoids wasting time and money repeating already patented work. The monopoly right is given only in return for the disclosure of the invention in sufficient detail to enable someone "skilled in the art" (i.e. experienced in that particular craft or manufacture) to carry out the invention himself.
- **TECHNOLOGICAL INTELLIGENCE** much can be learned about industrial organizations from a study of their patents.

WHY SEARCH PATENTS

- In order to be patentable in the US, an invention has to be **NEW, USEFUL and UNOBVIOUS**. Therefore, the **patent literature is full of useful and practical ideas**
- **Patent information is current**, because (in most of the world) disclosure before patent application renders the invention unpatentable.
- **Studies have shown that 70-90% of the information in patents is never published anywhere else.**
- **The technical content of a patent is often available in your local language**, because protection in your country must be obtained in your country's patent office.

SEARCHING THE IP LIFECYCLE



TYPES OF PATENT SEARCHES



- State-of-the-art research
- Collection searches with categorization
- Competitive and technical landscaping
- Alerts
- FTO

- Patentability / Novelty searching
- Accelerated Examination

- Legal status searches
- Patent family searches
- Patent watches

- Validity
- Assignee searching to identify target licensees

- FTO
- Validity/opposition research
- Claim strength analysis
- Patent watches

OUTLINE

- WHAT IS A PATENT?
- WHAT IS A MARKUSH STRUCTURE?
- CASE STUDY; A TYPICAL PATENT SEARCH INVOLVING CHEMICAL STRUCTURES

A MARKUSH STRUCTURE HAS A FIXED “SCAFFOLD” AND VARIABLE PARTS



IT IS A CONVENIENT WAY OF ENUMERATING MANY POSSIBLE **SPECIFIC EMBODIMENTS**

- Describe the invention or structure as a Markush instead of saying

Either



or



or



or any of the other possible combinations and permutations

A MARKUSH CHEMICAL STRUCTURE HAS A FIXED “SCAFFOLD” AND VARIABLE PARTS

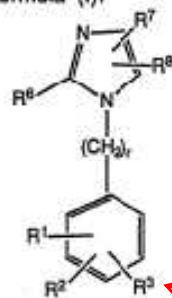
WO 91/14367

32

PCT/US91/00479

CLAIMS:

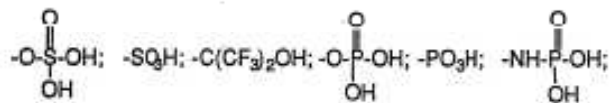
1. A method of treating a central nervous system
 5 (CNS) disorder mediated by AII in a mammal, comprising administering to the mammal an effective amount of a compound having the formula (I):



(I)

wherein

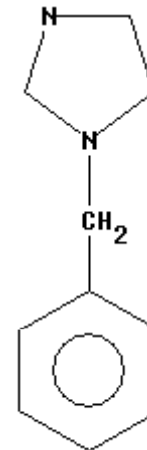
10 R¹ is 4-CO₂H; 4-CO₂R⁹;



15

4-NHSO₂CH₃; 4-NHSO₂CF₃; -CONHOR¹²;

- The fixed scaffold

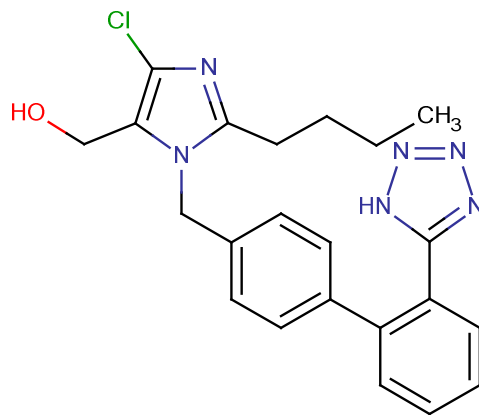


- The variable parts (only some highlighted)

- The actual claim takes 12 pages!

