Article

Innovation in Pharmaceutical Assistance

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Innovation is the driving force that is able to create and transform products, processes, and organization in the health system. Innovation in the field of pharmaceutical assistance covers a wide spectrum of aspects, from drug discovery to pharmaceutical care, contributing to the improvement in treatments through novel drugs or methods. This work will present the major characteristics of innovation with special emphasis on aspects pertaining to pharmaceutical assistance. The types and models of innovation, as well as the interaction between academia and industry, will be presented with examples of successful products and methods. In addition, the challenges and perspectives for innovation in pharmaceutical assistance will be discussed with a focus on drug discovery.

Keywords: Innovation. Drug discovery. Pharmaceutical care. Pharmaceutical assistance. Novel.

INTRODUCTION

Innovation is the "act or effect of innovation" that has accompanied humans since ancient times. The transformation of wood and bones into routine tools is an example of innovation. The word 'innovation' was derived from the Latin term '*innovatio*' and was first used in the Middle Ages to describe the act of renewing or changing a product or process. Nowadays, the concept of innovation has been incorrectly associated with the idea of invention. Rather, innovation must be considered as a process that modifies something without necessarily involving the introduction of new products/processes.

The central concept of the meaning of innovation refers to a renewal and is not directly related to creation and invention in conceptual terms. On the other hand, innovation may remain close to the concept of novelty, since the renewal of a product or process can create a completely new product or system of organization. The examples of innovation surround us in common objects that are present in our daily lives. The ballpoint pens,

derived from feather pens, represent an innovation, where there is no need for constant ink refills for writing.

Types of innovation

Innovation may be classified into several categories, including product, process, organization, and marketing. Product innovation is the driving force for pharmaceutical companies, facilitating improvements in the pharmaceutical, pharmacokinetic, and pharmacodynamic properties of drugs and medicines. One example is the discovery of the antifungal agent fosfluconazole (Prodif®) (1), a prodrug of fluconazole (2) (Rautio *et al.*, 2018)4-difluorophenyl (Figure 1).

Fluconazole (2), discovered and patented by Pfizer in 1981, is a triazole antifungal agent known to be effective against systemic fungal infections. However, limited water solubility (4 mg/mL) was one of its major drawbacks (Rautio *et al.*, 2018; Bentley *et al.*, 2002)4-difluorophenyl. In clinical practice, intravenous administration of fluconazole (2) required a large volume of the solution, making it difficult to handle for patients in critical condition. In contrast, fosfluconazole (1), the prodrug of fluconazole (1), demonstrated high water-solubility (100 mg/mL), thus overcoming its limitation. Fosfluconazole (1) is rapidly converted to fluconazole (2) *in vivo* (Figure

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1), with less than 4% of the unchanged prodrug excreted in the urine (Bentley *et al.*, 2002)4-difluorophenyl. This discovery of fosfluconazole is an example of product innovation that had advantages over an existing drug.

FIGURE 1 - Chemical structures of fosfluconazole (1), fluconazole (2), sofosbuvir (21) and JQ-1 (22).
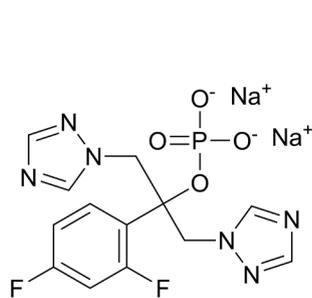
(**1**)
fosfluconazole
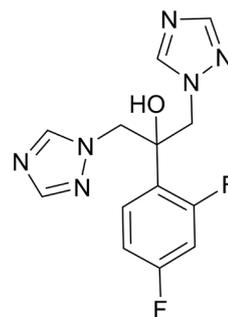
(**2**)
fluconazole

Inside-out process
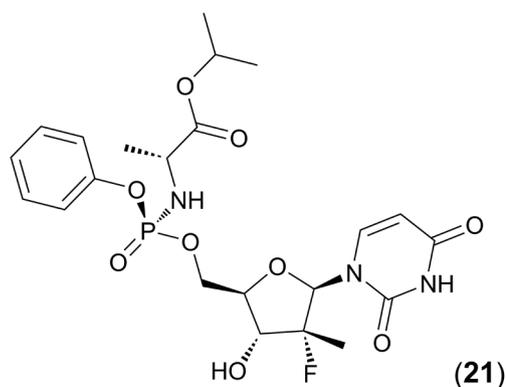
(**21**)
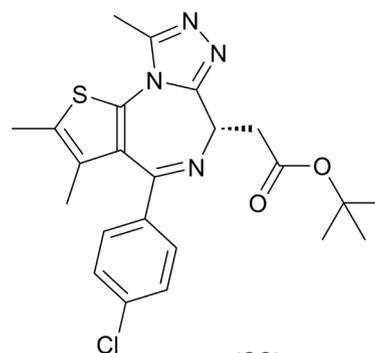
(**22**)

Process innovation involves the transformation of the means of execution, logistics, or production of services and products. Such examples in the pharmaceutical field range from modifications in the process of production of a pharmaceutical product to changes in the use of drugs by patients. The synthesis of vardenafil (14) at an industrial scale represents the concept of process innovation. The results of a collaborative study between three pharmaceutical companies (Bayer Pharmaceuticals, GlaxoSmithKline,

and Schering-Plow) indicated that the route of synthesis of vardenafil (14) had a major drawback, in the form of a modest overall yield of 25% from the synthetic intermediate (6) (Tian *et al.*, 2007) (Figure 2). In order to optimize the yield, a convergent synthetic route (route 2) was developed (Figure 2). The use of this modified route allowed 45% overall yield from the compound 2-ethoxybenzamide (6), representing an improvement of up to 20% compared to route 1 (Mao *et al.*, 2009).

