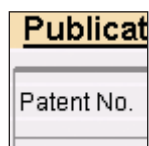


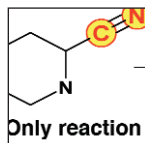
MDL[®] Patent Chemistry Database

Featuring “At the Bench” articles:



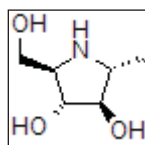
Page 2

Accessing three decades of patent chemistry
(2005 Vol 23 No 1)



Only reaction
Page 4

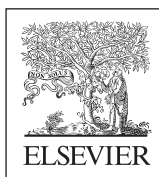
More effective synthesis planning
(2005 Vol 23 No 2)



Page 6

Better bioactivity profiling
(2005 Vol 23 No 3)

The structure-searchable MDL[®] Patent Chemistry Database provides scientists with indexed chemical reactions, substances and substance data from chemistry and life sciences patent documents (World, European since 1978, US since 1976). This series of reprinted articles from *Molecular Connection* newsmagazine demonstrates typical workflow scenarios in which the Patent Chemistry Database can improve the speed and efficiency of synthesis planning and drug discovery efforts.



Access to three decades of patent chemistry

Patents are an important and under-used source of information in chemistry and life sciences research. While many text-based systems exist for accessing patent information, structure-based searching offers a more powerful and flexible way for scientists to mine this vast pool of important information.

To support this need, Elsevier MDL released the new structure-searchable MDL® Patent Chemistry Database, specifically designed for research scientists and information professionals.

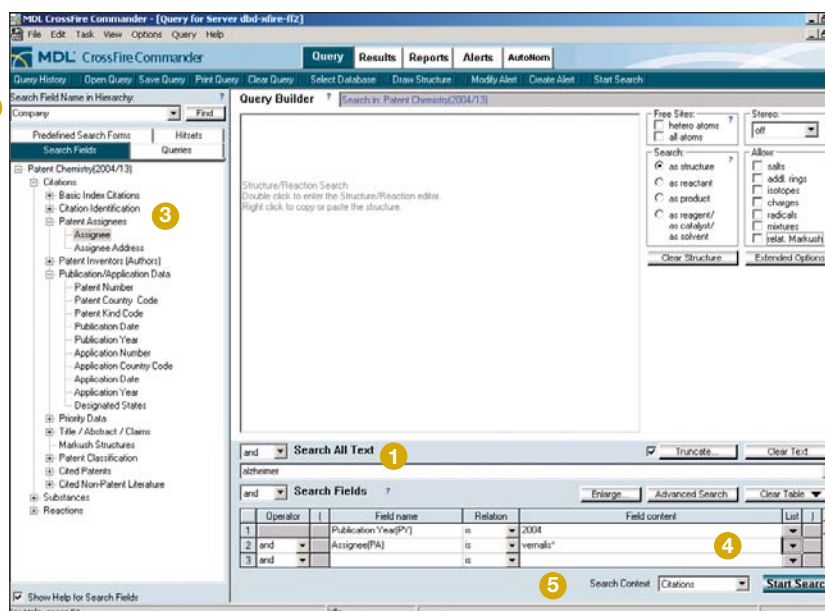


Figure 1 illustrates the steps for querying the Patent Chemistry Database using the MDL® CrossFire® Commander browser. The database can also be accessed through the DiscoveryGate® environment.

- 1 Search All Text:** Enter Alzheimer to search across the complete citation record (title, abstract, claims, etc.). The search system automatically applies left and right truncation (note Truncate check box) to find variants such as “Alzheimers”.
- 2 Search Field Name:** Enter Company and click Find. There is no field name Company, but the database reference guide suggests using the search field Patent Assignee. Use Locate in Tree from the guide menu.
- 3 Select Field Name:** Double click on Patent Assignee in the data field tree to copy this field to the Search Fields grid.
- 4 Enter Field Content:** Enter Vernalis* (use the asterisk to set right truncation and find expressions like “Vernalis Limited”), or select specific company names using the LIST button. Repeat steps 2-4 analogously to specify Publication Year=2004.
- 5 Search Context:** Select Citations from the Search Context drop-down menu to get citation records, which show the front-page data, claims text and all indexed structures and reactions as a hit set. Click Start Search.

