Patent Landscape Report on

Atazanavir

NOVEMBER 2011

PATENT LANDSCAPE REPORTS PROJECT

WIPO
WORLD INTELLECTUAL PROPERTY ORGANIZATION

The WIPO patent landscape report project is based on the Development Agenda project DA_19_30_31_01 "Developing Tools for Access to Patent Information" described in document CDIP/4/6, adopted by the Committee on Development and Intellectual Property (CDIP) at its fourth session held from November 16 to November 20, 2009.

The purpose of each report is three fold:

- It attempts to research and describe the patterns of patenting and innovation activity related to specific technologies in various domains such as health, food and agriculture, climate change related technologies, and others.
- WIPO attempts to collaborate for each report with institutional partners (IGOs, NGOs, public institutions of Member States) working in the respective field and having an interest in a specific topic. The collaborative work in the planning and evaluation phases may also serve as a vehicle for these institutions to familiarize themselves with the utilization and exploitation of patent information and related issues of patent protection. WIPO welcomes proposals for collaboration.
- Each report also serves as an illustrative example for retrieving patent information in the respective field and how search strategies may be tailored accordingly. It therefore includes detailed explanations of the particular search methodology, the databases used and well documented search queries that should ideally enable the reader to conduct a similar search.

Each report of this project is contracted out to an external firm selected in a tendering procedure. The tender is open to a limited number of bidders that were pre-selected based on their submission of an Expression of Interest (EOI). WIPO invites the submission of further EOIs by qualified providers.

More Information on the project, the ongoing work, and a compilation of reports published also by other institutions is available at: *www.wipo.int/patentscope/en/programs/patent_landscapes/pl_about.html*

For specific information, requests or proposals, please contact us at: patent.information@wipo.int

Patent Landscape Report on Atazanavir

A patent landscape report prepared

for the
World Intellectual Property Organization (WIPO)

by Thomson Reuters
IP Solutions, IP Consulting Group

In cooperation with the

Medicines Patent Pool (MPP)

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Contents

SECTION 1: THE TWO OBJECTIVES OF THE PROJECT

STUDYING DEVELOPMENT OF DRUGS THROUGH PATENTS

The specific example chosen to examine the evolution of the patent environment protecting an approved drug is the HIV drug, Atazanavir (ATZ). The focus is on Atazanavir itself, and excludes inventions that are useful generally for any of a long list of drugs, such as tablet preparation or device-mediated drug delivery.

The technical phases of drug patent protection evolve over many years and include protection of the drug composition *per se,* and later development including processes for synthesis, improvements to process, combination uses for the original indication, diversification to new indications, formulations of value for the specific drug, and so on.

Assignment may also evolve, and there may be different participants in the development of the drug, beginning with the originator of the composition, followed by participation of other entities such as new owners, licensed developer entities, clinical researchers, and others. Generic producers or improvers may also file at later times.

Global spread is a third evolutionary aspect, when development becomes active in many countries, including countries with emerging interest in local pharmaceutical development.

BEST PRACTICES FOR COLLECTING AND ANALYZING PATENTS

The second objective of the project is to provide insight into best practice for probing the patent literature in the pharmaceutical area, including utilization of indexing systems (non-proprietary or proprietary), and harnessing the expert-created[1] system of technical linkages between patents – i.e. the references (citations) between applications or patents and the art that preceded them in time.

ORGANIZATION OF THE REPORT

Using the example of Atazanavir, this report first describes some of the means to assemble collections through which drug development can be reliably studied. Once the collection process is laid out, the report goes on to cover various analytic approaches to probe the

[1] Patent references are created by patent examiners and applicants, each technical experts in the field in which they participate.

collection for nuggets of intelligence. It separates the activity of the developer of Atazanavir (Novartis and its licensee Bristol-Myers Squibb) from activity of other entities, and compares the two across a timeline. It identifies the inventions that reference standard phases of drug development including: composition discovery, establishing biological targets (pathway modulation effects), developing synthetic methods, formulating for treatment, describing best disease indications, investigating combinations, improving synthesis, and broadening uses. While there is a very rough linear relationship between them, new information developed either by the developer or externally can trigger iterations in developmental steps that break down any simple linear picture.

Because combination therapies involving more than one drug are such an integral part of pharmaceutical development, and because that is especially true for AIDS therapies, a separate chapter of the report will focus on combinations.

This report provides an integrated narrative that, at each step, draws attention to how the data elements satisfy the objectives, and explicitly points out the reasoning that allows inferences to be made.

Last, the report presents greater detail on use of various types of indexing and post-filing additions to the patent information.

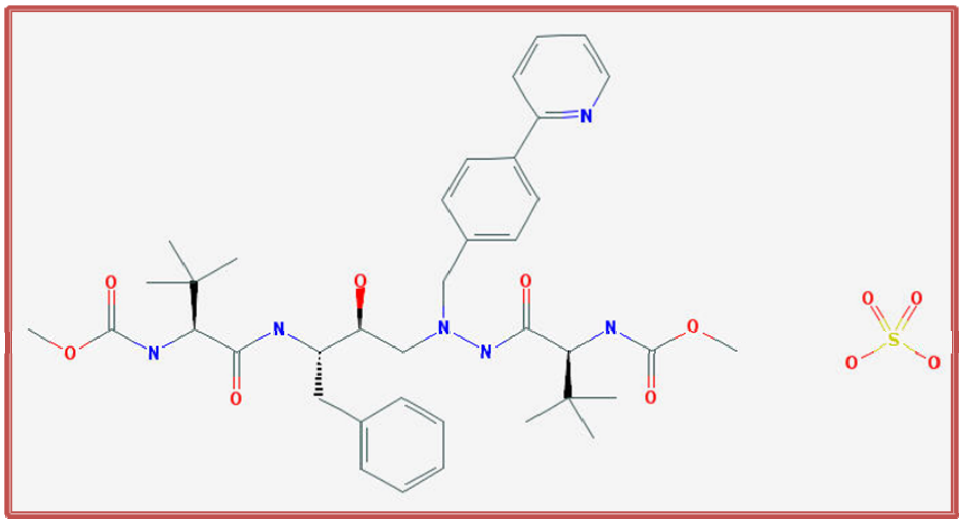
The Report Appendices include specific search strategies, a file containing bibliographic information on the collection and links to the documents, and clinical trials information.

SECTION 2: BUILDING A PATENT COLLECTION COVERING ATAZANAVIR

Atazanavir is a widely-used anti-HIV drug, approved in 2003 for use in treatment of HIV by the United States Food and Drug Administration (FDA). Atazanavir's target (the biomolecule or metabolic pathway that it perturbs) is the enzyme HIV protease, a protein produced from an AIDS virus gene. HIV protease is required for viral maturation. The underlying objective of the inventors was to design a compound that structurally mimicked the natural substrate to which the protease binds, thus preventing it from acting on its normal substrate. Thus Atazanavir belongs to a class of anti-HIV drugs called HIV-protease inhibitors, which are now numerous. The initial "indication" claimed for Atazanavir was HIV treatment, but there may be other indications uncovered through development.

Of course, to find patents about a particular drug, the best way is to search for it by name. This is easier said than done with chemical compounds, and in this section of the report, the "pre-clinical" and "clinical" names will be discussed, along with the strategies for assembling a collection that covers the development of the compound from beginning to end. Having confidence in the quality of the collection is crucial to the subsequent analysis.

Figure 1. Chemical Composition of Atazanavir Sulfate



When the initial patent application was made (1995), the compound in Fig 1 was not known as Atazanavir, which is its current non-proprietary generic name. Generic names are only applied to compounds after they have been approved for clinical investigation. It is usual also for the claims of the initial composition patent to cover not just one composition, but a range of compositions with different substitutions in various sites on the basic backbone structure. The backbone with variable substituents (shown as R groups in the variable positions) is called a Markush structure.

CHEMICAL NAMING

Chemical naming conventions are numerous, and there are many ways to describe the chemical structure of Atazanavir in words. This makes searching by name for patents on Atazanavir before it was given its clinical name more difficult.

The name given by the system of the International Union of Pure and Applied Chemistry (IUPAC) is methyl N-[(1S)-1-{[(2S,3S)-3-hydroxy-4-[(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethyl-N'-{[4-(7yridine-2-yl) phenyl] methyl} butane hydrazido]-1-phenylbutan-2-yl]carbamoyl}-2,2-dimethylpropyl]carbamate.

The inventors themselves created or proposed a range of compounds and referred to them as heterocyclic azahexane derivatives that had any of a number of substituents in 6 places on the basic backbone. (Markush claiming) Among these multiple compounds was the exact compound that later became known as Atazanavir.

Upon publication of chemical papers and patents, the Chemical Abstracts Service gives them identifying numbers known as CAS Registry Numbers[2]. There are other organizations that apply identifiers to chemical compounds, but the CAS system is globally recognized and used very frequently. The CAS Registry Number for Atazanavir is CAS-198904313-31-3.

SUPPLEMENTAL PROTECTION CERTIFICATES

Perhaps unexpectedly, it is usually quite easy to find founder composition inventions for a clinically investigated drug. For drugs, the owner typically files in the European Patent Office for a Supplementary Protection Certificate for the already granted patent, and this application and registration is recorded in the INPADOC Legal Status field (see Figure 2). When the SPC has been registered, the Legal Status field may also include the generic and/or proprietary (brand) name. In this example, searching for Atazanavir or Reyataz in this field finds the founder family, which includes the priority document. This founder patent family is the starting place for developing a "pre-clinical" patent collection that covers other patents by the owner or by others. The founding intellectual property for Atazanavir is a Swiss document that was filed in 1995, and was quickly followed by filings in other countries. The SPC was registered March 2, 2004, and its expiry is March 2, 2019.

This discussion of dates is significant to the searcher, because it identifies a gap between the invention of the drug in 1995 (priority date) and the earliest appearance (in 2001[3]) of the clinical names in patent application text fields other than in the INPADOC Legal Status field. Even in 2001, use of the clinical name for Atazanavir was not necessarily routine. For the

[2] http://www.cas.org/expertise/cascontent/registry/regsys.html

[3] Determined by searching.

Atazanavir example, the period between chemical naming and routine use of the clinical name is from 1995 to at least 2001. It is this gap that is challenging for the searcher to fill because the search strategies using “pre-clinical” chemical names are more difficult to devise and use. We will return to this issue in Chapter 4.

If the SPC approach fails to yield data because of the age of the drug or other factors, there are some alternatives. If the drug is still under patent protection, the relevant patents may be listed in the US FDA Orange Book[4]. The information may also be available from commercial products such as Thomson Reuters Pharma®

Another more laborious approach is to first find patents by the owner of the drug that mention the clinical name, and then perform a backward citation analysis to find the earliest predecessor document that covers the composition. This invention may or may not have been assigned to the owner at the time of its publication, but US reassignment and INPADOC legal status fields may clarify the chain of ownership.

[4] http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

Figure 2: Legal Status for Novartis Founder Patent

Date	Code Type	Country Code	Legal Status Text
27-Jul-05	REG	FI SPCF	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY PROTECTION CERTIFICATE APPLICATION FILED (FI)
05-Aug-05	REG	HK GR +	REFERENCE TO A NATIONAL CODE STANDARD PATENTS GRANTED IN HONG KONG (HK HK1018788)
08-Aug-05	REG	DK CTFF	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY PROTECTION CERTIFICATE FILED (DK)
12-Aug-05	REG	FR CR	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY CERTIFICATE OF PROTECTION LAID OPEN TO THE PUBLIC (EEC REGULATION OF 18 JUNE 1992) (05C0030, 20050705) (FR)
17-Aug-05	REG	GB CTFF	REFERENCE TO A NATIONAL CODE CERTIFICATE FILED (SPC/GB05/036: 20050721) (GB)
24-Aug-05	REG	IE SPCF	REFERENCE TO A NATIONAL CODE REQUEST FOR GRANT OF SUPPLEMENTARY PROTECTION CERTIFICATE (SPC023/2005, 20050728) (IE)
30-Aug-05	REG	SE SPCF	REFERENCE TO A NATIONAL CODE APPLICATION FOR SUPPLEMENTARY PROTECTION CERTIFICATE (0590027-9, 20040302) (SE)
30-Aug-05	REG	SE SPCF	REFERENCE TO A NATIONAL CODE APPLICATION FOR SUPPLEMENTARY PROTECTION CERTIFICATE (PRODUCT NAME: **REYATAZ, ATAZANAVIR;** NAT REG. NO/DATE: EG EU/1/03/267/001 20040302; FIRST REG.: EG EU/1/03/267/001 20040302) (SE)
01-Sep-05	REG	ES FG2A	REFERENCE TO A NATIONAL CODE DEFINITIVE PROTECTION (ES)
03-Oct-05	REG	LU CCP	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY PROTECTION CERTIFICATE (91189, EXPIRES: 20190302) (LU)
03-Oct-05	REG	NL AC1	REFERENCE TO A NATIONAL CODE APPLICATION FOR A SUPPLEMENTARY PROTECTION CERTIFICATE (NL)
14-Oct-05	REG	FR CP	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY CERTIFICATE OF PROTECTION FILED (FR)
01-Nov-05	REG	NL KC1	REFERENCE TO A NATIONAL CODE GRANT OF A SUPPLEMENTARY PROTECTION CERTIFICATE (300203, 20170414, EXPIRES: 20190301) (NL)
10-Jan-06	REG	SE SPCG +	REFERENCE TO A NATIONAL CODE GRANTED SUPPLEMENTARY PROTECTION CERTIFICATE (0590027-9) (SE)
10-Jan-06	REG	SE SPCG +	REFERENCE TO A NATIONAL CODE GRANTED SUPPLEMENTARY PROTECTION CERTIFICATE (SE)
01-Mar-06	REG	GB CTFG	REFERENCE TO A NATIONAL CODE CERTIFICATE GRANTED (SPC/GB05/036: 20060206, EXPIRES: 20190301) (GB)
30-Jun-06	REG	CH SPCG	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY PROTECTION CERTIFICATE GRANTED (PRODUCT NAME: **ATAZANAVIR;** REGISTRATION NUMBER/DATE: SWISSMEDIC 56288 06.05.2004) (CH)
12-Jul-06	REG	IE SPCG	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY PROTECTION CERTIFICATE GRANTED (SPC023/2005, 20060612, EXPIRES: 20190301) (IE
27-Apr-07	REG	FR CY	REFERENCE TO A NATIONAL CODE SUPPLEMENTARY CERTIFICATE OF PROTECTION GRANTED (EEC REGULATION OF 18 JUNE 1992) (PRODUCT NAME: **ATAZANAVIR** ET SES SELS PHARMACEUTIQUEMENT ACCEPTABLES; REGISTRATION NO/DATE IN FRANCE: EU/1/03/267/001 DU 20040302; REGISTRATION NO/DATE AT EEC: EU/1/03/237/001 DU 20040302) (FR)

CLINICAL NAMING

Clinical names are far more usable than chemical names from the searcher's point of view. They are distinctive and crucially, they are the same in any language. These names are the best resource for compiling a collection of patents that could be called "Clinical Collection" because they relate to the drug after it has begun to be tested clinically.

Figure 3. Time Sequence of Drug-Naming

MANUFACTURER NAMING

The inventors of Atazanavir were chemists at Novartis (then Ciba-Geigy). Novartis called the compounds that they were testing CGP-73547, CGP-75355 and CGP-75136. Novartis made an agreement with Bristol-Myers Squibb for further development, manufacturing, and clinical trials work. Bristol-Myers Squibb called the composition being tested BMS-232632, and this name was very commonly used in later publications.

GENERIC NAMING

The name Atazanavir is a non-proprietary generic name that will stay with the drug no matter which company makes or sells its bioequivalents in the future. Atazanavir follows a naming protocol (USAN – United States Adopted Name) that was selected for application to drugs in the same class (HIV-Protease Inhibitors). Usually a US manufacturer submits a candidate for its adopted name when the US FDA has approved an investigational new drug application (IND) and there are clinical trials starting. There is interaction between the USAN Council[5] and the International Nonproprietary Name (INN) Program of World Health Organization (WHO) to coordinate these names globally.

BRAND NAMING

Last, when the drug is tested and approved, it is known by a proprietary (brand) name registered for trademark protection by the company that owns/sells it. During the time when a composition is protected by a patent, only the originating company will have a brand

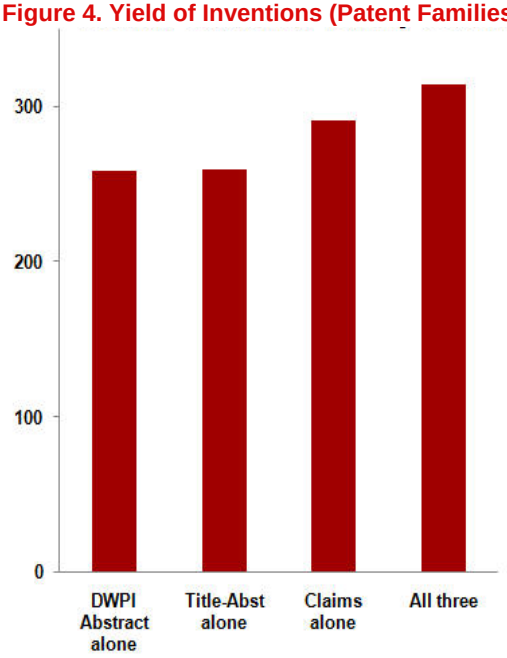
[5] A group co-sponsored by the American Medical Association, the United States Pharmacopeial Convention (USP), and the American Pharmacists Association http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.page

name, but after the patent protection expires, other companies may make the drug and give it other brand names. Atazanavir is still under patent protection, and is known as Reyataz®.

SECTION 3: PREPARING THE CLINICAL COLLECTION

The unique qualities of the clinical names means that they can be used in a search that is quite specific even without employing patent classification codes. The names also have the advantage of crossing many language barriers.

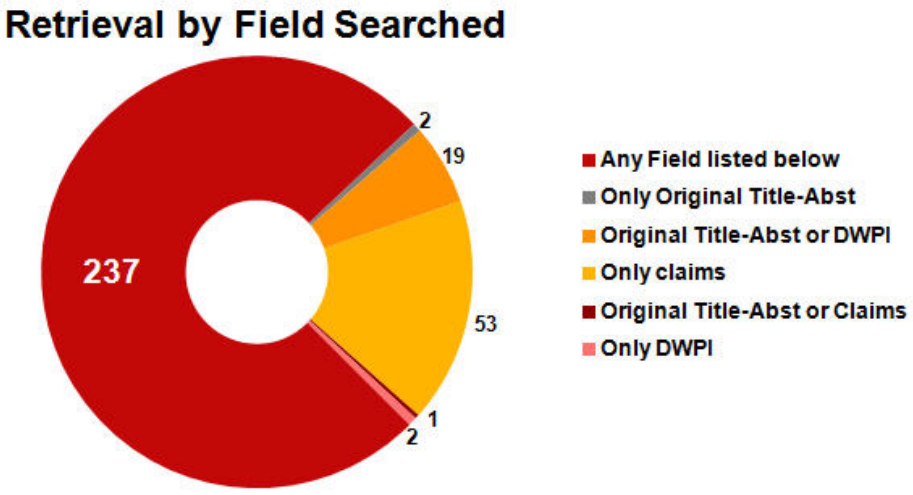
Figure 4. Yield of Inventions (Patent Families)



STAGE ONE STRATEGY

The stage-one strategy shown here uses the clinical names to search within the titles, abstracts and/or claims that are available in either in full text systems or INPADOC databases[6], as well as the Derwent enhanced abstracts (Derwent World Patents Index – DWPI). For the sake of comparability, the results are reported as counts of DWPI invention families. By searching text fields independently, it is possible to show which fields are useful for clinical name searching, and the chart in Figure 4 shows that all are reasonably similar, but that a combination of all three searches is the most complete. The detail on overlap between the collections is shown in Figure 5, and the overlap is atypically high because of the special qualities of clinical names. The text-mining exercise shown on the next page confirms the high relevancy of the documents retrieved with this approach.

