CHIRALITY AS A PATENT PROTECTION POLICY – AN EXAMPLE WITH CITALOPRAM

Lily Peikova[1], Manoela Manova[2], Ivanka Pencheva[1] and Guenka Petrova[2]
[1]Medical University – Sofia, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Sofia, Bulgaria
[2]Medical University – Sofia, Faculty of Pharmacy, Department of Social Pharmacy and Pharmacoeconomics, Sofia, Bulgaria
Correspondence to: Guenka Petrova
E-mail: guenka_petrova@hotmail.com

ABSTRACT

The aim of this study was to analyze the patent protection policy of citalopram as an example for protection of a biologically active chiral structure. A three-step search methodology of patent expiration date, EPO database was performed, and an expanded search was done via the INPADOC patent family system. The patents found were systematized according to the main International Patent Classification (IPC) class, C07 subclasses, and were analyzed by patent claim.

Our search methodology revealed 189 patents for citalopram issued during 1990-2010. The patents from IPC class A61K are divided among patents for composition (31%), salts and crystallization forms (38%), and combinations (31%). The patents from class C07 are almost equally allocated among subclasses C07C (acyclic or carbocyclic compounds – 49 patents) and C07D (heterocyclic compounds – 59 patents), with 5 additional patents from class C07B (general methods of organic chemistry). By C07 IPC subclass the distribution of issued patents is mainly for C07D (heterocyclic compounds) that correspond to the main active biological structure. By type of claim the patents for methods (n = 29) and processes (n = 20) are almost equally represented. There are only two patents for composition – for pharmaceutical composition containing citalopram and for the crystalline base of citalopram, whereas the patents for methods for preparation were nine.

Our study showed that the number of patents from class C07, which protect the substance, is almost double compared with other classes. The chiral structure of citalopram might also explain the fact that the patents within class C07 are more than those in class A61K. It is evident that the companies prefer to protect both the main structure and the chiral enantiomers.

Biotechnol. & Biotechnol. Eq. 2012, **26**(3), 3058-3061

Keywords: citalopram, chirality, patent protection, chemical structure protection

Introduction

The chirality of molecules was first reported in 1815 by the French Physician Jean Baptist Biot (10). Stereoisomerism in molecules can occur because the component atoms are arranged in 3-dimensional space. The pharmacological and toxicological activities of chiral drug enantiomers have attracted special attention in recent years as a result of the substantial progress in the synthesis, analysis and separation of chiral molecules. In addition, the interest in drug stereochemistry is further strengthened by the growing understanding of the potential importance of the differential biological properties of the enantiomers of chiral medicines given as racemic mixtures.

Different approaches in patent protection policy of the chiral molecules have been reported, which formulated our interest in the topic. The aim of the present study was to analyze the patent protection policy of citalopram as an example for protection of a biologically active chiral structure.

Background of the problem

The pharmaceutical companies could not benefit from the pharmaceuticals' patent protection during the whole period of patent validity and aim to increase the patent life cycle of their products (22, 29). In the beginning of 1990 the patent protection period was extended from 15 to 20 years with the TRIPS (trade-related aspects of intellectual property rights) agreement and in 1992 the supplementary protection certificate was introduced providing another 5 years of protection (34). In addition to that the companies often introduce separated patents for new application, dosage form, changes in the manufacturing process, and even changes in the colouring and benchmarking. When the inventor of the first therapeutic application of a pharmaceutical product is granted a patent, they block all other possible inventors.

In contrast with the USA, the European Union also grants an additional patent for new therapeutic application (5). Most of the European patent laws differ from the USA ones because they exclude the patent protection of the therapeutic and diagnostic methods, but grant patents for the means of application of these methods (20). The European patent Office formulated the following pretension: "usage of compound X for manufacturing of pharmaceutical product with application Y". Such a way of formulation refers to the manufacturing and to the therapeutic method and thus is not forbidden by law.

The influence of the patent protection policy on pharmaceuticals' life cycle has been studied in respect of the marketing authorization research process, pricing and reimbursement procedures, which could take up almost 8 out of 20 years of patent validity (2, 8, 16, 21, 30, 32). The

supplementary protection certificate could add 5 years, thus increasing the expiry date to 17 years of patent monopoly but for some authors this is still not enough. According to Bale (6, 7) in 1980 the patent exclusivity of 20 years led to 10 years of market exclusivity, while in 2000 this period was shortened to 5 years due to faster appearance of therapeutic competitors within the therapeutic group. On the other hand the changes of the data exclusivity period from 8 to 11 years led to a delay of 3 to 5 years in the generic competition (15).