Updated every two weeks, MDL Patent Chemistry Database contains about 2.4 million reactions, about 3 million organic, inorganic, organometallic (and polymeric*) compounds and related information from approximately 400,000 organic chemistry and life sciences patent publications (covering U.S. patents since 1976, World and European patents since 1978). The database includes:

- Complete reaction texts for easily checking a reaction’s relevance
- InfoChem ClassCodes to find similar reactions in other databases and group them according to similarity
- Markush reaction display* together with claims text for exploring the scope of a patent and the claimed reactions
- Location (page)* of the reaction in the original patent document for quick reference

The MDL Patent Chemistry Database can assist researchers in monitoring competitors and industry trends, designing new synthetic methods, developing drug profiles and selecting and optimizing leads. The database helps researchers quickly understand the scope and relevance of patents, allowing more effective synthesis planning and better bioactivity profiling.

The MDL Patent Chemistry Database brings patent claim texts and Markush structures/reactions¹ to the desktop in an easy-to-view format, enabling researchers to check the relevance of located patents quickly and easily.

The workflows illustrated on the following pages demonstrate the search capabilities of the database in typical work scenarios such as using reaction searching for more effective synthesis planning (pages 4-5) and structure searching for better bioactivity profiling (pages 6-7).

The scenario beginning on this page introduces a simple text search to see if a company is active in a particular therapeutic area, in this case whether Vernalis Research had any patent applications on anti-Alzheimer agents published in 2004.

Figure 2 displays the results of searching the Patent Chemistry Database for Alzheimer's drug patents assigned to Vernalis Research in 2004. From this, scientists can quickly assess all the relevant information and determine whether this particular Vernalis patent has a bearing on the project under consideration.

- 1 The database highlights the retrieved hit term, the patent assignee name, for clear viewing.
- 2 The database includes a table of the main patent equivalents of a patent family (including the designated states for World and European patents) with each patent number linked to the original patent document.
- 3 To facilitate more effective searches, the complete claim text for the patent can be searched in combination with a structure/reaction search.
- 4 By seeing the claim text alongside the main Markush¹ structures/reactions, scientists can easily check the relevance of a located patent. Right-clicking on the structure formula shows the expanded Markush formula with the complete substituent list. Markush structure search is not possible today.

Patent Assignees

Name	Address
Vernalis Research Limited	Winnersh GB 1

Publication/Application Data 1-4

Patent No.	Kind Code	Publ. Date	Appl. No.	Filing Date	Indexed Patent
WO2001/2409	A1	2001/01/11	WO2000-GB2517	2000/06/30	1
EP1192164	A1	2002/04/03	EP2000-940670	2000/06/30	2
US6787541	B1	2004/09/07	US2002-958948 GB1999-15437	2002/03/13 1999/07/01	yes

Note 1 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CR, CU, CY, CZ, DE, DK, DM, DZ, EE, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GR, OW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KP, KR, IZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MG, MK, ML, MN, MR, MW, MX, MZ, NE, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, SN, SZ, TD, TG, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

Note 2 AL, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LT, LU, LV, MC, MK, NL, RO, SI

Title / Abstract / Claims

Title Thieno- and furopyrimidine derivatives as A2A-receptor antagonists

Abstract Compounds of formula (I), wherein X is S. Compounds can be used for treating a disorder in which the blocking of purine receptors is beneficial.