FIGURE 2 - Two industrial synthetic routes for vardenafil (14) preparation.
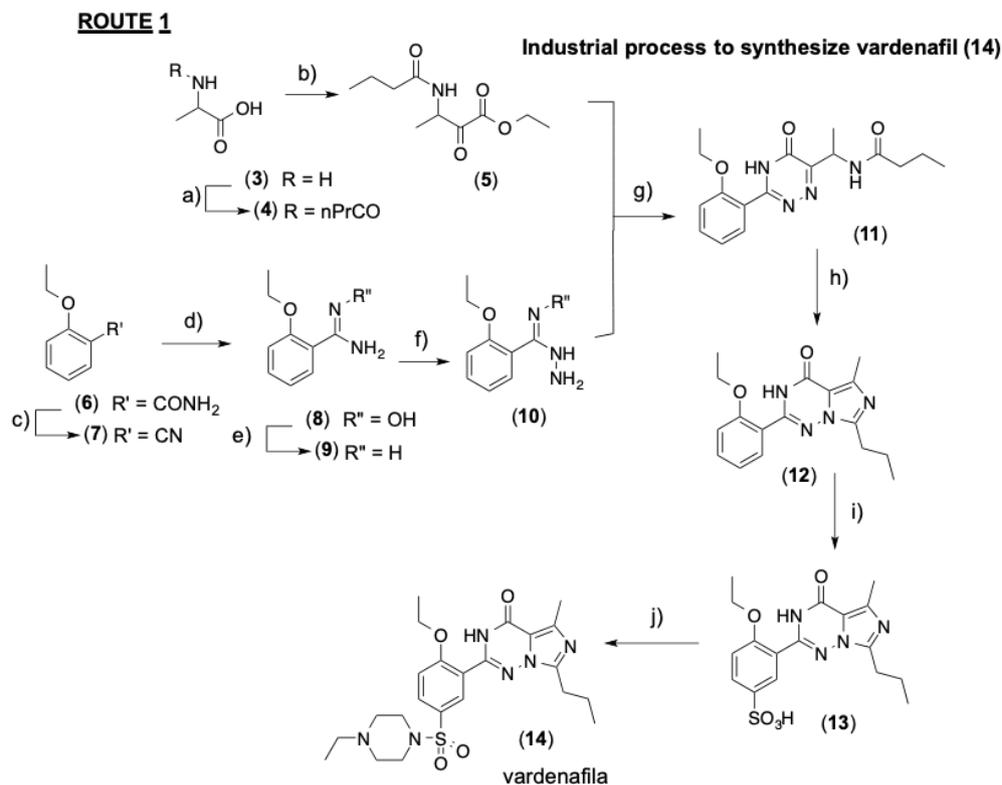
Reactive and conditions: a) n-PrCOCl, NaOH; b) ClCOCO$_2$Et, DMAP, THF; c) SOCl$_2$, toluene; d) NH$_2$OH.HCl, i-PrOH; e) H$_2$, Pd-C, AcOH; f) N$_2$H$_4$.H$_2$O, MeOH; g) MeOH; h) AcCl, AcOH; i) H$_2$SO$_4$; j) SOCl$_2$, 1-ethylpiperazine.

ROUTE 2
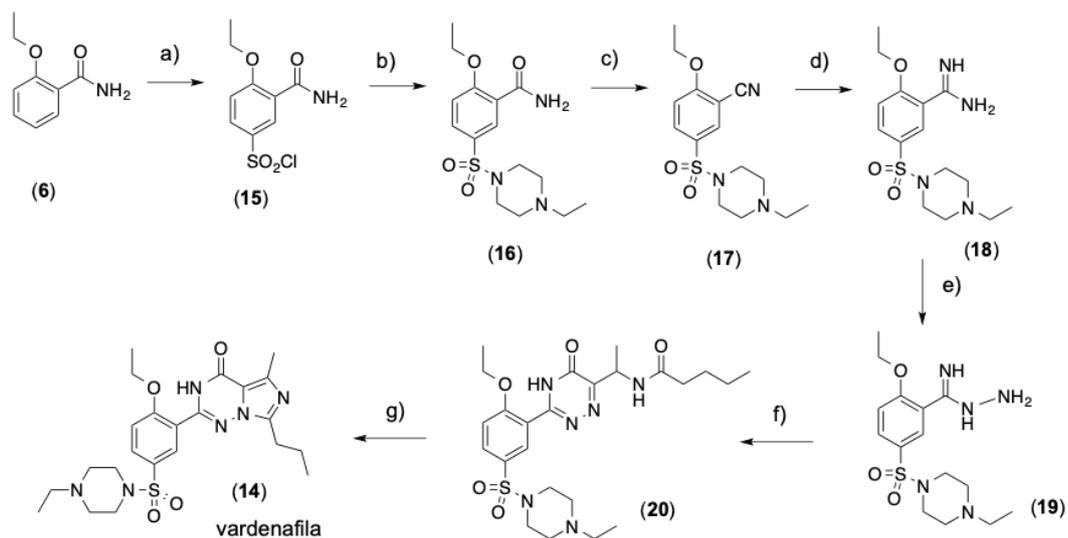
Reactive and conditions: a) ClSO$_3$H, dichloromethane, < 20 °C; b) 1-ethylpiperazine, rt; c) POCl$_3$, 80 – 90 °C; d) LiHDMS, THF, rt; e) N$_2$H$_4$.H$_2$O, EtOH, rt; f) EtOH, reflux; g) POCl3, 70 °C.

Another example of process innovation is the Directly Observed Treatment Strategy (DOTS). The DOTS approach represents a new paradigm in the treatment of tuberculosis. Currently recommended by the World Health Organization, it is a classic example of process innovation involving the use of medicines. It was initially formulated by the physician Karel Styblo (1921–1998) and was used during the 1970s to control the disease in some African countries such as Tanzania, Malawi, and Mozambique (Bleed *et al.*, 2000).

The basic principle of the process involved direct supervision by the health professional regarding the patient's intake of the medication. DOTS was subsequently expanded to include other components, such as a) smear-case detection of symptomatic patients suspected to have pulmonary tuberculosis; b) documentation and registration of information concerning the treatment of the patient, including data on clinical evolution; c) supply of medicines used to treat tuberculosis; and d) agreement with the government to include disease-control policies among the national health priorities. DOTS as an innovative process transformed the treatment of tuberculosis in these African countries, increasing the patient cure rates from 40% to 80% (Grzybowski, 1991).

Another category of innovation called 'organizational innovation' refers to the inclusion of a new organizational system in the operational routine of a particular company or organization, allowing for a reorientation of the way of work, as well as its external relations. Organizational innovation is commonly applied within the scope of management to optimize the functioning of a particular organization or company. A classic example is the organization of companies in assembly lines, as proposed by Frederick Taylor (1856–1915) during the early part of the twentieth century, based on the principle that systematization of work could increase productivity (Taylor, 1911).

In the Brazilian health system, the implementation of policies such as the Family Health Strategy (ESF) has been described as an example of organizational innovation. ESF, originated from Family Health Program, was initially constitute by a team which included a doctor, a nurse, one or two nursing technicians, and up to six community agents. After, the team as well as the healthcare actions were expanded, and other health professionals were included as part of Family Health Support Centers (NASF). ESF strategy aims to decentralize the Public Health System allowing Brazilian municipalities being responsible for the healthcare of their inhabitants. Regarding this aspect, the ESF created perspectives to design more appropriate health policies to guarantee healthcare in cities with different needs and characteristics. This program disrupted the traditional centralized system that was aligned to medicine positivism, which was technically based on the doctor and focused on the binomial disease/hospital as the only way to treat patients. ESF expanded this professional relationship to a multi-professional team that acted directly in the patient's environment, facilitating a new type of organization in the country's health system (Soratto *et al.*, 2015).