The origin of specific areas in pharmaceuticals' patent protection lies in the chemical and biological specificity of medicines, as well as in the structure of the patent systems and their functioning. A pharmaceutical product could be granted different patents, which are geographically valid and not internationally:

- patent for the active ingredient, its ethers, salts, esters, amides, ets., which are usually the soluble forms of the active ingredient (International Patent Classification, IPC class C07D);
- patent for physiological metabolites, or contrary for the so-called prodrugs that later metabolize in the human body into therapeutically active molecules (IPC class C07D);
- patent for the method of synthesis or formulation of the active substance known as indirect protection of the compounds (IPC class C07D);
- patent method for dosage form formulation (IPC class A61K);
- patent for therapeutic application (IPC class A61P);
- patent for second therapeutic application (usually as part of the data exclusivity).

This variety of patents has resulted in several specific patenting approaches, which have been reported in the literature. The main goal of such approaches is to extend the real patent protection period for the active compounds and to put barriers in front of the competitors.

If the active compound possesses a main structure with different substitutes at the same biologically active centers, the approach often used is that of substituting with different atoms or molecules, and the competitors should try to guess the wide rage of possibilities. In case the compound contains an easily separable hydrolyzing molecule, it might be useful for the inventor to put a claim on the main active molecule that is the same for all active compounds, thus blocking a variety of possible derivatives.

If the molecule is a prodrug that later metabolizes into an active compound, the protection is widened to all possible metabolizing compounds. This is applicable when the physicological process is short.

The patenting of chiral structures has been analyzed by Mansfield et al. (24), who focused on the connection between the patenting of enantiomers and the differences in their therapeutic effect. The authors discovered that when the patent of the racemic mixture approaches its expiration date companies started to develop products containing only therapeutically active enantiomers, a process knows as "chiral switch". Companies often claim that this process will benefit the therapy due to improved purity, better clinical effect, safety and pharmacokinetics. Mansfield et al. (24) analyzed the evidences for escitalopram, esomeprazole and levosalbutamol, but considered that the higher efficacy is mostly marketing rather than innovative claim. Enantiomers have also been used to replace the first generation products as is the case with citalopram and escitalopram, omeprazole and esomeprazole, zopiclone and eszopiclone, but the evidence for a better therapeutic effect is questionable.

The consecutive patenting of one main compound, then salt, then ester, then other soluble form is known as "evergreen" protection of pharmaceuticals. Another possibility is the so-called "hermetic protection", when the product is withdrawn from the market and introduced again with a new claim after 4-5 years. Such a practice has been observed when the products possess polymorph forms. Similar is the case of patenting one of the polymorph forms and then claiming another form as a new molecule, and trying to block both of them due to the impurity of the first one with the "new" form (33).

The studies on the patent protection of antidepressants are relatively limited and focus on the juridical case for patent violation (29), information about the status of the active patents and territory of protection (9, 14, 15), barriers to the generic entrance on the market (18, 28), requirements and practice of patents maintaining (26), influence of the patent protection on the market (12), as well as on the legislation (19). Serious concerns have been raised that the monopoly higher prices of patented products could negatively impact the access to medicines and thus, the mental public health (13, 25). Manufacturers working on the preformulation of the active substances invest more in promotion and thus additionally hamper the access (18).

Citalopram ((*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzo-furan-5-carbonitrile)), first introduced with the trade name Celexa (11), belongs to the group of selective serotonin reuptake inhibitors (SSRIs). It is authorized for therapy of severe depression and panic, but is also of label used for anxiety disorders. Citalopram has been studied for diabetes neuropathy (31), premature ejaculation (4), pathologic crying after insult (3). In 2009 the main patent of the racemate expired. The chiral structure allows expanding the patent protection for both enantiomers (1).

Materials and Methods

A three-step search methodology was applied that was previously described (23). First the patent expiration date was clarified, then the EPO database was searched with the key word 'citalopram', and an expanded search was performed via the INPADOC patent family system to clarify the geographic protection. The patents found were systematized according to

the main IPC class, C07 subclasses and analyzed by patent claim.

Results and Discussion

The first juridical case in Great Britain for patents of citalopram is based on the different methods for production of racemic mixture and separated production of (+) and (-) enantiomers (17). Two years after the expiration of the main patent in 1987 a patent for enantiomers separation was issued. The first decision is that the manufacturer only extract the (+) enantiomer but after appeal the court decided that the patent is valid because it explains how a qualified person could extract the (+) enantiomer and the process of purification is novel.

For the orodispersible tablets of escitalopram produced by Lundbeck a patent was issued 3 years after the patent expiration in 2002 (27). The patent was issued in Great Britain and with small technical differences in the USA. This strategy actually increases the effective patent till the year 2014.

Our search methodology revealed 189 patents for citalopram issued during 1990-2010. They fall into several IPC classes (**Table 1**). The patents from class A61K are divided among patents for composition (31%), salts and crystallization forms (38%), and combinations (31%), all possessing the probable pharmaceutical effect. The patents from class C07, which are of major interest in this study, are almost equally allocated among sub classes C07C (acyclic or carbocyclic compounds – 49 patents) and C07D (heterocyclic compounds – 59 patents), as well there are 5 patents from class C07B (general methods of organic chemistry).