Claims What is claimed is: 1. A compound of formula (I):
[Figure]
wherein: X is S; R₁ and R₂ are independently selected from hydrogen, alkyl, aryl, hydroxy, alkoxy, arylloxy, cyano, nitro, CO₂R₇, COR₇, OCOR₇, CONR₇R₈, CONR₇NR₈R₉, OCONR₇R₈, NR₇R₈, NR₇COR NR₇CONR₈R₉, NR₇CO₂R₈, NR₇SO₂R₈, NR₇CONR₈NR₉R₁₀, NR₇NR₈CO₂R₉, NR₇NR₈CONR₉R₁₀.

encephalitic Parkinsonism, Parkinsonism induced by poisoning, post-traumatic Parkinson's disease, progressive supranuclear palsy, Huntingtons disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystoma-Parkinsonism, spasticity, Alzheimer's disease or other disorders of the basal ganglia which result in dyskinesias. 40. A method according to claim 27 wherein the subject is human.

Language English
Number of Pages 60
Indexing Status fully indexed

Markush Structures

Markush PRN 3907725, 3907726
PRN=3907725 PRN=3907726

Compressed MARKUSH. Right-click to expand details

Compressed MARKUSH. Right-click to expand details

4

Markush Structure: C1=NC2=C(N1)N=CN=C2C3=CC=CC=C3R1

Label	Value	Size	Attributes	Substituted by	Frequency
R1	H				
R2	H				
R3	H				
R4	H				
R5	H				
R6	H				
R7	H				
R8	H				
R9	H				
R10	H				

More effective synthesis planning

Reaction searching in MDL[®] Patent Chemistry Database

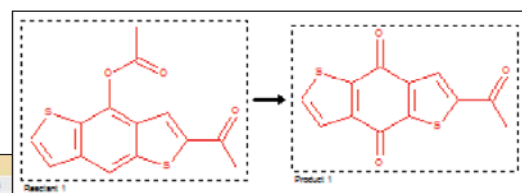
The previous exercise showed how scientists and information professionals can use a text search of the new MDL Patent Chemistry Database to quickly determine if a company is active in a particular therapeutic area.

This scenario illustrates a reaction search in Patent Chemistry Database, and then show how reaction classification with InfoChem ClassCodes enables scientists to rapidly find similar reactions in MDL and other databases that might be useful in synthesis planning.

(The following examples illustrate the use of MDL[®] CrossFire Commander to search Patent Chemistry Database. The database can also be accessed through DiscoveryGate[®].)

Figure 1 illustrates how to query for reactions in the Patent Chemistry Database.

- 1 Click **Select Database** and choose Patent Chemistry Database from the menu.
- 2 Click on **Draw Structure** and then enter the reaction query.
- 3 To perform a substructure search, select **all atoms** under **Free sites**.
- 4 To modify the query, select data fields from the hierarchy tree (click to add).
- 5 Next to **Search Context**, select **Reactions**.
- 6 Click **Start Search**.



