

Research on Pharmaceuticals Patents in Times of Big Data: A Contribution of the Web 2.0 for Medicinal Chemistry

Jorge Magalhães^{1*}, Luc Quoniam², Vitor Ferreira³, Patrícia Ferreira⁴ and Núbia Boechat⁵

¹Oswaldo Cruz Foundation/FIOCRUZ-Farmanguinhos, Capes Fellow 12.298-3 (Brazil), Aix-Marseille University, France

²University du Sud Toulon-Var, Aix-Marseille University, France

³Department of Organic Chemistry, Institute of Chemistry, Fluminense Federal University, Niteroi, RJ, Brazil

⁴Pharmacy School, Fluminense Federal University, RJ, Brazil

⁵Oswaldo Cruz Foundation/FIOCRUZ-Farmanguinhos, 21041-250 RJ, Brazil

Abstract

This work aims to demonstrate the use of tools of Information Science applied to pharmaceutical patents. Given that existence of big data in the new century providing a massive and growing wave of information, it becomes necessary for new ways to rescue data and analyze them consistently. In the public health area is no different, especially with regard to intellectual property for new potential molecules to treat diseases of the global population. The triazoles were used as a study case due the great interest these compounds arouse in the pharmaceutical industry due their biological activities. In this regards, the approach are by consulting databases indexed (PubMed, Web of Science, Medline, Scopus, SciFinder Scholar), beyond to use search engines for data mining and software's from collaborative intelligence to generate graphical analysis. The results demonstrate the potential of four series of triazoles derivatives and illustrate several correlations between patent and pharmaceutical industry extracted from the deep web.

Keywords: Patent; Intellectual property; Web 2.0; Heterocycles; Triazoles; Big data; Technological trends; Competitive intelligence; Information science

Introduction

Intellectual property capital is an important asset for businesses, and knowledge is becoming increasingly crucial for competitiveness, technology and therefore economic development. This is particularly true for technology-intensive sectors, where knowledge is regarded as a company's most valuable asset [1]. Therefore, it is very important for organizations to have good understand of the importance of the intellectual property in order to invest in research, development and innovation (R, D and I) if they want to stay active and competitive in the market.

However, researchers and people that make decisions without access to appropriate information leads to inaccurate decisions and sometimes disastrous. Decisions based on facts and on reliable information are more likely to generate good results and it still gives decision makers face every day. The information appropriately and in a timely manner, by which they can make decisions, develops effective strategies and acting proactively. This action can be called competitive strategy when it involves the placement of a business, which maximizes the value of the organization's capabilities and distinguish the company from its competitors [2].

When a decision is based into reliable information and the appropriate time it is not only regarded as a competitive strategy but also strategic for the success of the business. In this approach we have intelligence - the area that deals with the strategic analysis in the organization's business and still answers questions that decision makers are faced in every day. Thus, the responses coming from the strategic issues became Competitive Intelligence (CI) and not just information for portals. This is the differential knowledge. The activities of companies, research groups, institutions and national governments are effective when they attribute value and quality their information. These critical factors are crucial for organizations' success in their domestic and international planning, whatever their long- and short-term strategies [3].

Information science has tools that can help organizations produce, treat, store and manage data on any activities or processes, resulting in more effective management for innovation. With the increasingly turbulent, complex and competitive conditions in the markets in which companies operate, the use of industrial/intellectual property has become a way of assuring the continuation of their activities into the future by protecting innovations and restricting how their competitors can act. The industrial property information contained in patents identifies the latest science and technology developments, which also makes it a powerful competitive weapon [4].

It is widely known that the mechanisms for mining information have developed from "manuals" to dedicated portals or websites (from Web 1.0 to Web 2.0)—we have progressed towards mass information that is obtainable by automated means. This new paradigm allows huge quantities of data to be downloaded in different formats, but it cannot process this data to produce indicators that can actually help decision-makers. This is why studies are required using information science, such as technology trends [5].

The pharmaceutical sector is one of the areas of more investment and intensive research which constantly need accurate and updated information. In 2012, according to IMS Health (2012), global pharmaceutical industry surpassed US\$ 950 billion in sales with trend to reach US\$ 1,2 trillion by 2016 and they seek constant innovation of their products and processes [6-8]. According to the Oslo Manual published by the Organization for Economic Cooperation and

***Corresponding author:** Jorge Magalhaes, Oswaldo Cruz Foundation/FIOCRUZ—Farmanguinhos, Capes Fellow 12.298-3 (Brazil), Aix-Marseille University, E-mail: jorgemagalhaes@fiocruz.br

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Development (OECD), there are four kinds of innovation: product innovation, process innovation, organizational innovation and marketing innovation, as well as a combination of any of the above.

In 21st century, the speed information generation is unprecedented in the world. The data are practically instantaneous. Since proliferation of the internet, the information flow without restrictions as to distance and availability. Thus, the question arises of screening ability, interpretation and conversion of large amounts of existing information. [9,10].

Brownstein (2008) et al, argues that internet has become a critical medium for clinicians, public health practitioners, and laypeople seeking health information. Data about diseases and outbreaks are disseminated not only through online announcements by government agencies but also through informal channels, ranging from press reports to blogs to chat rooms to analyses of Web searches. Collectively, these sources provide a view of global health that is fundamentally different from that yielded by the disease reporting of the traditional public health infrastructure [11].