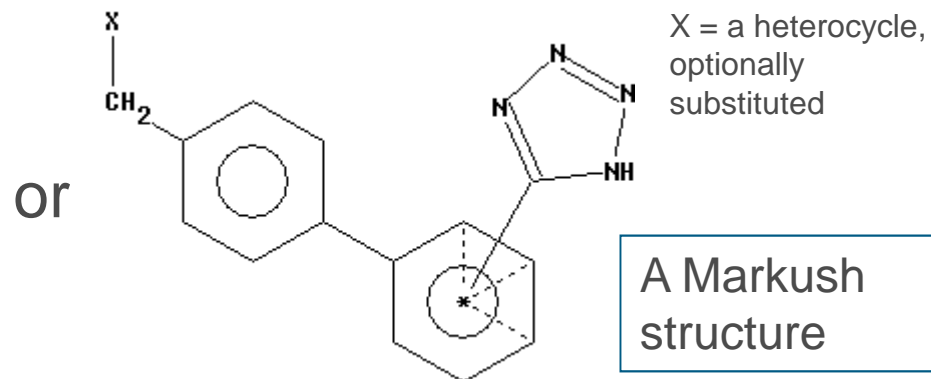
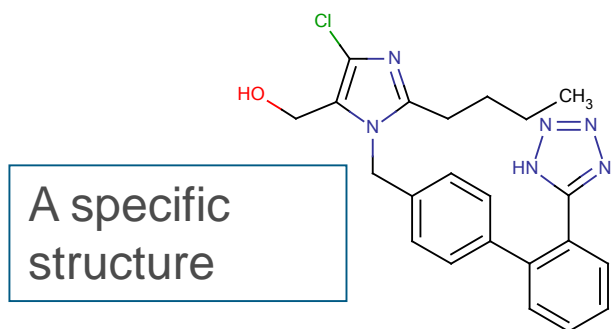
IT IS A CONVENIENT WAY OF ENUMERATING MANY POSSIBLE **SPECIFIC** EMBODIMENTS

- If the Markush structure from the previous slide had 11 possible values (e.g. R1 could be just the values on the previous page, not the 30++ in the actual patent) and 10 of those structures were printed per page, it would require a stack of paper OVER 2,000,000 miles tall.
- Only one of them is Merck's blockbuster losartan (Cozaar and Hyzaar).



THE PROBLEM

- Given a specific structure, or a range of a specific structures, how do you make sure you know whether what you have is patented or clear from patents?
- That is, how do you know if



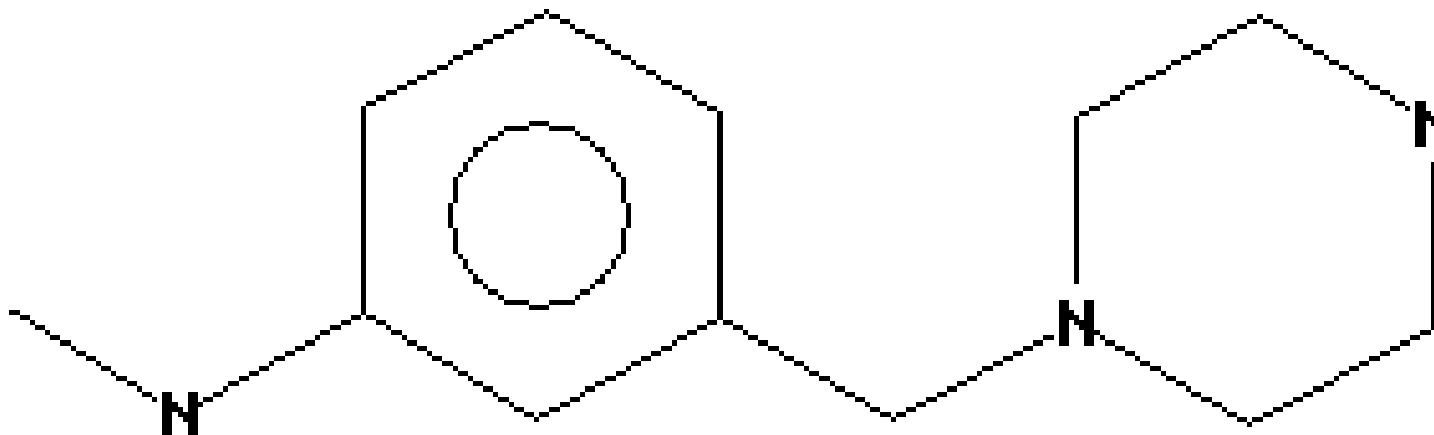
is covered by existing patents? (which is especially tough in the very likely event that the patents do not mention our structures by name!)

