UNIVERSIDADE DE SÃO PAULO

FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO

Application of continuous flow processes in the synthesis of fentanyl opioids

Aplicação de processos em fluxo contínuo na síntese de opioides fentanílicos

ARTUR DE LARA LIMA VAZ

Ribeirão Preto
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Concentration Area: Natural and Synthetic Products

Supervisor: Prof. Dr. Giuliano Cesar Clososki

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In memoriam

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“Upon those who step into the same rivers,

different and ever different waters

flow down.”

Heraclitus, ca. 500 BCE

Resumo

Vaz, A. L. L. **Aplicação de processos em fluxo contínuo na síntese de opioides fentanílicos.** 2022. 157p. Tese de Doutorado. Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2022.

Fentanila e análogos são opioides sintéticos da classe das fenilpiperidinas descobertos por Janssen et al. em 1959, e se mostraram os mais potentes anestésicos já conhecidos chegando a possuir dezenas de milhares de vezes o poder analgésico da morfina. Neste trabalho, a preparação da Fentanila e análogos foi investigada em condições de fluxo contínuo. Isto foi feito com a preparação em múltiplas etapas com uso de metodologias clássicas de síntese, adaptações de tais métodos a condições em fluxo, e desenvolvimento de novas estratégias sintéticas, envolvendo reações como adição de aza-Michael, aminação redutiva, desproteções por transferência catalítica de hidrogênio, entre outras. É mostrado aqui que as metodologias discutidas foram exitosas na preparação da Fentanila e precursores, bem como da remifentanila, um anestésico de alta potência e rápida ação e metabolismo de grande importância clínica. A metodologia sintética aqui investigada pode ser de interesse no escalonamento da preparação desta classe de opioides sintéticos por meios de técnicas de fluxo contínuo.

Palavras-chave: Fentanila, síntese orgânica, fluxo contínuo.

Abstract

Vaz, A. L. L. **Application of continuous flow processes in the synthesis of fentanyl opioids.** 2022. 157p. PhD Thesis. Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2022.

Fentanyl and fentanyl analogues are fully synthetic opioids of the phenylpiperidine class discovered by Janssen et al. in 1959, found to be the most potent anesthetics known so far, reaching tens of hundreds of times the analgesic potency of morphine. In this work, the preparation of fentanyl, and fentanyl analogues, under continuous flow conditions was investigated. This was accomplished by the multi-step preparation under common batch methodologies, by adaptation of such methods to continuous flow settings, and development of novel synthetic strategies, involving reactions such as aza-Michael addition, reductive amination, catalytic hydrogen transfer deprotection, and others. It is shown that the methodologies here discussed were successful in the preparation of fentanyl and its precursors, as well as of remifentanil, a high potent, fast-acting anesthetic, with great clinical importance. The synthetic methodology here investigated may be of interest in the up-scaling of the preparation of this class of synthetic opioids by means of continuous flow techniques.

Keywords: Fentanyl, organic synthesis, continuous flow.

Table of Contents

1. Thesis Introduction

1.1. Opioids, its medical relevance and socio-economical settings.

Opioids, organic substances with molecular structures and psycho- and physiological effects similar to those of morphine, have been, in modern medicine, as important in the management of pain as antibiotics have been in the treatment and prevention of infections. The human awareness and usage of these substances, however, largely predate the discovery of penicillin by Fleming in 1928. In fact, archaeobotanical registers of the cultivation of the poppy plant (*Papaver somniferum*) trace it to at least the Neolithic period (CHEVALIER; MARINOVA; PEÑA-CHOCARRO, 2014). Opioids have, then, been used by mankind for millennia for its pain relief, sleep- and euphoria inducing effects. Chemically classified as alkaloids, they are primarily present in the latex of the plant (figure 1), which contains at least fifty of such compounds, e.g. narceine, codeine, papaverine, thebaine and morphine itself (FOXCROFT, 2017), which amounts to around 20% of its contents.

