UNIVERSITAT DE BARCELONA

Synthetic approaches towards organic products of pharmaceutical interest

Beatrice Elena Jora

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FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

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BEATRICE ELENA JORA

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Synthetic approaches towards organic products of pharmaceutical interest

Memòria presentada per Beatrice Elena Jora per optar al títol de doctor per la Universitat de Barcelona

Director i tutor: Prof. Dr. Santiago Vázquez Cruz

Doctoranda: Beatrice Elena Jora

El treball experimental recollit en aquesta memòria s'ha realitzat al Laboratori de Química Farmacèutica del Departament de Farmacologia, Toxicologia i Química Terapèutica de la Facultat de Farmàcia i Ciències de l'Alimentació de la Universitat de Barcelona, sota la direcció del Prof. Dr. Santiago Vázquez Cruz.

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Resum

La present tesi se centra en l'estudi i la síntesi de tres principis actius (API, segons les sigles en anglès) amb activitat terapèutica. Tot i que aquests compostos són disponibles comercialment, les seves rutes de síntesi són molt antigues i per tant, requereixen un procés d'optimització i innovació sempre que sigui possible. El treball es dividirà en dos blocs en funció de la diana terapèutica: la primera part se centra en la síntesi i optimització d'un agent antipsicòtic, mentre que la segona part es basa en la preparació i optimització de fàrmacs antihipertensius. Pel que fa aquest darrer capítol, es presenta l'estudi i síntesi de dos APIs que formen part de la mateixa família de compostos.

Tenint en compte que molts dels processos de obtenció d'aquests compostos descrits en la bibliografia manquen de reproductibilitat o que aporten poca informació, és necessari investigar i millorar les condicions de reacció. Amb aquesta finalitat, es busquen els punts més crítics que afecten al procés de síntesi.

La optimització del desenvolupament de les rutes de síntesi implica abordar una sèrie de criteris com per exemple l'ús de reactius i dissolvents no tòxics, detecció de riscos laborals, increment d'eficàcia de procés en termes de rendiment i costos, reducció del temps de reacció, increment de la qualitat de producte, aplicació d'operacions més senzilles entre altres exemples.

Tan bon punt com s'estableixen les millors condicions de reacció, es procedeix amb la replicació d'aquests experiments per estudiar la viabilitat del procediment. La obtenció de bons resultats dóna pas a l'escalat de procés a nivell de laboratori; d'aquesta manera se segueix amb l'avaluació continua dels aspectes més transcendentals. Els paràmetres que poden ser alterats durant l'escalat de procés poden ser molt variats: conversió més lenta dels reactius de partida a producte final, aparició o intensificació d'impureses, risc d'increment de temperatura etc.

Una vegada es consolida la metodologia per a sintetitzar aquests compostos i es comprova la robustesa del procés, es valora la possibilitat de protegir la informació de procés mitjançant una sol·licitud de patent. Tanmateix, l'objectiu general de la present tesi radica en la fabricació d'aquests compostos a nivell industrial complint requeriments GMP.

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General introduction

BioPharma Synergies (BPS) is a business intermediary focused on knowledge and technology transfer from pharmaceutical companies that do not comply European Union (EU) quality standards. The objective of the Catalan company is to provide practical guidance for chemical corporations to explore their processes complying EU legislation.

Moreover, BPS offers technical advice through the Research and Development and Innovation (R&D&I) department affording reliable and robust outcomes based on Good Manufacturing Practice (GMP) activities at EU. Consequently, the pharmaceutical company has the option to manufacture on regulated market with no need to expand their installations around the world.

The benefits of GMP compliance are many such as control of manufacturing process, registration of proceedings and instructions, occupational risk prevention, regulatory compliance, adding value to the products in front of the competitors etc.

Due to the business partnership agreement, BPS is in charge of identifying and improving the vulnerable points of the project. Regarding this matter, the R&D&I team is responsible for the technical evaluation. Notwithstanding, the bibliographic research such as papers, patents, reviews, is the first step for investigating the procedures associated to the route of synthesis. Upon proper selection of the most representative methods for preparing the required compound, the technical team proceeds with the experimental part based on the information provided by the partner and complemented with the additional data from the literature.