OUTLINE

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- WHAT IS A MARKUSH STRUCTURE?
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CASE STUDY; A TYPICAL PATENT SEARCH

- Have compounds containing structure I (below) been disclosed before?
 - If so, have they been disclosed for the treatment of diabetes? Schizophrenia?



I

(ONE OF SEVERAL WAYS TO ENTER A QUERY)

The screenshot shows the Instant JChem 5.5.1 interface. The main window displays a 'Grid view for VMNs' with a table containing columns for 'Cdtid', 'Markush structure', and 'Markush st'. A 'Substructure' button is circled in red in the table. An 'Edit molecule' dialog box is open, showing a chemical structure of a piperidine ring connected to a benzene ring with a methyl group. The dialog box has a menu bar (File, Edit, View, Insert, Atom, Bond, Structure, Tools, Help) and a toolbar with various drawing tools. A vertical toolbar on the right contains element buttons for H, C, N, O, S, F, P, Cl, Br, and I. At the bottom of the dialog box are 'Set Query' and 'Cancel' buttons.

Click here to draw a structure

- 1- Draw the structure
- 2- Click on Set Query
- 3- Search

vmns: 58

Output

18

THE RESULTS;

Instant JChem 5.5.1

File Edit View Search Data Lists Tools Window Help

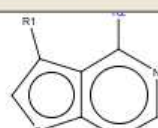
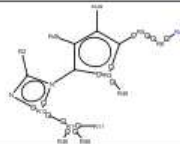
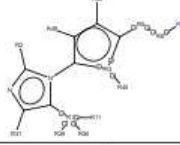


55 / 121

localdb [as admin]

- VMNs
 - Grid view for VMNs
- examples
 - Grid view for examples
 - Form view for examples
- Inventions
 - Grid view for Inventions
 - Form view for Inventions
- Inventions Examples
- Markush Numbers
 - Grid view for Markush Numbers
- V Examples
- README.txt