Figure 5. Retrieval of invention families by source field



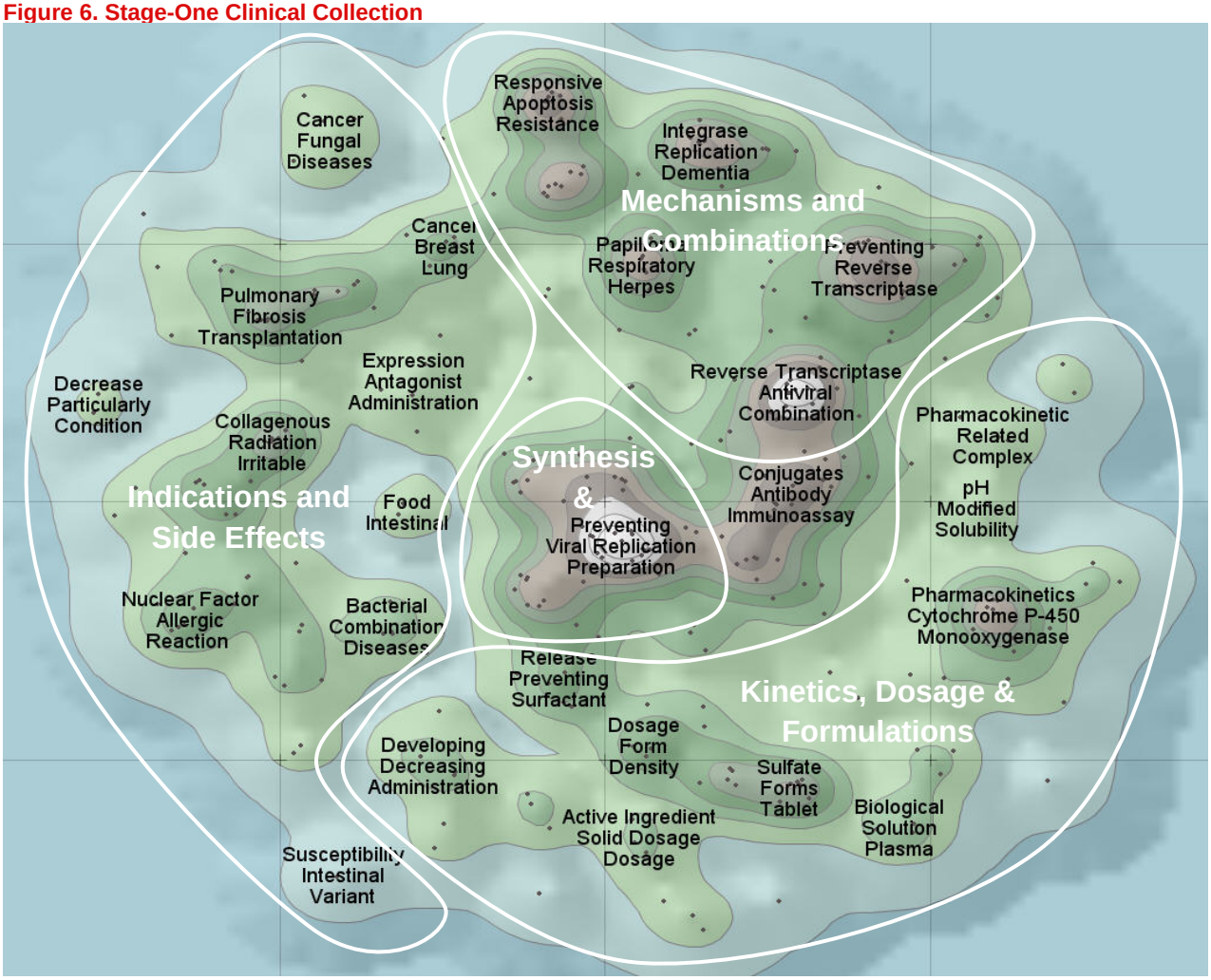
[6] The content that was probed also included the English text available for Asian documents on the Thomson Innovation platform.

A quickly-obtained overview of the contents of the initial (stage-one) clinical collection is provided by this map, covering the 314 patent families that were retrieved by using clinical names to search in the title, abstracts, claims, and DWPI enhanced abstracts. All of these documents contain one or more of the names Atazanavir, Reyataz or the BMS or CGP testing names within a title, abstract, claims (i.e., a field that indicates the term is central to the invention).

ThemeScape® map algorithms operate on the DWPI enhanced abstracts (all in English) to find relationships based on shared terminology, and cluster the documents according to their terminology-relatedness. Each dot on the map represents one invention family, and each is placed on the map only once. Density is conveyed by pseudo-altitude. The axes are arbitrary, but distance is a representation of relatedness or lack thereof.

The map of the stage-one collection shows that there are many documents related to methods and synthesis (snow-capped peak indicates high density) and that there are 3 other general areas covering a) mechanisms of action and the use of combinations to attack more than one target, b) drug behavior in patients and management of dosage, especially in the face of susceptibility to cytochrome P-450 monooxygenase, and c) managing side effects in various organ systems, and usage of drug in different clinical settings.

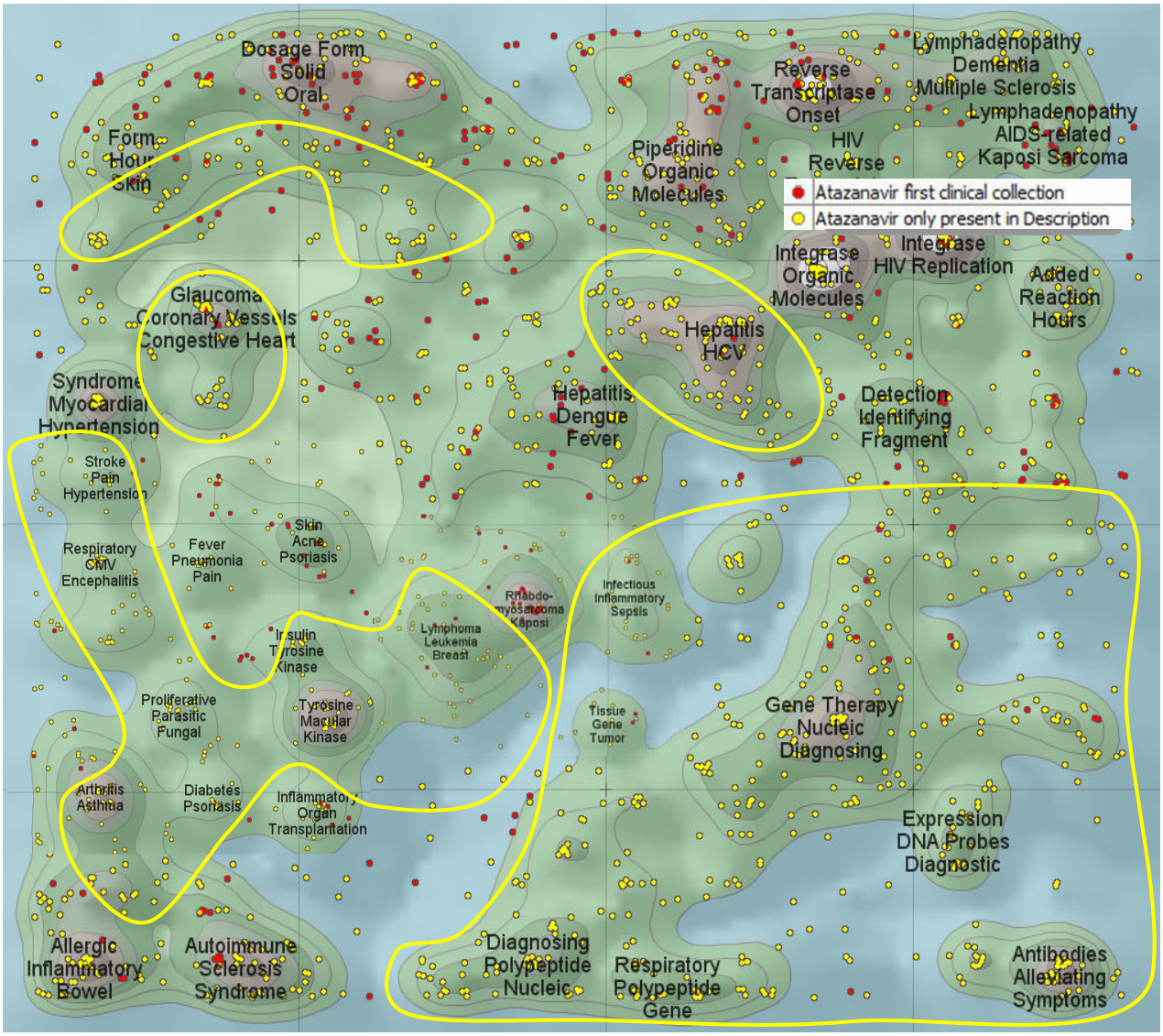
Figure 6. Stage-One Clinical Collection



STAGE TWO CLINICAL SEARCH

To be more comprehensive, it was necessary to search for clinical names in the description (specification) section of the document as well, though this opens the possibility of adding significant “noise” to the collection. Unlike the rather targeted result that was obtained from searching titles, abstracts, claims or enhanced abstracts, searching the description field with the clinical names returned a 6-7 fold higher number of invention families (either Inpadoc or DWPI families), but this retrieval was likely to include a high fraction of documents outside the desired scope. To diagnose the quality of the collection, the ThemeScape map below shows the Stage-One documents and the new documents added by the Stage-Two search mixed together. There are large regions in the map where very few inventions of the Stage-One collection are located (areas outlined in yellow). If we assume Stage-One is an indicator of higher relevance, that means the relevance in Stage-One-poor areas of the map is questionable. It is clear that the documents retrieved by searching the description need to be reviewed to remove those that are not truly oriented toward Atazanavir development. This is where use of either classification codes or other filtering methods becomes critical.

Figure 7. Stage-Two Clinical Collection – Map shows collection improvement is needed



Removal of major off-topic areas

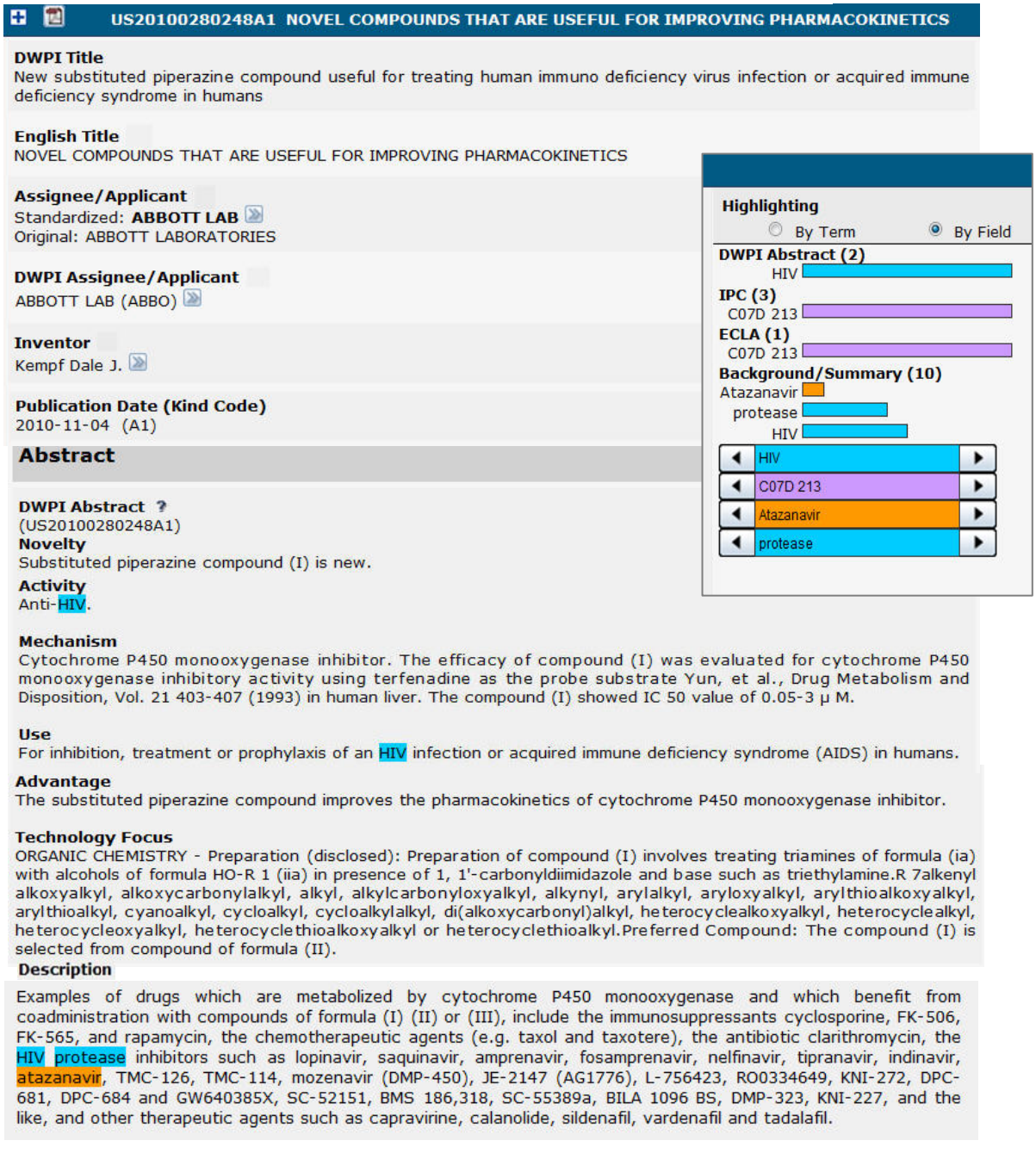
Two areas were removed as completely as possible from the description-based collection. One was development of devices meant for drug delivery. Such documents often mention a list of drugs (including Atazanavir) for which the device is deemed applicable, but these records are off-topic for assessing drug development and were removed. The second exclusion area was isolation of genetic material for the purpose of understanding molecular structure of drug targets and detecting genetic sequences. These more fundamental inventions were removed because they are not directly in the Atazanavir drug development pathway, even though Atazanavir may be cited as an example in the documents. About 400 records (20%) of the description-based collection could be removed in this manner, and the new map in Figure 8 shows that now the mixture of the Stage-One and the cleaned-up description-based collection yields a much-improved map, with the Stage-One collection documents spread more evenly throughout.

Figure 8. Stage-3 Clinical Collection after Improvement

CLINICAL COLLECTION

This is an example of a very useful invention found by searching in the description for the clinical name Atazanavir. It is a compound that could be used in combination with various HIV protease inhibitor drugs (including Atazanavir) to maintain the effective dose using a lower amount of drug. As noted from the highlighting key, the term Atazanavir appears in the description but not elsewhere in the abstract or claims, and hence it was only found by searching the description field. The broad set of documents obtained in this way was narrowed using a classification code strategy. The code **C07D 213**/, covers compounds of the Atazanavir type, was one way to isolate relevant documents from the excessively broad list generated by searching the description. For more on classification codes, see Chapter 9.

Figure 9 Retrieved using "clinical" name Atazanavir vs the text of the description



SECTION 4: PREPARING THE CHEMICAL COLLECTION

MULTI-FACETED APPROACH

A number of approaches are useful to prepare a collection of pre-clinical patents covering the same or similar compounds, even though the Atazanavir name was not yet available. These approaches are applicable even when access to enhanced content such as the Derwent World Patent Index is not available, and all have been used in this report.

List of search approaches:

1. Identifying founder compositions by using the SPC filing registration found in the Legal Status field. In later documents this field is also likely to contain the generic or brand name of the drug.
2. Searching for key terms selected from the unique parts of the chemical name (± classification codes)
3. Searching for CAS codes in the description field
4. Searching for founding inventor names together with their developer company names to select potentially related documents from the company's holdings.
5. Searching target key terms together with developer company names.
6. Searching for documents that cite patents owned by the companies involved in development.

The results from such searches do overlap with one another, and may also overlap with the clinical collection. After cross-deduplication, they will often need further review to determine if they are sufficiently on-topic. It is expected that this list will contain many fewer documents than are present in the clinical collection, because the volume of patents is typically lower before the discovery phase moves into clinical development. However, these documents should help fill in the "gap" period mentioned earlier, the period between the first composition patent, and the beginnings of clinical testing. The details for these search strategies are provided in Appendix A.

THE FOUNDER PATENT AND ITS DOWNSTREAM CITATIONS

After finding the founder patent, its citations (Listed in Figure 11) can also be used to trace the pathway to further development or new inventions. This citation map was made by starting from the founder patent (at the center) and filling in patents or applications that referred directly to the founder. These later-published references are arranged by year of publication in clockwise fashion around the diagram. The earliest references are in 1999 from the owner's collaborator (Bristol-Myers Squibb) and a competitor (Abbott) making a different drug in the same protease inhibitor class. In 2000, there is another "self" reference and 3 references from a provider of intermediates (Sumika/Sumitomo). Later there are references from companies targeting protease inhibitors for indications other than AIDS, and still later, some companies devising synthetic methods or trying to create a variation on the original composition by substituting deuterium for hydrogen in the compound. There are only 3 "self references" from Bristol-Myers Squibb, and these likely represent follow-on work improving the invention, or making new findings based on it.

Figure 10. Citation Map of Founder Patent

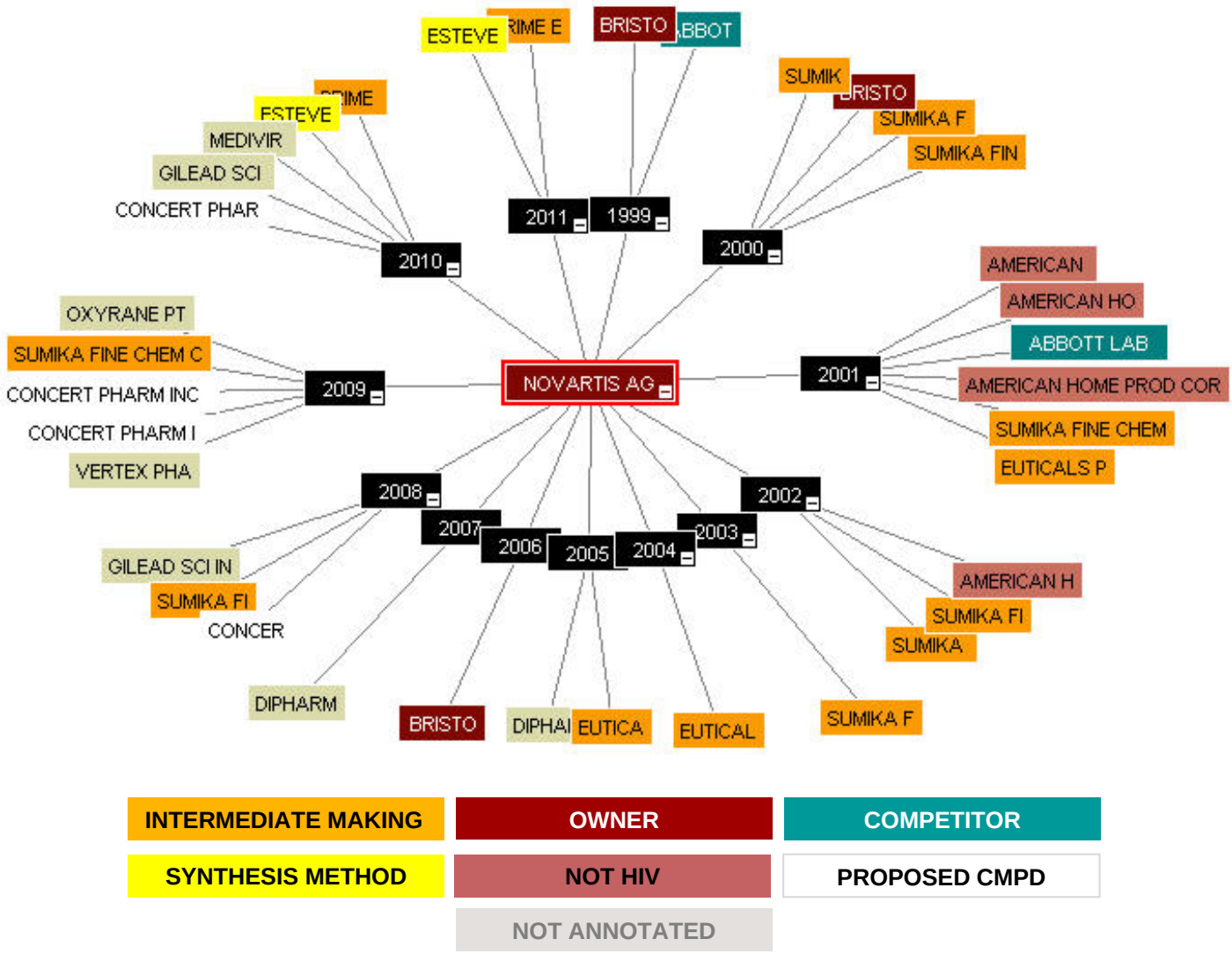


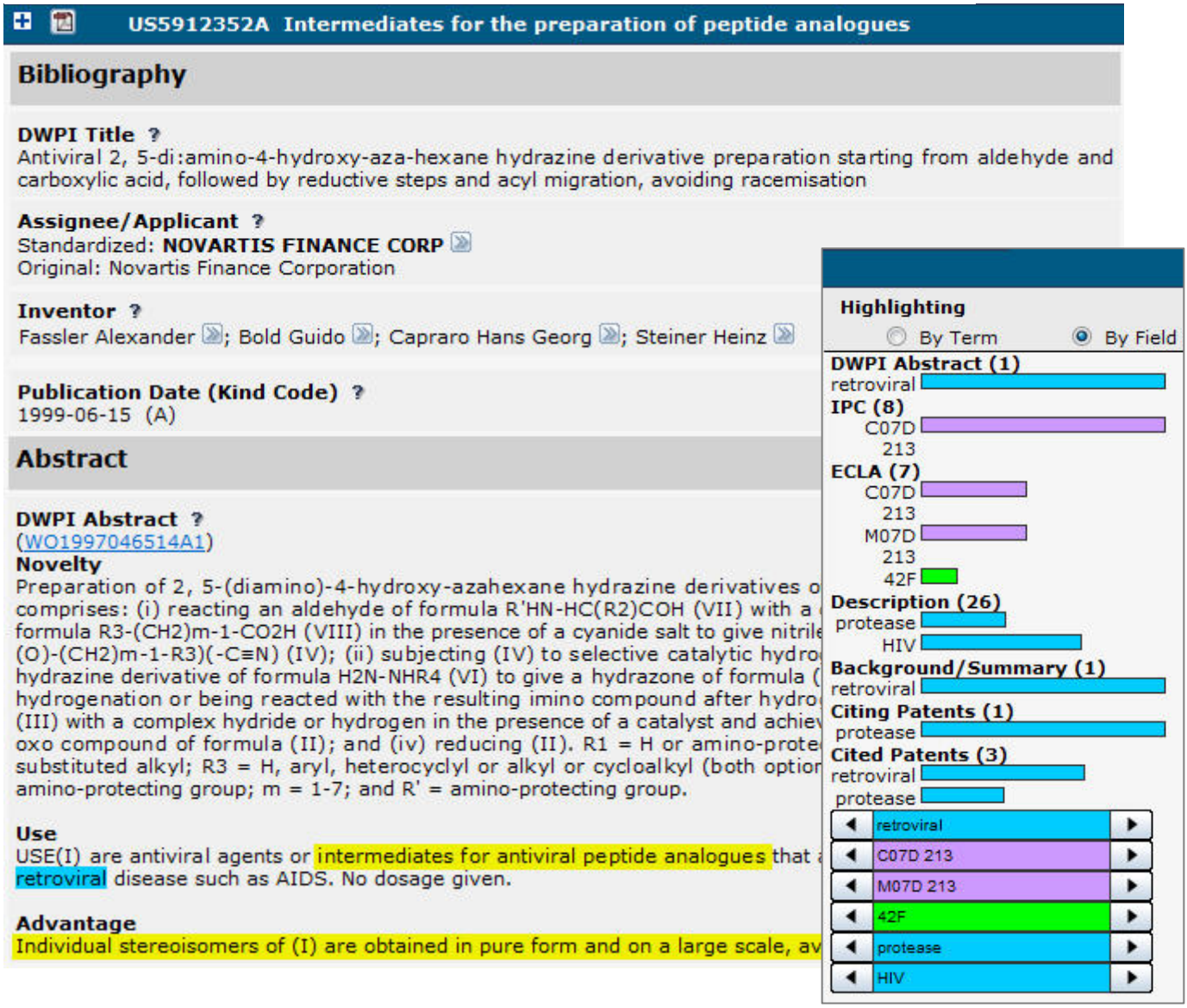
Figure 11 List of Documents Citing Founder