Reaction Details	
Topic of Interest	Preparation
Example Name	1
Example Title	1 Example 1 2-Acetyl-4,8-dihydrobenzo[1,2-b:4,5-b']dithiophene-4,8-dione (9)
Example Text	To a stirring mixture of acetyl chloride (5.1 g, 65 mmol) and AlCl ₃ (8.7 g, 65 mmol) in 1,2-dichloroethane (200 mL) under N ₂ was added dropwise a solution of 4-acetoxybenzo[1,2-b:4,5-b']dithiophene (7.7 g) (8 g, 32.3 mmol) in 1,2-dichloroethane (90 mL). After stirring for 4 h, this solution was poured into dilute HCl and the aqueous layer was extracted with CHCl ₃ three times. The combined extracts were washed with saturated NaHCO ₃ and water, dried over anhydrous MgSO ₄ , and concentrated under reduced pressure to give 7.5 g of the crude intermediate 4-acetoxy-2-acetylbenzo[1,2-b:4,5-b']dithiophene (8). To a suspension of crude 8 (7.5 g) in HOAc (30 mL) was added CrO ₃ (5.7 g, 57 mmol). After stirring for 1 h, i-PrOH (20 mL) and CHCl ₃ (300 mL) were added and stirred for 30 min. The resulting solution was poured into ice water, and the aqueous layer was extracted with CHCl ₃ three times. The combined extracts were dried over anhydrous MgSO ₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, CHCl ₃) to give 9 (mp 223-225 deg. C) in a 45 percent yield. IR (KBr) 1850, 1670 (C=O) cm ⁻¹ . ¹ H NMR (CDCl ₃) δ 2.67 (s, 3H, CH ₃), 7.88 (d, J=5.1 Hz, 1H, H-7), 7.74 (d, J=5.1 Hz, 1H, H-6), 8.12 (s, 1H, H-3); ¹³ C NMR (CDCl ₃) δ 26.9 (C-2-CH ₃), 126.9 (C-7), 129.4 (C-3), 134.3 (C-6), 170.0 (C-4), 174.4 (C-8), 190.7 (C-2-C=O); MS m/z 262 (M ⁺). Anal. (C ₁₂ H ₆ O ₃ S ₂) C, 12.9. H, 0.5. S, 86.6.
Location in Patent	3
Product PRN	168333 2-acetyl-4,8-dihydrobenzo[1,2-b:4,5-b']dithiophene-4,8-dione
Yield (percent)	45 %
Purification	4 aqueous workup, column chromatography, silica gel, chloroform
Stage Number	1
Reactant PRN	168335 4-acetoxy-2-acetylbenzo[1,2-b:4,5-b']dithiophene
Reagent PRN	218086 chromium(VI) oxide
Solvent PRN	227897 acetic acid
Time	5 1 h
Ref. 1	6 Frontpage/Claim: 132; Fulltext: LitLink ; Patent: University of North Carolina at Chapel Hill; Publ.: US6337346 B1 (2002/01/08); Appl.: US2000-651357 (2000/08/30)

Figure 2 shows a typical hit record from the reaction search described in Figure 1. From the database record, researchers can quickly evaluate the relevance of a patent.

- 1 **Complete example text** including example number and title as given in the original patent document
- 2 **Spectral data** (including peaks) of the product
- 3 **Location in Patent** specifies the page on which this reaction appears in the original patent publication (available from December 2003)
- 4 **Substance dossier**: a product registry number (PRN) links to the product record with all substance data and related reactions
- 5 **Frontpage/Claim** link leads to the corresponding database citation record including indexed structures and reactions
- 6 **Link to full-text document**: Clicking on **LitLink** connects to the original patent document at a patent provider (e.g., Espacenet, US Patent Server, MicroPatent, Delphion)

The DiscoveryGate reaction collection

MDL Patent Chemistry Database—and all DiscoveryGate reaction databases—are indexed with InfoChem ClassCodes. This classification relates 17 million reactions from different databases, giving researchers the ability to immediately compare a reaction to similar reactions and group similar reactions.

With the simple steps outlined below, scientists planning a synthesis can acquire the entire reaction text of a published reaction and locate an overview of the complete methodology from another database.

In the next issue: Learn how to use the MDL Patent Chemistry Database for better bioactivity profiling.

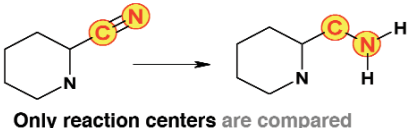
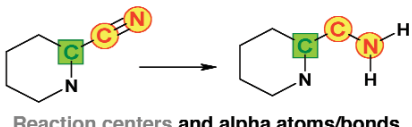
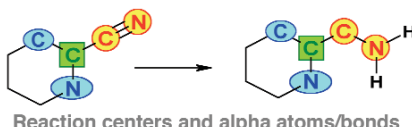
Reaction Similarity	ClassCode
 <p>Only reaction centers are compared</p>	<p>Broad RX.BCODE</p>
 <p>Reaction centers and alpha atoms/bonds are compared</p>	<p>Medium RX.MCODE</p>
 <p>Reaction centers and alpha atoms/bonds and beta atoms/bonds are compared</p>	<p>Narrow RX.NCODE</p>