In this context, in which the world's technological per-capita capacity to store information has roughly doubled every 40 months since the 1980s, becomes indispensable new ways to capture and manage these data. In 2012, for example, the quantity of information created everyday it was 2.5 quintillion (2.5×10^{18}) bytes of data [12,13].

Analyzing big data in the pharmaceutical field and specifically in the area of patents, it is possible to observe 5785 documents in database PubMed with the term "patents medicines". These documents comprise more than 40 years of research involving more than 100 countries, 820 cities worldwide, plus 1600 scientific journals (Lancet BMJ, Soc. Sci. Med, etc.) and over 13,700 experts. Figure 1 shows the distribution of countries where there are more records of research in this area.

The amount of experts and data for R,D&I in this area is concentrated in North America and Europe, requiring the constant socialization of knowledge and investment of other nations. Therefore, it is pressing to consider the technological evolution, Big data and Web 2.0 (combination of the technology allowing the customers to actually interact with the information). Data volume needs to be treated to aid in the science management and decision makers to improve the health care of their populations [14-16].

So, improving health of the people, mainly in the developing and undeveloped countries depends on the development and deployment of many varieties of health innovations, including new drugs, vaccines, devices, and diagnostics, as well as new techniques in process

engineering and manufacturing, management approaches, software, and policies in health systems and services [17-19].

For this case study, it was highlight product and process innovation opportunities for the chemical compounds of triazoles. The motivation for this choice was because this five-member heterocycles family has been studied for over a century as an important class of heterocyclic compounds. Until now it remains attracting considerable attention due to their broad range of biological activities. Recently, several compounds of this family have been reported as having anti-inflammatory, antiplatelet, antimicrobial, trypanocidal, antimycobacterial, antitumoral and antiviral properties and also activity against several neglected diseases. Therefore, many recent studies have focused on triazoles compounds as target structures and evaluated them in several new biological targets [20,21].

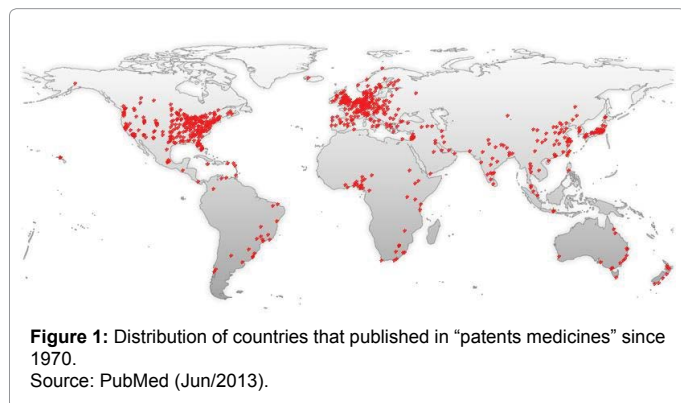
Thereby, aid to discover potential new treatments for diseases of the global population, since innovation can impact even established and approved markets, linking economic development to improved sanitation conditions and therefore yielding more sustainable lifestyles.

Methodology of Research

This study involves big data in patents which they were extracted using data mining. After, treated in a cluster engineering Lingo3G carrot2-version 3.6.2 as well as Google trend©2013 and PubMed database. Bibliographical references were also consulted on indexed scientific databases such as Scielo, Web of Science, Scopus and Lilacs. In addition to get massive information in the world and demonstrate advance in patents pharmaceutical.

Withal, the information contained in a patent document is recognized worldwide as an important source of data for innovation purposes. By making use of information science tools, such as technology foresight, it was possible to observe perspective and patent applications in the 1H-1,2,3-, 2H-1,2,3-, 1H-1,2,4- and 4H-1,2,4-triazole derivatives in the therapeutically patents, covering the development of new chemical entities and new pharmaceuticals.

The database used to access the patent documents was World Intellectual Property Organization (WIPO) and SciFinder® from Chemical Abstracts Service (a division of the American Chemical Society). This database is very broad, containing patent applications filed since 1907 by the leading patent offices in the world and it can be accessed using filters to obtain only the information of interest. The main advantage of SciFinder® is that substances can be searched for just using the CAS RN (Chemical Abstracts Service Registry Number). Next, the patent documents were filtered and exported transported for further treatment of data and subsequently analyse it to identify trends and make correlations in software spread sheets Microsoft Excel Office 2010®. In this context, five foresight indicators were analysed: (a) patents relating to processes (synthesis and/or formulation); (b) main assignees, i.e. the companies that have filed the most patent applications, since these are the ones that protect their R&D most in the sector; (c) top countries, i.e. the countries in which the greatest number of priority patent applications have been filed, which, in the vast majority of cases, are also the countries where the technology is being developed; (d) information about the first patent for the drug, date and respective assignee; (e) patents filed in Brazil, number of patents filed in the country, and the main assignees; (f) trends over time of patenting, since this indicates the rise or decline in companies' interest in investing in certain technologies.



Results and Discussion

In the *Information Society or Knowledge*, information is vital for the process of decision making by governments, corporations, institutions etc. With the expansion of the media and therefore the democratization of information, about 80% of the necessary information to support the decision-making processes is available. Thus, this statement should facilitate the data searches, but paradoxically with information from open and closed bases there is a great difficulty in systematizing and process the significant amounts of data. So, one of the solutions is the use of software analysis [14].

Information from sources closed (20%) have value expressive. They are provided for paid bases or through foundations, networking of information gatherers or still by intelligence analysts and managers. Moreover, it is not enough to produce information in time; it must make it available to anyone who has a real need to know it. In another context, it is crucial to protect the knowledge generated when it is used for strategic issues in the Organization. Thus, intelligence is a strategic tool that enables senior management to use it for their competitiveness and identify the main driving forces beyond predicting the future direction of the market. It is a process where information from multiple sources is collected, interpreted and communicated to those who need them to decide [22,23].