Finally, marketing innovation involves the introduction of significant changes in the product design or even packaging, positioning, promotion, or pricing, in order to increase sales. The changes may refer to the appearance or shape of the product that does not alter its functional characteristics. In addition, marketing innovation should consist of implementing a method that has not been previously used. An example of marketing innovation is the change in the packaging form of a cosmetic product and its promotion to attract male consumers (Tigre, 2014).

Models of innovation

The innovation of new products in pharmaceutical companies is a complex process. Traditionally, internal research centers in major pharmaceutical companies utilized great talents and ideas to carry out the discovery of modern medicines, with scarce external cooperation. In general, the acquisition of new technologies was common and did not involve the establishment of mutual collaborative partnerships. At the beginning of the 21st century, significant social changes, catalyzed by the information era and scientific advances, changed the scene of innovation. Wide access to information and access to technology contributed to the development of emerging centers outside the walls of the industries,

leading to the emergence of spinoffs or startups, mainly in developing countries. During this period of "innovation crisis", there was a reduction in the number of drugs discovered in big companies. Due to this situation, the model of innovation in the pharmaceutical industry was questioned and alternative models were developed (Pammolli, Magazzini, Riccaboni, 2011).

In 2003, professor Henry Chesbrough described the term 'open innovation', which represented a new dimension wherein organizations would not only use internal ideas, but also external inputs, in order to aggregate competencies, accelerate development, and reduce the number of failures/friction during the process. The advantages of open innovation included the establishment of collaborative networks, introduction of new ideas with an innovative profile, complementarity in the execution of the project in which responsibilities were shared among employees to achieve a common goal, and reduction of research costs (Chesbrough, 2003).

Recently, the term 'open innovation' has been used to address different areas, but in essence, it maintains the idea of external collaboration in the process of innovation. Among the described models of open innovation, the outside-in process, inside-out process, and coupled process have been discussed below (Enkel, Gassmann, Chesbrough, 2009).

Outside-in process

The open innovation model named 'outside-in' integrates suppliers, customers, and knowledge outside the company with an aim to increase knowledge promoting innovation. An example of the outside-in process used by the pharmaceutical industry is 'crowdsourcing'. In this model, external contributors such as patients or collaborators in academia can add new ideas or suggest strategies to the industry. This method has been followed by AstraZeneca on the platform patientslikeme.com (www. patientslikeme.com), a digital platform on which patients share concerns regarding their illnesses and treatments, facilitating a connection of the industry to the real needs of patients (Bentzien, Bharadwaj, Thompson, 2015).

An example of the open innovation crowdsourcing directed to academia is the platform InnoCentive developed by the pharmaceutical company Eli Lilly (https://www.innocentive.com/lilly/). This platform was initially available on the parent website, on which company scientists published their ideas and problems and other scientists around the world were able to contribute toward solving them. This approach was so successful that InnoCentive ended up establishing itself as an independent company (Enkel, Gassmann, Chesbrough, 2009).

Inside-out process

The open innovation model called 'inside-out' is based on the premise that internal innovations, which are not necessarily used by the company, can be made available to the external environment, allowing others to use it (Enkel, Gassmann, Chesbrough, 2009). This model aims to externalize the generated knowledge in order to bring innovation to the market faster than the one that would have been carried out in isolation. Using this strategy, organizations commonly earn profits through the licensing of intellectual property or technology transfer (Chesbrough, Chen, 2015). Spinoffs and startups in the pharmaceutical and biotechnology field often use this type of open innovation to develop new technologies at their companies, which are later licensed or transferred to large companies. Some situations involve not only the acquisition of technologies but also the purchase and merge of the entire company, leading to the formation of pharmaceutical giants.

An example of this model is related to the discovery of PSI-7977 (21) by the company Pharmasset. Founded in 1988 by two medicinal chemists from Emory University (Raymond Schinazi and Dennis Liotta), the company has developed several antivirals agents, including the compound PSI-7977 (21), a potent antiviral used for the treatment of hepatitis C. Following the promising *in vitro* and *in vivo* results using PSI–7977 (21), the technology was acquired by the pharmaceutical company Gilead. The compound PSI–7977 (21), later called sofosbuvir (21), received approval from the US FDA in 2013 (Figure 1). Furthermore, Gilead also chose to acquire the company in November 2011 for a value of 11.2 billion dollars (Roy, King, 2016).

Another example of an inside-out open innovation that was not created in the company environment is the discovery of the bromodomain inhibitor JQ–1 (22) (Figure 1). Bromodomains are epigenetic targets that are capable of recognizing acetylated lysine residues, thus influencing a number of processes related to gene transcription (Dutra *et al.*, 2017). *In vitro* and *in vivo* studies on the compound JQ–1 (22) have demonstrated its efficacy against a rare and aggressive form of cancer, named NUT midline carcinoma (Filippakopoulos *et al.*, 2010). The researcher James Bradner and his team from the Dana-Farber Cancer Institute decided that instead of protecting intellectual property regarding JQ–1 (22), they would make the information available to the community through an open innovation system, called the "social experiment". Until the end of 2018, more than 100 patents of new bromodomain inhibitors were filed in patent repositories by different pharmaceutical companies (Scott, 2016).

Similar open innovation approaches have been utilized by research organizations, including the Structural Genomics Consortium, Institute of Cancer Research in London, Broad Institute of Harvard, and Massachusetts Institute of Technology in Cambridge (Massachusetts, United States). The type of proposal by researchers also facilitates the development of a new organizational arrangement of the type of research carried out in institutes and universities.

Coupling model of innovation

The coupling model of innovation occurs when organizations collaborate with each other and merge both outside-in and inside-out innovation strategies, thereby enabling cooperation in networks. Several types of cooperation can be developed, including joint ventures and partnerships with universities and research centers (Schuhmacher *et al.*, 2013;in particular, how to manage stagnating research and development (R&D

Schuhmacher, Gassmann, Hinder, 2016)defined as the successful approval and launch of new medicines (output.

In the pharmaceutical industry, partnerships between large companies have facilitated the discovery of several drugs (Abou-Gharbia, Childers, 2014). Table I shows some of the partnerships developed by the pharmaceutical company Bristol-Myers-Squibb. A joint venture involving the companies Bristol-Myers-Squibb and Pfizer has led to the discovery of apixaban (27) (Eliquis®), a direct inhibitor of the Xa factor, that is used as an anticoagulant. This drug (27) can be used orally and has fewer adverse effects than warfarin, which is an anticoagulant with a narrow therapeutic margin. Thus, apixaban (27) may present a new alternative to the use of warfarin (Hernandez, Zhang, Saba, 2017).