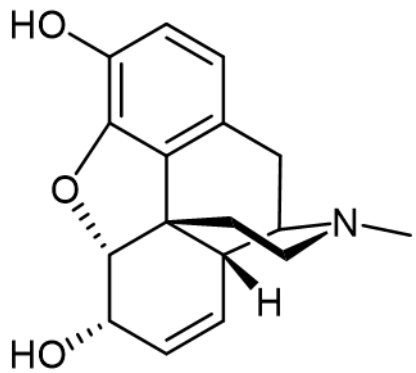

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Figure 1. Left: Molecular structure of morphine **1**. Right: Opium poppy plant drawing (Köhler's Medizinal-Pflanzen, Adolph Köhler, 1887)

Generally speaking, alkaloids (e.g. caffeine, morphine, quinine, etc.), are mainly characterized as secondary metabolites containing a nitrogen in their structure, but may differ greatly in their structural identity, as each arise from

distinct bio-synthetical pathways and precursors (O'CONNOR, 2010). As secondary metabolites, they are not strictly related to the plant's bio-energetic functions, but may play vital roles in the development, communication and survival of the plant that produces and houses them. In fact, from the vast variability of known secondary metabolites that have been discovered, most of their biological and ecological roles are yet to be fully elucidated. As expected, opioids derived from the opium poppy show many structural similarities, as all share the benzoisoquinoline biosynthesis pathway. They all have a common precursor, the (*S*)-reticuline (figure 2, structure **2**) (also a bioactive alkaloid), which itself is derived from L-tyrosine. Along their biosynthesis, however, different set of enzymatic reactions introduce/remove chemical bonds and rings, organic functions and oxidation states, and as the difference of their molecular structure arise, so does their resulting biological/pharmacological properties'.

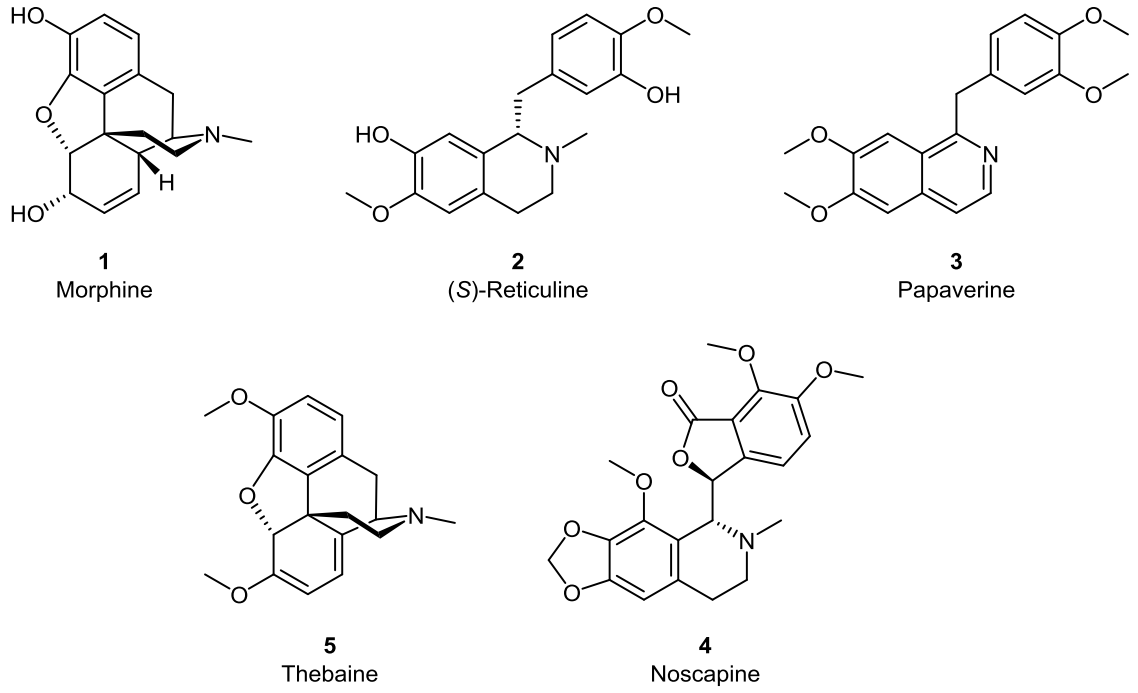


Figure 2. Molecular structure of (*S*)-reticuline (**2**) and various opioids.