Information society boom and market globalization have opened up new ways of using this concept which exists for a long time. In all ages, an enterprising man has always felt the need to be informed, to watch, to defend his "territory", to compare himself with others, i.e. to have the capacity to discern, to measure and to evaluate.

The expression Web 2.0, initially used by Darcy Di Nucci in 1999, refers to the second generation of Web design and development. Tim O'Reilly related this appellation, in 2004, to the idea of cumulative changes in the development of the Internet, as well as its new uses. Compared to 2.0, the early days of the Internet looked like a fake revolution. It was a replication of the traditional information publishing model which content produced by someone (a "knowledge holder") was imposed and addressed to others, despite the proclaimed possibility that everyone could publish themselves [24].

Therefore, traditional media models (television, radio, etc.) based on vertical communication remained. A fundamentally different model emerged with about 240 million Websites, in June 2009, and imposed its hegemony. The horizontal communication paradigm, i.e. "many to many" was henceforth dedicated and welcomed with new uses. Two types of phenomena had appeared simultaneously (Figure 2). On the one hand, the vertical communication (one to many) model gave way to a horizontal communication model of "many to many (n to n)" in which a speaker doubles as a facilitator. This is the extension of "peer-to-peer functioning in the organization of our societies; network technical architecture transposing into social interactions. On the other hand, this "flattening" of social relations, under the influence of the technical architecture of networks, was accompanied by a community phenomenon [3-25].

Therefore, aggregation of information and applications from different users and Websites are possible through the use of interoperable languages. This dimension of Web 2.0 constitutes its semantic nature, i.e. the possibility of applications to interact together. Semantic Web can therefore be defined as a set of interoperable online technologies and applications which interact with each other through a metadata system. These human-generated metadata can be compared

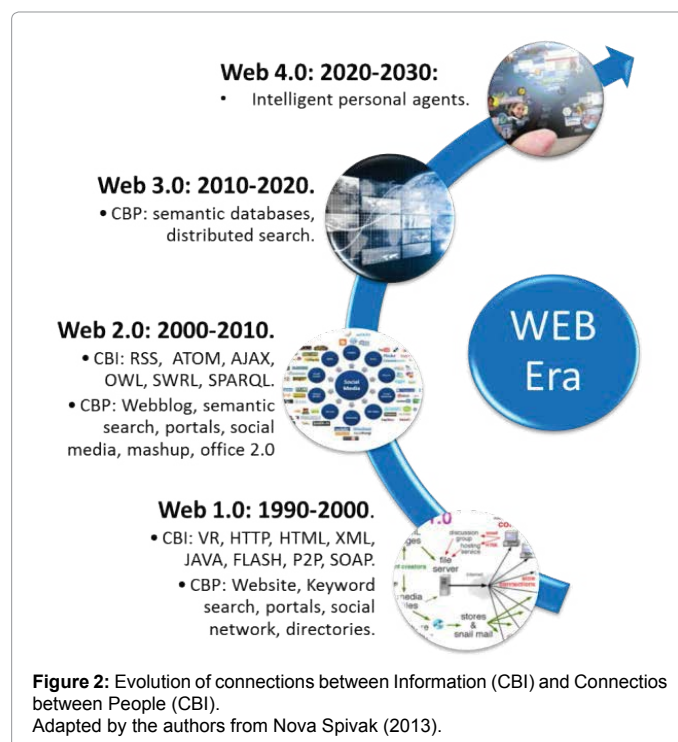
to neurons interconnected by synapses. Semantic Web is therefore a form of neural network leading to intelligent Web.

The phenomenon reflects a society where exchanges are more horizontal, networked, and where vertical hierarchy no longer exists. Speeches and organization types are changing, with valorizing individual involvement and working in ephemeral teams, around various projects. Adaptability and flexibility are the keywords. It is therefore necessary to analyze the relationship between social architecture and shared, collaborative, distributed computer application architectures. "2.0 Architecture" therefore should use a "many-to-many communication (n to n)" in order to ensure collective knowledge [3].

Concept of Big data is embedded within ecosystem that is part of a dataset much larger than software for data analysis. Internet is coming out of the virtual world, of the screens of PCs and becoming an element present in the physical world. Since the turn of the new century one can find "chips" on mobile phones, home appliances and cars. This new reality makes these devices can be connected to the World Wide Web. Thus, these connections generate a vast amount of data which there is a possibility to analyse and understand, more accurately, people's behaviour [12].

Amount of data in the world has been exploding. Companies capture trillions of bytes in information about their customers, suppliers, operations and millions of networked sensors are being implanted in the physical world in devices such as mobile phones and automobiles, sensing, creating, and communicating data [15]. Thus, because of the range of existing raw data and corresponding analysis, it must be draw an accurate representation and strategic. As the data analysis for makers' decision extends to all sectors, "health" cannot be different [26].

According to *Wikipedia Miner*¹, the term "Big data" is 43% related to the term "Health" within Wikipedia [27]. Somehow, indicates that



¹ Wikipedia Miner is a toolkit for tapping the rich semantics encoded within Wikipedia.

public health problem is enormous and require a multidisciplinary workforce. Thus, becomes necessary better information management of the “Knowledge Age” and technology. It should be regarded as an adaptation to the actual conditions of each local culture and collaboration of R, D&I through collaborative networks for the dissemination of knowledge beyond of development and the innovation. Working with the Information Sciences whatever application area includes a highly structured network since the processes involved in R,D and I drugs are increasingly complex due Big data, it is necessary multidisciplinary teams to establish a systemic vision. [14-28].