Another example of a drug developed through interaction between pharmaceutical companies, which has already been launched on the market, is Abilify®. The active ingredient aripiprazole (29) is an atypical antipsychotic used to treat schizophrenia and bipolar disorder (Table I). It was developed by a pharmaceutical company Otsuka in Japan but had the participation of Bristol-Myers-Squibb for the introduction of the drug in the US market. Aripiprazole (29) will have made billions of dollars until the expiry of its patent. Further collaboration between the technology company Proteus Digital Health and the pharmaceutical company Otsuka re-launched aripiprazole (29) on the market with the drug Abilify Mycite® (https://www.abilifymycite.com). Considering that a lack of adherence is one of the major challenges in the treatment of schizophrenia, through Abilify Mycite®, both companies have introduced a new technology by inserting sensors into medicine. After ingestion and subsequent contact with the stomach fluid, these sensors transmit electrical signals to devices attached to the patient's skin, which replicate signals received from the sensor to a cell phone containing an app. This app is in turn connected to the healthcare professional's computer, helping them monitor the patient's adherence (Mullard, 2015).

TABLE I - Drugs developed by Bristol-Myers-Squibb co-partnerships with other pharmaceutical companies (Abou-Gharbia, Childers, 2014).

Company	Medicine	Drug	Chemical structure	Therapeutic indication
Bristol-Myers-Squibb, Sanofi	Plavix®	clopidogrel (23)		Antiplatelet
Bristol-Myers-Squibb, Gilead e Merck	Atripla®	efavirenz (24), emtricitabine (25) e tenofovir disoproxil (26)		Antiretroviral –HIV
Bristol-Myers-Squibb, Pfizer	Eliquis®	apixaban (27)		Anti-coagulant
Bristol-Myers-Squibb, Novartis	Zelmac®	tegaserode (28)		Irritable bowel syndrome
Bristol-Myers-Squibb, Otsuka	Abilify®	aripiprazole (29)		Antipsychotic
Bristol-Myers-Squibb, AstraZeneca	Onglyza®	saxagliptine (30)		Hypoglycemic
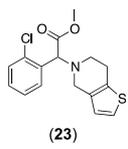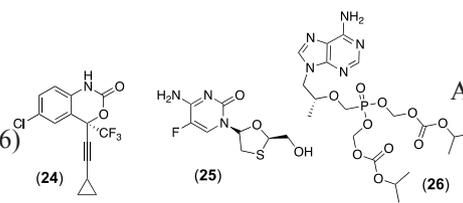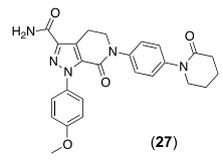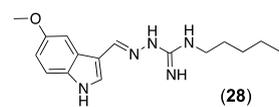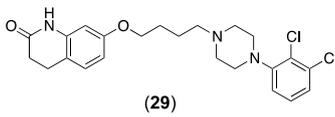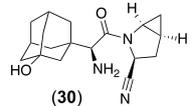
Open innovation and the contribution of universities to the discovery of novel drugs

Nowadays, it is known that the innovation model that had been used by pharmaceutical industries for several years is unsustainable in the face of current challenges, including high R&D costs, failures in the later stages of development, decrease in the numbers of drugs that achieve billions of sales, development of similar therapeutic products (me-too), increased regulatory requirements for the approval of drugs, and pressure of generic medicines leading to a reduction in industry revenues, among others (Melese *et al.*, 2009; Kneller, 2010; Bennani, 2011; Pammolli, Magazzini, Riccaboni, 2011).

The studies by Pammolli and collaborators have shown that the success rates of discovered drugs vary across therapeutic areas, ranging from 1.8 to 11.75%. For the antineoplastic industry, the total number of projects increased by 8% during the period from 2000 to 2007, compared to the period from 1990 to 1999. However, despite this increase, the percentage of success of a new anticancer drug reaching the market was only 1.8%

among 6566 projects evaluated. By the other hand, the percentage of success to discover a drug for genitourinary system and sex hormones have exhibited value of 11.75% among 865 projects evaluated (Pammolli, Magazzini, Riccaboni, 2011).

Therefore, it has become essential to search for new models of innovation that provide long-term sustainability. In the open innovation model, universities play an important role in generating knowledge and innovation, which may reduce the industry's effort in discovering new drugs. To this end, major pharmaceutical companies such as Pfizer, GlaxoSmithKline, Merck, and AstraZeneca have established partnerships with universities and research centers around the world (Hughes, 2008).

An analysis of the period from 1998 to 2007 has shown that about 76% of the 252 drugs that have been discovered during this period have been developed by pharmaceutical and biotechnology industries, while the remaining 24% have been developed with the participation of universities. Specifically, 66.67% of the drugs that were discovered in universities were transferred to biotechnology companies, while 33.33% were transferred to pharmaceutical companies (Kneller, 2010).

This is very different scenario, mainly considering the reality observed in previous years. For example, a study conducted by DiMasi and collaborators has shown that the pharmaceutical industry accounted for 93.3% of innovations between 1990 and 1999, while partnership with universities accounted modestly for only 3.5% and the public/government sector accounted for 3.2% (DiMasi, Hansen, Grabowski, 2003).

Despite these developments, the collaboration of universities with pharmaceutical companies can still be considered to be modest. In countries such as the United States, this interaction appears to be more fruitful, unlike others such as Japan, United Kingdom, Germany, Canada, Switzerland, and France, where university participation is still considered to be small (Kneller, 2010).

Several challenges related to the different visions of institutions make collaborative work difficult. The direct relationship between publication and funding, lack of patent policy, and the organizational management of information/knowledge generated in universities reduce the possibility of such interaction. Obviously, not all the areas and sectors of a university have innovative research that has the potential to reach the market, but for the areas that do, policies must be stimulated. Another aspect that hinders the interaction between universities and companies is the difference of interests pertaining to research topics.

A study conducted in the United States involving 78 drug research centers that were located mainly in US universities, showed that the focus of the research was based on themes such as cancer (86% of all researches), infectious disease (71% of all researches), and diseased orphans (36% of all researches), among others. These findings indicated that the research areas targeted at US universities did not have an identical interest in the industry (Frye *et al*., 2011). These differences between academic and business goals have distorted the interaction between academia and industry.