It was cited that, among the rich molecular composition of the opium poppy alkaloids, morphine is the prevalent one. As the archetypal opioid, its activity was eventually associated with its ability to bind to a specific group of G-protein coupled receptors that were found to be distributed on the central and peripheral nervous system, spinal cord, and digestive tract. (GOLDSTEIN; LOWNEY; PAL, 1971; OGURA; EGAN, 2013) Our current, most solidified

understanding of the opioid mechanism of action comprises three main types of receptor: Mu (**μ**), Kappa (**κ**) and Delta (**δ**) opioid receptors. As an ongoing research field, new receptor subtypes have been said to be identified. These studies have allowed us to distinguish their physiological roles in relation to their binding affinity to different agonists/antagonists (be it exogenous, like morphine and naloxone, or endogenous, such as endorphins and dynorphins) as well as in regard to their distribution on different tissues and organs. (DARCQ; KIEFFER, 2018)

While our greater understanding of opioids' intricate mechanism of action is a product of late 20th century scientific endeavour, their usefulness as potent analgesic, soporific and euphoric drug has been explored commercially for centuries. In fact, two wars were waged in the 19th century between the greatest imperialist force of the period, the United Kingdom and its East India Company, and Qing dinasty's China, with opium (and the right to impose its trade) playing a central role. (HANES; SANELLO, 2002) In the 20th century, one major autcome of the 2001 invasion of Afghanistan by the United States of America is the intensification of the production and exportings of opium and derivatives, mainly used in illegal drug production, which already accounted for a great share of the middle east country's gross domestic product (MCCOY, 2003), a trend that would only begin to be reverted in 2015. (UNITED NATIONS OFFICE ON DRUGS AND CRIME, 2016)

In the western world, opioid abuse has, from the late 90s to current days, been established as an ongoing crisis (BONNIE; FORD; PHILLIPS, 2017). The US has shown, in the last 3 decades, an unceased increase in deaths related to opioid abuse, both from illegal drugs use and from prescription medicines, surpassing 13 deaths per 100.000 individuals.