The surface web rescues up only 4% of all the information available in the world where the most relevant to the decision makers are in the deep web [29]. Figure 3 shows the global interest in “pharmaceutical industry” (blue color), “patent” (yellow color) and “triazole” (red color) by the search engine Google Trends. The numbers of searches into web for this term per country since 2004 are presented. The color darker in the country shows that this term has been more searched in a given period (North America). Beside the map is a list of the related terms searched for in the time.

If it considers only this data, it could be said that the interest in patents and the pharmaceutical industry has declined over the years which is not true. When is performed a search in the deep web data changes completely.

For example, examining in cluster engineering Carrot®, more than 31 million results are obtained only for the term “patent”. When

associated with “triazoles” the number drops to 16,800 documents. Facing the Big data, it used data mining by the AdunaLingo® software in order to rescue the most accurate and associated documents with the terms “patent” and “triazoles”. Thus, the data were restricted to 115 documents with the formation of 32 clusters as can be seen in Figure 4.

It becomes easier to analyse and make decisions in the correlations made. Can be observed that there are 16 compounds of formula connected to antifungal agents, which are in turn patent applications are established. Extending analysis it can observe other associations as novel triazole derivatives, synthesis and methods and preparation processing. It is noteworthy, that any information can be redeemed with a “click” in the area of interest to which the software will scan the data with more detailed analysis.

At the same time, an enormous amount of valuable information about patents and triazoles are found in Web-accessible information sources such as discussion sites, disease reporting networks and news outlets [11]. According to worldwide IP traffic will quadruple by 2015, nearly 3 billion people will be online, pushing the data created and shared to nearly 8 zettabytes. Notwithstanding, can be exemplified through the evolution of Wikipedia created in 2001. It has over 26 million articles written by 39 million people for 285 languages. The total revisions surpassed 1 billion in 2010 and they are conducted based on bibliographic sources often by scientific references. It is noteworthy, that the articles and/or reviews are done by registered users with doctoral, master and others degree.