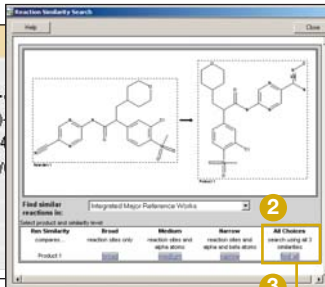
Figure 3 displays the principles of InfoChem ClassCodes.

Three levels of reaction similarity are defined—Broad, Medium and Narrow—depending on whether only reaction centers or also alpha and beta atoms/bonds are compared.

Reactions which are similar with respect to the similarity level have the same ClassCode.

Reaction Identification

Reaction RN	4966189
Reactant PRN	3259400 2-(3-Chloro-(tetrahydro-pyran-4-yl)-
Product PRN	3412781 2-(3-chloro-4-pyrazin-2-yl)-3-(tetrahy
Reaction Specification	full reaction
Entry Date (YYYY/MM/DD)	2004/03/28
Update Date (YYYY/MM/DD)	2004/03/28
Find Similar Reactions	click here



5.21.2.6.1 From nitriles

Nitriles (295) are the most frequently employed starting materials for this class of compounds. They react with hydroxylamine liberated usually from its hydrochloride with sodium carbonate, sodium or potassium hydroxide, or sodium ethoxide and the reaction mixture is kept for several hours at 60–80 °C to give (294) (Equation (85)) [9]. To avoid the separation of the product from sodium or potassium chloride a solution of five hydroxylamine in anhydrous methanol or ethanol is used [130]. The highest yields are obtained when 15% excess of hydroxylamine in benzene is used and the mixture is left for 48 h at 60 °C. The product separates as a practically pure crystalline material [189]. Diamidoximes (297) can, in principle, be prepared according to the same method from dinitriles, such as cyanogen (295) with hydroxylamine or alternatively, from its addition compounds with aniline, for example, diphenylformazine (296), which is treated with hydroxylamine hydrochloride (Scheme 34) [16] [17][26]. The best yields and the purest products are obtained if gaseous cyanogen is led directly in an aqueous hydroxylamine solution at 0 °C [82][CV166]. Polyacryamic amides [172] and polymers containing the acryamic amide function have been prepared from polyacrylonitrile of low molecular weight with a slight excess of hydroxylamine [168] [164].

$$\begin{array}{ccc}
 \text{R-CN} & \xrightarrow[\text{or NaOEt, KOEt, several hours}]{\text{NH}_2\text{OH} \cdot \text{HCl, NaOH or KOH}} & \text{R}-\text{C} \begin{array}{l} \text{NOH} \\ \text{NH}_2 \end{array} & (85)
 \end{array}$$

(295) (294)

Figure 4 shows how to find similar reactions using InfoChem ClassCodes.

- 1 Click the Find Similar Reactions link in a hit record from a reaction search in the Patent Chemistry Database.
- 2 Select the database you want to search (for example, ChemInform Reaction Library, other CrossFire databases, Current Synthetic Methodology, etc.)—in this case, Integrated Major Reference Works.
- 3 Select similarity level: Broad, Medium, Narrow or All Choices.
- 4 The hit record in Integrated Major Reference Works is an expert dossier evaluating the methodology with respect to highest yields and best reaction conditions for specific transformations. ■

Better bioactivity profiling

Export bioactivity data from MDL® Patent Chemistry Database to SAR tables

The ability to quickly find property data for substances of interest and create structure-activity relationship (SAR) tables is important to researchers in the lead discovery process.

This scenario demonstrates this type of bioactivity profiling with MDL Patent Chemistry Database, using the MDL® CrossFire® Commander browser.