Publication Number	Assignee/Applicant	Citing Company Category	Truncated Title - DWPI
US6087383A	Bristol Myers Squibb	Owner	New crystalline bisulfate salt of azapeptide HIV protease inhibitor, having high solubility and oral bioavailability
WO1999036404A1	Bristol Myers Squibb	Owner	New crystalline bisulfate salt of azapeptide HIV protease inhibitor, having high solubility and oral bioavailability
WO1997040029A1	Novartis	Owner	New heterocyclic aza:hexane derivatives are inhibitors of retroviral aspartate protease, useful for treating retroviral disease, e.g. AIDS
BG64774B1	Bristol Myers Squibb	Owner	Bisulfate salt of HIV protease inhibitor
US6251906B1	Abbott Laboratories	Competitor	New retroviral protease inhibitors useful in the treatment of HIV infection show no adverse side effects, such as low platelet count, renal toxicity or bone marrow
WO1999059994A1	Abbott Laboratories	Competitor	New urea or carbamate derivative for inhibiting proteases of retrovirus and human immunodeficiency virus
EP1274684B1	Prime European Therapeuticals	Intermediate	Preparation of arylpyridine compounds by reacting an arylmagnesium halide and a halopyridine in the presence of a zinc salt and palladium, useful as
US6765097B1	Prime European Therapeuticals	Intermediate	Preparation of arylpyridine compounds by reacting an arylmagnesium halide and a halopyridine in the presence of a zinc salt and palladium, useful as
EP2272831A1	Prime European Therapeuticals	Intermediate	Preparing 4-(2'-pyridyl)benzaldehyde comprises reacting arylmagnesium halide and halopyridine compound with zinc salt and palladium complex with bidentate
WO2010149356A1	Prime European Therapeuticals	Intermediate	Preparing 4-(2'-pyridyl)benzaldehyde comprises reacting arylmagnesium halide and halopyridine compound with zinc salt and palladium complex with bidentate
EP979820B1	Sumika Fine Chemicals	Intermediate	Preparation of pyridine-phenylmethylidene-hydrazine derivative useful as intermediate for anti-HIV drug
EP979820A1	Sumika Fine Chemicals	Intermediate	Preparation of pyridine-phenylmethylidene-hydrazine derivative useful as intermediate for anti-HIV drug
US6376678B1	Sumika Fine Chemicals	Intermediate	Preparation of hydrazine derivatives used as intermediate for anti-HIV drug comprises catalytically reducing hydrazone derivative and deactivating catalyst
US6365745B1	Sumika Fine Chemicals	Intermediate	Production of hydrazine starting materials for pharmaceutical product e.g. anti-AIDS agent, comprising reduction of hydrazone with base and metal
US6268503B1	Sumika Fine Chemicals	Intermediate	Preparation of pyridine-phenylmethylidene-hydrazine derivative useful as intermediate for anti-HIV drug
US6147218A	Sumika Fine Chemicals	Intermediate	Preparation of pyridine-phenylmethylidene-hydrazine derivative useful as intermediate for anti-HIV drug
US6096894A	Sumika Fine Chemicals	Intermediate	Preparation of 2-(p-alkylphenyl)pyridine comprises adding manganese dioxide and trimethylchlorosilane or manganese chloride to solvent and reacting p-
JP04222671B2	Sumitomo Chem	Intermediate	Preparation of hydrazine derivatives used as intermediate for anti-HIV drug comprises catalytically reducing hydrazone derivative and deactivating catalyst
JP04028945B2	Sumitomo Chem	Intermediate	Preparation of pyridine-phenylmethylidene-hydrazine derivative useful as intermediate for anti-HIV drug
WO2001027083A1	Norpharma	Intermediate	Preparation of arylpyridine compounds by reacting an arylmagnesium halide and a halopyridine in the presence of a zinc salt and palladium, useful as
WO2010146119A1	Esteve Química	Synthesis Method	Preparing atazanavir, useful to treat viral infection, comprises condensing 3-amino-4-phenyl-1-(N-(4-pyridin-2-yl-benzyl)-hydrazino)-butanol with 2-
EP2272830A1	Esteve Química	Synthesis Method	Preparing atazanavir, useful to treat viral infection, comprises condensing 3-amino-4-phenyl-1-(N-(4-pyridin-2-yl-benzyl)-hydrazino)-butanol with 2-
EP2003120B1	Concert Pharmaceuticals	Proposed Compound	New azepeptide compound useful in the manufacture of medicament for the treatment of HIV infection and virus infection, and for determining the
EP2003120B9	Concert Pharmaceuticals	Proposed Compound	New azepeptide compound useful in the manufacture of medicament for the treatment of HIV infection and virus infection, and for determining the
EP2003120A1	Concert Pharmaceuticals	Proposed Compound	New azepeptide compound useful in the manufacture of medicament for the treatment of HIV infection and virus infection, and for determining the
EP2116532A1	Concert Pharmaceuticals	Proposed Compound	New deuterated atazanavir useful for the treatment of diseases e.g. HIV infection
US6335350B1	American Home Products	Not HIV	New substituted acetamide-containing thiourea compounds useful in the treatment of diseases associated with herpes viruses
US6255349B1	American Home Products	Not HIV	New alpha-alkylbenzyl containing thiourea having phenylenediamine group useful as herpes virus inhibitor
US6207715B1	American Home Products	Not HIV	Alpha-methylbenzyl-containing thioureas, used to inhibit viral replication of e.g. cytomegalovirus, herpes simplex, varicella zoster, Epstein-Barr, herpes viruses-
US6197803B1	American Home Products	Not HIV	New aryl-thiourea derivatives are useful for inhibiting replication of and treating infections caused by herpes virus, especially cytomegalovirus, varicella zoster
EP1555260B1	Dipharma Francis	Not Annotated	Deprotection of new tetrazole compounds in the preparation of angiotensin II antagonists such as losartan, involves reaction of tetrazole compounds with
EP1555260A1	Dipharma Francis	Not Annotated	Deprotection of new tetrazole compounds in the preparation of angiotensin II antagonists such as losartan, involves reaction of tetrazole compounds with
US7723380B2	Gilead Sciences	Not Annotated	New hydrazine containing amide compound useful in the treatment of HIV infection and herpes simplex virus diseases
WO2008011117A2	Gilead Sciences	Not Annotated	New hydrazine containing amide compound useful in the treatment of HIV infection and herpes simplex virus diseases
US7807677B2	Medivir	Not Annotated	New amide compounds are HIV protease inhibitors useful for the prophylaxis or treatment of HIV infection
WO2009130534A1	Oxyrane	Not Annotated	Making Atazanvir to treat HIV involves coupling (2R,3S)-1,2-epoxy-3-((N-(methoxycarbonyl)-L-tert-leucinyl)amino)-4-phenylbutane and N-(N-
AU2003298868B2	Vertex Pharma	Not Annotated	Composition useful for the treatment of cancers, comprises an apoptosis inducing anti-cancer agent, inosine-5'-monophosphate dehydrogenase inhibitor

CHEMICAL COLLECTION

This is an example of what was found by searching for chemical entities when the clinical name was not mentioned. The name Atazanavir is not mentioned because at the time of this application, the name had not been assigned. It is related to the production of an azapeptide intermediate with optically correct orientation of the constituents. It was found by use of a combination of key terms and chemical codes (discussed in more detail in Chapter 8).

Figure 12 Retrieved with key terms and codes and without using Atazanavir name

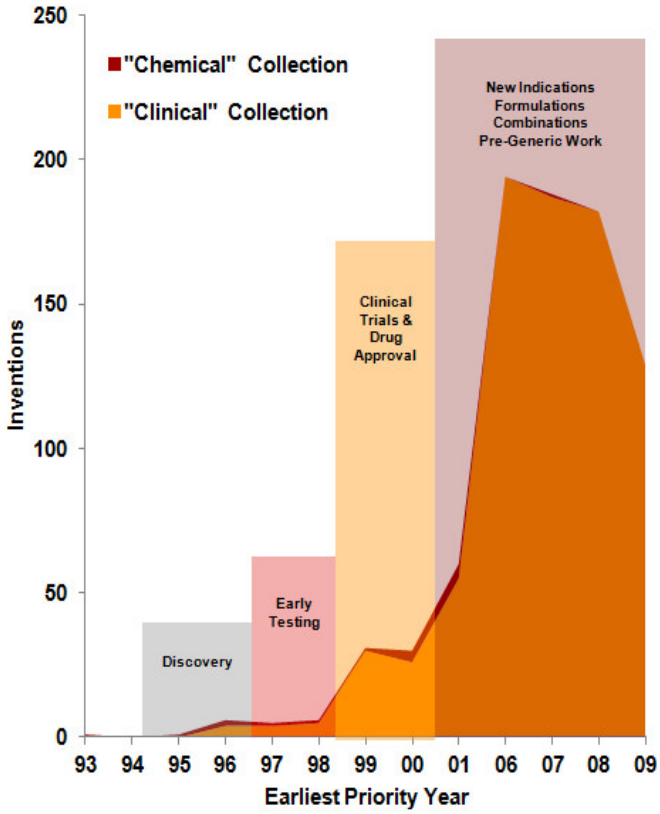


SUMMARY OF COLLECTION ASSEMBLY

As expected, the Pre-Clinical Collection is relatively small compared to the Clinical Collection (Figure 13). Its relative contribution is highest at the early discovery stage, and lower later on. Typical drug development stages are noted on the chart at right. Atazanavir was approved by the US FDA for HIV treatment in 2003. Note that after 2008 the data is incomplete because of publication lag.

Figure 13. Invention Timelines vs Developmental Stages

Earliest Priority Year	"Chemical" Collection	"Clinical" Collection	Invention Families
93	1		1
94			
95	1		1
96	2	4	6
97	1	4	5
98	1	5	6
99	1	30	31
00	4	26	30
01	5	55	60
06		194	194
07	1	187	188
08		182	182
09		129	129
All	19	1361	1380

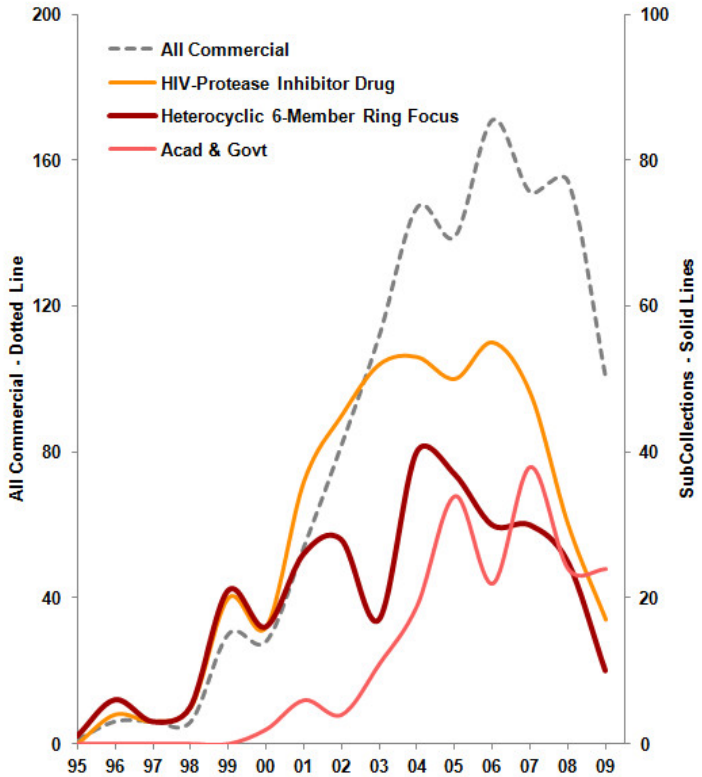


SECTION 5: GENERAL OVERVIEW OF THE COLLECTION

The collection contains inventions that are very specific to Atazanavir and cover compositions, processes and methods of use directly involving the drug, but it also includes contextual inventions that allow inferences to be made about the use of drugs in HIV treatment. For example, drug treatments may involve HIV-protease inhibitor drugs such as Atazanavir together with other anti-HIV treatments. Because of the issues of drug resistance in treatment of HIV infection or AIDS, it is standard practice to use co-administered or combination drugs, and this is reflected in the collection. It is also apparent that protease inhibitor drugs may have uses other than the treatment of HIV, and movement into other therapeutic areas is also covered in the collection.

Using this type of collection, the activity on Atazanavir can be examined either narrowly or more expansively depending on the kind of insights being sought. In the analysis that follows, examples of both approaches will be provided, and Figure 13 is a case in point. The chart in Figure 14 shows the earliest priority year (closest to date of invention) for several different subsets of documents from the collection. The “all commercial” set covers the majority of inventions in the collection except for those assigned to academic or government institutions, or individual inventors. This is a broad point of view. The other three timelines (second axis) cover smaller subsets, i.e. the inventions specifically covering HIV-protease inhibitor drugs (the drug class to which Atazanavir belongs), the inventions covering HIV protease inhibitor drugs that contain a six-membered heterocyclic ring structure (as Atazanavir does), and the inventions contributed to the field by academic and government inventors. The early documents in this collection come from the commercial sector, with academia and government mostly involved later.

Figure 14. Timelines for collection, including narrower subsets



EARLIEST PRIORITY COUNTRY

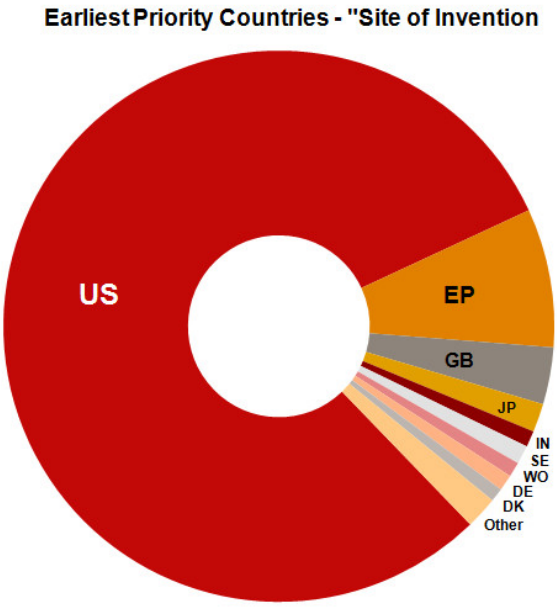
Determining the priority country (country of first filing) is the easiest way to get an idea of where inventions were made, and typically corresponds to a company location. Global companies may file in multiple countries if they have R&D facilities in each place. Most of the inventions in this collection were filed first in the US, and 70% of them were also filed in a PCT office (or have a priority in a PCT Office). This is partly explained because the pharmaceutical industry in general favors PCT filing. By examining the application number of a PCT filing, the country of origin of the application can be determined, and Figure 15 also shows the country of origin (receiving office) for the PCT applications.

Observations include: a) relatively low participation in this technical field by Japanese companies, whether measured through in-country priority filings or PCT filings, and b) noticeable but not large participation by India. The numbers of families that have grants in one or more authorities are also shown, and is 29% for the US and 35% for the EPO. The grant of a patent implies novelty, but the grant rate statistic is affected by the age of the invention, since young applications are not expected to grant in a time shorter than the normal pendency period.

Figure 15. Priority Country Information

Earliest Priority Country Code	Country or Authority Name	Inventions with no Granted Patrents	Inventions with ≥1 Granted Patent	# Records	% with grants
US	United States	785	320	1105	29%
EP	European Office	73	39	112	35%
GB	United Kingdom	32	14	46	30%
JP	Japan	14	9	23	39%
SE	Sweden	7	8	13	62%
DE	Germany	12	1	15	7%
IN	India	11	2	12	17%
WO	PCT	9	3	13	23%
DK	Denmark	10	1	11	9%
Other	13 Countries	20	10	30	33%
ALL		973	407	1380	29%

PCT Application Country Code	PCT Deposit Office	Count
US	United States	636
EP	European Patent Office	159
IB	International Bureau	46
CA	Canada	39
GB	United Kingdom	27
JP	Japan	20
SE	Sweden	14
IN	India	11
DK	Denmark	8
NL	Netherlands	5
IL	Israel	4
DE	Germany	3
FR	France	3
BE	Belgium	2
BR	Brazil	2
AU	Australia	2
CN	China	2
IT	Italy	2
ES	Spain	2
CZ	Czech Republic	1
SG	Singapore	1
Total		989



FAMILY MEMBER COUNTRIES

Looking at patent applications in another way, it is easy to see that the companies file for protection not only locally (priority country), but also in other regions where they expect to require protection for their product, or for manufacturing of their product. The average size of the DWPI families in this collection is 5 members (5 countries where filings have been made). Figure 16 presents a count of the inventions filed in various countries or authorities, and countries with high numbers are presumably viewed as potential markets by the developers, and may also be considered as potential sites for manufacturing. Regional filings in the European Patent Office may protect inventions in multiple European countries not listed here. Protection is Asia-Pacific countries is robust, as is protection in North and South America.

Figure 16. Countries Viewed as Markets

World Regions	Family Member Country Codes	Countries	National or Regional Filings
APAC	JP	Japan	554
APAC	AU	Australia	548
APAC	CN	China	376
APAC	IN	India	289
APAC	KR	South Korea	253
APAC	TW	Taiwan	207
APAC	NZ	New Zealand	82
APAC	PH	Philippines	36
APAC	VN	Viet Nam	21
APAC	SG	Singapore	14
APAC	MY	Myanmar	2
EMEA	EP	European Patent Office	763
EMEA	ZA	South Africa	170
EMEA	DE	Germany	122
EMEA	NO	Norway	118
EMEA	RU	Russia	70
EMEA	ES	Spain	61
EMEA	IL	Israel	24
EMEA	HU	Hungary	22
EMEA	CZ	Czech Republic	17
EMEA	SK	Slovakia	11
EMEA	NL	Netherlands	4
EMEA	GB	Great Britain	3
EMEA	PL	Poland	1
NA	US	United States	1114
NA	CA	Canada	356
NA	MX	Mexico	300
SA	BR	Brazil	145
Stateless	WO	PCT*	1184

* Patent Cooperation Treaty filings may be further prosecuted in many countries

SECTION 6: EXAMINING ASPECTS OF DRUG DEVELOPMENT

There are different invention aspects in drug development, including chemical compositions, biological target identification, use of combination therapies, development of drug formulations, and finding clinical indications (disease or condition to be treated) that are of interest to the companies active in the field. To study these, a natural language processing exercise[7] was performed and the categories created included those listed in Figure 17. Individual documents may be placed into multiple categories.