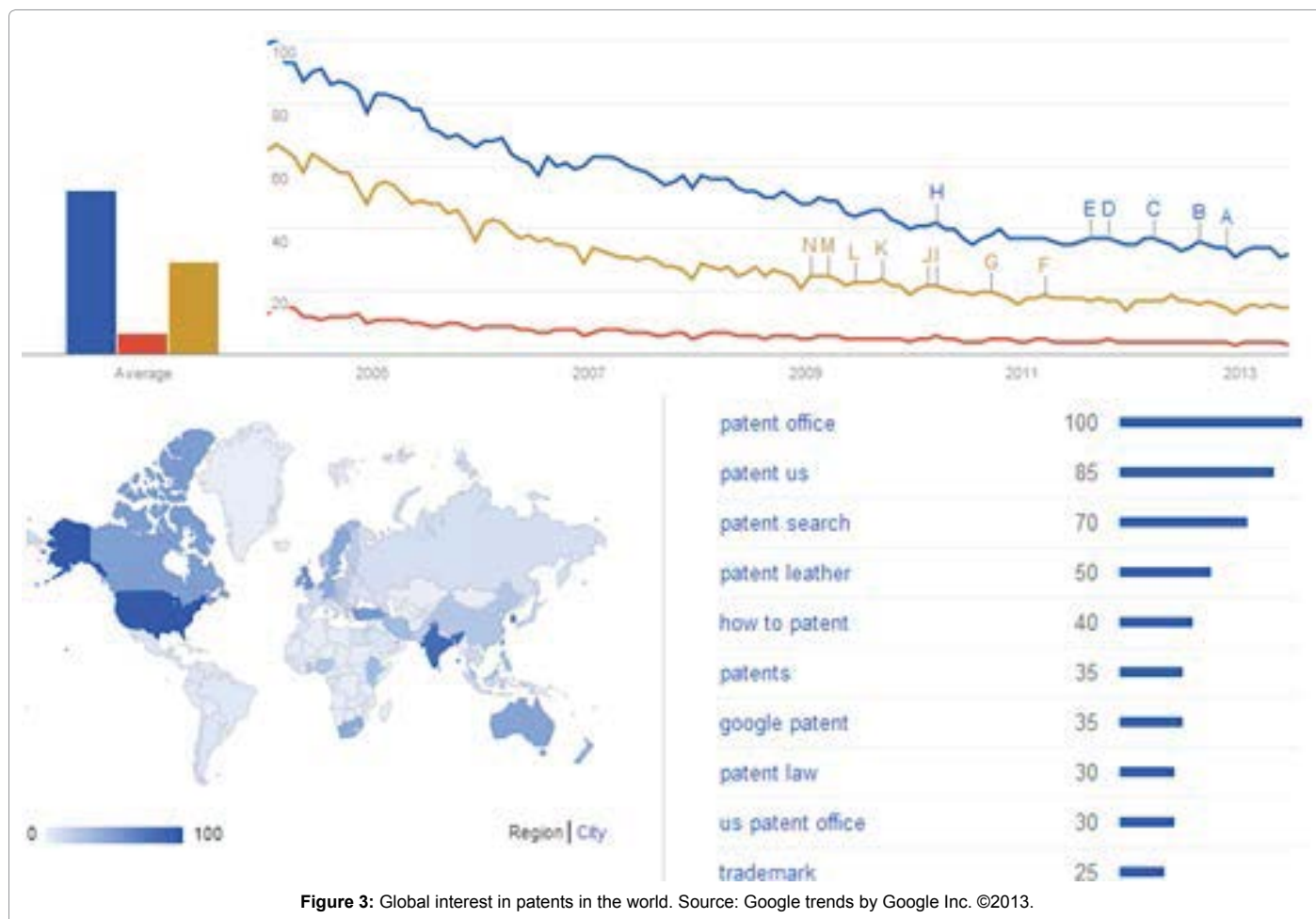
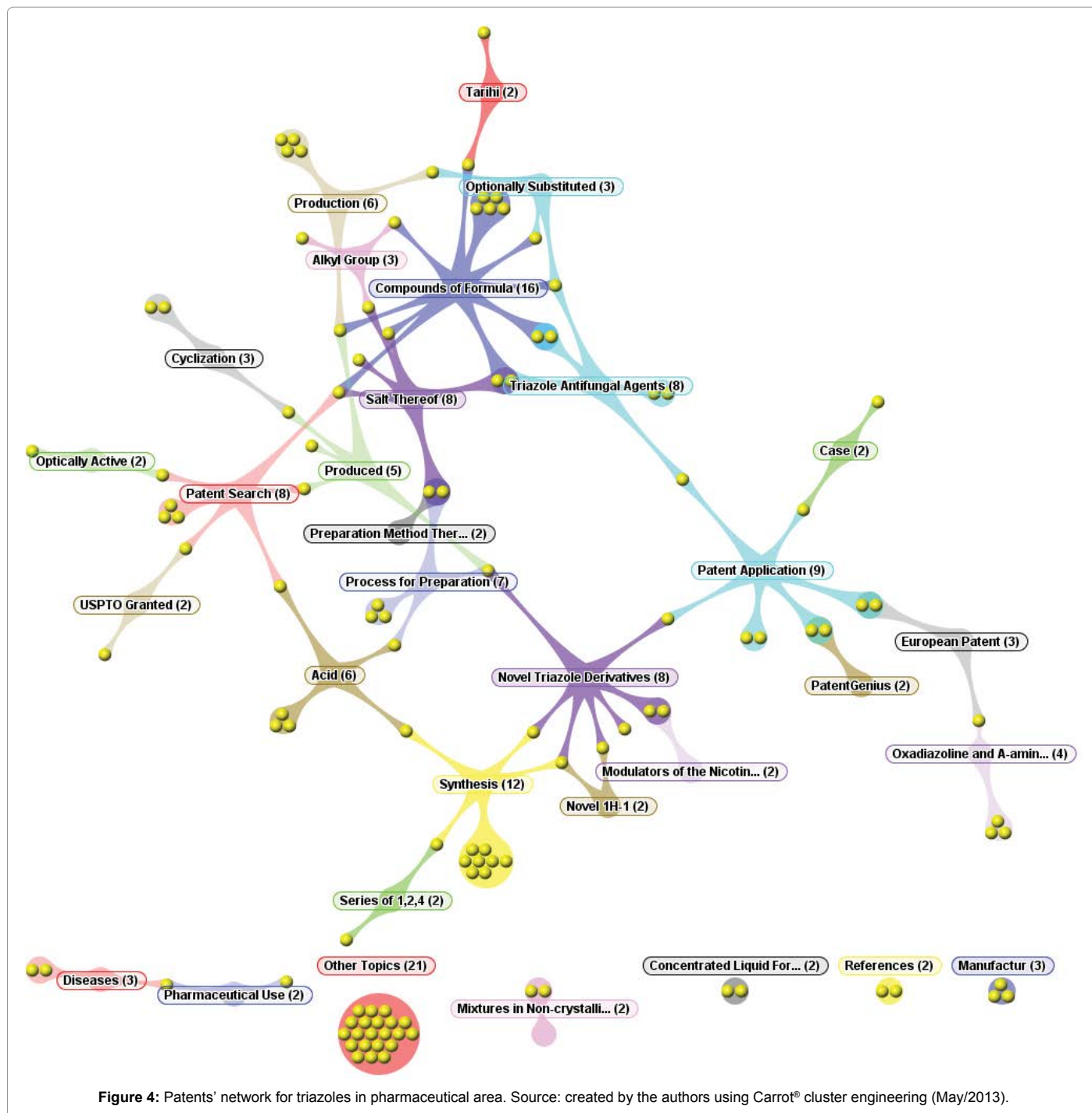


Figure 3: Global interest in patents in the world. Source: Google trends by Google Inc. ©2013.



Thereby, the data mining software known as Wikipedia Thesaurus Visualizer allows visualizing the network of relationship between the terms in question in this work as well as it calculates the interaction position between terms according to the concept of relativity among them. Figure 5 shows the interaction of articles with the topic “patent,” the pharmaceutical industry and “triazole”. With this application several analyses can be structured. In this example were excluded from the networks the node smaller and then intensified the more intense relationships (expressed through the nodes with highlighting colors).

Concentration demonstrated in each node, it can extract the

related articles on the subject in question. Likewise, view their closer relationship with the subject under consideration. Note that all relations triazoles are linked to the pharmaceutical industry by Janssen Pharmaceuticals and Chinese industry. On the other hand, the interaction is much stronger when approaching the issue of “patent” where the relationship intensifies with chemical patents, generic drugs, agreements etc. So, when analyse this new scenario of Big data leads to considering that this feature deserves to be studied to aid R,D and I in public health [11-17].