How to search substances and their data

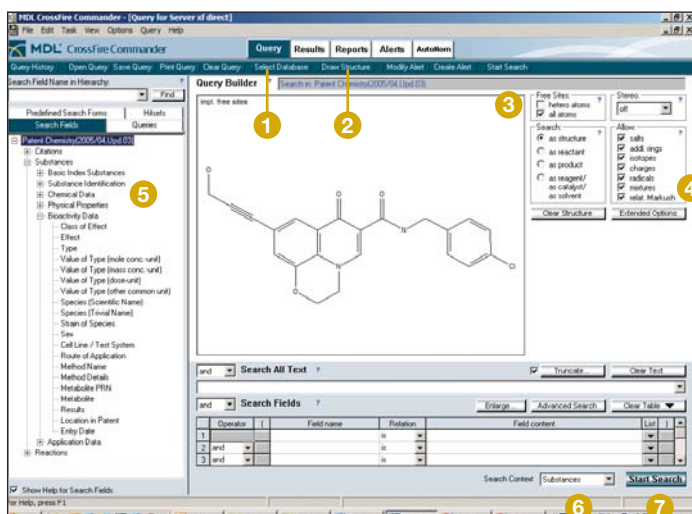


Figure 1 illustrates how to find substance data in the Patent Chemistry Database.

- 1 Click **Select Database** and choose **Patent Chemistry Database** from the menu.
- 2 Click **Draw Structure** and then enter the substance query.
- 3 For a substructure search, select **all atoms** under **Free Sites**.
- 4 Check **Allow related Markush** to get Markush structures that are related to your specific hit structures included in the hit set (this is not a Markush structure search).
- 5 **Data Search:** See the fields in the hierarchy tree, which are indexed in the area of bioactivity/application data.
- 6 Next to **Search Context**, select **Substances**.
- 7 Click **Start Search**.

Viewing the bioactivity and application data of a specific hit substance

Bioactivity Data	
Class of Effect	Pharmacology
Effect	antiviral
Type	IC50
Value of Type (mole conc.-unit)	1.2 µmol/l
Species (Scientific Name)	HCMV polymerase
Method Details	polymerase inhibition; DMSO; dithiotho
Results	inhibition of virus polymerase, IC50&/sub
Location in Patent	Page column 7-8
Ref. 1	Frontpage/Claim: 253, Fulltext: LitLink ; Patent; Pharmacia and Upjohn Company; Publ.: US6340680 B1 (2002/01/22), Appl.: US2000-672472 (2000/09/28)
Application Data	
Area of Use	Pharmaceuticals
Use	Antiviral drug
	compound of a pharmaceutically acceptable salt thereof is useful for treating or preventing a herpesviral infection and cytomegalovirus (CMV) in a mammal
Preferred Route of Application	parenteral, topical, oral, rectal
Preferred Dosage	1 - 30 mg/kg
Location in Patent	Page column 2.8
Ref. 1	Frontpage/Claim: 253, Fulltext: LitLink ; Patent; Pharmacia and Upjohn Company; Publ.: US6340680 B1 (2002/01/22), Appl.: US2000-672472 (2000/09/28)

Figure 2 shows a substance hit record from the search in Figure 1, including measured bioactivity and application data described in patents published since December 2003.

Besides the inhibition concentration shown here [1: Type=IC50], the bioactivity data field also may include effective concentrations (EC50), binding constants for drug-target interactions (K_i), lethal doses (e.g. LD50) and other parameters.

The record shown includes the **Location in Patent** [2], which is the page of the bioassay in the original publication, a **frontpage/claim** link [3] to the database citation record and a link [4] to the original document at a patent provider (e.g. EspaceNet, US Patent Server, MicroPatent, Delphion).