Welcome x Grid view for VMNs x

Query Browse

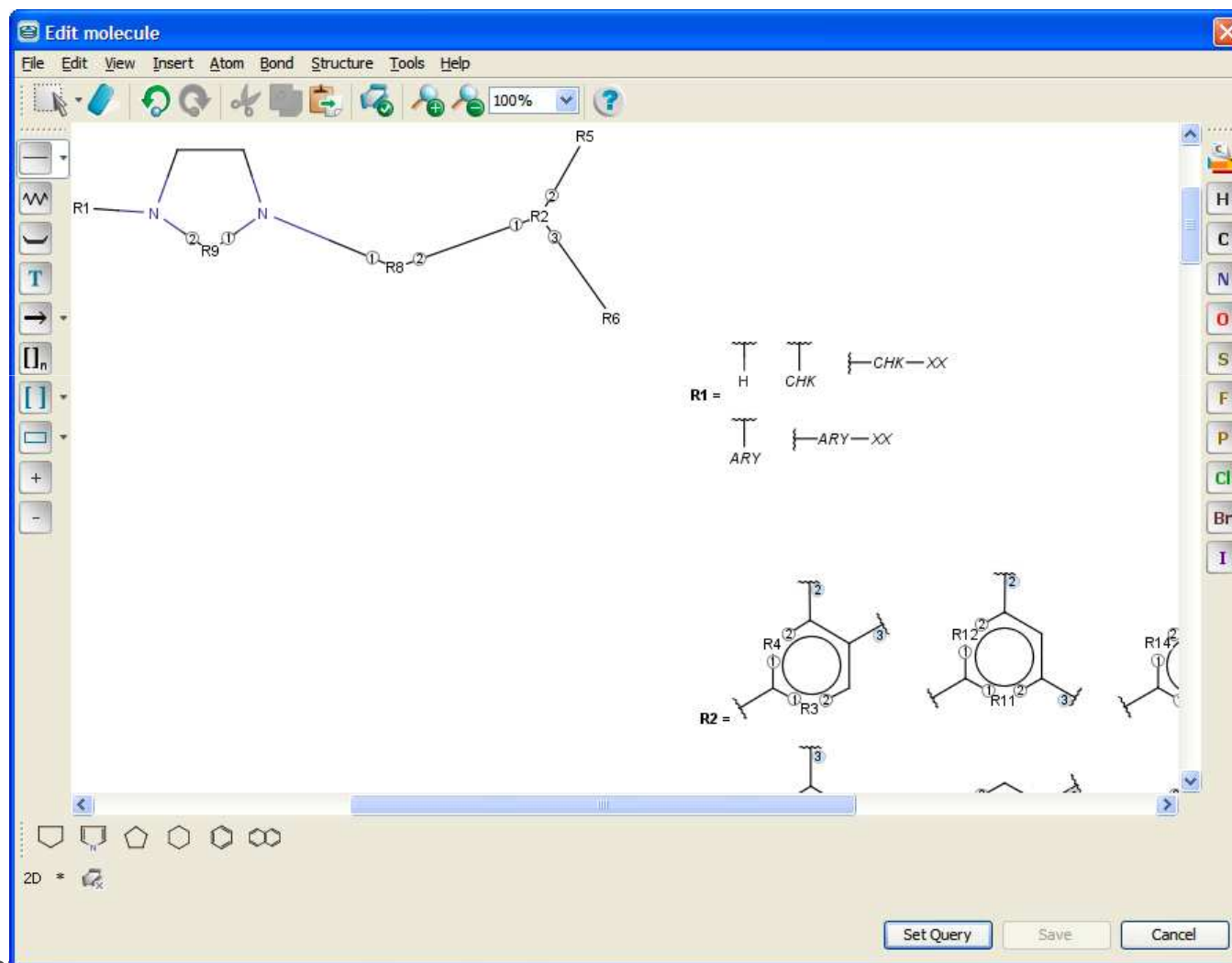
CdId	Markush structure	Markush structure number	path	enum count	Invention ID
51		0330-88101	woa1/2006/07/19/88mrk001.vmn	902704965	2006-503012
52		0331-02901	woa1/2006/07/87/75mrk001.vmn	-1	2006-513563
		0331-02902	woa1/2006/07/87/75mrk002.vmn	-1	2006-513563
		0331-02903	woa1/2006/07/87/75mrk003.vmn	-1	2006-513563
55		0331-69601	woa1/2006/08/13/32mrk001.vmn	381600	2006-539401

vmns: 121 out of 584 rows.

Output

What is the full value of this structure?

(SOME OF) THE FULL DEFINITION OF THIS STRUCTURE



EASY TO COMPARE THE QUERY STRUCTURE TO THE ANSWER STRUCTURE

Instant JChem 5.5.1

File Edit View Search Data Lists Tools Window Help

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Project: localdb [as admin]

- VMNs
 - Grid view for VMNs
- examples
 - Grid view for examples
 - Form view for examples
- Inventions
 - Grid view for Inventions
 - Form view for Inventions
- Inventions Examples
- Markush Numbers
 - Grid view for Markush Nu
- V Examples
- README.txt

Welcome x Grid view for VMNs x Markush Enumeration x

Markush structure

Query structure

Enumerate Display Filter Output

Alignment: Off On Partial clean

Colouring

Show R-groups

Enumerate

MarvinView

File Edit View Tools Pages Help

Query structure

Target structure

Specific examples of the Markush structure ALIGNED TO EASILY COMPARE TO QUERY

Output

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RESULTS CAN BE FILTERED TO FIND THE MOST INTERESTING COMBINATIONS

The screenshot displays the Instant JChem 5.5.1 interface. The main window shows a 'Markush Enumeration' task. The 'Markush structure' panel contains a template with substituents R1, R2, and R5. The 'Query structure' panel shows a specific chemical structure. A 'Chemical terms filter' dialog box is open, listing various filters such as 'Bioavailability', 'Ghose filter', 'Lead likeness', 'Lipinski rule of 5 (3 of 4)', 'Lipinski rule of 5 (4 of 4)', 'Muegge filter', and 'Rule of 3'. The 'Output' panel at the bottom shows a grid of generated chemical structures, with a button labeled 'Generated 40 structures'.