Considering that valuable information can be found in patents, these documents have to be carefully studied. State-of-the-art, priority date, patent validity, risk of infringement are some of the features to take into account before starting with the process development.

Furthermore, detection of critical aspects such as the use of toxic reagents or solvents, large reaction time, product isolation through organic solvent dryness, operational complexity, industrial hazards and environmental factors among others, is mandatory for ensuring process effectiveness and safety. Taking into account these preliminary conclusions, the R&D&I team presents a report with suggestions and explanations of the research evaluation.

Nevertheless, the final decision in relation to the project viability belongs to the finance and marketing departments of BPS. On one hand, the project refusal leads to the corresponding desertion, nevertheless, new drug programs and being considered. On the other hand, the

acceptance proposal involves freedom to operate, so the researchers will focus their efforts on the synthesis of Active Principle Ingredient (API) and process optimization. Modifications of route of synthesis have to be logical and consistent leading to a safer and cheaper process.

However, frequently, design and synthesis of completely new route of synthesis involve long time investigation and more capital for innovation of entire process.

With the optimized process in hand, the next step consists in increasing the batch product in laboratory. In order to validate the performances, outcomes have to be similar to those obtained in a smaller scale. Replication of selected reaction conditions on a higher production of API is critical. Usually, reaction progress can be slower due to inappropriate stirring mixture or temperature control not being constant over the time. Therefore, the reaction yield can be altered.

Regarding the purity product, this parameter can decay due to an increment of impurities concentration when the reaction is scaled up. For the detection and identification of undesirable chemicals, is extremely necessary the use of proper analytical techniques. Therefore, development of analytical methods is indispensable in order to monitor reactions and determine purity product.

Thus, in order to prevent these unpredictable situations, is mandatory to perform experiments using higher amounts of starting materials. Consequently, this operation provides useful information and preventive measures can be adopted if necessary for improving throughput and quality product.

Moreover, identification of potent hazards during scale-up process is an important tool for the correct risk assessment.

In summary, process validation is based on the design, development and scale-up activities, followed by its qualification in terms of reliable and reproducible results.

Upon final examination of the process confirming the viability of the route of synthesis, the next step consists in transferring the collected data from the laboratory to a chemical factory for preparing the requested API.

Bearing in mind that knowledge and technology transfer is a decisive factor in order to guarantee the key to success, the R&D&I team offers technical assessment to process manufacturer. Worth of mentioning here is the fact that the API's fabrication is carried out under GMP requirements.

General objectives

The previous aspects are in agreement with the general objectives established by BPS. Thus, the first goal of the Catalan company is to examine the plausibility and potentiality of the design and optimization of route of synthesis for a specific API.

Regarding this point, the first step is based on an exhaustive bibliographic research related to the existing procedures for preparing the selected compound. Nevertheless, this information can be used either as a complement to the data provided by the customer or being the main scientific resource if the external partner does not share any input.

Upon collecting and processing all the information found in data base, the R&D&I personnel will decide the most viable procedure for synthesizing the API. Further on, study and optimization of chemical process involves the experience and innovation provided by the skilled professional.

From a synthetic point of view, the proper election of reaction solvent is considered fundamental not only for its role as solubilizing reaction vehicle but also for the health risks. According to the classification of residual solvent by risk assessment, solvents class 1 such as benzene, carbon tetrachloride, 1,2 – dichloroethane must be avoided during the manufacturing process due to its connection with human carcinogens. In addition, manipulation of solvents class 2 like acetonitrile, dichloromethane, *N*,*N*-dimethylformamide, hexane etc should be limited due to their intrinsic toxicity. Ethanol, ethyl acetate, pentane etc are included in solvent class 3 because they present lower toxic potential. Finally, for solvent class 4 like petroleum ether no toxicological information was reported.

Optimal use of equivalent number of reagents is also one of objectives due to the economical impact on the total cost. Among the same lines, the reduction of reaction time can be translated to low-cost manufacturing process too.