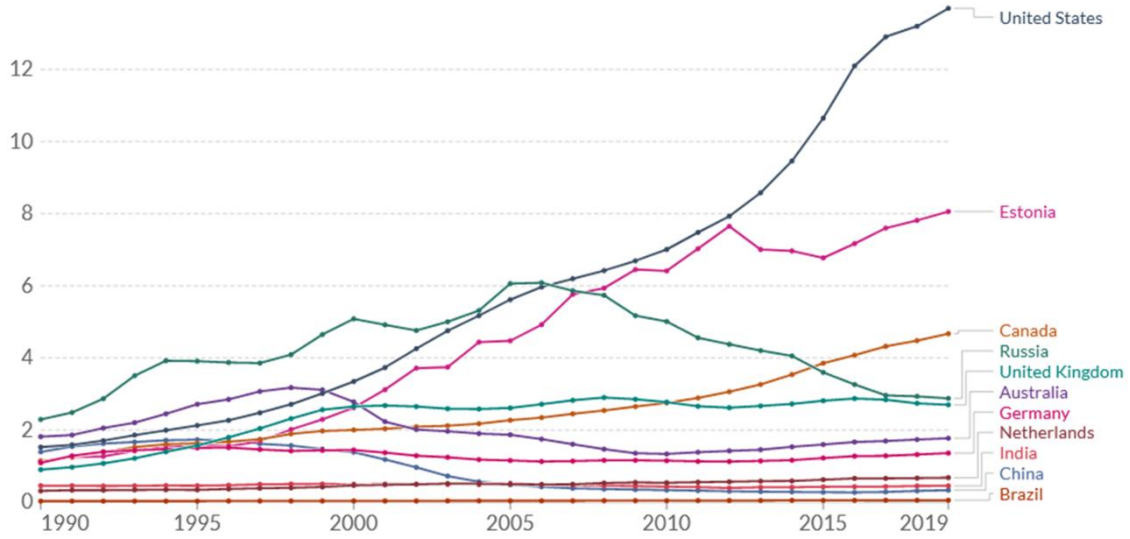


Figure 3. Death rate from opioid overdose, comparison among various countries from 1990 to 2019. Published at OurWorldInData.org, Institute for Health Metrics and Evaluation, Global Burden of Disease (2019). Retrieved 2021/09/22 from https://ourworldindata.org/illicit-drug-use#opioids.

Much of this particular scenario in the US has been credited to a trend of opioid overprescription by medical professionals, who are often encouraged by pressure from pharmaceutical companies' marketing campaings which tend to underplay the risks of opioid tolerance and addiction, as well as the country's inherent problems associated with a mostly privatized health care system. It's been reported that patients in the US tend to choose more immediate relief from pain instead of persuing more complex (and prohibitively expensive) diagnostic procedures and treatments, thus acquiring a chronic opioid dependence for an unresolved medical condition (MEIER, 2018). These elements, in conjunction to the ease of access to such drugs, have been alleged as the driving forces begind the opioid epidemic in the US. (Opioid Epidemic Ther. Community Model, 2019)

A global trend of increase in opioid consumption has been observed for the period between 2015 and 2019, including the South American continent, but such trend has shown disparate numbers regionally, with Brazil showing a slight decrease in morphine (or morphine equivalent) consumption per habitant in this time interval, while the same metric has shown a significant increase in our neighbor Uruguay. (JU et al., 2022) Clearly, the situation regarding opioid abuse

is a challenge to be reckoned, even in regions where such trends of abuse have not yet been observed, and health authorities and regulatory institutions should hold great concern for the subject.

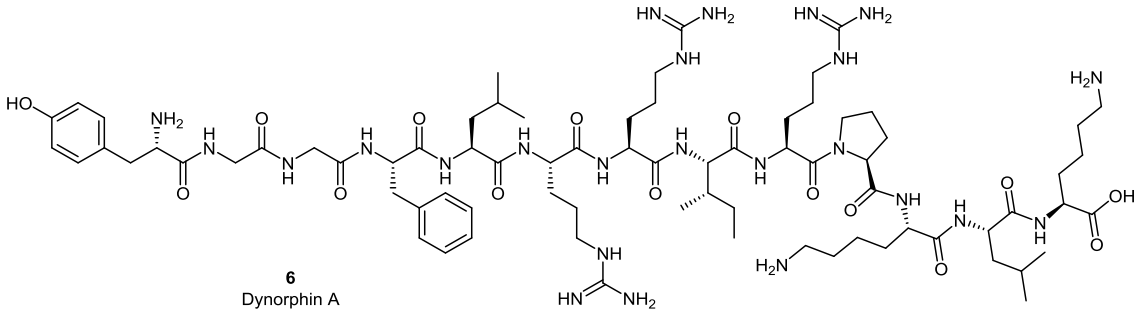


Figure 4. Molecular structure of the Dynorphin A polypeptide, the main endogenous κ receptor agonist.

With this important background context in mind, the medical importance of opioids in the management of pain is hardly disputed. Non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) may be the ordinary prescription choice for mild and moderate pain, but the intense pain associated with chronic conditions, cancer, and perioperative analgesia are often more adequately addressed with opioid administration. (SCHOLTEN et al., 2019)