Instant JChem 5.5.1

File Edit View Search Data Lists Tools Window Help

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Project: localdb [as admin]

- VMNs
 - Grid view for VMNs
- examples
- Inventions
- Inventions Examples
- Markush Numbers
- V Example
- README.txt

Welcome x Grid view for VMNs x Markush Enumeration x

Markush structure

Query structure

Enumerate Display Filter Output

Post-enumeration Chemical Terms filter:

Double click to edit ...

Chemical terms filter

Chemical terms expression Favourites...

- Favourites...
- Bioavailability
- Ghose filter
- Lead likeness
- Lipinski rule of 5 (3 of 4)
- Lipinski rule of 5 (4 of 4)
- Muegge filter
- Rule of 3

OK Cancel

Generated 40 structures

Output

VERY IMPORTANTLY, RESULTS CAN BE EXPORTED IN MACHINE READABLE FORM

Instant JChem 5.5.1

File Edit View Search Data Lists Tools Window Help

55 / 121

Proj... Lists and que... Welcome x Grid view for VMNs x Markush Enumeration x

localdb [as admin]

- VMNs
 - Grid view for VMNs
 - examples
 - Inventions
 - Inventions Examples
 - Markush Numbers
 - V Examples
 - README.txt

Markush structure

Query structure

Enumerate Display Filter Output

Post-enumeration Chemical Terms filter:

Double click to edit ...

Full enumeration of this structure produces 6230719694472768 (~ 10¹⁶) structures

Output

ChemAxon extended Smiles (*.cxsmiles)
Daylight Smiles (*.smi, *.smiles)
MDL SD file (*.sdf)
ChemAxon MRV format (*.mrv)


BENEFITS OF EXPORTABILITY

- Output of Markush search can be imported into other computational chemistry software automatically, without having to be re-drawn
- Subsequent steps can be used to calculate suitability of Markushes or specifics for drugs or other applications
- HUGE time saver



AND OF COURSE YOU CAN FIND THE PATENTS CONTAINING THE STRUCTURE

The screenshot displays the Instant JChem 5.5.1 software interface. The main window shows a search for a chemical structure in a patent database. The search results are displayed in a table with the following data:

Cld	Markush structure	Markush structure number	enum count
1		0331-69601	381600

The interface also shows the following information:

- ID:** 2006-539401
- Title:** New substituted arylamine compounds are 5-hydroxytryptamine receptor modulators
- Assignees:** EPIX DELAWARE INC (EPIX), PREDIX PHARM HOLDINGS INC (PRED)
- Patents:** WO2006081332-A1 *, US20060205737-A1, NO200704324-A, AU2006209216-A1, EP1856075-A1

At the bottom of the window, a status bar indicates: "Inventions: 67 out of 300 rows. vmns: 1 out of 584 rows. V Examples: 28 out of 9,680 rows."

THE MARKUSH IN THE PATENT MATCHES OUR QUERY AS FOLLOWS;

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 August 2006 (03.08.2006)

PCT

(10) International Publication Number
WO 2006/081332 A1

(51) International Patent Classification:
C07D 295/12 (2006.01) C07D 311/68 (2006.01)
A61K 31/495 (2006.01) C07D 317/62 (2006.01)
A61K 31/496 (2006.01) C07D 319/18 (2006.01)
C07D 243/08 (2006.01) C07D 333/66 (2006.01)

(21) International Application Number:
PCT/US2006/002718

(22) International Filing Date: 25 January 2006 (25.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/646,957 25 January 2005 (25.01.2005) US
60/701,853 22 July 2005 (22.07.2005) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:
US 60/646,957 (CIP)
Filed on 25 January 2005 (25.01.2005)
US 60/701,853 (CIP)
Filed on 22 July 2005 (22.07.2005)

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(74) Agent: **KAVANAUGH, Theresa C.**; Goodwin Procter LLP, Exchange Place, 53 State street, Boston, MA 02109 (US).