However, the abovementioned factors are intrinsically associated to the quality product. Impurities-derived synthesis can be formed as a consequence of handling excess of molar equivalent reagent or due to prolonged reaction time. Scaling-up the process can contribute to an increment of unwanted compound levels. Consequently, purification compounds through recrystallization or manipulating anti-solvent during washing product (slurry) is one of the targets for this project.

Taking into account the need of detection and identification of impurities, our goal is to develop a robust analytical method for quality assessment. In order to meet specifications, it is mandatory to ensure quality product. Moreover, our intention is the preparation of these undesirable products since it represents a very attractive added value for quality control.

CHAPTER 1

Synthesis and optimization of [redacted]

Chapter I. Synthesis and optimization of [redacted]

1. General introduction antipsychotic drugs

1.1. Mental disorders

The mental illness is a general health condition that affects the mood, personality and behavior of a person. These pathologies can be classified in different groups such as eating (like bulimia and anorexia nervosa), psychotic (for example, schizophrenia) and mood disorders (depression, bipolar illness), among others. Nevertheless, in 2020 the most common dysfunctions were related to anxiety and depression due to the COVID-19 pandemic situation[1]. However, mental diseases with low incidence on the population such as schizophrenia also require special attention and treatment.

1.2. Schizophrenia

Schizophrenia is a complex chronic psychiatric disease defined by incoherent thoughts, nonsensical speech and behavior, hallucinations and psychosis (loss of contact with reality)[2,3].

Taking into account that schizophrenia is a heterogeneous disorder, several factors contribute to the development of this disease. In agreement with the genetic studies, proteins such as dysbindin, D-amino acid oxidase activator (DAOA), Disrupted in schizophrenia 1 (DISC1), neuregulin 1, catechol-*O*-methyltransferase (COMT) are structurally altered leading to genetic mutations or gene polymorphism.[4]

Furthermore, the environmental aspect is a cause in developing schizophrenia. Due to the cytokine response of a pregnant woman to the exposure to viral infections, the brain fetus can be damaged. The increased level of stress hormones, malnutrition or birth complications are risk components as well for schizophrenia.[4]

[1] https://www.who.int/news-room/fact-sheets/detail/mental-disorders
[2] K. Iwamoto, T. Kato, *The Neuroscientist*, **2006**, *12*, 349 – 361
[3] M. P. van den Heuvel, A. Fornito, *Neuropsychol Rev.*, **2014**, *24*, 32 – 48
[4] C. A. Ross, Russell L. Margolis, S. A.J. Reading, M. Pletnikov, J. T. Coyle, *Neuron.,* **2006**, *52*, 139 - 153

Additionally, recent studies have proved reasonable data supporting the association of the minority ethnic group, growing up in urban areas or cannabis consumption with this psychotic condition.[5]

However, a Danish investigation showed that around 30% of the people suffering from psychiatric family history were more likely to develop schizophrenia. In contrast, only 6% of schizophrenia patients were associated to a family background of this condition.[6]

According to the medical terminology, there are two groups of symptoms in schizophrenia, the positive and negative ones[7]. The positive symptoms are characterized by the increase of normal functions such as hallucinations, delusional beliefs or bizarre motor behavior. In order to manage these symptoms, the antipsychotic drugs are usually used to minimize these effects[8].

Regarding the negative symptoms, they are defined by the reduction or lack of normal behaviors affecting the psychological response[9]. Thus, the most common examples are the asociality (absence of motivation to establish social relationships), anhedonia (incapacity of feeling pleasure) and avolition (absence of motivation to perform any activity or task). Moreover, negative symptoms are classified in two categories, the implicit ones to schizophrenia, known as primary negative symptoms, and those that derive from positive symptoms or as a side-issue of antipsychotic medication, the secondary negative symptoms.

Nevertheless, there is an unmet medical need to treat these negative symptoms due to the complexity of distinguishing between the primary and secondary negative symptoms[10]. Although the secondary symptoms can respond well to the antipsychotic treatment, the primary ones are more difficult to manage due to the unclear neural mechanism and interactions with other symptoms.

