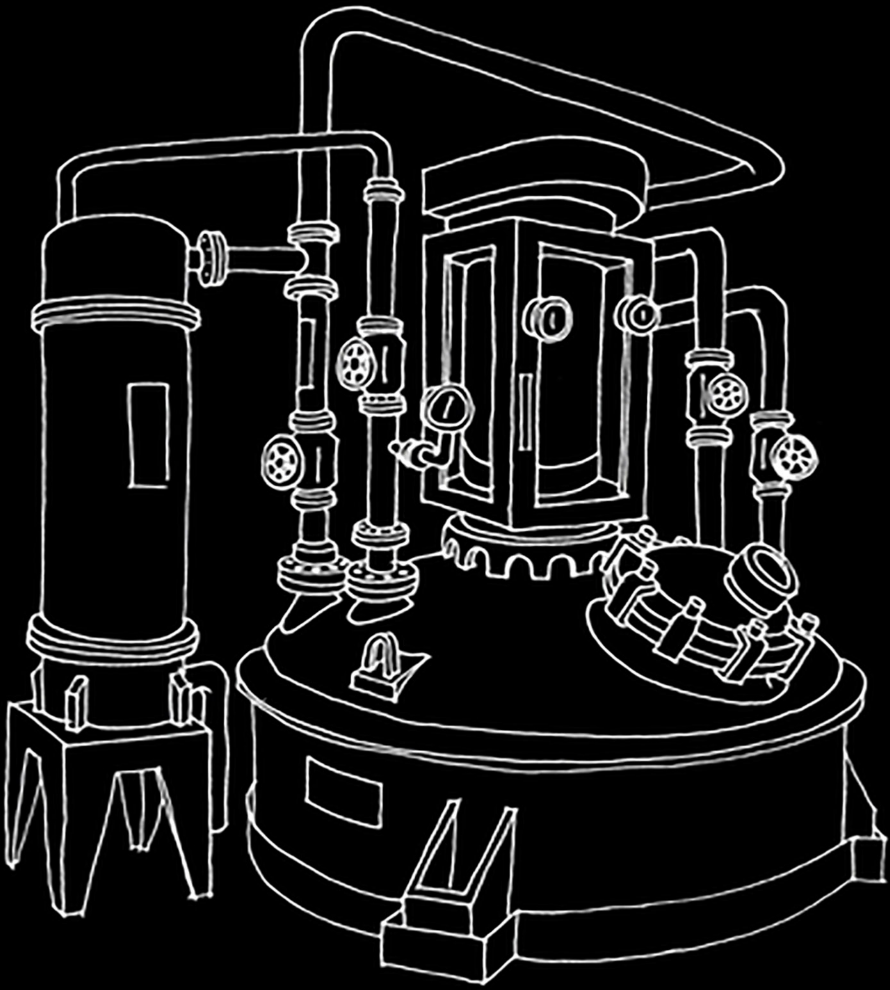
Pedro Paulo Santos | William Heggie



Retrosynthesis in the Manufacture of Generic Drugs

Selected Case Studies

WILEY

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To
Pedro, Rita, Isabel,
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CONTENTS

PREFACE

This book aims to illustrate how the retrosynthetic tool, widely used by academics in the search for synthetic routes used to prepare novel organic compounds, is applied in the Pharmaceutical Industry. However, merely finding a viable synthetic route is not sufficient. Many different options have to be considered and evaluated, as there exist numerous constraints on the industrialist in terms of what can and what cannot be reduced to practice. The reader will be guided through the various steps leading to the “best” processes and the limits encountered if these are put into practise on an industrial scale. Thereafter, an evaluation the potential each process has for implementation is presented.

A great deal of information is presented from both the patent and academic literature. The more serious reader can use this as a basis for further study and thought but for those who have neither time nor necessity the material is presented in such a way that it can be appreciated without delving into excessive detail.