TABLE 1

Issued patents for citalopram by IPC class

IPC class	A61K	A61P	C07C	C07D	C07B
Number of issued patents	52	24	49	59	5

By C07 IPC subclass the distribution of issued patents is mainly for C07D (heterocyclic compounds) that correspond with the main active biological structure. The year 2006 was the most active in terms of granted patents, followed by 2002, then 2001, and 2007 (**Fig. 1**).

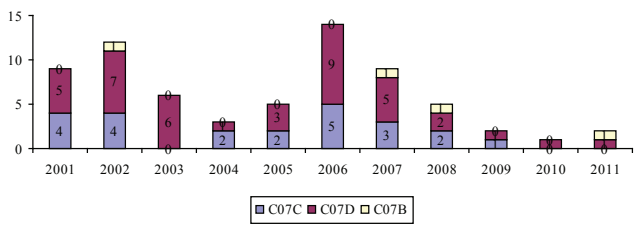

Fig. 1. Yearly distribution of C07 patents by subclasses.

By type of claim the patents for methods (n = 29) and processes (n = 20) are almost equally represented. The search retrieved only two patents for composition – for pharmaceutical composition containing citalopram (granted in 2003) and for the crystalline base of citalopram (granted in 2006). We also placed the 9 patents for methods for preparation in one category due to the lack of clarification. Thus in general the patents for methods prevail. The low number of patents for composition is reasonable due to the known compound and its structure (**Fig. 2**).

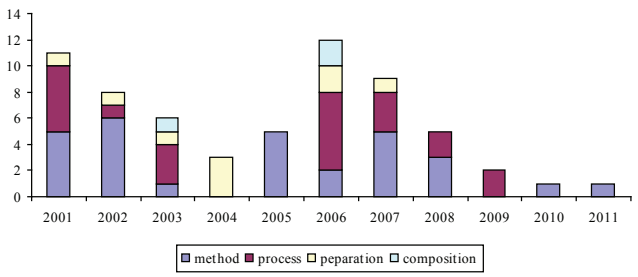

Fig. 2. Yearly distribution of C07 patents according to the main claim.

Going in details year by year, it is seen that in 1987 the first patent issued was for ring closure preparation of citalopram and enantiomers, as well as acid addition salt. This patent covers the main structure and enantiomers as well as possible salts. In 2001 one process of synthesis of citalopram, one for purification, crystallization, and one for production of citalopram and intermediates were described. Thus the protection is widened for intermediates and types of structures. One of the patents granted in 2002 is a new one for the preparation of citalopram by halogenation of 5-cyanophthalide to give an intermediate which is reacted with organometallic 4-fluorophenyl halide or 4-fluorophenylborane to give a benzophenone compound convertible to citalopram and covers also pro-products convertible to citalopram. Two of the patents from the same year are also for manufacturing of citalopram and intermediates. One of the patents issued in 2005 covers also the antidepressive effect of citalopram and intermediates. In 2007 a patent was issued for both enantiomers, that is, for the process of preparation of racemic citalopram diol and/or S- or R- citalopram diols and the use of such diols for the preparation of racemic citalopram, R-citalopram and/or S-citalopram. Similar patents were issued in 2008, 2009 and 2010.

Our study confirms what was previously mentioned, i.e. that the companies try to expand the real patent life of their products through increasing the active protection of the main active substance. The fact that the number of patents from class C07, which are protecting the substance, is almost double in comparison with other classes supports such a conclusion. Thus it appears that the patent search is a complex process because it should reveal the logically created staged policy of protection with its actual chemical and market meaning.

In our study we found patents not only for the main molecule preparation but also for enatiomers separately or together with the main molecule preparation. There were also patents found for salts and esters, which confirms the wide aspects of patent

protection. For some of them it appears that the enantiomers are more potent than the racemic mixture, which is evident from the better therapeutic effect of S-citalopram, later proven with clinical studies. This makes the patent search a complex process that should focus on the additional patents, modification of the molecule, differences in the effectiveness of the active substance and or intermediates. This explains the fact that we found a lot of patents for enantiomers or intermediates.

The chiral structure of the citalopram might also explain and the fact that the patents within class C07 are more than those from class A61K, in contrast with previous studies. It is evident that the companies prefer to protect both the main structure and the chiral enantiomers.

Conclusions

We could conclude that the chemical structure is an important factor in companies' patent protection policy and that the chiral structure is connected with more patents issued on the chemical substance than for the pharmaceutical activity.

Acknowledgements

This work was published with financial support from the "Human Resources Development" Operational Programme, "Science – Business" Scheme (Grant № BG051PO001-3.3-05/0001).

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