Under a risk of oversimplification, it can be said that the **μ** agonistic abilities of opioids are the most credited for their desirable analgesic effects as well as, in good extent, for its respiratory depressing and euphoriant ones. Also, as expected, it is recognized that exogenous opioids typically show non-specific ligand behaviors. Different opioids have, each, a distinct set of affinities for each of the three known opioid receptor types. In more recent studies, they have been agued to show different affinities for receptor subtypes (μ_1, μ_2, κ_1, κ_2, etc.). These type/subtype affinity profiles are likely to dictate each opioid's pharmacodynamic properties, that is, the degree with which, for example, a certain opioid will exert its preferable analgesic effect in the central nervous system (CNS), while showing reduced undesired gastroenterological effects or delayed onset of tolerance. (DREWES et al., 2013; PASTERNAK, 2010) Extending this concept, it is also acknowledged that certain opioids may possess mixed agonistic/antagonistic effects, that is, with agonistic effects for certain receptor types while showing antagonistic effects on others. This has

been shown to be the case of nalbuphine (figure 5, structure **10**). In comparison to morphine, nalbuphine was found to have a pronounced agonistic affinity for **κ** receptors while showing moderate agonistic to antagonistic effect for **μ** receptors, and overall low **δ** receptor affinity, an observation that helps to explain its ability to exert strong analgesia while having little to no euphoriant effect. (SCHUMACHER; BASBAUM; NAIDU, 2017)

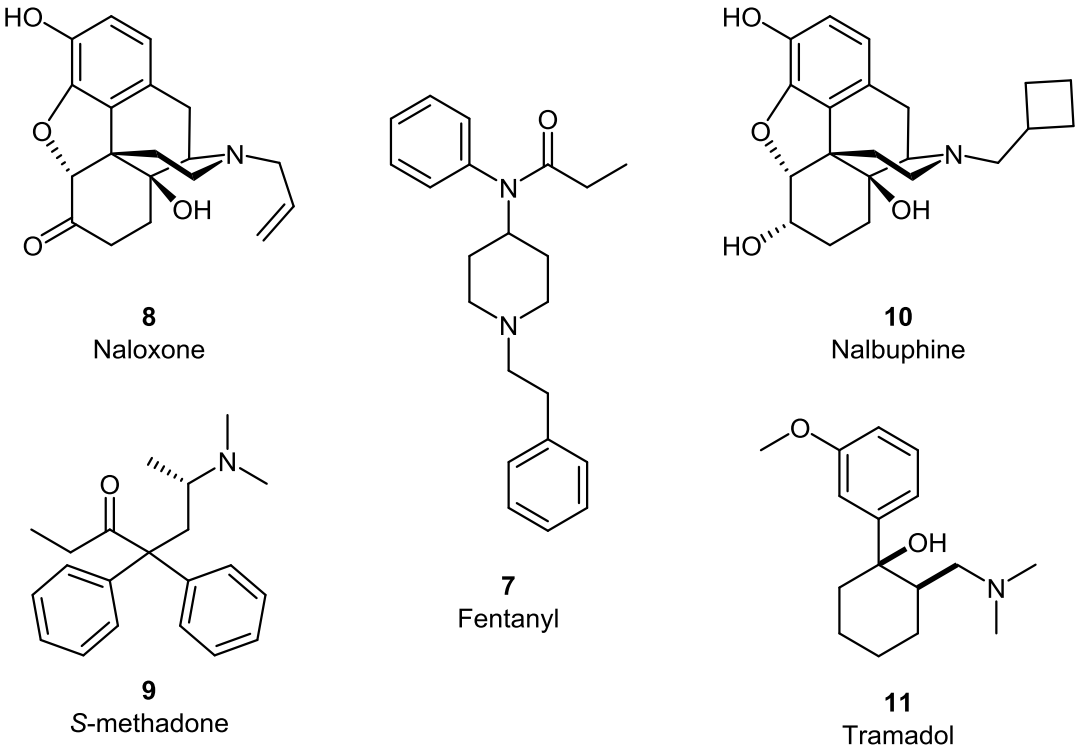


Figure 5. Naloxone, a non-specific opioid antagonist. Nalbuphine, a mixed agonist/antagonist. *S*-Methadone, an atypical opioid with good oral bioavailability used in addiction treatment. Tramadol, a μ-selective pro-drug with weak analgesic potency. Fentanyl, a strong μ-selective agonist.