William Heggie
Pedro Paulo Santos

A NOTE ABOUT THE BOOK AND ITS USE

Books on process chemistry usually use many short schemes, each referring to a particular synthetic route. This methodology makes comparison of different synthetic routes somewhat difficult and we can lose sight of the fact that frequently some intermediates are common in several processes. A unique feature of this book is the use of “reaction maps” (schemes identified with a letter coding). Whenever possible, similar strategies will be included in the same scheme.

The reaction maps collect several processes in the same scheme according to the intermediates used during the synthetic process. This allows easy comparison of the different routes which give the same molecule or intermediate. An analogy with an Underground Map can be made, where lots of lines (synthetic routes) are combined in the same chart to provide a map (our reaction map). For instance, if we travel in a city having a collection of schemes for each subway line as a guide we may be easily disoriented. Instead, the use of a map of the whole underground network where interconnections can be easily identified will be much more efficient and clear.

Each reaction in these maps will be coded with a scheme letter/reaction number (example, A22 means reaction 22 of scheme A) and the reaction conditions are included at the end of each chapter. In this way the reader can easily spot which reactants/conditions were used for the chemical transformation. In cases where the reactions have been used by several authors a summary of the conditions will be included.

The patent references in the book will be in company/year format (assignee/priority date). This system will allow the evolution of different synthetic routes to the molecule to be observed in accordance with the date of its disclosure (or discovery). If relevant, “references from peer review journals” will be also included.

ABBREVIATIONS

2-MeCBS	2-methyl-CBS-oxazaborolidine; 1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2*c*][1,3,2]oxazaborole
Ac	acetyl
acac	acetylacetone
AEAI	asymmetric enolate addition to imine
AHT	asymmetric hydrogen transfer
AIBN	azobisisobutyronitrile
all	allyl
alloc	allyloxycarbonyl
anh.	anhydrous
API	active pharmaceutical ingredient
aq.	aqueous
Ar	aryl
AS	asymmetric synthesis
ASA	acetylsalicylic acid
B_2pin_2	bis(pinacolato)diboron
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate
BBB	blood brain barrier
BIMAH	1-(1*H*-benzimidazol-2-yl)ethanamine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
BIPHEPHOS	6,6'-[(3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)bis(oxy)]-bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)
bmim	1-butyl-3-methylimidazolium
BMS	borane dimethylsulfide
Bn	benzyl
BnEZT	benzyl ezetimibe
Boc	*t*-butyloxycarbonyl
BSA	bis(trimethylsilyl)acetamide
BTHF	borane tetrahydrofuran complex
Bu	butyl
Bz	benzoyl
CA	chiral auxiliary
CAH	catalytic asymmetric hydrogenation
CAN	ceric ammonium nitrate
cat.	catalyst
CBS	Corey-Bakshi-Shibata
Cbz	carbobenzyloxy
CDI	1,1'-carbonyldiimidazole
cod	1,5-cyclooctadiene
conc.	concentrated
Cp	cyclopentadienyl
CSA	camphor-10-sulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DAIPEN	1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine
dba	dibenzylideneacetone
DBSA	4-dodecylbenzenesulfonic acid
DBTA	dibenzoyl tartaric acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCDMH	1,3-dichloro-5,5-dimethyl hydantoin
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHP	3,4-dihydro-2*H*-pyran

DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIC	*N*,*N*'-diisopropylcarbodiimide
dil	diluted
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIP-Cl	B-chlorodiisopinocampheylborane
DIPEA	*N*,*N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMC	dimethylcarbonate
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPEN	1,2-diphenylethylenediamine
DPMS	diphenylmethyl silyl
DPPA	diphenyl phosphoryl azide
DPPB	1,4-bis(diphenylphosphino)butane
dppbz	1,2-bis(diphenylphosphino)benzene
dppf	1,1'-ferrocenediyl-bis(diphenylphosphine)
DPPP	1,3-bis(diphenylphosphino)propane
DPTTA	di-*p*-toluyl-D-tartaric acid
dr	diastereomeric ratio
dtbpf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
E1cB	Elimination Unimolecular conjugate Base
EAS	electrophilic aromatic substitution
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethyl-carbodiimide
ee	enantiomeric excess
EP	European Pharmacopoeia
eq.	equivalent
Et	ethyl
EWG	electron withdrawing group
EZT	Ezetimibe
FGA	functional group addition
FGI	functional group interconversion
Fmoc	9-fluorenylmethoxycarbonyl
g	gas or gram
GABA	γ-aminobutyric acid
h	hour
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
hfacac	hexafluoroacetylacetone
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HWE	Horner-Wardsworth-Emmons
i	iso
Ipc_2BCl	diisopinocamphenylchloroborane
kg	kilogram
KRED	ketoreductase
LG	leaving group
LiHMDS	lithium bis(trimethylsilyl)amide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
MCPBA	3-chloroperbenzoic acid
MCR	multicomponent reactions
Me	methyl
MEK	methyl ethyl ketone
MIBK	methyl isobutyl ketone
ML	mother liquor
MOM	methoxymethyl
morph.	morpholine
Ms	methanesulfonyl
MS	molecular sieve
MTBE	methyl *tert*-butyl ether
MW	microwave
n	normal
NAD	nicotinamide adenine dinucleotide
NaDCC	sodium dichloroisocyanurate
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NCE	new chemical entity
NCS	*N*-chlorosuccinimide
NI	not isolated

NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
op	optical purity
PCC	pyridinium chlorochromate
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
Phth	phthalimide
pin	pinacolato
Piv	pivaloyl
PLE	pig-liver esterase
PLP	pyridoxal phosphate
PMB	*p*-methoxybenzyl
PMHS	polymethylhydrosiloxane
PMP	*p*-methoxyphenyl
PNBA	*p*-nitrobenzoic acid
PPA	polyphosphoric acid
PPTS	pyridine *p*-toluenesulfonate
Pr	propyl
py	pyridine
QA	quinic acid
QN	7-chlorquinolin-2-yl
RCM	ring-closing metathesis
rt	room temperature
S/C	substrate-catalyst ratio
SA	shikimic acid in Oseltamivir chapter, salicylic acid in Sitagliptin chapter
SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SES	2-(trimethylsilyl)ethanesulfonyl
SM	starting material
SMB	simulated moving bed
S_N	nucleophilic substitution
t	*tert*
t	ton
TA	tartaric acid
TBA	tetrabutylammonium
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TCCA	trichloroisocyanuric acid
TEBA	benzyltriethylammonium chloride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanosulfonyl
TFA	trifluoracetic acid
TFAA	trifluoracetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
ThPD	bis(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)methane
THTP	4,5,6,7-tetrahydrothieno-[3,2-*c*]-pyridine in the Clopidogrel chapter; 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine in the Sitagliptin chapter
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	tetramethylsilyl
Tol	toluyl
TpEA	2-(thiophen-2-yl)ethanamine
Tr	trityl
Ts	*p*-toluenesulfonyl
UK	United Kingdom
USA	United States of America
USD	United States Dollar
USP	United States Pharmacopeia
v	volume
w	weight
WW	Worldwide
Xyl-BINAP	1,1'-binaphthalene-2,2'-diylbis[bis(3,5-dimethylphenyl)phosphine]
YNR	yield not reported

1 INTRODUCTION

Retrosynthetic analysis is a powerful tool, first developed by E.J. Corey in the late 1960s, and extensively used by modern organic chemists to plan the syntheses of organic molecules. This book applies this technique to a series of important Drug Substances, also known as Active Pharmaceutical Ingredients (APIs). It is not our intention to teach, or even briefly review, the principles of retrosynthetic analysis. This is now a major part of any advanced organic chemistry course and many excellent publications, including the book: The Logic of Chemical Synthesis, New York: Wiley (1995) by E. J. Corey and X-M. Cheng, have been published. The reader is strongly advised to review the main tenets of retrosynthesis to be able to take maximum advantage of this volume.

In an academic setting the major goals of organic synthesis are:

i) to establish that the molecule (generally complex) can be synthesized;
ii) to establish new and novel synthetic routes to molecules that have already been synthesized and
iii) to demonstrate the applicability of new reactions to the synthesis of organic molecules.