Regarding to assess the size of therapeutic patents for triazoles

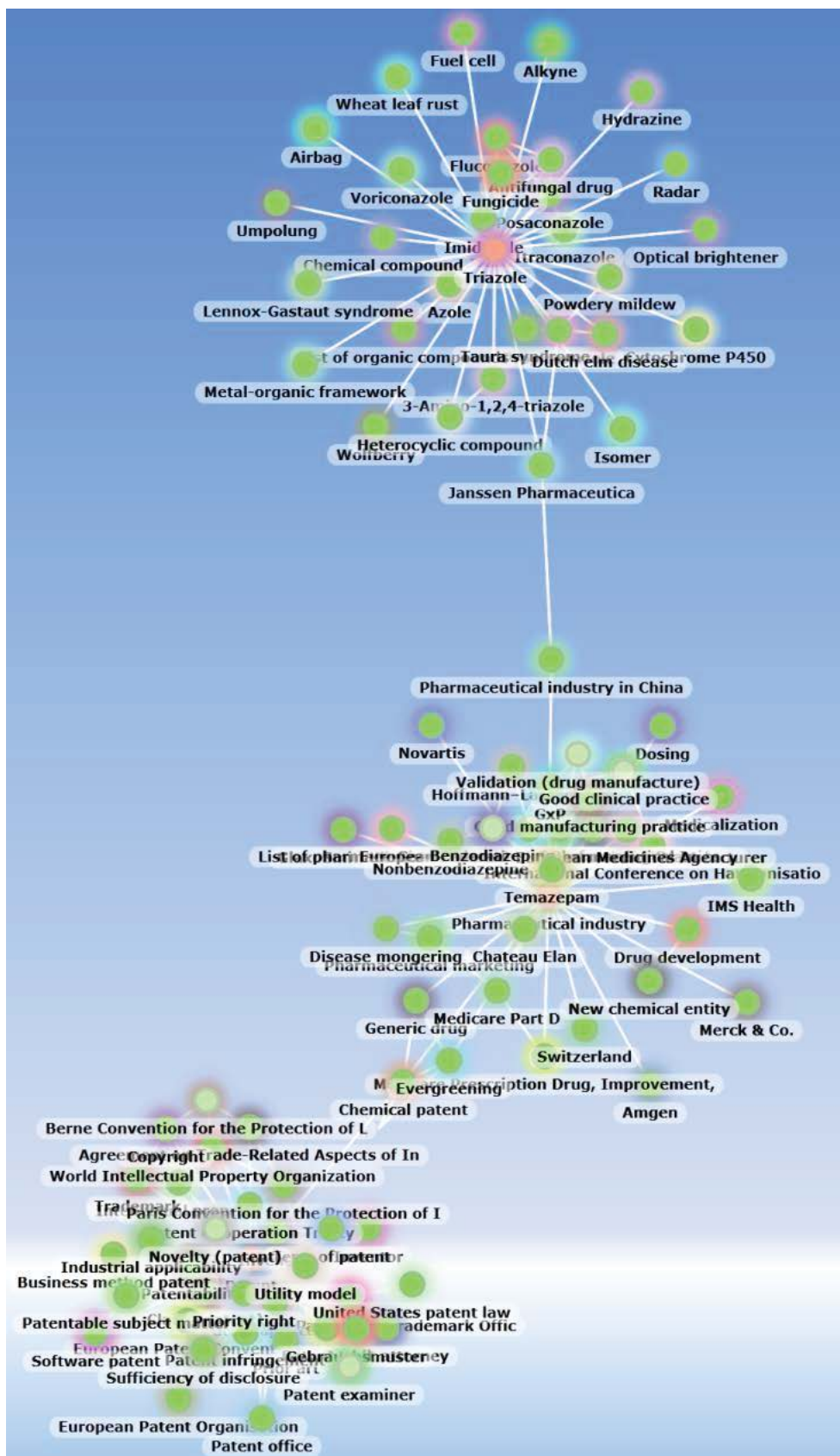
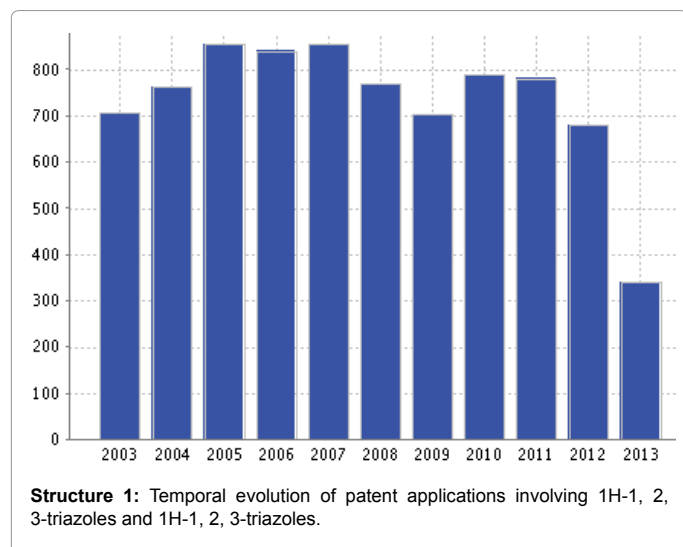
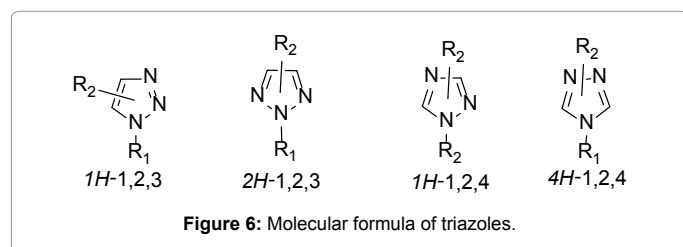


Figure 5: Patents' network for triazoles in pharmaceutical area. Source: created by the authors using Carrot® cluster engineering (May/2013).