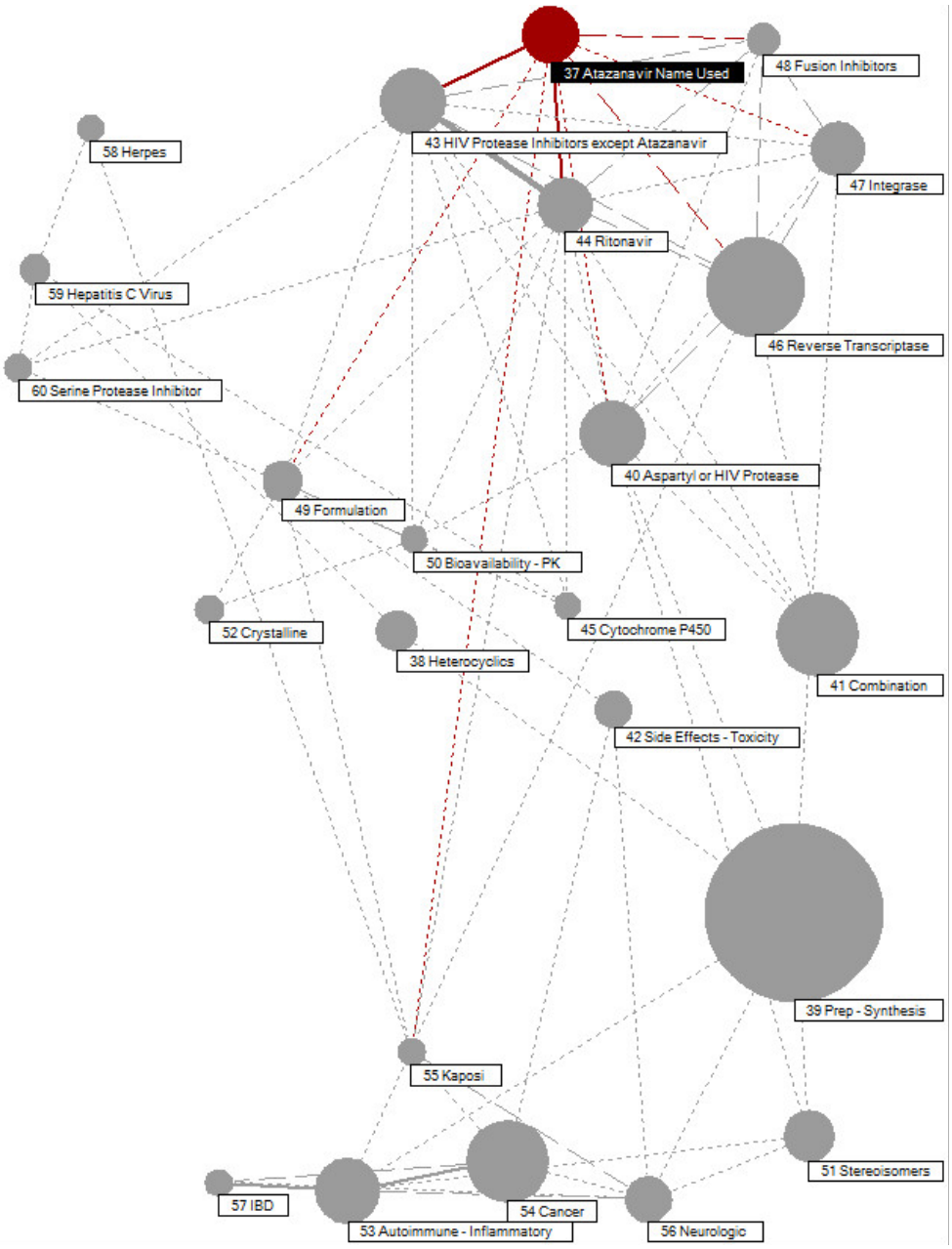
Figure 17. Categories

	Categories	Hits
Chemistry & Target	Founder	1
	Combined Collections with C07D 213/	134
	Atazanavir Name Used	279
	Heterocyclic	199
	Prep - Synthesis	851
	Aspartyl or HIV Protease	316
Combinations	Combination	397
	Side Effects - Toxicity	184
	HIV Protease Inhibitors except Atazanavir	318
	Ritonavir	264
	Cytochrome P450	84
	Reverse Transcriptase	469
	Integrase	262
	Fusion Inhibitors	162
Formulations	Formulation	197
	Bioavailability - PK	129
	Stereoisomers	248
	Crystalline	53
Indications	Autoimmune - Inflammatory	310
	Cancer	394
	Kaposi	114
	Neurologic	228
	IBD	131
	Herpes	106
	Hepatitis C Virus	152
	Serine Protease Inhibitor	50

7 This exercise employed the Thomson Data Analyser® Application. If NLP processing is not available, this approach can be mimicked by sub-searching the collection with specific searches aimed at the specialized areas, or by the labor-intense method of manual categorization.

The crossover between categories is visualized in this autocorrelation map[8] (Figure 18). A linkage means that there are inventions where the linked categories co-exist. By far the largest category deals with synthesis (lower right), and linkages upward from the synthesis node connect with formulations, pharmacokinetics, side-effects, etc, while the set of linkages in the lower left lead to different clinical indications in which the protease inhibitor is usable. At the top right, different anti-viral biochemical targets are clustered, with the linkages among them reflecting drug combinations that mix drugs that are aimed at different targets. On the far left are some isolated nodes that link the serine protease inhibitor target with two indications in which it is involved. The highlighted node (red) is Atazanavir, which has prominent links (red lines) to inventions involving Ritonavir and other protease inhibitor drugs, and reflective of combinations.

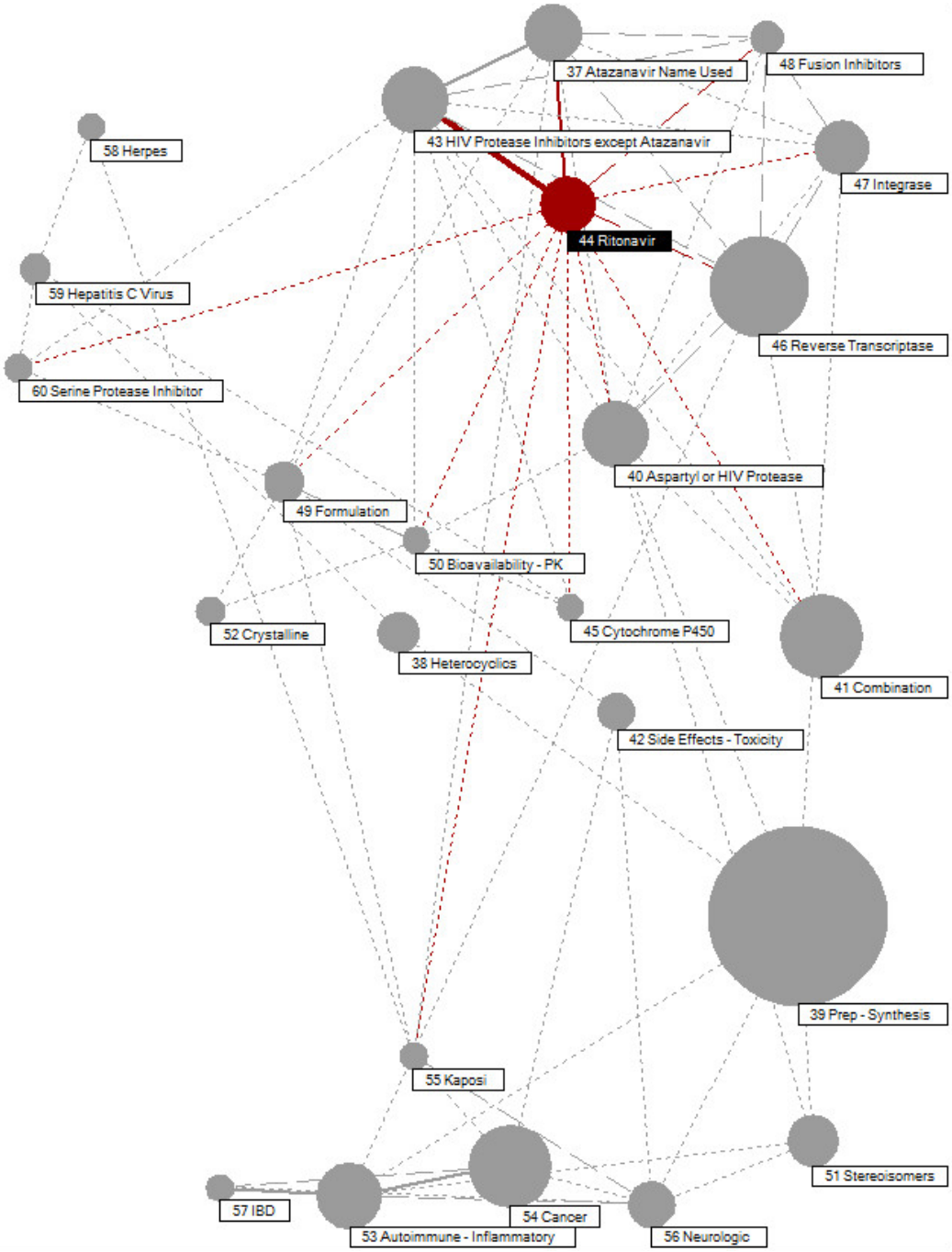
Figure 18. Correlation between inventive categories – Atazanavir highlighted



[8] Performed using Thomson Data Analyzer

In this view of the same correlation map (Figure 19), the Ritonavir node is highlighted (red), and the thickness of the red linkage lines shows that Ritonavir is more often involved in combinations with other protease inhibitors than is Atazanavir (as visualized on the preceding page). It also has more linkages, especially to bioavailability and to cytochrome P450, as well as to the serine protease inhibitor node that relates to Hepatitis C treatment. This is discussed further in Chapter 8 on Combinations.

Figure 19. Correlation between inventive categories – Ritonavir highlighted

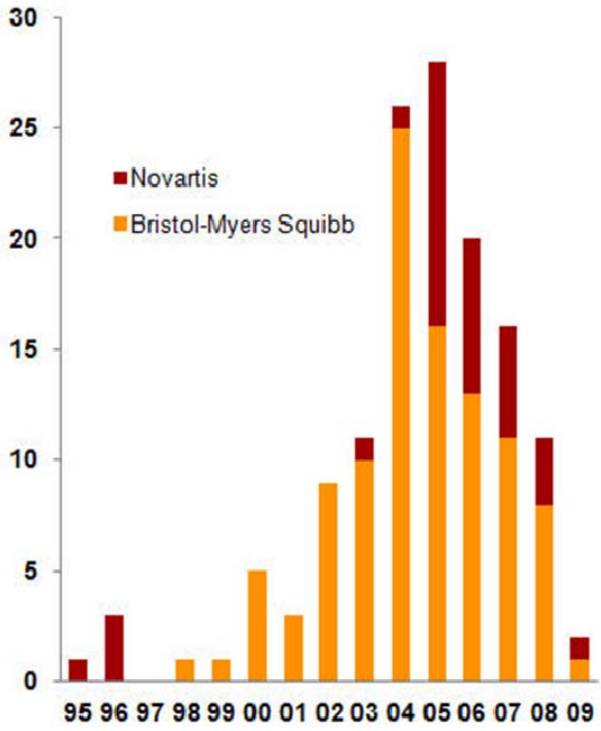


THE DEVELOPER'S OWN TIMELINE

The Atazanavir-related inventions belonging to Novartis and Bristol-Myers Squibb have a time line of development that began in 1995 with the founder composition patent, and was punctuated in 2003 by the approval of the drug for an HIV/AIDS indication.

The summary in Figure 20 shows the division of labor between Novartis and Bristol-Myers Squibb. A point to remember is that the categories are overlapping. The founder patent was developed by Novartis (then Ciba-Geigy), and while Novartis did a considerable amount of chemical work on the compound and its synthesis, the lion's share of the synthesis work was done at BMS in preparation for scale up, formulation for treatment, and so on.

Figure 20 ATZ-related inventions of Novartis and Bristol-Myers Squibb by Priority Year



In the case of combinations (Figure 21), Novartis mentioned them more generically in its inventions, while the BMS patents were more specific about which types of drugs would be valuable in combination. In terms of diversification to other clinical indications, Novartis appears to be taking the lead, but both companies are working on cancer, anti-inflammatory and neurologic indications, which may or may not be an indicator of future direction.

Figure 21. Atazanavir Patenting by Novartis and Bristol-Myers Squibb

Categories	Novartis	Bristol-Myers Squibb	All
All Records - Counts	33	100	133
Founder	1		1
Still Pending	18	30	48
Aspartyl or HIV Protease	3	51	54
Prep - Synthesis	26	77	103
Formulation	1	17	18
Bioavailability - PK	2	2	4
Cytochrome P450		1	1
Stereoisomers	6	17	23
Crystalline		11	11
Side Effects - Toxicity		15	15
Combination	20	16	36
HIV Protease Inhibitors except Atazanavir		14	14
Ritonavir		10	10
Reverse Transcriptase		33	33
Integrase		31	31
Fusion Inhibitors		19	19
HIV-AIDS Indication (Code)	22	2	24
Autoimmune - Inflammatory	18	14	32
Cancer	16	13	29
Neurologic	12	13	25
IBD	14		14
Hepatitis C Virus	6		6

The three sections of Figure 22 follow the development of the combined Novartis and BMS portfolio on Atazanavir. The top section of the table shows that the portfolio includes granted patents and also pending applications that were filed since 2002. The inventions found by chemical searching were filed beginning in 1995, but the clinically-oriented collection begins in 1999, with the Atazanavir name per se appearing in 2001. From the beginning, in 1995, utility for treatment of HIV was claimed, and Atazanavir was of course, not the first composition in this drug class, with multiple predecessors in the class, led by Roche's Saquinavir that had was approved by the FDA in 1995, and which is now off-patent.

The mid-section of the table reviews the different aspects of drug development mentioned in patents in the Novartis-BMS portfolio. Use of the drug in combination was included in the founder patent, since much had already been learned about combination treatment of HIV by 1995. Patenting of synthetic approaches persists over the entire time frame, and formulation patents are noted starting in 1998. Specific combinations begin to appear in 1998, and combinations addressing both the same (PI) and different targets are mentioned, with the latest being viral fusion inhibitors.

Figure 22. Timelines for Atazanavir Development Categories

Novartis and BMS	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	# Records
Founder - Identified with SPC	1															1
Inventions with Grants	1	3		1	1	5	3	7	9	17	19	13	6			85
Pending Applications								1	2	8	8	7	10	10	2	48
Pre-Clinical Collection (Chemical Search)	1	3		1		3			2		2	1				13
Clinical Collection					1	2	3	8	9	25	25	19	16	10	2	120
Atazanavir Name Used							1		1	6		1	4			13
Inventions with A61P/ code for HIV (Main Clinical Indication)	1	1			1	1	2	1	1	6	1	3	1	5		24

Developmental Stages	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	# Records
Aspartyl or HIV Protease	1	2		1		2	1	1	5	14	9	8	7	3		54
Combination	1					1	2	1	2	7	11	7	3		1	36
Prep - Synthesis		1		1		5	2	7	8	16	25	16	12	9	1	103
Bioavailability - PK		1		1							1			1		4
Stereoisomers		1				1			1		5	4	8	2	1	23
Formulation				1	1		1	1		4	2		4	4		18
Crystalline				1						5	3		1	1		11
Reverse Transcriptase					1	1		1	4	12	6	3	3	2		33
HIV Protease Inhibitors except Atazanavir						1	1		1	7			4			14
Cytochrome P450							1									1
Integrase									3	15	6	2	3	2		31
Ritonavir									1	5			4			10
Side Effects - Toxicity									1	2	2	3	6	1		15
Fusion Inhibitors										8	5	2	2	2		19

Diversification to other Clinical Indications	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	# Records
Autoimmune - Inflammatory									1	2	11	7	8	2	1	32
Cancer										1	11	7	7	2	1	29
Neurologic									1		8	6	7	2	1	25
IBD										1	8	3	2			14
Hepatitis C Virus											3		3			6

The last section of the table deals with clinical indications other than HIV infection, and these were not filed until after approval for the HIV indication was received.

Several of the representative patents held by Novartis and Bristol-Myers Squibb are listed in Figure 23. A list of all the ATZ patents in the collection that are held by Novartis/BMS is provided in an Appendix.

Figure 23 Representative Patents from Novartis and Bristol-Myers Squibb

Earliest Priority Year	Publication Number	Title - DWPI	Unified Assignee	Comment
1995	WO1997019055A1	New aza-hexane derivatives as substrate isostere(s) of retroviral aspartate protease(s) used to treat retrovirus(es) e.g. HIV-1 and HIV-2 , AIDS, SIV and FIV	NOVARTIS AG	Founder Composition
	US5912352A	Antiviral 2,5-di:amino-4-hydroxy-aza-hexane hydrazine derivative preparation starting from aldehyde and carboxylic acid, followed by reductive steps and acyl migration, avoiding racemisation	NOVARTIS AG	Synthesis
1998	US6087383A	New crystalline bisulfate salt of azapeptide HIV protease inhibitor, having high solubility and oral bioavailability	BRISTOL MYERS SQUIBB CO	Bioavailability
2001	US20030045501A1	Reduction of elevated plasma low-density lipoproteins and/or triglyceride levels in human immunodeficiency virus-infected patient, by administering atazanavir for the offending human	BRISTOL MYERS SQUIBB CO	Lower Side-Effects
	WO2004062613A2	New amine derivatives are HIV integrase inhibitors useful to treat HIV infections	BRISTOL MYERS SQUIBB CO	Two-target Combination
	WO2005058248A2	Use of atazanavir or its salt and at least one other HIV protease inhibitor (e.g. ritonavir) for treating HIV infection, where the	BRISTOL MYERS SQUIBB CO	Rescue Combination
	US20050267131A1	New bicyclic heterocyclic compounds are HIV integrase inhibitors, useful to treat HIV infections and AIDS	BRISTOL MYERS SQUIBB CO	Two-target Combination
	US7829720B2	Preparation of atazanavir bisulfate form A crystals, useful for treatment of disease caused by retroviruses, involves reacting atazanavir free base with concentrated sulfuric acid, and	BRISTOL MYERS SQUIBB CO	Improved Synthesis
2006	US20070207985A1	New substituted triazine derivatives useful for treating, preventing, or slowing the progression of e.g. diabetes, obesity, dyslipidemia, hypertension, cognitive impairment and metabolic	BRISTOL MYERS SQUIBB CO	Other Indication Combination
	WO2009002823A2	Compressed tablet useful for treating HIV infection in a patient comprises raltegravir and granules containing atazanavir sulfate	BRISTOL MYERS SQUIBB CO	Oral Formulation

CATEGORIES WITH HIGHEST EMPHASIS

When the entire collection is compared by category, and the categories with the highest emphasis within each assignee group is noted, similarities and differences in assignee emphasis can be noted (Figure 24).

The commercial entities are relatively similar in chemical and formulation emphasis, with their highest focus on synthesis, and stereospecific synthesis in particular. Most of the drug candidates for this target (viral protease) are peptide mimetics which must stereospecifically bind to a site on the surface of the target. Commercial focus on this issue is understandable since the efficacy, cost of goods and reduction of side-effects all rest on the effectiveness of stereospecific synthesis of a drug with multiple stereoisomeric centers (molecular linkages which are required to be in the appropriate orientation, left-handed or right-handed).

In the area of combinations, Novartis/BMS places slightly more emphasis on combinations with other protease inhibitors and reverse transcriptase inhibitors than with integrase. It also emphasizes auto-immune indications and cancer but there is little evidence of pursuit of neurologic or other anti-viral indications.

Figure 24. Emphasis on Categories in Drug Development

	Categories	Commercial	Top Commercial	Novartis - BMS	Acad & Govt	# Records
Chemistry	Atazanavir Name Used	240	198	12	35	279
	Heterocyclics	188	115	15	11	199
	Prep - Synthesis	787	579	95	60	851
	Aspartyl or HIV Protease	287	250	47	29	316
Combinations	Combination	348	208	35	43	397
	Side Effects - Toxicity	149	75	15	31	184
	HIV Protease Inhibitors except Atazanavir	269	198	13	45	318
	Ritonavir	225	165	10	35	264
	Cytochrome P450	82	45	1	2	84
	Reverse Transcriptase	400	308	32	64	469
	Integrase	233	190	31	29	262
	Fusion Inhibitors	137	104	19	25	162
Formulations	Formulation	170	99	17	22	197
	Bioavailability - PK	123	90	2	5	129
	Stereoisomers	238	200	20	10	248
	Crystalline	53	32	10		53
Indications	Autoimmune - Inflammatory	285	178	31	22	310
	Cancer	329	185	29	58	394
	Kaposi	96	68		16	114
	Neurologic	194	131	23	29	228
	IBD	122	73	14	8	131
	Herpes	74	28		29	106
	Hepatitis C Virus	133	74	6	19	152
	Serine Protease Inhibitor	48	22		2	50

COMPARING TECHNICAL EMPHASIS OF TOP COMPANIES

The categories listed above allowed creation of a matrix (Figure 25) that compares each company for activity in different technical areas. The companies selected for the matrix are a sampling (44 of 288) of the full list available in Appendix B, and include those companies that have an approved HIV-protease inhibitor drug.