Some types of partnerships in establishing relationships between universities and companies have been described (Melese *et al*., 2009), some of which are highlighted below:

a) Company-researcher: in this model, the company establishes a direct partnership with the researcher by providing funds for collaborative work. Although it is the starting point for interaction, it does not allow the collaboration of other researchers.

b) Company-university: in this model, the company signs a wide agreement with the university, financing a series of research groups depending on their interest. The establishment of an agreement can facilitate the entry of other researchers. However, working with a single company can limit the scope of research at the university, although it is seen by the company as an extension of its R&D activities.

c) Company-consortium of universities: in this model, the company builds a consortium involving several universities that are focused on a specific objective. This model expands the number of collaborators in different universities, facilitating concerted efforts toward a common goal.

d) Company-financing of a university's research institute: in this model, one or more companies donate to research institutes or create new institutes

within universities. The company has access to researchers and their knowledge, while the university receives funds to sustain research in a specific area.

e) Consortium between companies: in this model, some companies form a consortium and collaborate with medical academic centers present in the universities, in order to solve non-competitive innovation challenges, for example, the search for biomarkers in certain diseases.

f) Competition: the company invests on multiple researchers to investigate the same topic; the first team to achieve the objectives receives more financial resources for the next step. The information is not shared, and the team that wins is not always the most qualified to take the project to the next step.

g) Fee for service: in this model, the university offers a certain service of interest to the company, which in turn pays for the work. Generally, the aim is to avail specific services of technologies that the university possess, and the company is not interested in acquiring them at that time.

The models are not limited to the types presented here and may be adapted according to the needs of the company or the university to suit the interests of both parties.

Examples of successful interaction between academia and the pharmaceutical industry

The interaction between academia and industry has contributed to the discovery of several therapeutic drugs, namely paclitaxel (31), vorinostat (32), darunavir (33), raltitrexed (34), adefovir dipivoxil (35), tenofovir disoproxil fumarate (36), lamivudine (37), valrubicin (38), carboplatin (39), temozolomide (40), dexrazoxane (41), pemetrexed (42), and zidovudine (43) (Figure 3) (Frearson, Wyatt, 2010).

FIGURE 3 - Examples of drugs developed through academia-industry interaction.

paclitaxel (31)

vorinostat (32)

darunavir (33)

raltitrexede (34)

lamivudine (37)

valrubicin (38)

carboplatin (39)

adefovir dipivoxil (35)

tenofovir disoproxil fumarato (36)

temozolamide (40)

dexrazoxan (41)

pemetrexede (42)
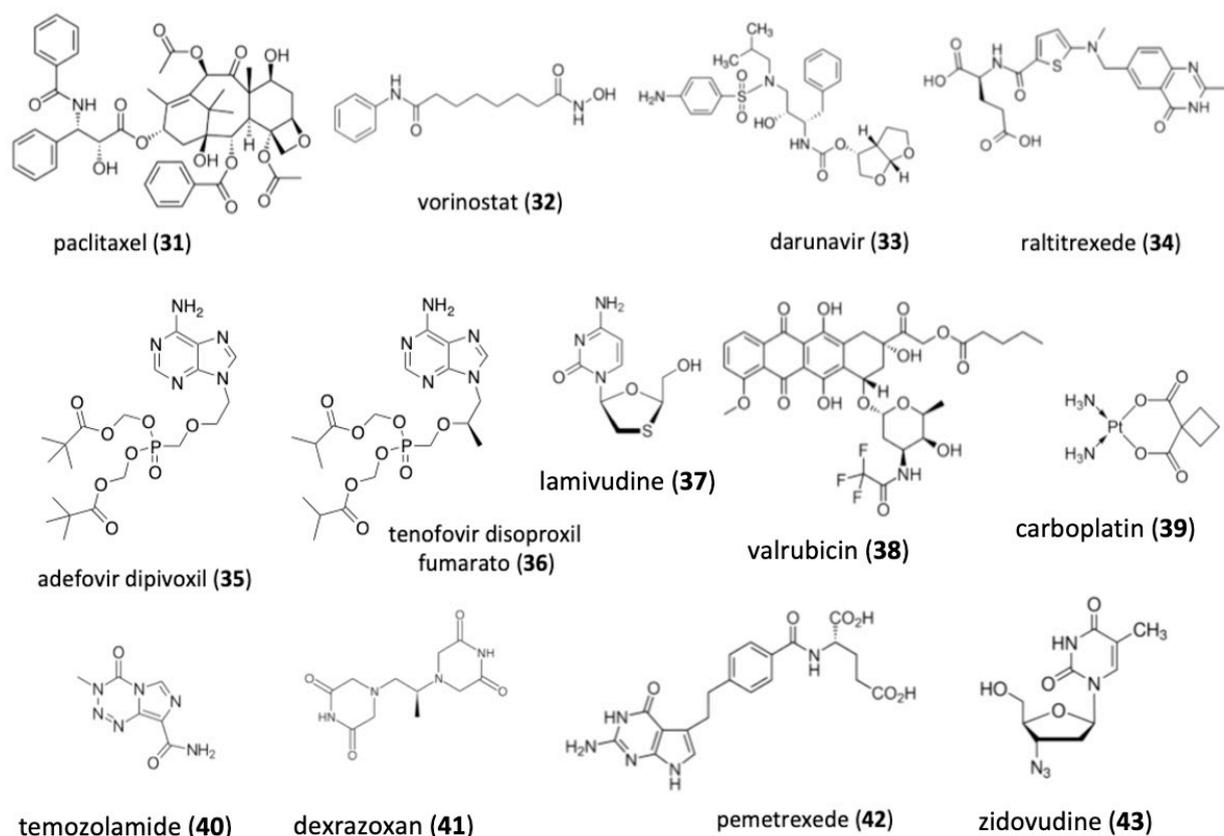
zidovudine (43)

The therapeutic class of antiviral agents is a classic example of the fruitful interaction between academia and industry in the promotion of new-drug discovery. Historically, one of the first examples of this was zidovudine (43), also called azidothymidine (AZT) (Figure 3). This drug was synthesized in 1964 by researchers at the Michigan Cancer Foundation (USA), and was further evaluated against cancer, although without success (BRODER, 2010). In 1974, researchers at the Max Planck Institute (Germany) demonstrated the effect of AZT against a type of murine leukemia retrovirus, called the Friend virus (Ostertag *et al.*, 1974). In 1983, researchers at the Pasteur Institute in Paris demonstrated the effect of this drug against HIV. Realizing the potential shown by the drug, the pharmaceutical company Burroughs-Wellcome, which had already developed acyclovir in collaboration with the National Cancer Institute in the United States, began clinical trials following the FDA's approval of the drug in 1987 for HIV treatment (Cihlar, Ray, 2010) nucleoside analog 3'-azidothymidine (AZT.