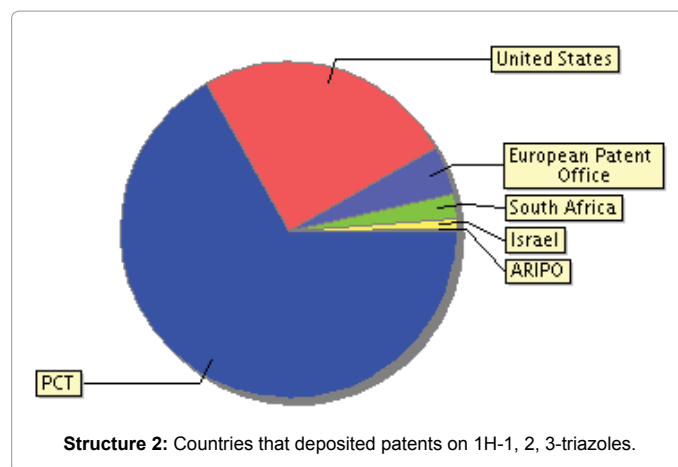
(important area for medicinal chemistry), it searched the compounds databases in Patentscope (WIPO) and SciFinder® using 1H-1,2,3-triazole and 1H-1,2,4-triazole as key words. The molecular formulas can be seen in Figure 6.

Ferreira et al. [20] observed existence of 4,078 compounds in the period between 2008 and 2011. In this new approach (2008-2013), there was an increase of about 50% in interest in substances triazoles. In the Structure 1 it is possible to observe a constant number of deposited patent from 2003 (707) to 2012 (681). Until May 2013 have already been requested 341 patents, suggesting that these compounds remain promising candidates in this area of research. The most countries containing reserve markets through patents filed by companies already holding patents are those belonging to the PCT² market. In this regard, the U.S. stands out.

The Patentscope platform selected 8,661 results involving 1H-1,2,3-triazoles. Applying a filter for the period between 2009 and 2013 reduced the results to 2,643 compounds and when the search was restricted to “pharmaceutical,” 7,039 compounds were obtained. The results were further refined by selecting the term “therapeutic” without the key words “treatment” and “pharmaceutical,” which generated a database of 6,319 compounds. Structure 2 shows the priority countries with global patent deposits—PCT countries holds 67% (4,221 patents) followed by U.S (1,581), EPO (European Patent Office) countries (296) and the Israel (3) and the ARIPO (African Regional Intellectual Property Organization) countries 9.



² The PCT is a multilateral treaty that allows apply for patent protection for an invention simultaneously in many countries through the filing of a single international patent request. This Treaty is administered by WIPO (World Intellectual Property Organization) and has 147 signatory countries (through June 2012). The PCT was concluded in 1970, amended in 1979, and modified in 1984 and 2001. It is open to States party to the Paris Convention for the Protection of Industrial Property (1883).

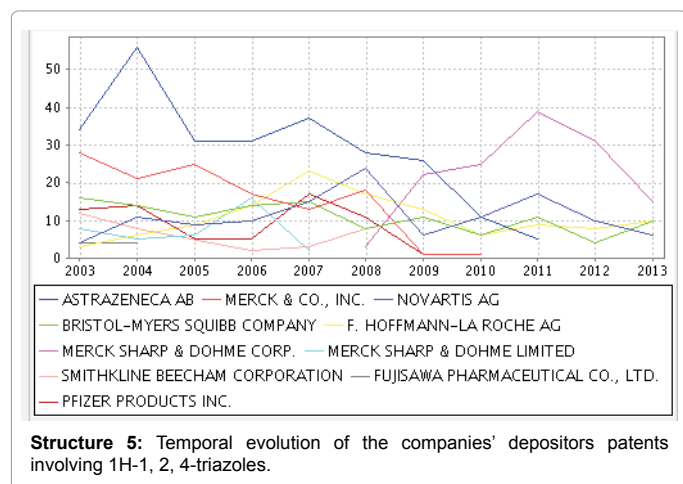
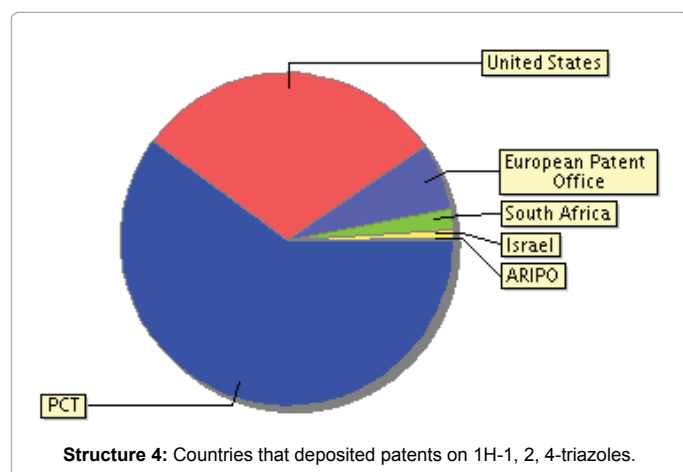
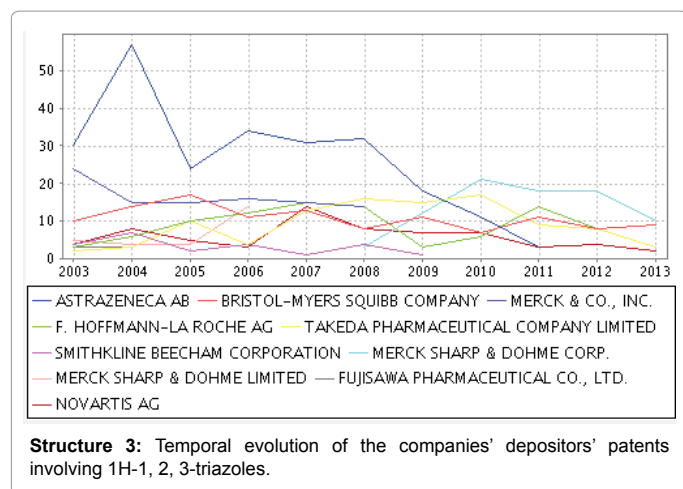