[5] J. van Os, G. Kenis, B. P. F. Rutten, *Nature*, **2010**, *468*, 203 – 212
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[9] S. Galderisi, S. Kaiser, I. Bitter, M. Nordentoft, A. Mucci , M. Sabé , G. M. Giordano, M. Ø. Nielsen, L. B. Glenthøj, P. Pezzella, P. Falkai, S. Dollfus and W. Gaebel, *Eur. Psychiatry*, **2021**, *64*, 1 – 15
[10] I. Bègue, S. Kaiser, M. Kirschner, *Neurosci. Biobehav. Rev.*, **2020**, *116*, 74 – 88

1.3. Treatment

Of note, the antipsychotic drugs are cataloged in two groups, the classical or typical medication, known as first-generation antipsychotics (FGAPs) and the atypical class, also called as second-generation antipsychotics (SGAPs).

The FGAP drugs such as haloperidol, mosapramine, pipamperone, zotepine etc, act by blocking the D2 dopamine receptors in brain, thus they are effective for patients with the first-episode of psychosis.[11,12] Nevertheless, they also present side-effects such as extrapyramidal symptoms (EPS), being dystonia (muscle spasms and contractions) and tardive diskinesia (involuntary movements) two examples well known among others.

According to the chemical structure, the most common typical neuroleptic classes to treat psychosis episodes are the butyrophenones (benperidol, droperidol, haloperidol, pipamperone), phenothiazines (promazine, thioridazine, perphenazine) and thioxanthenes (clopenthixol, flupenthixol) among others (figure 1).

[11] S. Miyamoto, G. E. Duncan, C. E. Marx, J. A. Lieberman, *Mol. Psychiatry*, **2005**, *10*, 79–104.
[12] P. Dazzan, K. D. Morgan, K. Orr, G. Hutchinson, X. Chitnis, J. Suckling, P. Fearon, P. K. McGuire, R. M. Mallett, P. B Jones, J. Leff, R. M. Murray, *Neuropsychopharmacol.*, **2005**, *30*, 765 – 774.