Other examples of antiretroviral reverse transcriptase inhibitors are adefovir dipivoxil (35) and tenofovir disoproxil fumarate (36) (Figure 3). Adefovir dipivoxil (35) is used for the treatment of hepatitis B, while tenofovir disoproxil fumarate (36) is used against both HIV and hepatitis B virus. Both the drugs were developed through collaboration between the pharmaceutical company Gilead and the Institute of Organic Chemistry and Biochemistry of the Czech Republic/Rega Institute of Belgium. The first studies on acyclic nucleoside phosphonates started in 1986, following the discovery of the broad-spectrum antiviral activity of the compound [(S)–9-(3-hydroxy–2-phosphonylmethoxypropyl) adenine] ((S)-HPMPA) (44) (Figure 4). Using the molecular simplification of this compound (44), both adefovir (45) and tenofovir (46) were synthesized and evaluated against viruses of the family Retroviridae. In order to improve the pharmacokinetic profile of both compounds, the prodrugs adefovir dipivoxil (35) and tenofovir disoproxil fumarate (36) were developed (De Clercq, 2015).

The interaction of research institutes such as the Dana-Faber Cancer Institute (USA) with the company Endo Pharmaceuticals has allowed the reintroduction of valrubicin (38) for the treatment of bladder cancer. The drug (38) is administered by intravesical instillation using a catheter that is introduced into the bladder through the urethra. Although its anticancer effect has been known since 1980, it was approved by FDA in 1997 for bladder treatment in patients that were recalcitrant to the intravesical instillation of Calmette-Guerin bacillus (BCG) (Steinberg *et al.*, 2001).

FIGURE 4 - Development of adefovir dipivoxil (35) and tenofovir disoproxil fumarate (36) as a result of academia-industry interaction.
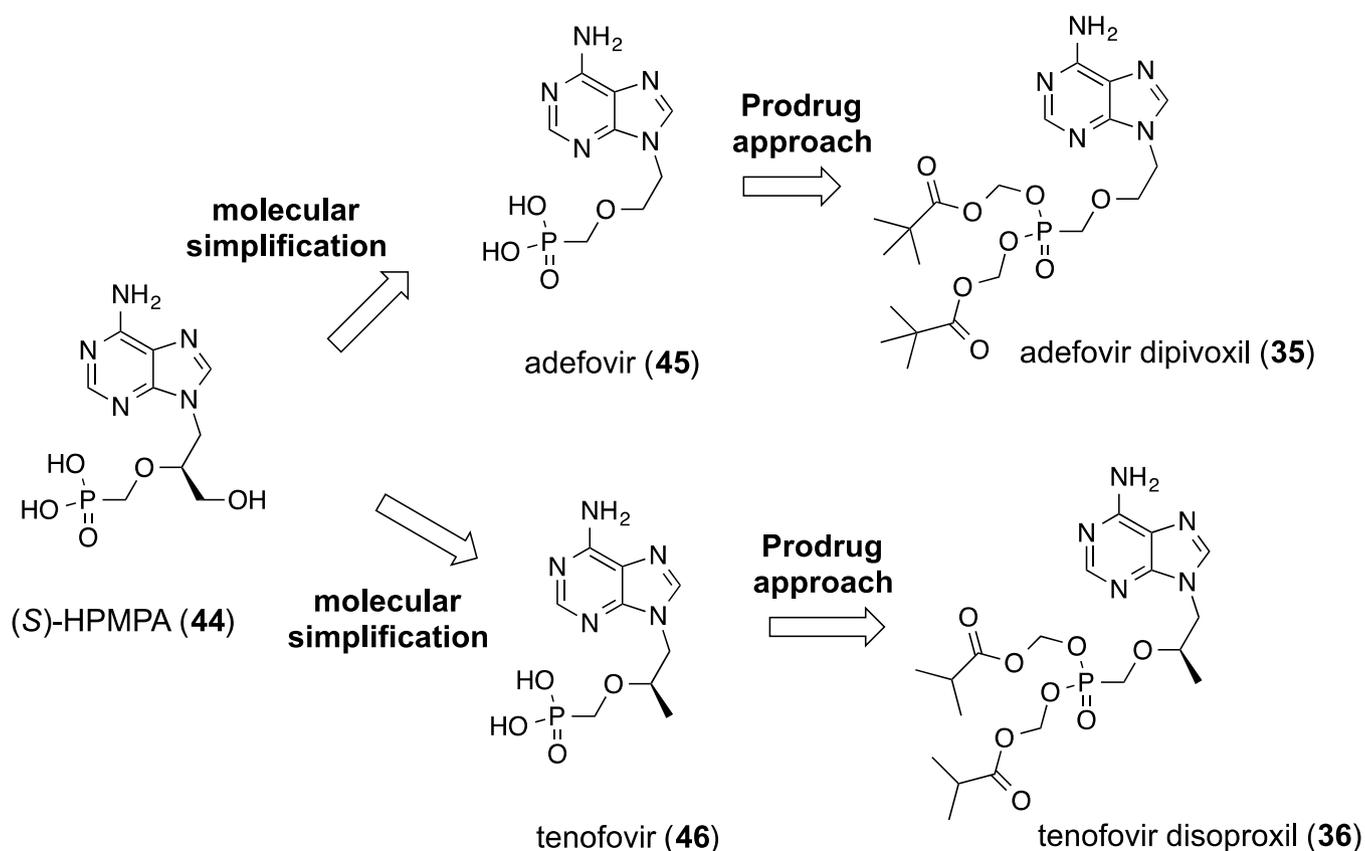
The alkylating agent temozolomide (40) is an antineoplastic drug used for the treatment of multiform glioblastoma (Figure 5). It was discovered by Malcolm Stevens and collaborators from the University of Aston (England), and was later developed by the pharmaceutical company Schering-Plow (Newlands *et al*., 1997). In 2008, it achieved revenue worth one billion dollars. The research leading to the discovery of temozolomide (40) began in the late 1970s after reports that described the anticancer activity of trienes. At the same time, Y. Fulmer Shealy from the Southern Research Institute in Birmingham (United States) discovered the drug dacarbazine (47) (Figure 5). In 1975, the FDA approved this trienic compound for the treatment of malignant

metastatic melanoma, and its development resulted from collaborative work with the pharmaceutical company Bayer. Using this derivative with the aim of searching for imidazo tetrazine heterocyclic systems, Malcolm Stevens and colleagues developed mitozolamide, also called azolastone (48) (Fairbairn *et al*., 2000)which exhibits resistance to inactivation by O6-benzylguanine (O6-beG. However, phase 2 clinical studies demonstrated that this compound (48) induced severe spinal suppression. Thus, in collaboration with Schering-Plow, a molecular simplification was performed, wherein the alkyl halide present in mitozolamide (48) was removed, leading to the discovery of temozolomide (40) (Figure 5) (Newlands *et al*., 1997).