There are few, if any, restrictions to carrying out these syntheses on a small scale in the laboratory. Overall yield, transformation efficiencies, potential hazards and effluent treatment, although undoubtedly important, are not showstoppers in this setting. If the synthesis produces enough material, at a milligram scale or less, which allows the end product to be characterized, then it is deemed successful. Obviously, no synthesis starts with the most rudimentary starting materials but relies on what is easily accessible. For an academic synthesis, the major source of starting materials is a chemical products catalogue such as that of Sigma-Aldrich. The vast majority of the thousands of chemicals listed have extremely limited availability and the price in many cases is enormous. Woodward's total synthesis of cephalosporin C started with L-(+)-cysteine, which was more expensive than Cephalosporin C itself, so it might appear that the undertaking of such a synthesis is illogical. However, the objective of the study was to demonstrate the conversion of a structurally simple molecule into a more complex one following a rationally designed synthesis. We return to this theme at the end of this introduction.

When carrying out a synthesis of an API on an industrial scale different constraints apply. The objective of any Pharmaceutical Company, whether originator or generic, is to get the product to market and maximise profitability for as long as possible. Hence, the design of a synthesis for industrial production has a significant number of limitations. The Process Chemist, as well as having a broad knowledge of synthetic transformations, an in-depth understanding of chemical group compatible and a well-founded acquaintance with the conditions necessary to carry out a plethora of chemical reactions, also has to appreciate what is viable on a large scale.

The retrosynthetic process will uncover a number of options for the construction of any molecule as no molecular entity has only one approach to its preparation. Nonetheless, not all of the possibilities will have the same degree of success when the chemistry is put into practice. The Process Chemist can, however, make a fairly accurate appraisal of what is more likely to work and what is not by applying basic chemical wisdom. Priorities for laboratory testing can be identified, but it should be stressed that those routes that have potential for success can only be confirmed after laboratory testing. Generally speaking, a particular route must be able to provide final product, API, in high yield and purity in addition to being feasible on a large scale. The product must be free of potentially toxic materials, some of which need to be controlled down to ppb levels. If time allows, it is prudent to do some quick trials on a route that current wisdom may have excluded, as sometimes happy surprises can occur.

Chemical considerations and laboratory verification are key in determining the success of any proposed synthetic route but additional factors have to be taken into consideration for operation in a chemical production plant. There are certain reactions that are comparatively more difficult to implement on a large scale than others. Amongst these are: highly exothermic reactions; Reactions requiring very high or low temperatures; Reactions requiring fast heating and cooling; Reactions using highly toxic reagents and that require containment; Reactions which generate large

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quantities of waste; Reactions done under high dilution; Reactions which require a high degree of control i.e. temperature, pressure and time. Whilst all of these reactions can be carried out at scale, if they can be avoided by using simpler, easier alternatives large scale manufacturing becomes more sustainable.

Again it is not our intention in this book to discuss the details of and the requirements imposed by large scale manufacturing. There are many excellent publications dealing with this topic. However, it is useful to mention some of the more salient points for each of the cases mentioned above.

Highly exothermic reactions

Highly exothermic reactions generate large amounts of heat over a very short time. On an industrial scale, the removal of this excess energy is problematic as the area to volume ratio of large vessels is relatively small. When this excess energy cannot be removed run away reactions, sometimes explosively, occur with grave consequences to both health and the environment. Many serious industrial accidents have occurred in this way.

Reactions requiring very high or low temperatures

One way to control highly exothermic reactions is to carry these out at low temperatures where the reaction rate is greatly reduced and hence the release of energy is slower and more easily removed from the reaction medium. However, expensive specialized equipment to achieve and maintain homogeneous low temperature conditions is necessary. Reactions requiring high temperatures (nominally above 150 ºC) also require specialized equipment and materials resistant to chemicals and reagents at these elevated temperatures. Pyrolysis reactions at extremely high temperatures are practically never carried out in the fine chemical industry. These reactions require rapid cooling immediately following the transformation as the reaction products are subject to decomposition under these extreme conditions.