Several companies were identified as those that sought the technology to develop these compounds, some of which are involved in development partnerships for the deposit of patents. In period analysed, ten companies deposited patents related to these compounds, including Astrazeneca AB, Bristol-Myers Squibb Company, Merck and Co. Inc, F. Hoffmann-La Roche AG, Takeda Pharmaceutical Company Limited etc. The countries containing the most reserve markets through patents filed by companies already holding patents are those belonging to the PCT (Patent Cooperation Treaty) market, as noted in Structure 2. The deposit-to-deposit PCT ensures priority in many countries, and it provides substantial holders for future innovation in these markets. The U.S. has used these systems to protect the triazole compounds. By analyzing the scope of triazole patents, we found that, in general, the triazoles that have been patented during this period of time relate to several types of diseases and their possible treatments. Structure 3 shows the registers of the companies for 1H-1, 2, 3-triazoles were promising. Top 5 companies that patent ascending order are Astrazeneca held 284 patents, Bristol-Myers Squibb Company held 133 patents, Merck & Co. Inc, held 130 patents and Takeda Pharmaceutical Company Limited held 101 patents.

These are examples of 1H-1, 2, 4-triazoles used as drugs in various therapies which demonstrate the importance of the triazole core in the pharmaceutical field. Initially, the search selected 14,108 references for 1H-1, 2, 4-triazoles. Applying a filter for “pharmaceutical”, 9,634 compounds remained. These results were further refined by selecting the term “therapeutic” which generated a database of 8,610 entries for therapeutic 1H-1, 2, 4-triazoles. During the enquired period of time, the PCT countries held 60% (6,324 patents) of the total global deposits, and U.S. had 2,635 patents, followed by EPO countries (549), South Africa (175), Israel (77) and ARIPO countries with 9 (Structure 4).

Structure 5 shows mainly companies’ deposited patents related to these compounds, including Astrazeneca AB held 301, Merck & Co. Inc, F. (173), Novartis AG (141), Bristol-Myers Squibb Company (139), Hoffmann-La Roche AG (136), Merck Sharp & Dohme Corp. (135), Merck Sharp & Dohme Limited (128), Smithkline Beecham Corporation (115), Fujisawa Pharmaceutical Co. Ltd (84) and Pfizer Products Inc. (80). Again, we emphasize that this provides the scope of substantial holders for future innovation in these markets. The U.S. used these systems to protect the triazole compounds. From an analysis of the scope of these patents, we see that, in general, the 1H-1, 2, 4-triazoles patented during this period cover several types of diseases and their possible treatments.

Compounds containing 1H-1, 2, 4-triazoles have a broad spectrum



of application and therapeutic use, as indicated by the technology trends analyzed in this study. They cover patent protection for numerous treatments, including rheumatoid arthritis, bacterial infection, lupus erythematosus, multiple myeloma, psoriasis, lymphoma, neoplasm, multiple sclerosis and pulmonary fibrosis [20-30].

Final Considerations

- The existence of the Big data is a reality requiring new

approaches to treat the information, especially in the field of intellectual property. So, R,D and I should be always use to collaboration via Web 2.0 of the Information Science area.

- Intensity with which companies and scientists devote their energy to developing and filing patents to protect their innovations demonstrates how they are strategically important some technologies. In this sense, by observing the progress of certain products over the years, it is possible to deduce the technological importance of the products/processes in question, which indicates where most effort is concentrated.
- Research in pharmaceutical patents using web 2.0 tools may contribute to new approaches to R, D and I in the chemical area, because as research conducted with cluster engine as well as the prospecting in the chemical compounds demonstrates that triazoles are still an excellent alternative in the discovery of new compounds.
- This class of triazoles remains essential in antifungal treatments, but several new bioactive compounds have also been discovered for the treatment of cancer, tuberculosis and many other diseases. With regards to their organic syntheses, new routes of preparation that are more environmentally friendly and compatible with the current paradigms of sustainable chemistry are still needed.
- Overall, the medicinal chemistry area still has much to contribute to the development of important new drugs. So, combined with multidisciplinary teams from other areas of science such as the Information Sciences, the process for R, D & I becomes much better to establish a systemic vision.

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