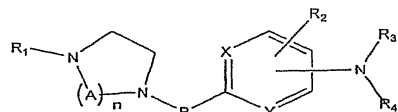
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published: with international search report

[Continued on next page]

(54) Title: SUBSTITUTED ARYLAMINE COMPOUNDS AND THEIR USE AS 5-HT₆ MODULATORS



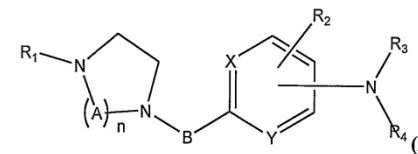
(I)

or alkyl ester thereof; a sulfone; haloalkyl or haloalkoxy; acetaldehyde; carboxamide; carbonyl; alkoxyaminocarbonyl; or substituted arylalkylamino; - R₃ and R₄ independently are hydrogen, substituted or unsubstituted alkyl, aryl, alkylaryl, heteroaryl or alkylheteroaryl, or, taken together, R₃ and R₄ form one substituted or unsubstituted aryl, alkylaryl, heteroaryl or alkylheteroaryl group; - B, when present, is lower alkyl; and - X and Y are independently C or N; and use of these compounds and their pharmaceutical compositions, e.g., in the treatment, modulation and/or prevention of physiological conditions associated with serotonin action, such as in treating obesity, and obesity-related disorders, e.g., cardiovascular disease, digestive disease, respiratory disease, cancer and type II diabetes; and psychological disorders such as schizophrenia, are disclosed.

CLAIMS

What is claimed is:

1. A compound having the formula



5

and pharmaceutically acceptable salts and/or esters thereof, wherein

- n is 0, 1, 2, 3, or 4;

- A, when present is a lower alkyl group;

- R₁ is hydrogen or substituted or unsubstituted alkyl or aryl;

10 - R₂ is hydrogen; halo; nitro; cyano, lower alkoxy; carboxylate salt acid or alkyl ester thereof; a sulfone; haloalkyl or haloalkoxy; acetaldehyde; carboxamide; carbonyl; alkoxyaminocarbonyl; or substituted arylalkylamino;

- R₃ and R₄ independently are hydrogen, substituted or unsubstituted alkyl, aryl, alkylaryl, heteroaryl or alkylheteroaryl, or, taken together, R₃ and R₄ form one substituted or unsubstituted aryl, alkylaryl, heteroaryl or alkylheteroaryl group;

15

- B, when present, is lower alkyl; and

- X and Y are independently C or N.

2. The 15 50. A pharmaceutical composition comprising the compound of claim 1 in an amount effective to treat schizophrenia, and a pharmaceutically-acceptable carrier.

3. The 51. A method of treating schizophrenia, comprising administering to a patient in need thereof a pharmaceutical composition comprising the compound of claim 1 in an amount effective to treat the schizophrenia.

4. The 52. A method of treating schizophrenia, comprising diagnosing a patient in need of treatment and administering to a patient in need thereof a therapy including a pharmaceutical composition comprising the compound of claim 1 in an amount effective to treat the schizophrenia.

5. The 53. A method of treating an obesity-related disorder, comprising administering to a patient in need thereof a pharmaceutical composition comprising the compound of claim 1 in an amount effective to treat the obesity-related disorder.

6. The 54. The method of claim 53, wherein the obesity-related disorder is selected from the group consisting of cardiovascular disease, digestive disease, respiratory disease, cancer and type II diabetes.

SOME FOLLOW UP POSSIBILITIES

- **If this were a Patentability search**, the attorney will either decide not to file (because the compound we looked for was already claimed) or look for new patentable matter (new syntheses, new uses, ...)
- **If this were a Validity search**, the attorney might ask whether the patent was applied for before or after the invention date, or your filing date. You might have to license this patent.
- **If this were a Freedom to Operate search**, the attorney would ask the legal status of this patent.

SUMMARY

- Patents are both technical and legal documents describing inventions. Inventors have to describe their inventions in sufficient detail for one “skilled in the art” to reproduce it. Patents also allow their owners to prevent others from practicing the invention without permission.
- The patent literature should be searched
 - Before beginning research to assess the state of the art, and keep from “reinventing the wheel”
 - Before applying for a patent to make sure nobody else has disclosed the invention
 - Before practicing the invention to make sure you do not infringe someone else’s patent
 - To test the validity of someone else’s patent
- Chemical patents are especially hard to search because so much of the information is structural rather than text
- The Markush on ChemAxon’s Instant Jchem offer a way of finding chemical structures in patents that are both explicit (e.g. “Amoxicillin”) and implicit (e.g. “Compounds of Formula I where R = ...”)



QUESTIONS?



THANK YOU

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Product Specialist

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