Reactions requiring fast heating and cooling

Suffice it to say that it takes a long time to heat and cool a large mass. Heat transfer is dependent on surface area. Surface area increases less (n^2 correlation) in comparison to mass/volume (n^3 correlation) on scale up. This causes problems for the Process Chemist, even to the extent that scaling up some reactions might turn out to be impractical. If the kinetics of a synthetic reaction increases greatly with temperature, and the kinetics of competing/impurity forming reactions do not, then fast heating to high temperatures so that the desired reaction goes to completion in the shortest possible time, helps keep impurities to low levels. Likewise, decomposition of the product can be controlled by fast cooling. Obviously, for large volumes of reactants, heating and cooling times are much longer than in the laboratory. It is no surprise that occasionally new impurities are observed and known impurities increase on scale up. Simulating times, temperature gradients and other variables that are expected at large scale in small scale equipment will establish whether this is true or not, and the Process Chemist will have to find alternative reaction conditions if this turns out to be the case. Flow chemistry, still in its infancy in the Pharmaceutical Industry, can resolve these types of situations and is an attractive alternative to classical batch chemistry.

Reactions using highly toxic reagents and that require containment

It is self-evident that plant personnel, the general populace and the environment need to be protected from noxious materials. Supply and transport of toxic chemicals can pose difficult logistic problems. Facilities which are designed to handle highly toxic materials are expensive to build and require constant monitoring to ensure that no harmful leakage occurs. Disastrous accidents, where large amounts are released into the environment, can have serious and even fatal consequences. Where possible companies avoid such materials and only highly specialized companies have adequate facilities to carry out this type of chemistry. In many instances, the waste products are also highly toxic and require special care in their disposal.

Reactions which generate large quantities of waste

Chemical reactions generally use stoichiometric quantities of reagents that are transformed into waste products. Few of these materials are environmentally friendly and their disposal poses problems for the chemical industry. Indeed, the major part of the bad publicity that the chemical industry, including the Pharmaceutical Sector, derives from this issue. The problem is exacerbated when more than one equivalent of reagent is required, resulting in a corresponding increase in effluent, and when toxic wastes are involved. Although recycling is an acceptable option, in the vast majority of cases recycling is not achievable. Even so, if the cost of recycling exceeds that of waste disposal, it may not be a choice worth considering. Hence, one of the principal focuses for the Process Chemist has become the application of green chemistry and catalytic reactions wherever possible.

Reactions done under high dilution

Aside from the fact that reactions carried out at high dilution require a much larger plant and bigger equipment, they severely restrict throughput, thus reducing the overall quantities that can be produced in a given time. They are also much more energy and labour intensive as the large volumes of solvent need to be heated and cooled whilst handling takes more time. This all adds to the final cost of the drug substance, which may in turn reduce the economic viability of a drug.

Reactions which require a high degree of control i.e. temperature, pressure and time

The Process Chemist takes into consideration the limitations of the equipment that will be used for the industrial process that he/she develops. The gauges that measure variables on plant have limitations (as do those in a laboratory setting) although Good Manufacturing Practices (GMP) require that these are at least adequate to the task. There is no guarantee that the probes used for measurements accurately depict real values in the reaction mass as they are usually located in the jacket of the reactor and not in body of the liquid. Another issue is that, at industrial scale, the large mass of the material gives it a certain inertia. As a consequence, overshooting of programmed reaction parameters such as temperature is anticipated when fast heating is applied. The system then takes time to settle into a steady state where temperature fluctuation is minimal. It is therefore pointless to develop a process whose success depends on tight control of such reaction parameters. The process should be as "forgiving as possible" especially when multipurpose batch reactors are involved. Tight controls are only feasible in equipment, such as flow reactors, designed specifically for the purpose. Thus, robustness and reproducibility of a processes are important factors for its success on plant.