Figure 25. Emphasis Matrix for Selected Assignees

Selected Commercial Assignees	Has Approved Drug	Heterocyclics	C07D 213/00 and /42 - Chemically related	C07D 213/42 or /42F ECLA	Prep - Synthesis	A61P 31/18 - HIV specific	Aspartyl or HIV Protease	Combination	Side Effects - Toxicity	HIV Protease Inhibitors except Atazanavir	Ritonavir	Cytochrome P450	Reverse Transcriptase	Integrase	Fusion Inhibitors	Formulation	Bioavailability - PK	Stereoisomers	Crystalline	Autoimmune - Inflammatory	Cancer	Kaposi	Neurologic	IBD	Herpes	Hepatitis C Virus	Serine Protease Inhibitor	# Records
MERCK & CO INC	YES	33	2		119	36	68	60	3	6		1	71	55	2	5	10	52	9	61	54	2	10	15				134
BRISTOL MYERS SQUIBB CO	YES	9	7	6	70	23	45	15	15	13	10	1	32	31	19	16	1	14	10	14	13		12					92
TIBOTEC (J&J)	YES	9	2	1	64	40	18	12	3	9	6	4	24	5	1	8	17	57	1		2	16	35			9	4	78
GLAXOSMITHKLINE	YES	8	1		57	6	21	10	7	24	22		24	26	21	17	3	13	1	16	17	22	31	16	3	1		64
ABBOTT LABORATORIES	YES	6	6		33	5	21	10	3	23	23	6	10	7	7	13	15	14	6		1					17	3	48
ENANTA PHARM INC		19			34	2		29	2	21	21	24				4	4	9		4	22			4		22	19	40
GILEAD SCIENCES INC	YES	11	2		28	12	17	11	6	19	11	5	32	20	8	12	12	4	1		3	2				11	6	36
AGOURON (PFIZER)	YES	4	6		30	13	10	3	3	3	3	4	6	8	4		3	1	1	7	13	6	4	6	3	6		34
NOVARTIS AG	YES	6	3	2	25	1	2	20								1	1	6		17	16		11	14		6		31
BOEHRINGER INGELHEIM INT	YES	1	4		20	15		8	3	4	4	1	13	13			1	9								4	3	24
CYTOVIA INC		4			14				2	14	13		14							20	21	17		3		1		22
SCHERING CORP		2			16			5	4	1	1	4	1							14	1		1	2		9	5	18
ASTRAZENECA AB		1	2	2	16				2								3			15	4		15	4				16
SYNTA PHARMACEUTICALS CORP		4	1		12			3	4							1	1			10	13	3	8	7	6	1		14
MONOGRAM BIOSCIENCES INC					1		2	5		3	1		6	3												1		14
SEQUOIA PHARMACEUTICALS INC		5			8	1	10	1	2	2	2	8	6	2	1	3	8	4			4		6			1	1	13
VIROCHEM PHARMA INC					13	5		9	1	8	7	3	7	5	4	1		4		2	1		1	1	1	1		13
PANACOS PHARMACEUTICALS INC					10	1	5	7	2	7	6		9	1	4	3	4		1		4					1		13
GENZYME CORP		9	2		10	1												4		12	11	4		11	3			12
TRISTRATA INC		4			2			1	1	1			6			3	1	8		6	1		6		2			10
PHARMASSET INC		1			7	4		5	1				2			1			1			1	1			2		9
JAPAN TOBACCO INC		4			5	7	2	5	3	2	1		3	9														9
INTELLECTUAL VENTURES										5	5		1			1	3			5	7				2	1		8
PHARMACYCLICS INC			1		6		5	5	2				5			1	2	2	1	7	6		1	4				8
ARENA PHARM INC		1			7				4											3			4					8
TRIMERIS INC			1		3	1		5					3	2	4			1										8
CONCERT PHARMACEUTICALS INC			4	4	8	1	8	2	5	7	6		7	5	5	1	1											8
MUTUAL PHARMACEUTICAL COMPANY								2	1	4	4		1		1	1	1											8
IDENIX PHARMACEUTICALS INC					6	4		5	1	1	1	1	6	2	1	1	1	3				1	1			1		7
ASTEX THERAPEUTICS LTD		7			6			5	3							2	1		3	4	7	1	6	2				7
HOFFMANN LA ROCHE	YES		1	1	6	3	4			6	4		4	1	2		1											7
AICURIS GMBH & CO KG		1			6	4		7	2	2	2		5															7
NEKTAR THERAPEUTICS					5	2	1	1		4	2	1																7
NEW YORK BLOOD CT INC					2	3	1						1	1	2			1									1	6
ZIRUS INC							1						1												5	5		6
RFS PHARMA LLC		2			4	2		6	2			1	3	2	2	1	1			1	2	1	1			4		6
CDG THERAPEUTICS INC \ UNIV ILLINOIS					3	1			1			5				2				2	3		3	2	4	1		6
ICN PHARMACEUTICALS SWITZERLAND					1			5		6	6		6		6	1								6	1			6
ALDER BIOPHARMACEUTICALS INC					2			1	2											4	5		4	3				6
CERULEAN PHARMA INC					2			3	2							1				2	6		3	1				6
MONDOBIOTECH LAB AG					5	3		3	6							6				6	6	6	6					6
ONO PHARMACEUTICAL CO		4			6	5		2	4				6	6	5	3				5	6		2					6
RANBAXY LAB LTD			2	1	4	1	4	1		4	4	1	1			2	2		1									6
PROGENICS PHARM INC							2	2		2	2		5		6	2												6

In Figure 24, the darker colors highlight the top values in each column. The companies who have an approved HIV protease inhibitor (PI) drug are quite dominant with the exception of Roche, and interesting observations can be made about many companies.

Abbott and its collaborator **Enanta,** and to a lesser degree **Gilead** and **Schering**) are interested in serine proteases because serine protease inhibitors are useful in Hepatitis C therapy. **Abbott** and **Gilead** use the serine protease inhibitors in combination therapy for patients with both HIV and HCV, while **Schering** appears to be more focused on HCV per se.

Cytovia is interested in drugs inducing apoptosis for cancer treatment (including Kaposi's sarcoma), and they mention combination therapies with these drugs and PI and reverse transcriptase (RTI) drugs.

There are companies in the matrix that have no patents mentioning indications at all. These companies form an interesting subset (**Concert, Aicuris, Nektar, Ranbaxy, Progenics**) that includes suppliers of intermediates, and developers of improved processes or formulations that could position them to be generic suppliers when the drugs are off-patent.

ACTIVITY TIMELINES OF SELECTED COMPANIES

The timelines for the inventive activity in the same companies (using earliest priority year for each invention) are presented in Figure 26. The companies are ranked on the **recency** of their activity. This presentation approach draws attention to recently active companies.

Novartis, with the founder patents, has the earliest appearance in Figure 25, and it has persistent later activity, as does its developer Bristol Myers Squibb. The top rank in the table belongs to Enanta, a company with collaborative relationship to Abbott, also highly ranked in the table. Zirus (Herpes), Aicuris (synthesis) and Ranbaxy (synthesis) are all recent entrants in the field of the collection. Abbott, GSK and Merck all have significant Atazanavir-relevant activity recently, mostly relating to combination therapy regimens or other indications. Recent Boehringer and Schering activity relate to other HIV targets (Boehringer) or Hepatitis Virus (Schering). The latter observations are suggested by a comparison with Figure 24 where technology emphasis was covered.

Figure 26. Heat Diagram of Activity timelines

Select Assignee	Earliest Priority Years															# Inventions
	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	
ENANTA PHARM INC												4	12	9	15	40
GILEAD SCIENCES INC								3	4	3	1	6	8	8	4	36
ABBOTT LABORATORIES								4	18	1	11	5		5	4	48
ZIRUS INC														2	4	6
GLAXOSMITHKLINE							1	7	3	2	7	15	14	12	3	64
AICURIS GMBH & CO KG														4	3	7
MERCK & CO INC		4	3	5	19	14	23	19	6	15	10	7	6	2	3	134
RANBAXY LAB LTD											1			2	3	6
BOEHRINGER INGELHEIM INT								1	3	4	1	4	8		3	24
CONCERT PHARMACEUTICALS INC													4	2	2	8
BRISTOL MYERS SQUIBB CO					1	2	3	8	10	24	14	12	11	8	1	92
SCHERING CORP						1					1	4	7	5	1	18
NOVARTIS AG	1	2								1	12	7	5	3	1	31
NEKTAR THERAPEUTICS									1				2	3	1	7
AMPLYX PHARMACEUTICALS INC											1	1		1	1	3
EUTICALS PRIME EUROP THERAPEUTICALS					1			1							1	3
ESTEVE QUIMICA SA															1	1
INTELLECTUAL VENTURES														8		8
SYNTA PHARMACEUTICALS CORP												4	5	5		14
SEQUOIA PHARMACEUTICALS INC								3	1	2		1	1	5		13
TIBOTEC (J&J)					1	2	9	11	11	17	10	11	9	3		78
VIROCHEM PHARMA INC									4	4	1	1		3		13
ARDEA BIOSCIENCES INC													1	2		3
PROGENICS PHARM INC											1		4	1		6
AUSPEX PHARMACEUTICALS INC												1	2	1		4
ALTIRIS THERAPEUTICS INC													2	1		3
PHARMACYCLICS INC									2	1	1	2	1	1		8
CYTOVIA INC								4	5	2	6	4		1		22
AGOURON (PFIZER)							3		6	8	10	5	2			34
PANACOS PHARMACEUTICALS INC								1	2	4	2	2	2			13
MONOGRAM BIOSCIENCES INC							2	1		3	5	1	2			14
PHARMASSET INC							3		2		1	1	2			9
ALBA THERAPEUTICS CORP												3	1			4
HOFFMANN LA ROCHE									1	3		2	1			7
LIAONING LIFENG SCI & TECHNOLOGY DEV CO LTD													1			1
TRISTRATA INC										2	3	5				10
ASTRAZENECA AB								3	2	7		4				16
GENZYME CORP							1		5	2	3	1				12
BAYER HEALTHCARE AG										1	3					4
SUMITOMO					1			1	1							3
ELAN PHARM INC						1										1

PATENT QUALITY INDICATORS FOR SELECTED COMPANIES

Some objective measurements can be made to assess patent quality. Two of these are the ratio of applications that are successfully prosecuted to obtain patent grants, and the breadth of geographic filing. Figure 27 provides information on these aspects of patent strength.

As a measure of grant success and hence novelty, each invention that has received a grant in at least one examining authority was counted, and is presented as a ratio of total filings.

As one measure of geographic breadth, the number of inventions filed in China, the European Office, Japan and the United States was determined and is reflected in the Thomson Reuters Quad Patent Index®. This measurement is not just about protection in large markets, but is also a measure of company confidence, since the investment required for geographically broad filing is substantial. Both measurements are lag indicators, and can underestimate companies that are recent entrants to the field. The table is ranked on grant ratio, and top values are highlighted.

Figure 27. Quality indicators

Selected Commercial Assignees	Invention Count	Number of Families with ≥1 Grants	Grant Ratio	Filed in EP-US-JP-CN	Thomson Reuters Quad Patent Index®
ELAN PHARM INC	1	1	1.00	0	0.00
BRISTOL MYERS SQUIBB CO	92	62	0.67	30	0.33
TIBOTEC (J&J)	78	48	0.62	52	0.67
MERCK & CO INC	134	80	0.60	19	0.14
GENZYME CORP	12	7	0.58	4	0.33
PHARMASSET INC	9	4	0.44	3	0.33
HOFFMANN LA ROCHE	7	3	0.43	4	0.57
NOVARTIS AG	31	13	0.42	23	0.74
ASTRAZENECA AB	16	6	0.38	9	0.56
PHARMACYCLICS INC	8	3	0.38	3	0.38
CYTOVIA INC	22	8	0.36	4	0.18
ABBOTT LABORATORIES	48	16	0.33	10	0.21
EUTICALS PRIME EUROP THERAPEUTICALS	3	1	0.33	0	0.00
SUMITOMO	3	1	0.33	0	0.00
AGOURON (PFIZER)	34	11	0.32	9	0.26
PANACOS PHARMACEUTICALS INC	13	4	0.31	5	0.38
SEQUOIA PHARMACEUTICALS INC	13	4	0.31	4	0.31
VIROCHEM PHARMA INC	13	4	0.31	1	0.08
BOEHRINGER INGELHEIM INT	24	7	0.29	6	0.25
GILEAD SCIENCES INC	36	9	0.25	12	0.33
BAYER HEALTHCARE AG	4	1	0.25	1	0.25
GLAXOSMITHKLINE	64	13	0.20	8	0.13
TRISTRATA INC	10	2	0.20	3	0.30
MONOGRAM BIOSCIENCES INC	14	2	0.14	3	0.21
NEKTAR THERAPEUTICS	7	1	0.14	1	0.14
CONCERT PHARMACEUTICALS INC	8	1	0.13	1	0.13
SCHERING CORP	18	1	0.06	5	0.28
LIAONING LIFENG SCI & TECHNOLOGY DEV CO	1	0	0.00	1	1.00
ALBA THERAPEUTICS CORP	4	0	0.00	1	0.25
PROGENICS PHARM INC	6	0	0.00	1	0.17
ENANTA PHARM INC	40	0	0.00	2	0.05
SYNTA PHARMACEUTICALS CORP	14	0	0.00	0	0.00
INTELLECTUAL VENTURES	8	0	0.00	0	0.00
AICURIS GMBH & CO KG	7	0	0.00	0	0.00
RANBAXY LAB LTD	6	0	0.00	0	0.00
ZIRUS INC	6	0	0.00	0	0.00
AUSPEX PHARMACEUTICALS INC	4	0	0.00	0	0.00
ALTIRIS THERAPEUTICS INC	3	0	0.00	0	0.00
AMPLYX PHARMACEUTICALS INC	3	0	0.00	0	0.00
ARDEA BIOSCIENCES INC	3	0	0.00	0	0.00
ESTEVE QUIMICA SA	1	0	0.00	0	0.00

SECTION 7: SPECIFIC ELEMENTS OF DEVELOPMENT

FOUNDER COMPOSITIONS

The founder composition for Atazanavir, invented at Novartis (then Ciba-Geigy) was presented earlier as a citation map (Figure 10), but the map is repeated here showing both forward and backward citations (Figure 29). The backward references represent earlier art referenced by Novartis, and because the patent was issued, it implies that the composition that was later named Atazanavir was new compared to earlier art. The earlier art includes work by Novartis, Abbott, Merck and Roche (Figure 30). The Roche document is particularly interesting. The map in Figure 31 is a forward citation map from the highlighted Roche patent, and it is extraordinarily highly cited, as well as being the founder case for a Roche protease inhibitor drug. As can be seen from the 3-generation citation map in Figure 31, the Roche patent is far more highly cited than the Atazanavir document, and contains 3950 citing documents published between 1990 and 2011. This high rate of citation is probably because it was the ground-breaker for this class of drugs, showing in 1989 that the HIV-aspartyl protease target was amenable to inhibition that resulted in disease modulation. Looking for very highly and persistently cited documents such as the Roche patent, and then analyzing their downstream references can allow insight into how the most foundational work in a field was followed up.

Figure 29. Citation map of the founder composition patent for Atazanavir

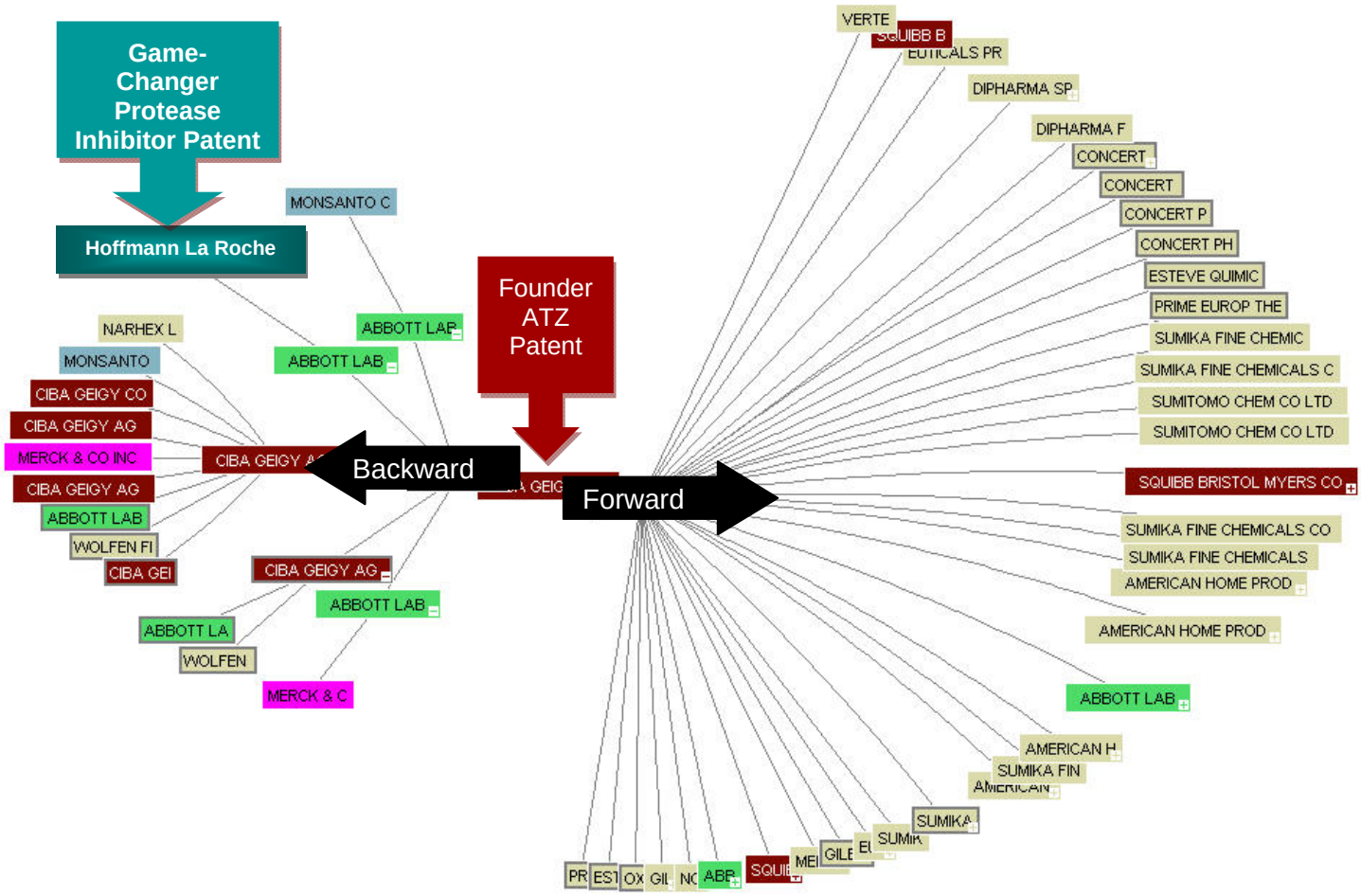


Figure 30. References made by the Founder Patent

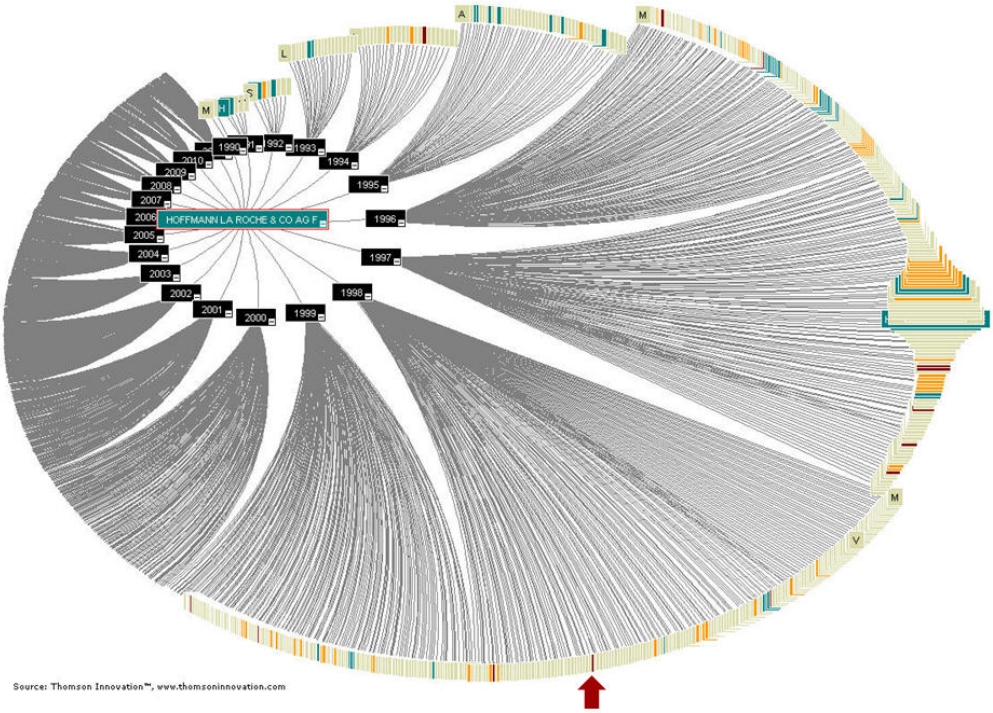
Publication Number	Publication Number	Assignee/Applicant	Truncated Title - DWPI
WO1994014436A1	**WO1994014436A1**	Abbott Laboratories	New di:heterocyclyl-substd. carbonate cpds. used as HIV protease inhibiting anti-retroviral agents esp. for treating AIDS
WO1994019332A1	**WO1994019332A1**	Abbott Laboratories	New di(thio)acyl derivs. of 1-hydrazino-2-hydroxyalkyl-3-amine cpds. useful in treatment of retroviral infections
EP402646A1	**EP402646A1**	Abbott Laboratories	New retro-viral protease cpds. for treatment of hiv 1 and 2
EP486948A2	**EP486948A2**	Abbott Laboratories	New retroviral protease inhibitors e.g. 2-hydroxy-1,4-butane-di:amine derivs., used for treating HIV
EP521827A1	**EP521827A1**	Ciba Geigy	New hydrazine derivs. useful as gag protease inhibitors for treatment of AIDS
EP604368A1	**EP604368A1**	Ciba Geigy	New 2-acyloxy:alkyl-hydrazine derivs. are used as retroviral protease inhibitors giving high blood levels esp. for treating AIDS.
US4794109A	**US4794109A**	Ciba Geigy	Antibacterial 2-heterocyclyl:alkyl-2 penem cpds. prepd. e.g. by cyclisation of 1-carboxy-phosphoranylidene-methyl-4-heterocyclyl-
EP236734A2	**EP236734A2**	Ciba Geigy	New 5-amino-4-hydroxy-valeric acid peptide derivs. useful as renin inhibitors, esp. hypotensives
EP532466A2	**EP532466A2**	Ciba Geigy	New 5-amino-4-hydroxy hexanoic acid derivs. useful as HIV-1 aspartate protease inhibitors for treating AIDS
EP346847A2	**EP346847A2**	F. Hoffmann-La Roche	New cyclic aminoacid derivs. useful as antiviral agents, esp. against HIV
EP491538A1	**EP491538A1**	Merck & Co.	Stereoselective prepn. of hydroxy ester, hydroxy amide and lactone by reacting N-protected-alpha-amino-aldehyde with homo enolate
EP337714A2	**EP337714A2**	Merck & Co.	New HIV protease inhibitors comprising amine protecting gp. linked to di:peptide isostere linked to aminoacid with small terminal gp.
WO1992008698A1	**WO1992008698A1**	Monsanto Company	New urea-contg. hydroxy:ethylamine derivatives are retroviral protease inhibitors for treating HIV infections
WO1992008699A1	**WO1992008699A1**	Monsanto Company	New urea-contg. hydroxy-ethylamine derivatives are retroviral protease inhibitors for treating HIV, cytomegalovirus and picornavirus etc.
WO1993018006A1	**WO1993018006A1**	Narhex Limited	New amine derivs. of oxo- and hydroxy-substd. hydrocarbon(s) are inhibitors of retroviral protease esp. aspartyl protease and HIV
DE1254461B	**DE1254461B**	Wolfen Filmfab	Hydrazine derivatives as additives to photographic emulsions