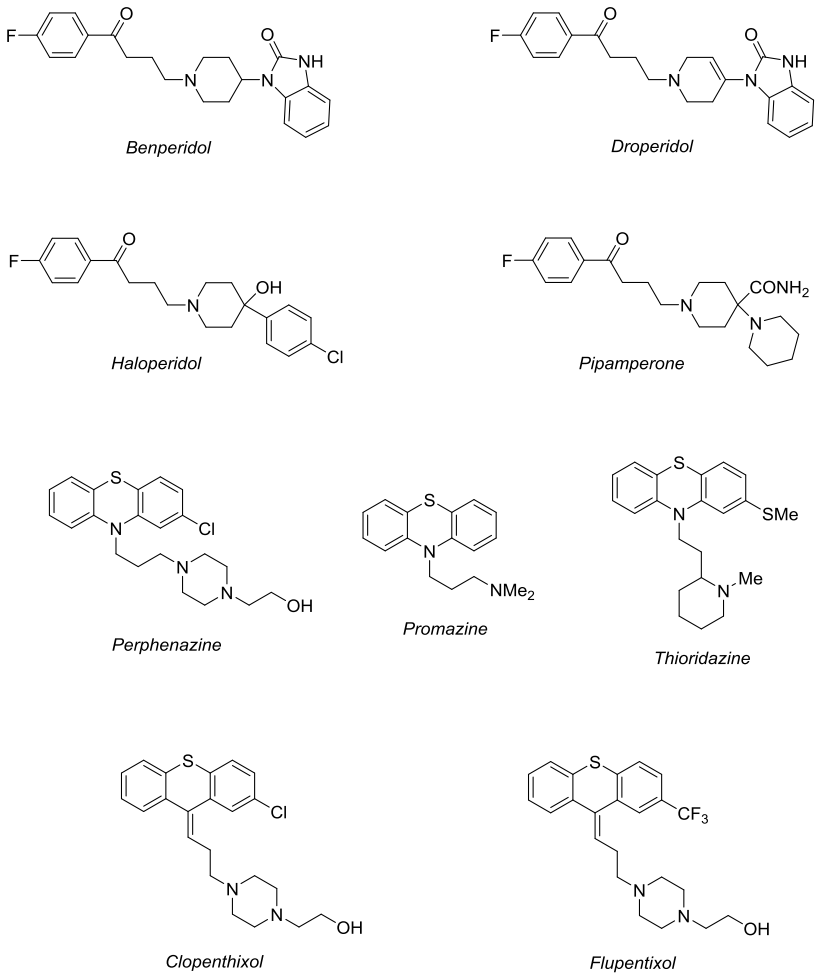

Figure 1. Typical antipsychotic drugs.

In relation to the SGAP drugs, the mechanism of action involves lower affinity and occupancy to the D2 dopamine receptors than the typical antipsychotics. In contrast, they present higher selectivity for the serotonin 5-HT_{2A} receptors such as 5-$HT_{2A/2C}$, 5-HT_{1A}, 5-HT_6 and 5-HT_7.[8,9,13] Depending on the selection of the atypical antipsychotic, such as aripiprazole, clozapine, risperidone etc (figure 2), these compounds present different activity for certain receptors due to their pharmacodynamic parameters.[14]

[13] I. Kusumi, S. Boku, Y. Takahashi, *Psychiatry Clin. Neurosci*., **2015**, *69*, 243–258.
[14] J. Horacek, V. Bubenikova-Valesova, M. Kopecek, T. Palenicek, C. Dockery, P. Mohr, C. Höschl, *Drugs*, **2006**, *20*, 389 – 409.

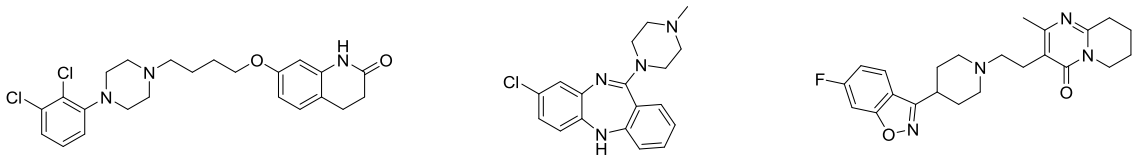

Figure 2. Atypical antipsychotic drugs.

However, either the FGAPs or SGAPs treatment has a direct impact on the conformation of the brain. For instance, it was detected that the use of atypical drugs was associated with an increase in thalamus volume.[9] Notwithstanding, the structural magnetic resonance imaging (MRI) showed that the exposure to the conventional antipsychotics causes a decrease of volume of frontal regions.

Although the use of atypical drugs to treat schizophrenia is attributed to a decreased number of adverse effects, the conventional medication is still prescribed to manage the symptoms of this mental disease.[15] Considering the great demand of the FGAPs, it is necessary to continue manufacturing these drugs.

Due to a strategic and commercial goal of BioPharma Synergyes (BPS) company, [redacted] was selected for the study of the synthetic route.

[15] https://www.alliedmarketresearch.com/antipsychotic-drugs-market

Introduction, objectives, results and discussion, conclusions, supporting material are encoded, from page 13 – 71.

Chapter 2. Synthesis and optimitzation of [redacted]

1. General introduction antihypertensive drugs

1.1. Cardiovascular diseases

Hypertension, also named high blood pressure (HBP), is one of the most common cardiovascular diseases and it is thought that approximately 1.28 billion adults around the world are being affected by this medical condition. Less than half of the cases, 42%, is being evaluated and receiving treatment.

The illness is caused by the blood circulation through the arteries at higher pressure. In order to know the blood pressure level, two agents are considered: the systolic and diastolic pressure. The first of them belongs to the above number and it represents the pressure when the heart pumps the blood. The last term is related to the bottom number and shows the pressure when the heart rests between the beats (Table 1).

Table 1. Blood pressure measurements.