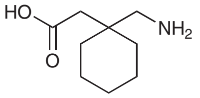
The analyses given in this book each start with a theoretical exercise where retrosynthetic principals are applied to the molecular entities of a selected number of important drugs to ascertain viable routes of synthesis. In each case, the applicability to an industrial scenario is assessed and conclusions drawn. Following this, the original literature is examined to evaluate which options had been studied and published. An attempt is made to evaluate which of the synthetic routes uncovered are eligible for introduction into a manufacturing scenario. It is hoped that the methodology exploited will aid the reader to uncover practical synthetic routes to other drug substances whether they be NCEs (New Chemical Entities) or generic APIs (Active Pharmaceutical Ingredients).

Finally, some observations on the origin of the information that is presented in this volume is in order. The two major sources that have been used are the patent literature and peer review journals. Other sources such as books, presentations/posters given at scientific conference and personal communications exist, but are not as comprehensive and/or as easily accessible.

There exist fundamental differences between these two types of literature. Peer review journals are mainly the province of academics whose careers are largely defined by what they publish. Consequently, academics focus on publishing as many original papers as possible. If the end point of the original postulate is reached experimentally, then the prime objective has been reached. A multitude of chemical syntheses, based on original and inspired chemistry, have been published where the accumulated yields are minimal, use chromatography to separate and purify intermediates and final product and are carried out on a milligram, or even a microgram, scale. The investigator does not concern him/herself by doing further work to optimize the route further from the point where it is acceptable for publication in a peer review journal. It is challenging to assess whether these synthetic routes could be viable at an industrial scale. We have made an attempt to do so using experience and common sense but, only process development and actual hands on experimentation can validly answer this question.

Patents are legal documents and can be regarded as contracts between a company (or individuals) and the state. Pharmaceutical companies submit a patent specification and, if after examination it is granted, the state allows the company a number of years (usually 20) to commercially exploit the invention without competition. The alternative would be to keep the invention secret (referred to as a trade secret). However, this is not an option for the Pharmaceutical Industry as, once the product is commercialized, it could be reverse engineered and competitors would very quickly enter into the market. To obtain a patent is not straightforward. The very first patent of a drug (a product patent) need only describe, almost in a rudimentary fashion, how it can be prepared. Thereafter, subsequent patents which describe new and novel ways to produce the drug substance (process patents) have to establish superiority over what is known in the Prior Art (the sum of all publications related to the subject matter of the patent). Patent offices worldwide have experienced patent examiners who assess patent novelty and inventiveness and only after they have approved the patent claims, does the patent proceed to grant. However, it cannot be presumed that the work of assessing the suitability of processes therein described to be implemented industrially has been done. The patent examiner only looks at novelty and inventiveness, which may not necessarily signify that the process is industrially practicable. There is an additional constraint when trying to interpret the content of patent literature. It is required by law to include the best examples that allow a patent to be reduced to practice. This is obviously not in the patentee's interest – no-one willingly lays bare their manufacturing knowhow for competitors to copy. Hence, patents are published revealing numerous options to carry out the process, usually before real industrial development work has been done. In this way companies can "disguise" their chosen route in an avalanche of information whist still revealing the best examples at the time of patent application. Once more we have used common sense and experience to interpret which processes are worthy of application in a manufacturing scenario, but as was the case for academic syntheses, only experimentation can give definitive answers.

2 GABAPENTIN



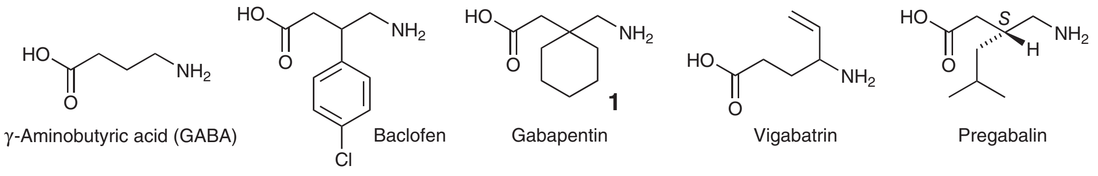
Year of discovery: 1974 Warner-Lambert Company
First WW Approval: 05 February 1993 (UK)
US approval: 30 December 1993
Drug category: Calcium channel ligand, structurally related to γ-aminobutyric acid (GABA)
Uses: Antipsychotic; Analgesic (non-narcotic); Antidepressant; Antimigraine; Anticonvulsant