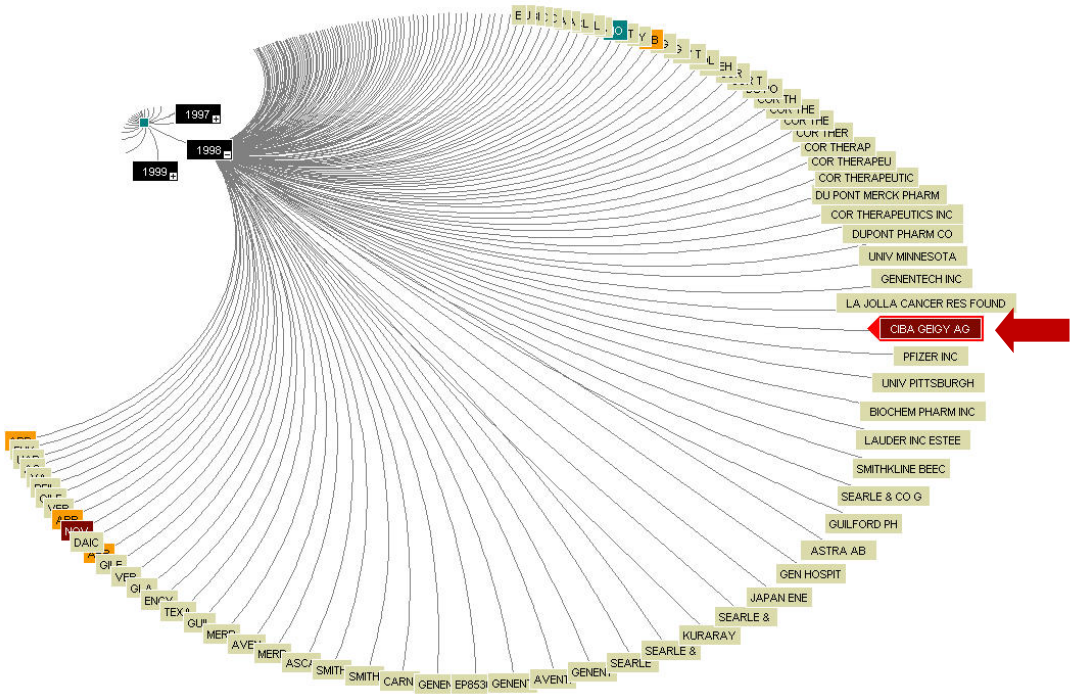
PROTEASE INHIBITOR BREAK-THROUGH

In Figure 31, the Roche citation map for its protease inhibitor patent is arranged to show 1st to 3rd generation citations according to their year of publication. In the first few years, citation was at a low frequency because the original document was still in the early stages of being noticed. The rate of citation then picked up speed, with an average rate of 280 references per year since 2000. The arrow points out the founder patent for the Novartis drug Atazanavir, which is within the 1998 branch of the map, and this branch is expanded in the view below. Along with ATZ, many of the drugs later approved for inhibition of HIV protease referred to the original Roche patent, and are therefore included among the citing references in this cite map.

Figure 31. Citation Map of Roche's Early HIV Protease Invention

Publication Years	Citing Documents
1989	1
1990	2
1991	5
1992	8
1993	20
1994	24
1995	45
1996	120
1997	115
1998	164
1999	156
2000	187
2001	221
2002	268
2003	335
2004	255
2005	252
2006	295
2007	273
2008	288
2009	297
2010	371
2011	248
All	3950





FORMULATIONS

Even before a drug is approved, it is crucial to be able to make it in a form a) that is usable in clinical trials, b) that has reasonable bioavailability, i.e. can be given in feasible doses and by practical routes, and c) that has an appropriate half-life in the body. Early in development, in 1998, Bristol-Myers Squibb developed a method to make a better form of Atazanavir, a sulfated version of the drug that was more stable and had higher bioavailability than the form used in early preclinical testing (Figure 32). After approval, it is also typical to find other efforts to improve these qualities.

Figure 32 Formulation Development

WO1999036404A1 BISULFATE SALT OF HIV PROTEASE INHIBITOR

Bibliography

DWPI Title ?
New crystalline bisulfate salt of azapeptide HIV protease inhibitor, having high solubility and oral bioavailability

DWPI Assignee/Applicant ?
BRISTOL-MYERS SQUIBB CO (BRIM-C)

Inventor ?
SINGH Janak; PUDIPEDDI Madhusudhan; LINDRUD Mark D.

DWPI Inventor ?
LINDREED M; LINDRUD M D; MADHUSUDHAN P; PUDIPEDDI M; SINGH J

Application Number / Date ?
WO1998US27382A / 1998-12-22

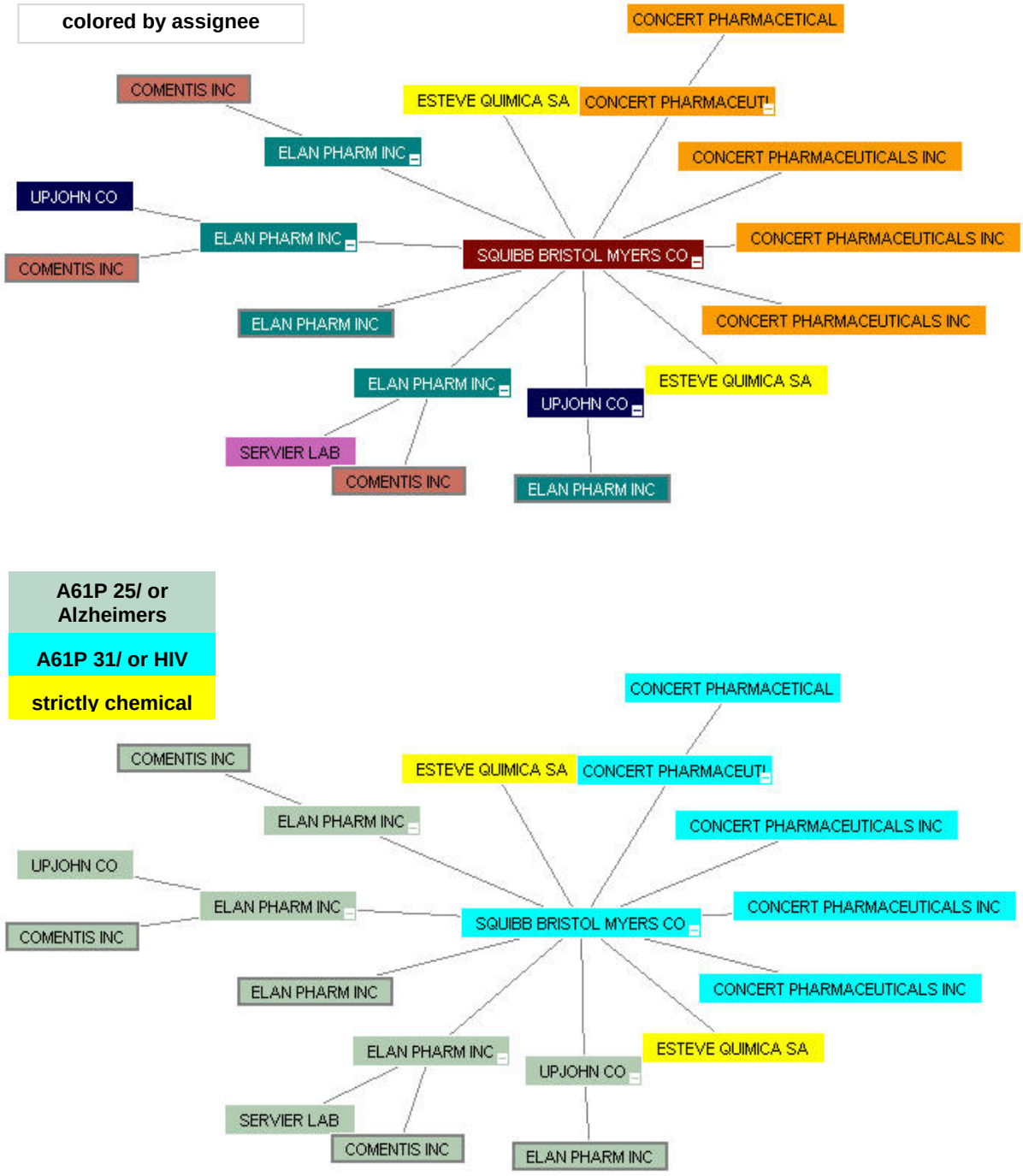
Abstract

DWPI Abstract ?
(WO1999036404A1)
Novelty
The bisulfate salt (I) of [3S-(3R*, 8'R, 9'R*, 12R*)]-3, 12-bis- (1, 1-dimethylethyl)-8-hydroxy-4, 11-dioxo-9-(phenylmethyl)- 6-[[4-(2-pyridinyl)-phenylmethyl]-2, 5, 6, 10, 13-pentaazatetradecane dioic acid dimethyl ester is new.

Advantage
(I) has superior aqueous solubility and dissolution behavior compared to other salts, as well as high stability and significantly improved oral bioavailability in animals compared with the free base (II) (see).In tests in dogs, the absolute oral bioavailability of (I) was 20% when administered in unformulated solid form placed in a gelatin capsule; whereas crystalline (II) showed minimal bioavailability under these conditions. In solubility studies, (II) had a solubility of less than 1 mg/ml in water at pH 1.8 adjusted with sulfuric acid, compared with 4-5 mg/ml for (I) at a comparable pH.(I) also showed excellent solid state physical stability when stored at 40°C and 75% relative humidity for as long as 9 months, whereas the methanesulfonate, hydrochloride and sulfate salts showed significant changes in thermal behavior when stored under these conditions for as long as two weeks.

Downstream citation to the Bristol Myers Squibb patent covering the sulfated form of Atazanavir is shown in Figure 33. The top citation map shows that several different assignees cited the patent, and the bottom map is identical except that the colors are changed to highlight the purpose of the companies who cited Bristol-Myers Squibb. On the right of the lower version, the aqua colored patents are coded A61P 31/ which is the International Patent Classification Code (IPC)[9] for HIV treatment. These companies are developing forms of Atazanavir that can be used in HIV. On the left, the light green colored nodes bear the code (A61P 25/) indicating that they are interested in developing Atazanavir or derivatives of it as treatments for Alzheimers disease. The yellow nodes do not mention disease treatment, but are focused on chemistry of Atazanavir.

Figure 33 Formulation patent and follow-on activity



[9] See Section 9 for a more extended discussion of Patent Classification

Figure 34. References to Bristol Myers Squibb formulation patent refer to different disease targets

Publication Number	Target	Assignee/Applicant	Truncated Title - DWPI
WO1999036404A1	HIV	Bristol-Myers Squibb	New crystalline bisulfate salt of azapeptide HIV protease inhibitor, having high solubility and oral bioavailability
WO2010132663A1	HIV	Concert Pharmaceticals	New pegylated forms of deuterium substituted atazanavir sulfate compounds are HIV protease inhibitors useful for
EP2003120B1	HIV	Concert Pharmaceticals	New azepeptide compound useful in the manufacture of medicament for the treatment of HIV infection and virus
EP2003120A1	HIV	Concert Pharmaceticals	New azepeptide compound useful in the manufacture of medicament for the treatment of HIV infection and virus
EP2116532A1	HIV	Concert Pharmaceticals	New deuterated atazanavir useful for the treatment of diseases e.g. HIV infection
US7432389B2	Alzheimers	Elan Pharmaceuticals	New disubstituted amine derivatives, useful for treating Alzheimer's disease and other degenerative diseases
US7034182B2	Alzheimers	Elan Pharmaceuticals	New disubstituted amine derivatives, useful for treating Alzheimer's disease and other degenerative diseases
WO2002094768A2	Alzheimers	Elan Pharmaceuticals	New aza hydroxylated ethyl amine compounds as e.g. Beta-secretase activity inhibitors, useful for the treatment of e.g.
WO2010146119A1	Chemical	Esteve Química	Preparing atazanavir, useful to treat viral infection, comprises condensing 3-amino-4-phenyl-1-(N-(4-pyridin-2-yl-benzyl)-
EP2272830A1	Chemical	Esteve Química	Preparing atazanavir, useful to treat viral infection, comprises condensing 3-amino-4-phenyl-1-(N-(4-pyridin-2-yl-benzyl)-
US7576120B2	Alzheimers	Les Laboratoires Servier	New azabicyclic derivative useful to treat e.g. cognitive deficits associated with brain aging, neurodegenerative diseases,
US7504420B2	Alzheimers	Oklahoma Medical Res Found	New isophthalamide derivatives as beta secretase inhibitor useful for treating Alzheimer's disease
WO2004052348A2	Alzheimers	Pharmacia & Upjohn	Composition, useful to treat disorders involving cholinergic hypofunction, comprises an alpha-7 nicotinic acetylcholine
US6960664B2	Alzheimers	Pharmacia & Upjohn	New aza hydroxylated ethyl amine compounds as e.g. Beta-secretase activity inhibitors, useful for the treatment of e.g.

SYNTHESIS IMPROVEMENTS

As development of a drug continues, various entities may become interested in manufacture, especially if a way can be found to manufacture a drug more cheaply. Such companies can potentially make the drug for the patent holder, or if the composition patent has expired, the process could be sold or licensed to others for manufacture of competing generic products. The patent application shown in Figure 35 is a method of synthesis for Atazanavir that is stated to be cost effective for large scale manufacture.

Figure 35 Synthesis Stage of Development

CN101391978B Novel synthesis method of HIV-1 protease inhibiter atazanavir

Bibliography

DWPI Title ?
Novel method for synthesizing HIV-1 protease inhibitor atazanavir, involves carrying out nucleophilic substitution reaction between benzyl hydrazine and methyl carbamate derivatives to prepare azahexane derivative

English Title ?
Novel synthesis method of HIV-1 protease inhibiter atazanavir

DWPI Assignee/Applicant ?
SHANGHAI INST MATERIA MEDICA (SHAN); SHANGHAI PHARM INST CHINESE ACAD SCI (SHAN)

Inventor ?
LONG Ya-qiu; FAN Xing; SONG Yan-li

Publication Date (Kind Code) ?
2009-03-25 (A)

Abstract

DWPI Abstract ?
(CN101391978A_)
Novelty
HIV-1 protease inhibitor atazanavir synthesizing involves carrying out a nucleophilic substitution reaction between N-1-[N-(methoxycarbonyl)-L-tert.-leucinyl]-N-2-[4-(2-pyridyl)-benzyl]hydrazine and (S)-1-((S)-4-chloro-3-carbonyl-1-phenylbutan-2-yl-2-amino)-3, 3-dimethyl-1-carbonylbutan-2-yl-methyl carbamate at 0-80° C for 2-24 hours to prepare 1-[4-(2-pyridyl)phenyl]-5(S)-2, 5-bis{[N-(methoxycarbonyl)-L-tert.-leucinyl]amino}-4-carbonyl-6-phenyl-2-azahexane.

Detailed Description
The HIV-1 protease inhibitor atazanavir is synthesized by carrying out a nucleophilic substitution reaction between N-1-[N-(methoxycarbonyl)-L-tert.-leucinyl]-N-2-[4-(2-pyridyl)-benzyl]hydrazine and (S)-1-((S)-4-chloro-3-carbonyl-1-phenylbutan-2-yl-2-amino)-3, 3-dimethyl-1-carbonylbutan-2-yl-methyl carbamate at 0-80° C for 2-24 hours to prepare 1-[4-(2-pyridyl)phenyl]-5(S)-2, 5-bis{[N-(methoxycarbonyl)-L-tert.-leucinyl]amino}-4-carbonyl-6-phenyl-2-azahexane. The 1-[4-(2-pyridyl)phenyl]-5(S)-2, 5-bis{[N-(methoxycarbonyl)-L-tert.-leucinyl]amino}-4-carbonyl-6-phenyl-2-azahexane is reduced at -78° C to 60° C for 2-24 hours to prepare 1-[4-(2-pyridyl)phenyl]-5(S)-2, 5-bis{[N-(methoxycarbonyl)-L-tert.-leucinyl]amino}-4(S)-hydroxy-6-phenyl-2-azahexane.

Advantage
The HIV-1 protease inhibitor atazanavir synthesizing method enables to prepare HIV-1 protease inhibitor atazanavir conveniently with high yield in simple and cost effective manner and is suitable for large scale production of atazanavir.

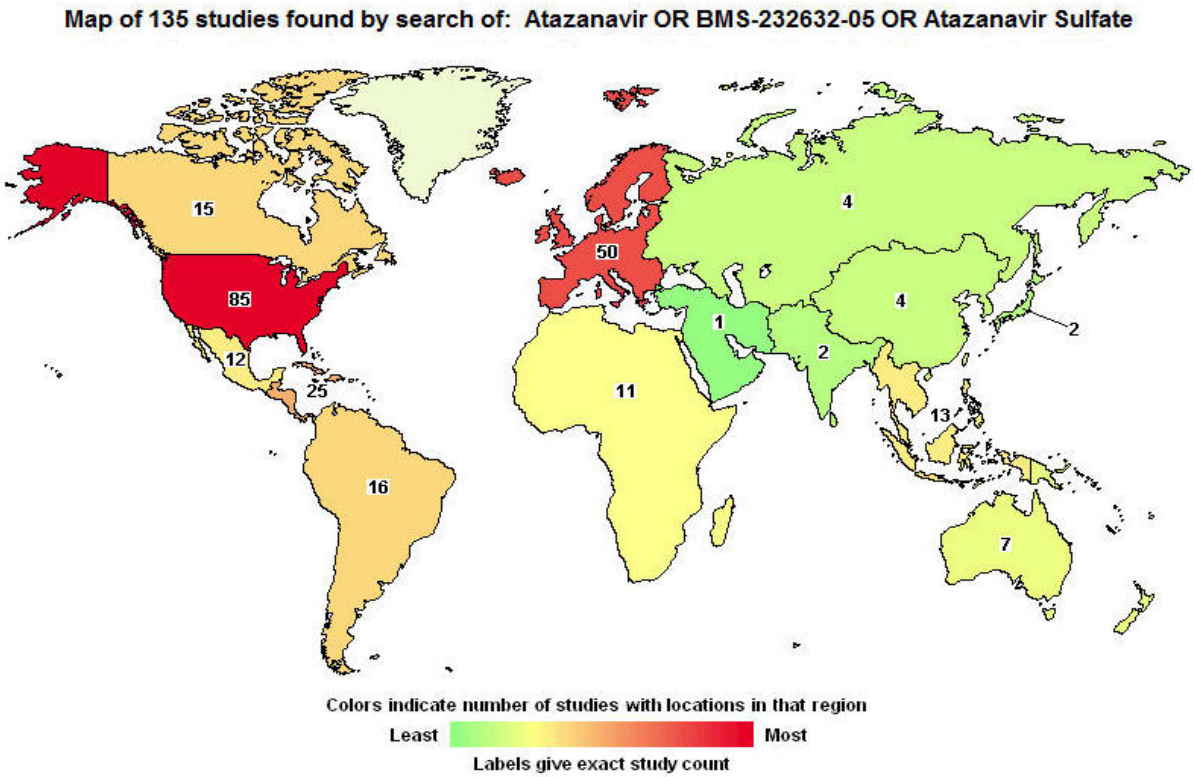
PROPRIETARY DRUGS AND LITIGATION

The owners of proprietary drugs that are protected by patents do assert their patent rights against companies they believe are infringing. In the case of Atazanavir, Novartis and Bristol Myers Squibb filed suit[10] on April 1, 2010 against Teva Pharmaceuticals after being notified that Teva had applied to the US FDA for an ANDA (Abbreviated New Drug Application) for Atazanavir before expiration of the Novartis and Bristol Myers Squibb patents US 5,849,911 and US 6,087,383. The suit alleges infringement by Teva and remains to be decided at time of writing. The existence of US lawsuits is recorded with the US PTO and is searchable in the US patent data.

CLINICAL TRIALS AND PATENTING

Most clinical trials do not give rise to patents because they are meant to test the safety and efficacy of the drug in established and already-patented forms, but they can contribute information supporting drug regimens that have already been claimed in patents. The US National Institutes of Health website where clinical trials information is collected is http://clinicaltrials.gov. The information in Figure 36 on trials of Atazanavir was collected from that site. A list of 420 clinical trials on HIV-protease inhibitors, including subject, sponsors, phase and status is provided in Appendix C. Another useful site for clinical information is the European Bioinformatics Institute site https://www.ebi.ac.uk/, part of the European Molecular Biology Laboratory.