FIGURE 5 - Examples of drugs agents developed through university-business interaction.
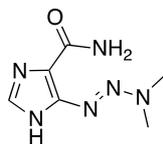
dacarbazin (**47**)
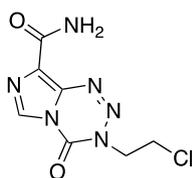
mitozolamide (**48**)
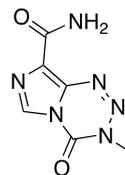
temozolamide (**40**)
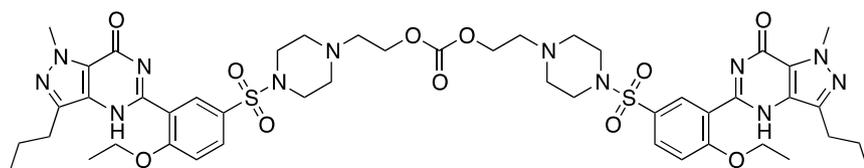
lodenafil carbonate (**49**)
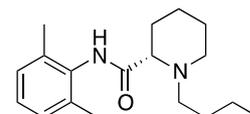
levobupivacaine (**50**)

Pemetrexede (42) is a pyrrolopyrimidine derivative that is able to inhibit thymidylate synthase, glycinamide ribonucleotide formyltransferase and dihydrofolate reductase, which makes it useful in the treatment of cancer (Figure 3). As an isolated agent, it is recommended for the treatment of non-small cell lung cancer patients with non-squamous cell histology after prior chemotherapy. In combination with cisplatin, it has been recommended for the treatment of patients with malignant pleural mesothelioma that is either unresectable or not amenable to curative surgery (Hazarika *et al*., 2004). Pemetrexede (42) was discovered by Edward C. Taylor of the Princeton University (United States) and subsequently developed by the pharmaceutical company Eli Lilly after receiving approval of FDA in 2004 (Taylor, Patel, 1992).

It is beyond the scope of this review to discuss the examples of accidental university-business interaction, but it has to be emphasized that this interaction reduces costs, allows access to new technologies and knowledge, and promotes collaboration between academia and industry. From the perspective of academia, the discovery of new drugs allows the acquisition of royalties, which further accelerates research by setting tangible goals to achieve an innovative product.

Innovation in Brazil: challenges for interaction between academia and industry in the discovery of new drugs

In order to understand the context of innovation in Brazil, it is necessary to revisit the political background for describing this process in the country. From 1930, the Brazilian government began to formulate and coordinate national development. Several public institutions were created for the purpose of enabling the country's industrial development. Until the mid-1960s, the state's bidding policy was focused on investment in science. At that time, several agencies, such as the National Council for Scientific and Technological Development (CNPq) (1951) and the National Bank for Economic and Social Development (BNDES) (1952), were created at the federal level with an aim of promoting scientific and human resources.

During the military government (1964-1985), regulatory policies were planned to encourage the technological modernization of the country through the absorption of foreign technology. In 1967, the organization Financier of Studies and Projects (FINEP) was created to manage and provide resources for the financing of projects and programs for economic development. The early initiatives to encourage university-company

interactions were taken, but the country was still dependent on external technology.

From the beginning of the New Republic (1985) until the later part of the 1990s, several transformations in the Science and Technology Policy took place. Based on the neoliberal logic, it was imagined that the opening of a Brazilian market could promote innovation within companies, as they would face pressure from external competition. However, due to the fragility of the newly-formed industry, a high degree of restructuring was observed. In 1985, the Ministry of Science, Technology, Innovations, and Communications (MCTIC) was created. During this period, the government provided the stimulus for investment in research and development (R&D) in national public companies.

The regulatory framework for innovation in Brazil was complemented by the Technological Innovation Law No. 10,973 (December second, 2004) (Brasil, 2004). This represented an important milestone for national science and technology and laid the foundations for relationships between academia and industry. The Technological Innovation Law No. 10,973 was organized in three guiding axes: a) the creation of a conducive environment for strategic partnerships between universities, technological institutes, and companies; b) encouraging the participation of scientific and technological institutes in the process of innovation; and c) stimulus for innovation within each industry.

The purpose of the Technological Innovation Law was to stimulate partnerships between the public sector, private sector, and academia, aiming at generating knowledge that could be transformed into innovative products or processes that would reach the market. After some years and the identification of certain obstacles, the Law was reformulated on February 7th, 2018 vide the Decree No. 9283, making the partnership regime clearer and more flexible, simplifying accountability, and distributing financial resources between company and university, among others (Brasil, 2018).

In the area of pharmaceuticals, innovation in the research and development of new drugs is still nascent, in contrast to pharmaceutical technology development. With the external acquisition of active ingredients, the innovation process in the national pharmaceutical industry is still restricted to generic drugs. However, this situation is changing in certain national industries. One such example is the pharmaceutical laboratory Cristália, which holds about 105 filed and/or granted patents, many of which are in collaboration with Brazilian universities. The company has invested in innovations for some years and has been a new center for research, development, and innovation since 2009. According to the company, about 25% of the projects under development are focused on radical innovations. An example of innovation from the Cristália laboratory is the dimer of lodenafil carbonate (49) called Helleva®, which is considered to be the first synthetic drug developed in Brazil (Figure 5). For the development of this compound, the laboratory collaborated with researchers from the State University of Campinas (UNICAMP) for the pre-clinical and clinical trials (Phase 1) (Mendes *et al*., 2012)a key mediator that stimulates soluble guanylyl cyclase to increase cGMP levels causing penile erection. Phosphodiesterase 5 (PDE5.

Another example of successful collaboration between academia and industry was the development of the anesthetic drug Novabupi® (Figure 5). This drug was developed through interaction between the pharmaceutical laboratory Cristália and the research group headed by Professor Maria dos Prazeres Barbalho Simonetti from the University of São Paulo (USP). The collaborators collectively owned a patent for a process of the enantiomeric enrichment of bupivacaine, which allowed the development of a product containing 75% of the levobupivacaine eutomer (50), rather than commercialization of the racemic mixture. This approach reduced the adverse effects of racemic mixtures, such as cardiac arrhythmias, and represented a type of incremental innovation (Sudo *et al*., 2001).

### Radical vs. incremental innovations

In order to differentiate between innovation processes that present a true divergence from the state of the art from those that promote improvements in previously known elements, the terms radical innovation and incremental innovation have been introduced. Radical innovation results in products or processes with no apparent similarity to the existing ones. This type

of innovation can access new segments and capture a large market share due to the absence of competitors. For example, in the field of drug discovery, it can be the first representative of a certain therapeutic class (Alt, Helmstädter, 2018).