Classification	Systolic reading (mm Hg)	Diastolic reading (mm Hg)
Normal	< 120	< 80
Elevated	120 - 129	< 80
High blood pressure (stage 1)	130 - 139	80 – 89
High blood pressure (stage 2)	> 140	> 90

Depending on the risk factors (age, diet, lifestyle) and the type of hypertension which can be either primary (also called as essential hypertension, it might be developed by different causes such as family history, lifestyle conditions) or secondary HBP (induced by a medical condition like kidney, thyroid or adrenal disease or being a side effect of some medication), several treatments are used to control the blood pressure.

1.2. Treatment

The medication for hypertension comprises angiotensin-converting enzyme (ACE) inhibitors that dilate or enlarge the blood vessels (e.g., enalapril, ramipiril and lisinopril). Due to the presence of side effects using ACE drugs, like persistent dry cough, the angiotensin II receptor blockers (ARBs) are an option to treat hypertension[16]. These drugs bind selectively to the angiotensin II AT_1 receptor on the blood vessels and block the cellular action of the angiotensin II, the hormone responsible for narrowing the vessels. Drugs like losartan or valsartan (the "sartans") help to relax the blood vessels and so to stabilize blood pressure.

Another strategy to manage HBP involves the use of beta blockers agents. Compounds such as atenolol and bisoprolol act by blocking selectively the action of adrenaline in the heart; hence, less force is required to drain the blood through the body, whereupon, blood pressure is reduced too.

Releasing the excess of water and salt from the body through the urine, allows the reduction of fluid volume in blood vessels, which have a direct effect in lowering blood pressure. For this reason, diuretics like indapamide and bendroflumethiazide are prescribed as antihypertensive drugs.

One more current treatment for HBP encompasses the calcium channel blockers (CCBs). The reduction of calcium flow entering cells of the heart empowers the blood vessels relaxation. Consequently, more oxygenated blood arrives to the heart and finally the blood pressure is reduced. Determined by the chemical structure, there are two classes of CCBs: dihydropyridines and non-dihydropyridines CCB drugs. The first category mentioned above presents high vascular selectivity and therefore is recommended as antihypertensive drug (Figure 1). Meanwhile, non-dihydropyridines compounds (phenylalkylamines like verapamil drug) are more likely to be used for angina treatment because they don't exhibit such vasodilatory properties, in turns; they are very effective to regulate the heart rhythms.

[16] A. Barreras, C. Gurk-Turner, *BUMC Proceedings*, **2003**, *16*, 123 – 126.