Figure 36 Atazanavir Clinical Trials



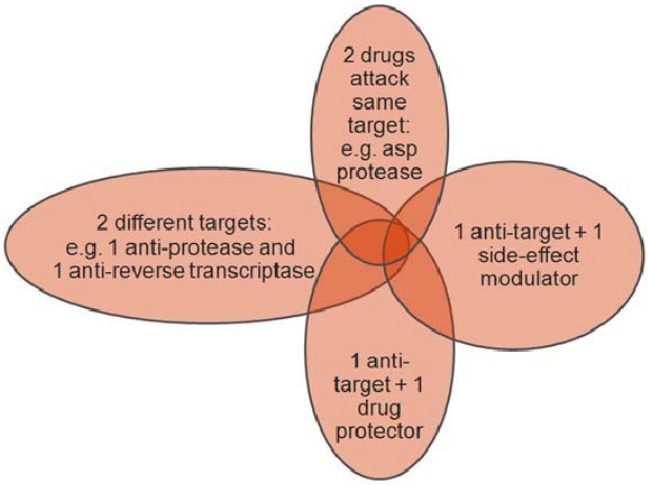
[10] Case Number 1:11-cv-00353 Court: Delaware

SECTION 8: DRUG COMBINATIONS

COMBINATION TYPES

“Combination” is a term of art in drug development and this specific word reliably appears in patent applications that cover a drug therapy that involves more than one bioactive agent. The types of drug combinations may differ, and common ones are diagrammed in Figure 37.

Figure 27 Types of Combinations



There are some combinations aimed at preventing development of drug resistance (biochemical or genetic adaptation), others aimed at preventing drug degradation (meaning that less drug would be required for therapeutic effect), and still others meant to mitigate unavoidable side-effects caused by the drug. All have been employed in the case of Atazanavir. The overlap in the diagram is meant to convey that some combinations have more than one strategy behind them, and also that there may be combinations that employ more than 2 therapeutic entities.

Examples for some combination types are provided on the following pages, followed by an overlap matrix that allows each kind of combination to be identified.

TWO DRUGS DIRECTED AT THE SAME TARGET

Multiple drugs exist in the HIV-protease inhibitor class. Drugs affecting the same target in the HIV replication pathway are often used together to reduce the ability of HIV to develop drug resistance by developing variants. Treating with two drugs attacking the same target reduces the chances that effective variants will arise, or as in the example shown in Figure 38, help to overcome resistance that has begun to develop.

Figure 38. Combination using two PI drugs and aimed at rescue

WO2005058248A2 A METHOD OF TREATING HIV INFECTION IN ATAZANAVIR RESISTANT PATIENTS USING A COMBINATION OF ATAZANAVIR AND ANOTHER PROTEASE INHIBITOR

Bibliography

DWPI Title ?
Use of atazanavir or its salt and at least one other HIV protease inhibitor (e.g. ritonavir) for treating HIV infection, where the infecting HIV strain has become resistant to atazanavir

DWPI Assignee/Applicant ?
BRISTOL-MYERS SQUIBB CO (BRIM-C); COLONNO R J (COLO-I); FRIBORG J (FRIB-I); ROSE R E (ROSE-I)

Inventor ?
COLONNO Richard J., US FRIBORG JR. Jacques, US ROSE Ronald E., US

Publication Date (Kind Code) ?
2005-06-30 (A2)

DWPI Accession / Update ?
2005-479195 / 200548

Application Number / Date ?
WO2004US41968A / 2004-12-14

Priority Number / Date / Country ?
US2003529678P / 2003-12-15 / US
US2003532746P / 2003-12-23 / US
WO2004US41968A / 2004-12-14 / US

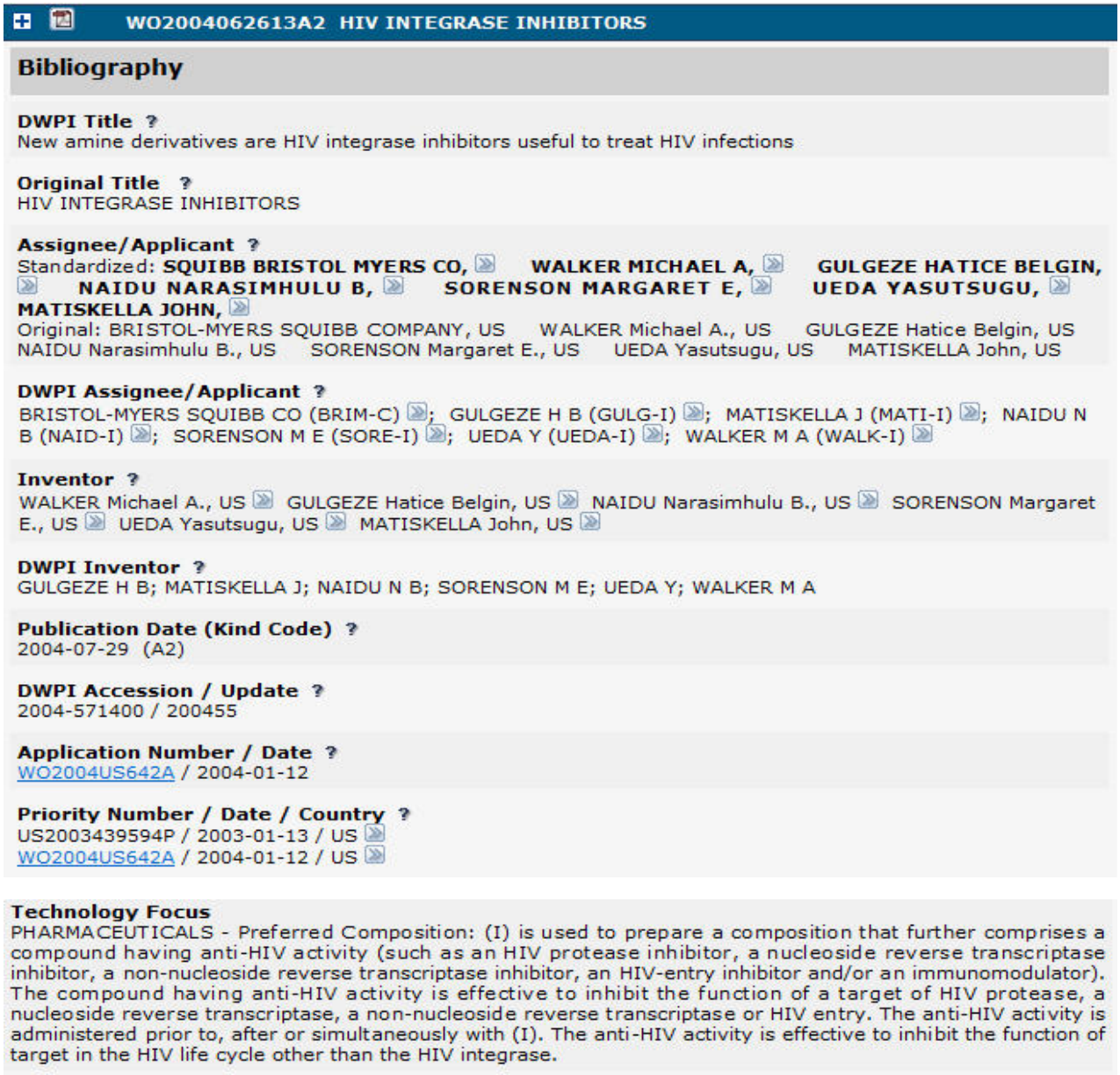
Abstract

DWPI Abstract ?
(WO2005058248A2)
Novelty
Treating HIV infection in a human patient, where the infecting HIV strain has become resistant to atazanavir, comprising administration of atazanavir (I) or its salt and at least one other HIV protease inhibitor (II), is new.
Detailed Description
An INDEPENDENT CLAIM is also included for enhancing the effectiveness of a second HIV protease inhibitor in treating HIV infection in a human patient whose HIV strain has become resistant to (I) or its salt, comprising administration of (I) or its salt, which is effective in maintaining the resistant strain, in combination with the second HIV protease inhibitor.
Activity
Anti-HIV.No biological data given.
Mechanism
HIV protease inhibitor.
Use
(I) and (II) are useful for treating HIV infection in human, where the infecting HIV strain is resistant to atazanavir. (claimed).
Advantage
(I) and (II) are effective in treating HIV infection, where the infecting strain is resistant to (I). The amount of (II) administered to the human patient in combination with (I) or its salt is less than the amount required in the absence of (I) (all claimed). (II) is a potent and effective antiretroviral. (I) is a potent inhibitor of HIV-1 protease.
Technology Focus
BIOLOGY - Preferred Method: The resistance is manifested by the existence of a signature mutation consisting of the Ile50Leu mutation in the HIV protease and the amount of (I) is sufficient to maintain the existence of the Ile50Leu mutation in the HIV protease.
PHARMACEUTICALS - (II) is saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir or lopinavir.

TWO DRUGS DIRECTED AT DIFFERENT TARGETS

Another way to fight an agent like a virus is to attack it at different steps of the viral life cycle, including viral uptake by cells, entry of viral nucleic acids or proteins into the replication, transcription, or translation processes they require, viral assembly proteins like HIV protease, and processes for exit from the cell. Integrase inhibitors prevent integration of viral coding regions into the DNA of the host cell. In the example in Figure 39, the integrase inhibitor treatment is performed in combination with an inhibitor of other targets, one of which is HIV protease.

Figure 39 Multi-Target Combination



Citations to this document mainly come from Bristol-Myers Squibb itself, and from Takeda and Merck (Angeletti). In Figure 40, all the nodes with red borders mention Atazanavir by name, and as in the case of the record shown, are discussing cocktails of drugs with multiple targets. The Takeda applications do not mention Atazanavir, and instead they are targeting dipeptidyl peptidase as a means to interfere with various other disease entities. Takeda acquired at least one of its lead compounds by acquisition of Syrrx Inc.

Figure 40 Citations to the Integrase Combination Patent

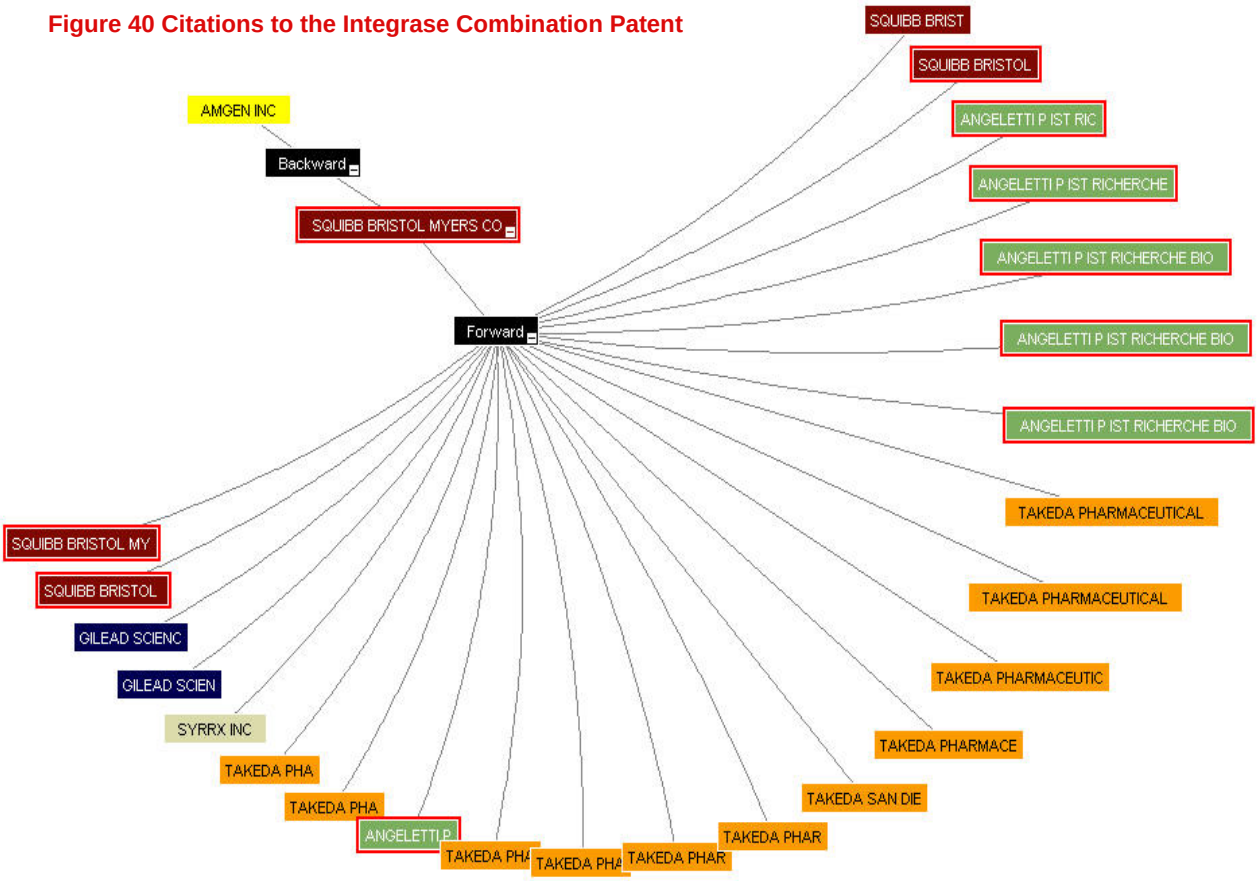


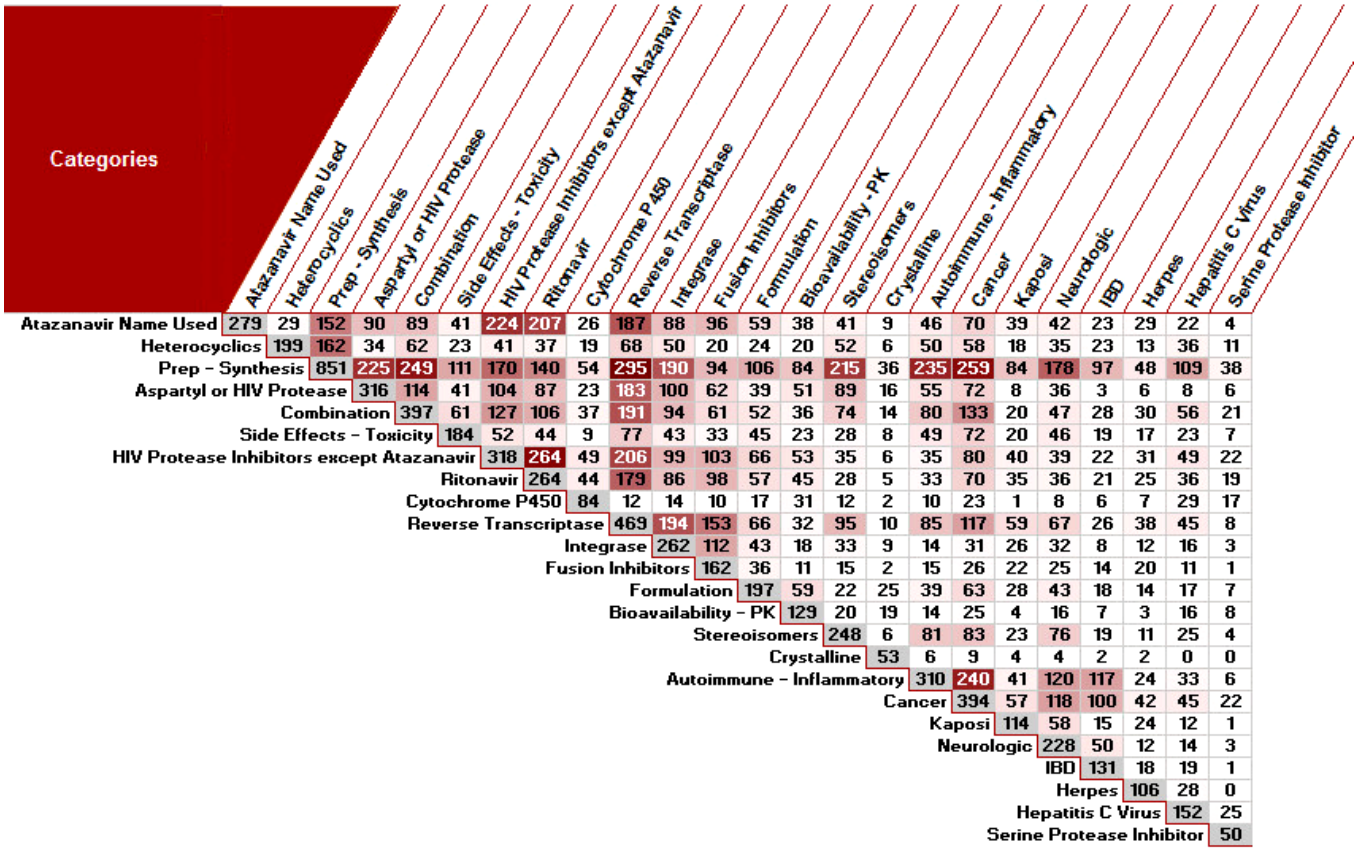
Figure 41. Patents citing Bristol Myers Integrase-ATZ combination patent

Publication Number	Assignee/applicant	ATZ	Truncated Title - DWPI
US7115601B2	Bristol Myers Squibb		New spirocycle-substituted pyrimidinecarboxamides are HIV integrase inhibitors, useful for treating HIV infection and AIDS
WO2004062613A2	Bristol Myers Squibb		New amine derivatives are HIV integrase inhibitors useful to treat HIV infections
EP1756069A2	Bristol Myers Squibb		New spirocycle-substituted pyrimidinecarboxamides are HIV integrase inhibitors, useful for treating HIV infection and AIDS
WO2007064619A1	Bristol Myers Squibb		New bicyclic pyrimidinone derivatives useful for treating HIV infections and AIDS
WO2011046873A1	Bristol Myers Squibb		New 5-hydroxy-3H-pyridin-4-one compounds are HIV integrase inhibitors, useful for treating AIDS and HIV infection
WO2008154246A1	Bristol Myers Squibb		New pyrimidinone compounds used in the preparation of composition for treating HIV infections and acquired immune deficiency syndrome
US7820660B2	Instituto Angeletti (Merck)		New dihydroxypyrimidine carboxamide derivatives useful for the treatment of prevention of infection by HIV and for the treatment,
US7169780B2	Instituto Angeletti (Merck)		New dihydroxypyrimidine carboxamide derivatives useful for the treatment of prevention of infection by HIV and for the treatment,
US7459452B2	Instituto Angeletti (Merck)		New dihydroxypyrimidine carboxamide derivatives are HIV integrase inhibitors used for treating infection by HIV and AIDS
US7435734B2	Instituto Angeletti (Merck)		New dihydroxypyrimidine carboxamide derivatives useful for the treatment of prevention of infection by HIV and for the treatment,
US7232819B2	Instituto Angeletti (Merck)		New dihydroxypyrimidine carboxamide derivatives are HIV integrase inhibitors used for treating infection by HIV and AIDS
US7217713B2	Instituto Angeletti (Merck)		New dihydroxypyrimidine carboxamide derivatives useful for the treatment of prevention of infection by HIV and for the treatment,
WO2005070901A2	Gilead Sciences		New pyrimidyl phosphonate compounds useful as HIV integrase inhibitors for treatment of e.g. HIV infection, AIDS, AIDS-related complex
WO2005016911A1	Syrrx Inc		New pyrimidine derivatives are dipeptidyl peptidase inhibitors useful to treat e.g. diabetes, cancer, autoimmune disorders, rheumatoid
US7470700B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors useful to treat e.g. diabetes, cancer, autoimmune disorders, rheumatoid
US7550590B2	Takeda		New heterocyclic compounds are dipeptidyl peptidase IV inhibitors useful to treat e.g. type 2 diabetes mellitus, obesity, autoimmune
US7579357B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors useful to treat e.g. diabetes, cancer, autoimmune disorders, rheumatoid
US7687625B2	Takeda		New heterocyclic compounds are dipeptidyl peptidase IV inhibitors useful to treat e.g. type 2 diabetes mellitus, obesity, autoimmune
US7781584B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors, useful for treating e.g. diabetes, cancer, rheumatoid arthritis, psoriasis,
US7790736B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors useful to treat e.g. diabetes, cancer, autoimmune disorders, rheumatoid
US7790734B2	Takeda		New heterocyclic derivatives are dipeptidyl peptidase IV inhibitors useful to treat e.g. diabetes, cancer, autoimmune disorders,
US7807689B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors, useful for treating e.g. diabetes, cancer, rheumatoid arthritis, psoriasis,
US7872124B2	Takeda		New azaheteroaryl compounds are dipeptidyl peptidase IV inhibitors used for treating and preventing e.g. diabetes, obesity, organ
US7906523B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors, useful for treating e.g. diabetes, cancer, rheumatoid arthritis, psoriasis,
US7723344B2	Takeda		New pyrimidine derivatives are dipeptidyl peptidase inhibitors useful to treat e.g. diabetes, cancer, autoimmune disorders, rheumatoid

USING OVERLAP TO FIND COMBINATIONS OF INTEREST

By segmenting the collection into overlapping subcollections dealing with specific topics, it is possible to develop a matrix that documents the overlap and allows the user to focus on inventions that include overlaps of specific interest. In Figure 42, this has been performed for the Atazanavir collection. Areas of high overlap, such as the use of protease inhibitors together with reverse transcriptase inhibitors and integrase inhibitors are notable, as is the focus on Inflammatory Disease and Cancer. This matrix was created using an application (Thomson Data Analyzer®) that allows click-through to the records of interest. The Excel Appendix permits a similar focusing by using filtering.