Gabapentin (**1**) resulted from the search for synthetic analogues of γ-aminobutyric acid (GABA), a natural inhibitor of neurotransmission in the mammalian brain. GABA itself cannot enter the central nervous system by systemic administration; hence, a more lipophilic derivative was sought. Both GABA and Gabapentin are γ-amino acids (Figure 2.1), the higher lipophilicity of Gabapentin resulting from the presence of the cyclohexane ring. Contrary to the desired result it was found that Gabapentin does not interact with the GABA receptor in the brain but does display activity due to binding to a protein subunit that regulates a calcium ion channel.

In 1993, Gabapentin was initially approved to control seizures and was marketed by Pfizer under the trademark Neurotin®. Later, the drug was also approved (2002) for neuropathic neuralgia and some other uses anticipated, for example, in anxiety and in panic disorders.

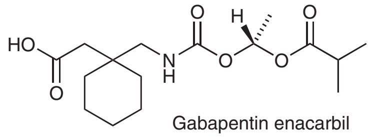
In the aftermath of the success of Gabapentin, a new more active and potent derivative, Pregabalin, emerged and was marketed as Lyrica® by Pfizer from 2004 onwards.

Gabapentin and Pregabalin belong to a class of drugs known as gabapentinoids. Recent studies have revealed that the Large-neutral Amino acid Transporter 1 (LAT-1), which is found in the membranes of the Blood Brain barrier (BBB), transports Gabapentin across the BBB explaining the uptake of the drug to the brain. This discovery facilitated the development of gabapentin prodrugs, such as Gabapentin enacarbil (Figure 2.2), which more easily cross the BBB.



γ-Aminobutyric acid (GABA) Baclofen Gabapentin **1** Vigabatrin Pregabalin

FIGURE 2.1 GABA AND SOME SYNTHETIC API ANALOGUES



Gabapentin enacarbil

FIGURE 2.2 GABAPENTENTIN ENACARBIL CHEMICAL STRUCTURE

Retrosynthesis in the Manufacture of Generic Drugs: Selected Case Studies, First Edition, Pedro Paulo Santos and William Heggie.

2.1 WORLDWIDE SALES AND PATENT STATUS

The following graphs illustrate how research carried out in the pharmaceutical industry towards the production of the API and worldwide sales of the finished drug product evolved.

- US basic patent term 02/05/1995 (US4087544, WarnerL1974), USA Product Patent term extension 16/01/2000.
- Annual production[1]: 2019, 3,997.3 t; 2018, 3,851.6 t; 2017, 3,743.0 t.
- Annual WW sales[1]: 2019, 1377M USD; 2018, 1401.3M USD; 2017, 1346.9M USD.

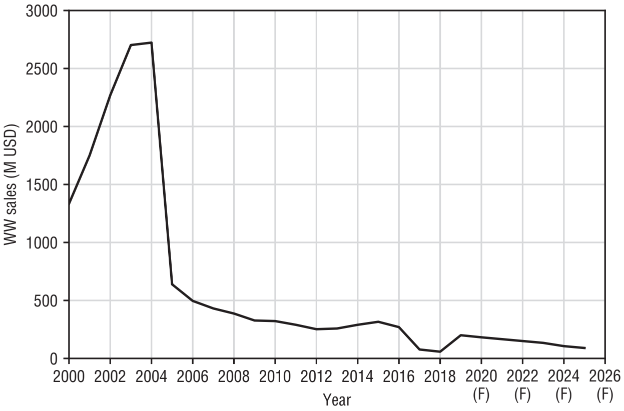


Figure 2.3 Gabapentin WW sales evolution (in M USD)