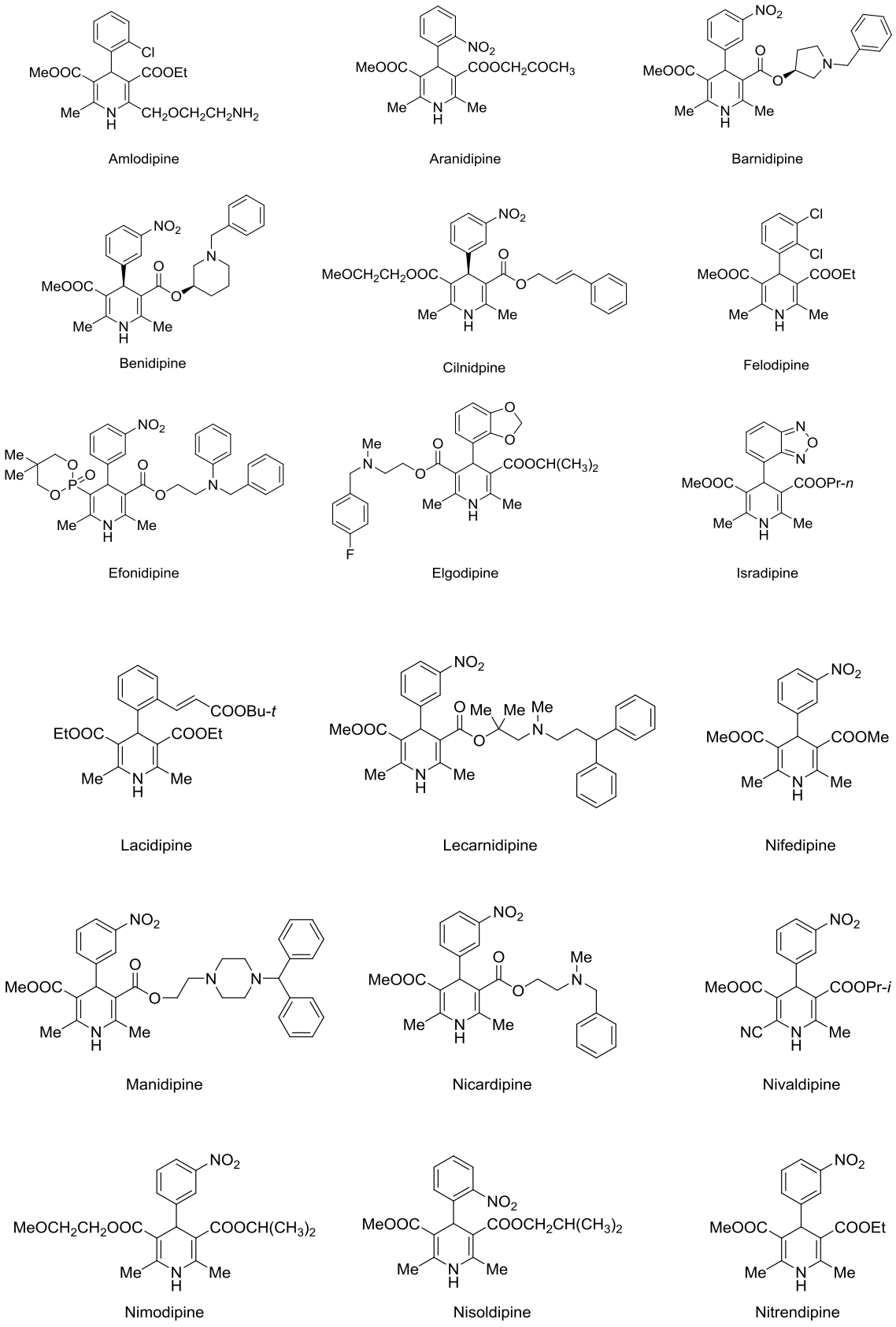

Figure 1. Clinically approved antihypertensive drugs.

1.3. 1,4-Dihydropyridine CCBs

The 1, 4-dihydropyridine (1,4-DHP) nucleus is an interesting scaffold in medicinal chemistry because of its broad range of pharmacological properties like antitumor[17,18], antitubercular[19], antiviral[20], antimicrobial[21] and anticoagulant[22] activities. Above all these beneficial effects, 1,4-DHP derivatives have been highly prescribed in the treatment of cardiovascular diseases as calcium channel blocking agents.

Nowadays four generations of 1,4-DHPs are well known and commercially available.[23] Nifedipine is a first-generation agent and was prescribed as a treatment for the hypertension and angina pectoris. Although it was a powerful vasodilator, its short-acting and rapid onset of its activity were key aspects to be considered. As a result, a second-generation of 1,4-DHPs, nicardipine, led to a moderate duration and some adverse effects, such as tachycardia and headache were decreased. Next, 1,4-DHP's, amlodipine, nitrendipine and manidipine, became more efficient and safer since the third-generation was proved to have a long acting, slow onset and limited side effects. The mechanism of action of these three generations is based on the inhibition of vascular L-type Ca^{2+} channels. Moreover, the enhanced lipophilicity of the fourth-generation drugs, such as cilnidipine and lercanidipine, could be translated into a reduction of adverse effects.[24] The main difference among these two compounds was the mode of action since cilnidipine acts like a dual inhibitor by blocking the N and L-type Ca^{2+} channels.