Figure 42. Overlap between Subject matter Categories Identifies size of Overlapping Set



Categories	Atazanavir Name Used	Heterocyclics	Prep - Synthesis	Aspartyl or HIV Protease	Combination	Side Effects - Toxicity	HIV Protease Inhibitors except Atazanavir	Ritonavir	Cytochrome P450	Reverse Transcriptase	Integrase	Fusion Inhibitors	Formulation	Bioavailability - PK	Stereoisomers	Crystalline	Autoimmune - Inflammatory	Cancer	Kaposi	Neurologic	IBD	Herpes	Hepatitis C Virus	Serine Protease Inhibitor
Atazanavir Name Used	279	29	152	90	89	41	224	207	26	187	88	96	59	38	41	9	46	70	39	42	23	29	22	4
Heterocyclics	199	162	34	62	23	41	37	19	68	50	20	24	20	52	6	50	58	18	35	23	13	36	11	
Prep - Synthesis	851	225	249	111	170	140	54	295	190	94	106	84	215	36	235	259	84	178	97	48	109	38		
Aspartyl or HIV Protease	316	114	41	104	87	23	183	100	62	39	51	89	16	55	72	8	36	3	6	8	6			
Combination	397	61	127	106	37	191	94	61	52	36	74	14	80	133	20	47	28	30	56	21				
Side Effects - Toxicity	184	52	44	9	77	43	33	45	23	28	8	49	72	20	46	19	17	23	7					
HIV Protease Inhibitors except Atazanavir	318	264	49	206	99	103	66	53	35	6	35	80	40	39	22	31	49	22						
Ritonavir	264	44	179	86	98	57	45	28	5	33	70	35	36	21	25	36	19							
Cytochrome P450	84	12	14	10	17	31	12	2	10	23	1	8	6	7	29	17								
Reverse Transcriptase	469	194	153	66	32	95	10	85	117	59	67	26	38	45	8									
Integrase	262	112	43	18	33	9	14	31	26	32	8	12	16	3										
Fusion Inhibitors	162	36	11	15	2	15	26	22	25	14	20	11	1											
Formulation	197	59	22	25	39	63	28	43	18	14	17	7												
Bioavailability - PK	129	20	19	14	25	4	16	7	3	16	8													
Stereoisomers	248	6	81	83	23	76	19	11	25	4														
Crystalline	53	6	9	4	4	2	2	0	0															
Autoimmune - Inflammatory	310	240	41	120	117	24	33	6																
Cancer	394	57	118	100	42	45	22																	
Kaposi	114	58	15	24	12	1																		
Neurologic	228	50	12	14	3																			
IBD	131	18	19	1																				
Herpes	106	28	0																					
Hepatitis C Virus	152	25																						
Serine Protease Inhibitor	50																							

SECTION 9: USE OF CLASSIFICATION SYSTEMS TO ASSIST SEARCHING

Rather than looking through the classification systems to try to identify applicable codes by inspection, it is often worthwhile to use a small, precise collection to determine codes actually used by the examiners, leveraging the examiners' expertise by determining how they have classified highly relevant documents. The codes identified this way can then be used either to search more widely in combination with key terms, or to restrict the range of an unfocused collection to a more relevant set. A comparison of patent classifications was performed for the small set of documents that was closest to the Atazanavir composition invention. The intention in all classification systems is that several or even multiple codes be applied to the same invention, because most inventions involve several aspects that are covered by different codes. If only a single code is used without also limiting with either key terms or another code, the retrieval will contain a variety of inventions that have a common aspect, but otherwise might be quite diverse.

INTERNATIONAL PATENT CLASSIFICATION AND RELATED SYSTEMS

The IPC codes were the classification system deemed most widely useful, since they are applicable regardless of country of origin, and are widely available in search systems[11]. Areas in two sections of the International Patent Classification system (IPC) were prominent in the collection (Figure 43). Section C covers Chemistry, and Section A covers medicines. The Section C chemical codes of interest were established long ago, (IPC version 2), and they were in use over the entire span of Atazanavir development. In contrast, the Section A anti-viral codes were introduced much later and do not cover the whole time span of the collection[12].

Figure 43. Highest Relevance IPC

C	**SECTION C — CHEMISTRY; METALLURGY**
C07	**ORGANIC CHEMISTRY**
C07D	**HETEROCYCLIC COMPOUNDS [2]**
	Heterocyclic compounds having only nitrogen as ring hetero atom [2]
C07D 213/00	**Heterocyclic compounds containing six-membered rings, not condensed with other rings, with one nitrogen atom as the only ring hetero atom and three or more double bonds between ring members or between ring members and non-ring members [2]**
C07D 213/02	· having three double bonds between ring members or between ring members and non-ring members [2]
C07D 213/04	· · having no bond between the ring nitrogen atom and a non-ring member or having only hydrogen or carbon atoms directly attached to the ring nitrogen atom [2]
C07D 213/24	· · · with substituted hydrocarbon radicals attached to ring carbon atoms [2]
C07D 213/36	· · · · Radicals substituted by singly-bound nitrogen atoms (nitro radicals C07D 213/26) [2]
C07D 213/38	· · · · · having only hydrogen or hydrocarbon radicals attached to the substituent nitrogen atom [2]
C07D 213/40	· · · · · Acylated substituent nitrogen atom [2]
C07D 213/42	· · · · · having hetero atoms attached to the substituent nitrogen atom (nitro radicals C07D 213/26) [2]

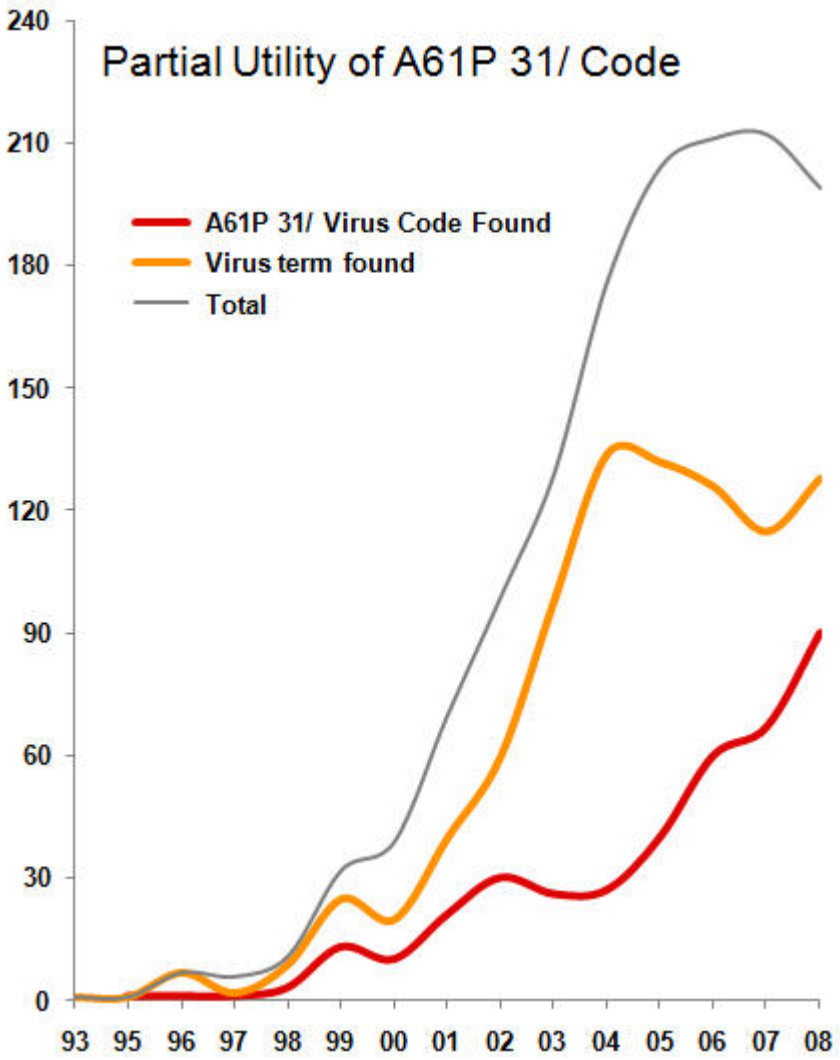
A	**SECTION A — HUMAN NECESSITIES**
A61	**MEDICAL OR VETERINARY SCIENCE; HYGIENE**
A61P	**SPECIFIC THERAPEUTIC ACTIVITY OF CHEMICAL COMPOUNDS OR MEDICINAL PREPARATIONS [7]**
A61P 31/00	**Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics [7]**
A61P 31/12	· Antivirals [7]
A61P 31/14	· · for RNA viruses [7]
A61P 31/16	· · · for influenza or rhinoviruses [7]
A61P 31/18	· · · for HIV [7]

[11] http://www.wipo.int/classifications/ipc/ipc8/

[12] Even though the code reform in 2005 involved automated application of new codes to the backfile when earlier family members existed, the A61P 31/ codes are present only on a minority fraction of documents in the early part of the Atazanavir collection.

The utility of the HIV-specific A61P 31/ code is not as good for the early part of the collection. In Figure 44 its appearance is compared to the appearance of virus or HIV terms in the titles and abstracts of the documents, and the two deviate from one another substantially prior to 2007. A61P 31/ is not totally absent in the earlier period (as a result of the backfile reclassification, which propagated the code to documents with later family members that were directly classified as A61P 31/).

Figure 44. Tracking the A61P 31/ code in the collection



Since there are three other code systems based on the IPC sytem, these were compared with one another in parallel. ECLA codes (European Classifications) are based on the IPC system, but are more detailed. ICO codes[13] (in-computer only) are internal codes that are applied and used by EPO examiners and only appear in electronic records. They have as a section code the alphabet letter offset 10 characters from the letter on the standard code series (e.g. M for C). The Japanese patent offfice also has its own classification (FI codes)

[13] The ICO codes are not generally available except through a few proprietary systems. The ICO section used for this report was kindly provided by Heiko Wongel of the European Patent Office.

based on the IPC, but with sometimes very significant differences. This system is only used on JP documents.

Because the Section C codes were more consistent over the collection period, the top chemical codes appearing in each classification system were ranked within that system, and the rankings were pooled in the table shown in Figure 45. The C07D 213/ codes (highlighted) have the most activity in all the code systems (IPC, ECLA, FI and ICO). The ICO codes in particular are interesting, because they subdivide C07D 213/42 into M07D 312/42C and M07D 213/42F (42F is very specific to hydrazine-type compositions, which include Atazanavir)

Figure 45. Observed Code Summary - IPC, ECLA, ICO and JP FI

Code Source	Code (IPC, ECLA, ICO, JP FI)	Normalized Usage Rate
ICO	M07C 102/08	
IPC-8	C07C 271/00	
ECLA	C07C 271/22	
JP FI	C07C 271/22	
ECLA	C07C 275/24	
JP FI	C07C 275/24	
ECLA	C07C 281/02	
ECLA	C07C 281/04	
IPC-8	C07C 311/00	
JP FI	C07C 311/06	
IPC-8	C07D 209/00	
IPC-8	C07D 211/00	
IPC-8	C07D 213/00	
JP FI	C07D 213/26	
ECLA	C07D 213/42	
IPC-8	C07D 213/42	
JP FI	C07D 213/42	
ICO	M07D 213/42C	
ICO	M07D 213/42F	
JP FI	C07D 213/48	
JP FI	C07D 213/53	
IPC-8	C07D 213/56	
IPC-8	C07D 213/75	
IPC-8	C07D 213/81	

Code Source	Code (IPC, ECLA, ICO, JP FI)	Normalized Usage Rate
IPC-8	C07D 215/00	
IPC-8	C07D 231/00	
IPC-8	C07D 239/00	
IPC-8	C07D 241/00	
ECLA	C07D 241/12	
JP FI	C07D 241/12	
ECLA	M07D 241/12C	
ECLA	C07D 257/04	
JP FI	C07D 257/04-E	
IPC-8	C07D 261/00	
ECLA	C07D 261/08	
JP FI	C07D 261/08	
ECLA	M07D 261/08	
IPC-8	C07D 277/00	
JP FI	C07D 277/28	
IPC-8	C07D 295/00	
JP FI	C07D 303/36	
IPC-8	C07D 307/00	
JP FI	C07D 317/58	
IPC-8	C07D 333/00	
ECLA	C07D 333/20	
JP FI	C07D 333/20	
ECLA	M07D 333/20	
ECLA	C07D 333/34	
ECLA	M07D 333/34	
IPC-8	C07D 333/38	
JP FI	C07D 333/58	

Code Source	Code (IPC, ECLA, ICO, JP FI)	Normalized Usage Rate
IPC-8	C07D 401/00	
IPC-8	C07D 401/04	
ECLA	C07D 401/12	
IPC-8	C07D 401/12	
ECLA	M07D 401/12	
IPC-8	C07D 405/00	
ECLA	C07D 405/12	
IPC-8	C07D 405/12	
ECLA	M07D 405/12	
IPC-8	C07D 409/00	
ECLA	C07D 409/12	
ECLA	M07D 409/12	
ECLA	C07D 409/14	
ECLA	M07D 409/14	
IPC-8	C07D 413/00	
IPC-8	C07D 417/00	
IPC-8	C07D 417/12	
IPC-8	C07D 417/14	
IPC-8	C07D 471/00	
IPC-8	C07D 471/04	
ECLA	C07F 009/58G	

US CLASSIFICATION SYSTEM

The US classification system is much older than the International Classification Codes, and is organized quite differently. It is entirely numerical, and each Class has many divisions that are organized hierarchically, but the hierarchical numbering is not nested in the way that the IPC codes are more likely to be. This means that the relatedness one class/subclass to another cannot be determined from the numbers themselves, but rather must be investigated one by one using the code descriptions provided by the US Patent and Trademark Office.

The most common US codes found in the chemical subcollection are shown in Figure 46. But the numbers after the class designation (first 3 digits), do not convey hierarchical relationships. The hierarchical relationships are solely conveyed by the level of indentation under the primary US Class, as shown in Figure 47.

Figure 46 US Codes found in the targeted Chemical Collection

US Class/Subclass	Count	Description
514/357	5	Six-member hetero ring with Nitrogen
424/465	4	Drugs: capsule improvement
546/332	3	Plural acyclic nitrogens bonded directly to the same carbon or single bonded directly to each other
546/329	2	Nitrogen attached indirectly to the six-membered hetero ring by nonionic bonding
564/148	2	Unsaturated hetero ring attached indirectly to the isoquinoline ring system by nonionic bonding
023/295R	1	Chem:Phys Proc:Crystallization
514/007	1	Lipids
514/019	1	Neoplasia
514/245	1	Nitrogen bonded directly to ring carbon of the hetero ring
514/2521	1	1,2 diazine attached directly or indirectly to an additional hetero ring by nonionic bonding
514/2634	1	Nitrogen bonded directly to ring carbon of the purine ring system (e.g., adenine, etc.)
514/2663	1	Chalcogen bonded directly to a ring carbon of the 1,3-diazine ring of the quinazoline ring system
514/269	1	Pyrimidines with chalcogen bonded directly to a ring carbon of said pyrimidine moiety
514/272	1	Nitrogen bonded directly to the 1,3-diazine at 2-position
514/313	1	Nitrogen, other than as nitro or nitroso, attached directly to the six membered hetero ring by nonionic bonding
514/337	1	The additional hetero ring is one of the cyclos in a polycyclo ring system
514/371	1	C=X bonded directly to the nitrogen which is bonded directly to the thiazole ring (X is chalcogen)
514/378	1	5-member ring 1,2-oxazoles (including hydrogenated)
514/415	1	The bicyclo ring system consists of the five-membered hetero ring and a benzene ring (e.g., indole, etc.)
514/469	1	Polycyclo ring system having the hetero ring as one of the cyclos

Figure 47 Sample of the classification hierarchy for US Code 546/332

CLASS 546, ORGANIC COMPOUNDS -- PART OF THE CLASS 532-570 SERIES

ORGANIC COMPOUNDS (CLASS 532, SUBCLASS 1)

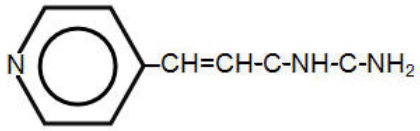
. HETEROCYCLIC CARBON COMPOUNDS CONTAINING A HETERO RING HAVING CHALCOGEN (I.E., OXYGEN, SULFUR, SELENIUM, OR TELLURIUM) OR NITROGEN AS THE ONLY RING HETERO ATOMS (Class 540, subclass 1)

1 **.. Hetero ring is six-membered consisting of one nitrogen and five carbons:**

329 **... Nitrogen attached indirectly to the six-membered hetero ring by nonionic bonding:**

332 **.... Plural acyclic nitrogens bonded directly to the same carbon or single bonded directly to each other:**

Simple Example:



DERWENT MANUAL CODES

DWPI Manual Codes are the proprietary codes attached to Derwent abstracts by experienced reviewers. They are available to subscribers of various search interfaces (Dialog, STN, Thomson Innovation). Figure 48 shows the DWPI Manual Codes appearing most frequently in the precisely targeted collection. Those that are most specific are highlighted. These codes are recognizably hierarchical, and tend to bring subjects of shared interest closer together in the hierarchy, for example the B07-D04B code on production of compounds is followed immediately by the B07-D04C code on use of the same compounds. In this code system, a code for anti-retroviral (HIV) drugs was introduced at an earlier date than is the case for the IPC codes.

Figure 48. Observed DWPI Manual Code Selection

Count	Manual Code	Manual Code Definition
	B14-A02B1	Pharmaceutical activities -> Antimicrobials -> Antiviral [general] -> RNA viruses general and other -> Retrovirus
	B06-H	Heterocyclic fused ring -> Fused ring, general [general]
	B07-H	Heterocyclics, mononuclear -> Mononuclear heterocyclics [general]
	B14-D07C	Pharmaceutical activities -> Hormonal, antihormonal, enzyme inhibitors -> Antihydrolases general and other -> Antiproteases, antipeptide hydrolases general
	B14-A02	Pharmaceutical activities -> Antimicrobials -> Antiviral [general]
	B14-G01B	Pharmaceutical activities -> Drugs acting on the immune system -> Immunostimulant general and other -> Aids treatment
	B14-L06	Pharmaceutical activities -> Agonists/mimetics and antagonists/inhibitors not covered elsewhere -> Antagonist/inhibitor/antimetabolite general and other
	B10-A08	Aromatics and cycloaliphatics (mono and bicyclic only), aliphatics -> Aromatics and cycloaliphatics (mono+bicyclic only), aliphatics - with rarer chemical groups -> Aromatics and cycloaliphatics (mono and bicyclic only),
	B07-D04B	Heterocyclics, mononuclear -> Heterocyclics, mononuclear - sole hetero(s) nitrogen -> Pyridine [general] -> Pyridine (optionally substituted) production
	B07-D04C	Heterocyclics, mononuclear -> Heterocyclics, mononuclear - sole hetero(s) nitrogen -> Pyridine [general] -> Pyridine (optionally substituted) use
	B14-D06B	Pharmaceutical activities -> Hormonal, antihormonal, enzyme inhibitors -> HIV integrase inhibitor -> Antireverse transcriptase
	B14-C03	Pharmaceutical activities -> Anaesthetics and drugs relieving fever, inflammation and pain -> Antiinflammatory [general]
	B10-A10	Aromatics and cycloaliphatics (mono and bicyclic only), aliphatics -> Aromatics and cycloaliphatics (mono+bicyclic only), aliphatics - with rarer chemical groups -> Sulphone, sulphoxide
	B14-H01	Pharmaceutical activities -> Anticancer drugs -> Anticancer general and other
	B10-A12C	Aromatics and cycloaliphatics (mono and bicyclic only), aliphatics -> Aromatics and cycloaliphatics (mono+bicyclic only), aliphatics - with rarer chemical groups -> Carbamate [general]" -> Carbamic acid
	B10-A19	Aromatics and cycloaliphatics (mono and bicyclic only), aliphatics -> Aromatics and cycloaliphatics (mono+bicyclic only), aliphatics - with rarer chemical groups -> Hydrazine
	B10-D03	Aromatics and cycloaliphatics (mono and bicyclic only), aliphatics -> Aldehydes and carboxylic amides [general] -> Carboxylic amides
	B14-D03	Pharmaceutical activities -> Hormonal, antihormonal, enzyme inhibitors -> Enzyme inhibitors general and other
	B04-B03D	Natural products (or genetically engineered), polymers -> Animal, microbiological and general extracts -> Nucleosides and nucleotides [general] -> Modified nucleosides
	B14-A02A7	Pharmaceutical activities -> Antimicrobials -> Antiviral [general] -> DNA viruses general and other -> Hepatitis C treatment

SECTION 10: RECAP

The study presented here is aimed at providing a workflow useful for studying the patent landscape on drugs approved for treatment of one or more indications. The following checklist provides a quick review of the processes presented.

1. Learn the naming history of the drug
2. Use the generic clinical name to create a collection covering the later phases of development
3. Use SPC information, citation linkages, classification systems, and other approaches to find the founder composition patent and patents on the chemistry of the compound.
4. Categorize the types of activity in the field including new indications, improved formulations, combinations with improved outcomes, synthesis improvements and others.
5. Analyze the development of the drug by the originator and collaborators, using timelines, geographic reach and quality indicators where possible.
6. Analyze development by other contributors to the field using timelines, geographic reach and quality indicators, and compare the activity between the originator and its competitors.
7. Using highly cited founder patents, study the downstream development of the field, including improvement of the original drug and how it is used to treat the primary indication, as well as the arrival of second generation compounds that have new or better properties, new indications for use of the original drug, and new directions for manipulating the target pathway.

For more information contact WIPO at www.wipo.int

World Intellectual Property Organization
34, chemin des Colombettes
P.O. Box 18
CH-1211 Geneva 20
Switzerland

Telephone:
+4122 338 91 11
Fax:
+4122 733 54 28

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