In the pharmaceutical industry, there are several examples of radical innovation, including chlordiazepoxide (51) (1959), propranolol (52) (1964), cimetidine (53) (1971), omeprazole (54) (1979), celecoxib (55) (1993), and sildenafil (56) (1996), among others (Figure 6). These drugs represent previously unpublished chemical structures and unknown mechanisms of action. When radical innovations reach annual revenues of $ 1 billion or more, the drug is called a 'blockbuster'. One of

the most representative examples of a blockbuster drug is sildenafil (56) (Yamanaka, Kano, 2016).

In recent years, the open innovation model has facilitated the contribution of universities in the discovery of 'blockbuster' drugs, through the academia-industry interaction. One such example is pregabalin (57) (Lyrica®), developed by Pfizer and recommended for neuropathic pain, epilepsy, generalized anxiety disorder, and fibromyalgia. Pregabalin, was first discovered by the researcher Richard Bruce Silverman from the Northwestern University (United States), the patent for which was later transferred to Pfizer. In 2006, the drug earned about US $ 1.2 billion, representing a radical innovation from the academic world (Silverman, 2008).

FIGURE 6 - Examples of drugs developed through radical (51-57) and incremental (58-60) innovations.

Radical innovations

chlordiazepoxide (**51**)   propranolol (**52**)   cimetidine (**53**)   omeprazole (**54**)   celecoxib (**55**)


sildenafil (**56**)   pregabalin (**57**)

Incremental innovations

lansoprazole (**58**)   pantoprazole (**59**)   rabeprazole (**60**)
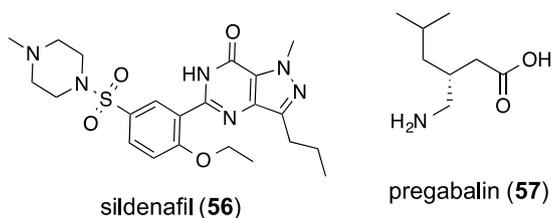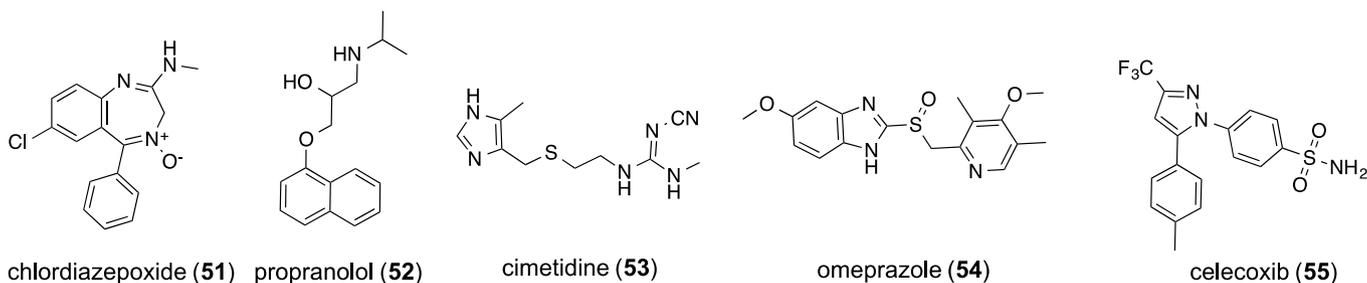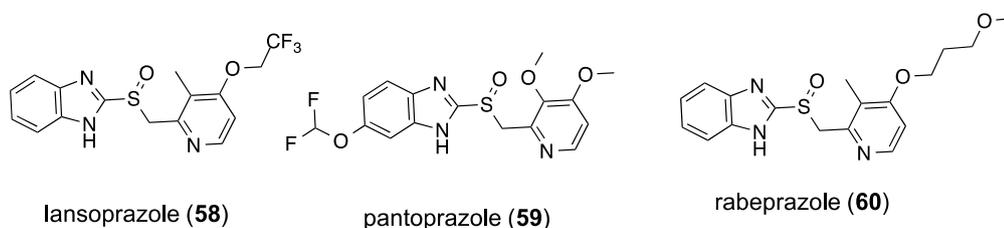
On the other hand, incremental innovation is the improved version of a product or process. In the area of new drugs, the design of analogs from radical innovations is referred to as "me-too". In general, these compounds demonstrate improved pharmaceutical efficacy, and better pharmacokinetic and/or pharmacodynamic profiles (Bennani, 2011; Alt, Helmstädter, 2018). Incremental innovation results in rapid access to the market that has already been acquired by a particular technology achieved by radical innovation (Bennani, 2011).

Omeprazole (54), an antiulcer drug, was an innovative drug, the discovery of which led to several incremental innovations. The drug (54), discovered in 1979 by Astra AD (now AstraZeneca), was launched in Europe in 1998 (Losec®) and the United States in 1990 (Prilosec®). At the time of its launch, it represented a radical innovation for the treatment of duodenal ulcers, and gastric and reflux esophagitis. From omeprazole (54), a number of 'me-too' drugs have been developed, such as lansoprazole (58), pantoprazole (59), and rabeprazole (60) (Figure 6). Pharmacokinetic differences, mainly associated with bioavailability, have been described for these 'me-too' drugs (Strand, Kim, Peura, 2017)safe, and effective agents for the management of a variety of acid-related disorders. Although all members in this class act in a similar fashion, inhibiting active parietal cell acid secretion, there are slight differences among PPIs relating to their pharmacokinetic properties, metabolism, and Food and Drug Administration (FDA.

CONCLUSION

The original concept of innovation represents the idea of renewing a product or process, adding previously unknown advantages to it. Innovation can be categorized into several types, including product, process, organizational and marketing. According to the model, the innovation may present characteristics of 'closed innovation' or 'open innovation'. There are also characteristics that classify the result of innovation as radical or incremental.

For several years, the pharmaceutical industry had worked with the concept of closed innovation, wherein the development occurred internally and external participation was rare. At the beginning of the 21st century, the concept of 'open innovation' solved the crisis of innovation that was being experienced by the pharmaceutical industry. In the new model, external participation in the company's innovation activities increased, allowing collaborative development among even the pharmaceutical companies themselves, something that was not imagined in the competitive environment of the early twentieth century.

However, the part of the success of the open model comes from partnerships established with universities or research centers, which have created new opportunities and added to business technology development. The examples of the discovery of novel antiviral and antineoplastic agents, which have been presented in this chapter, demonstrate the potential of interaction between the industry and academia in the generation of innovative products.

Interaction with companies can open up new avenues of financing for universities, provide access to technologies, and present a direct application of research with the development of new products or processes to society. In pharmaceutical assistance, innovation can be found at different levels such as, for example, the development of products/process that guarantee the appropriate use of medicines. Despite the advancements, university-company interaction in our country in the area of research of new drugs is still emerging, although initial steps have already been taken.

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