[redacted]

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[23] A. L. Wang, C. Iadecola, G. Wang, *J. Geriatr. Cardiol.*, **2017**, *14(1*), 67–72
[24] R. Gasser, W. Klein, H. Köppel, *J. Clin. Basic Cardiol*., **1999**, *2(2)*, 169 – 174

1.4. Chemical approaches to the synthesis of the 1,4-DHP scaffold

The 1,4-DHP scaffold can be synthesized in many ways, but the classical Hantzsch[25] reaction is still the most common approach. This methodology is focused on a multicomponent reaction (MCR) that involves the condensation of an aromatic aldehyde, 2 equivalents of a β-ketoester and ammonia in an alcoholic solvent.

More recently, several modifications of this procedure have been carried out in order to increase yield and to minimize process time. Hence, the use of ionic liquids[26] instead of organic solvents, microwave irradiation[27], metal[28] or Lewis catalysts[29] are some of the examples employed for improving the outcomes related to the purity, yield product and also to reduce reaction time. Although these implementations afforded good results, reproducing the reaction conditions on a large scale and the use of expensive catalysts, are two unviable challenges. Taking into account these considerations, we focused our attention on the typical synthetic methodology to prepare the 1,4-DHP skeleton.

[redacted]

[25] A. Hantzsch, *Liebigs Ann. Chem.*, *Liebigs Ann. Chem.*, **1882**, *215*, 1 – 82.
[26] J. S. Yadav, B. V. S. Reddy, A. K. Basak, A. V. Narsaiah, *Green Chem.,* **2003**, *5*, 60 – 63.
[27] M. Anniyappan, D. Muralidharan, P. T. Perumal, *Syn. Comm.*, **2002**, *32*, 659 – 663.
[28] S. B. Sapkal, K. F. Shelke, B. B. Shingate, M. S. Shingare, *Tetrahedron Lett.*, **2009**, *50*, 1742 – 1756.
[29] S. Ko, C. F. Yao, *Tetrahedron*, **2006**, *62*, 7293 – 7299.

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Introduction, objectives, results and discussion, conclusions, supporting material are encoded, from page 76 – 191.

CHAPTER 3

Synthesis and optimization of [redacted]

Chapter 3. Synthesis and optimization of [redacted]

Introduction, objectives, results and discussion, conclusions, supporting material are encoded, from page 192 – 253.

General conclusions

As final conclusions of this thesis, the route of synthesis of three APIs was optimized towards more efficient process within a shorter time, higher yields and more environmentally friendly processes.

In order to boost drug development, multiple features were studied such as replacement of toxic reagents or solvents by safer alternatives, reduction of number of synthetic steps, readjustment of molar equivalent of reagents, enhancement of process efficiency and throughput, optimization of purification procedures, innovation and improvement of analytical HPLC methods for monitoring reaction progress properly and consequently, correct quality assessment.

With the optimal process in hand, we implemented it on a higher scale of production, from milligrams to multigrams of product in the laboratory. Scale-up process empowered the disclosure of complex operations and detection of critical points such as conversion, yield and purity product. Furthermore, reproducibility of the reaction conditions working on an increased ratio was mandatory for validating the process. Nevertheless, safety and costs are critical factors for the scale-up procedure. Thus, preliminary study of the abovementioned parameters enables troubleshooting potential scale-up issues before increasing the output rate to pilot production.

Satisfactorily, the investigation and optimization of the route of synthesis of the three APIs led to excellent outcomes. Therefore, BPS initiated the manufacturing of two of these three drugs under GMPs requirements.

In addition, recently the Catalan company has received capital funding in form of a research grant from the CDTI (Ministry of Science and Technology, Spain) for starting with the validation batches for production scale.

Three lots of 30 kg (3 x 30 kg) are planned for the validation process of the first API which synthesis has been optimized in the present Thesis. For a second API, three batches of 5 kg (3 x 5 kg) are scheduled.

Upon validation at the production scale and approval from the regulatory authority, the next step will be the industrial manufacture of both compounds, at a scale 10 times higher than the validation batches, that is 300 Kg for the first API and 50 Kg for the second one. Finally,

the validation of the analytical method is also scheduled in order to perform the stability studies.