Source: Data from GlobalData [Online] https://globaldata.com/

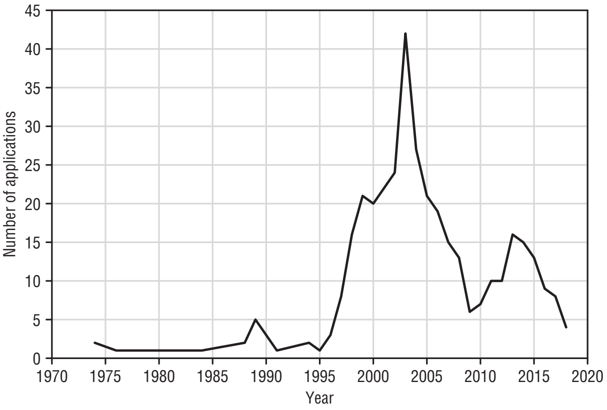


Figure 2.4 New Patent applications on Gabapentin filed by year

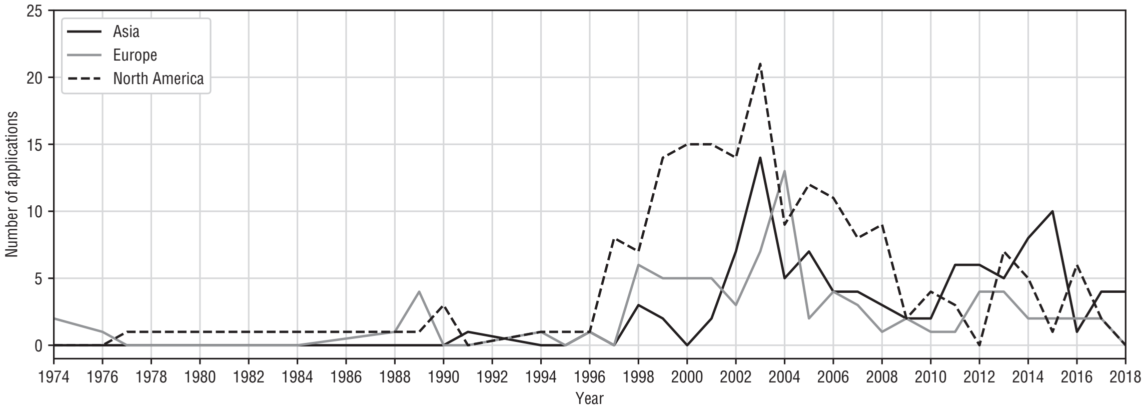


Figure 2.5 Patent applications on Gabapentin filed by region

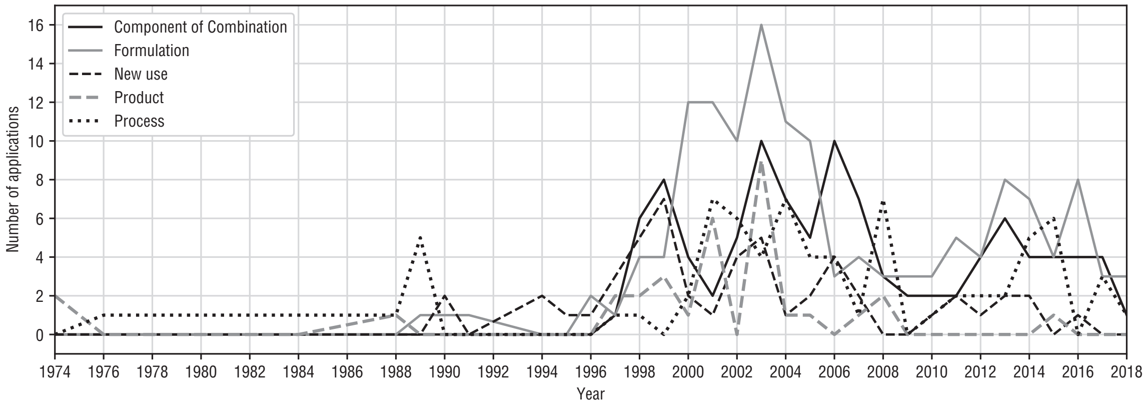


Figure 2.6 Patent applications on Gabapentin filed by type of patent

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[1] Newport Modular Platform – Clarivate Analytics [Online] https://clarivate.com/cortellis/ [2020, April]