Including the related Markush structures in a hit set

From December 2003 onwards specific substances—real or “prophetic” compounds—are linked to the corresponding “Related Markush Structure” in a given patent publication during the indexing process. Selecting the query option **Allow related Markush** includes these related Markush structures in the hit set. *Note: This is not a Markush structure search.*

Figure 3

In addition to the bioactivity data, the hit substance of Figure 2 shows **Patent-Specific Data** illustrating the **Compound Identifier in Patent** (2) label. In this case it is B-7, which the inventor used in the document to describe the specific compound (1).

Also shown is the **Related Markush Structure** (3), of which the hit substance is a representative. The corresponding Markush structure image appears in compressed form (4). Right clicking on the compressed form opens an expanded form (5).

Viewing the Markush Family

Figure 4

To view other specific examples (real or prophetic) that are representative of the Markush structure (1), click on the Markush link (2) to view the Markush Family (3).

Exporting bioactivity data to a SAR table

All four compounds shown in Figure 4 have bioactivity data (indicated by the red text “Bio” on top of the structure window) that can be easily exported to a structure-activity-relationship table.

Figure 5 shows how bioactivity data can be exported to a SAR table from the **Results** menu (1) using **Export Hits** (2). You can create your own export formats by clicking on **Settings** (3), or use the predefined export formats (4) delivered with CrossFire Commander 7.0 SP2 covering export to structure-data files (SDfiles), Microsoft Word, Microsoft Excel and HTML. To create a SAR table, use the export format **“Substance (Identification, Bioactivity) to SDfile”** (4) and import the SDfile into MDL® ISIS for EXCEL using the menu options **ISIS ⇒ Import ⇒ SDfile to worksheet**.

Structure	Compound RegNo	Molecular Formula	Class of Effect	Effect	Type	Value (mol/Cell)	Species (Scientific Name)	Location in Patent	Citation
	179350	C22H17ClN2O4	Pharmacology	antibial	IC50	1.2	>10M polymerase	Page column 7-8	253 Patent: Pharmacia and Upjohn Company, US 5,135,345 B1, US 5,200,012 C2, Appl. US 2000-07-2472 (2000/09/28)

Figure 6 shows one line of the SAR table created for the four Markush Family structures in Figure 4.

Structure	Compound RegNo	Effect	Type	Value (mol/Cell)	Species	Test System	Method Name	Location in Patent	Citation
	438188	B-glycosidase inhibition of	IS	330	Saccharomyces sp.	B-glycosidase (EC 3.2.1.21)	Kinetic analysis of B-glycosidase inhibition: Analysis of Glycosidase Inhibition Activity With CZE	Page/Page column sheet 3, 16, 22	241125 Patent: 200506976, 200505020, The Scripps Research Institute, US 677480, US 6,120,049 B2, 200404976, 2004 US 2002-803663, 200203242, 2002;
	438205	B-glycosidase inhibition of	IS	50	Saccharomyces sp.	B-glycosidase (EC 3.2.1.21)	Kinetic analysis of B-glycosidase inhibition: Analysis of Glycosidase Inhibition Activity With CZE	Page/Page column sheet 3, 16, 22	241125 Patent: 200506976, 200505020, The Scripps Research Institute, US 677480, US 6,120,049 B2, 200404976, 2004 US 2002-803663, 200203242, 2002;
	438182	B-glycosidase inhibition of	IS	28	Saccharomyces sp.	B-glycosidase (EC 3.2.1.21)	Kinetic analysis of B-glycosidase inhibition: Analysis of Glycosidase Inhibition Activity With CZE	Page/Page column sheet 3, 16, 22	241125 Patent: 200506976, 200505020, The Scripps Research Institute, US 677480, US 6,120,049 B2, 200404976, 2004 US 2002-803663, 200203242, 2002;

Figure 7 shows another SAR table with drug-target interactions showing the structure (1), the test system (5) (here proteins) and the species (4) together with the effect (2) and the corresponding drug-target interactions constants K_i (3). The table also includes the **Location in Patent** (6) where this bioassay appears and the citation (7), including patent assignee and publication/application number and date.

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PAT DBWF/02-06/5k