As is usual for psychoactive substances, the task of accurately evaluating the potency of opioids in regards to their analgesia/anesthesia is, in fact, not a trivial matter. On a molecular level, opioids can be ranked according to their affinity to opioid and other receptors in relation to their endogenous agonists. For this goal, one classical form of investigation has been in-vitro/ex-vivo essays where, for example, the capacity of an opioid analyte to displace an endogenous ligand is measured, in radiolabeled competition studies. (CHEN et al., 1993) One obvious drawback of such model is its inability to more accurately predict an opioid's behavior as an agonist/antagonist, in a complete

biological system, let alone its clinical efficacy, but it is nevertheless an important source of information, especially in initial drug triages. On animal models, on the other hand, antinociceptive effect trials are especially insightful, as they not only may help account for absorption/distribution issues inherent to biological systems, but allow for even richer information when utilizing genetically modified animals carrying knock-out versions of the genes responsible for various types of receptors. (DAHAN et al., 2001) Most important in the clinical setting, however, would be a form of comparison metric that would help health professionals formulating safe and proper opioid dosages. For this purpose, multiple health authorities have worked on elaborating guidelines for the proper prescription and administration of opioids, such as the US Center for Disease Control and Prevention's Guideline for Prescribing Opioids for Chronic Pain (DOWELL; HAEGERICH; CHOU, 2016), which takes into account continuously updated clinical and experimental information on opioid formulations' usage, like the long utilized "Defined Daily Dose" and "Morphine Equivalence Metric", developed in conjunction with the World Health Organization's Collaborating Centre for Drug Statistics Methodology and other agencies. (GILSON et al., 2013; NIELSEN et al., 2016; WASHINGTON STATE AGENCY MEDICAL DIRECTORS' GROUP, 2015) In this work, relative potency of different examples of opioids will be mentioned with these references in mind, otherwise are cited with the corresponding studies.

Opioids may also be arranged among three main categories according to their molecular nature:

- 4,5-epoxymorphinan, such as morphine, that may be of natural or semi-synthetic origin. Usually derived from opium, they have also been called opiates.
- Diphenylheptylamines, such as methadone (figure 5, structure **9**).
- Phenylpiperidines, such as fentanyl (figure 5, structure **7**) and loperamide.

While this classification may be useful for ease of categorization of these substances according to some common molecular features, it falls short on allowing for the prediction of their pharmacological properties, i.e. absorption,

distribution, toxicity and metabolism, or potency. These properties can vary greatly among members of each class. Naloxone (figure 5, structure **8**), for example, is structurally very similar to codeine and oxymorphone but a change of an *N*-methyl group for an *N*-allyl moiety grants its strong antagonistic effects. Loperamide, a phenylpiperidine derivate, is incapable of crossing the blood-brain barrier, and is prescribed for its gastrointestinal effects and is capable of controlling diarrhea while having no CNS effects. Fentanyl, on the other hand, possesses on of the strongest analgesic and respiratory depressant effects of known opioids. Nevertheless, this classification is still valuable in the clinical context, as well as for researchers and forensic toxicologists. (SHAFI et al., 2020)

1.2. Fentanyl and fentanyl analogues.

Fentanyl (figure 6, structure **7**) is a fully synthetic opioid of the phenylpiperidine class. Fentanyl and many structurally similar opioid candidates were originally synthesized by Paul Janssen in 1959. A fentanyl citrate formulation was firstly approved for use by the US FDA in 1972 and, by the 90s, it already accrued enough reports of misuse by both patients and clinicians for a notice to be issued by the american agency warning about dangers associated with formulations of the drug (ARMENIAN et al., 2018). In Brazil, fentanyl citrate has attained registration by the ANVISA in the late 80s for general anesthesia in the form of injectable solution of 50 ug/mL 5 mL ampoules (that is, 9.45*10^-5 mmol per mL) and 2.5 to 10 mg transdermal patches. Since then, various companies have acquired registration for similar formulations in similar concentrations, including veterinary for use.

This drug, as well as other 4-anilidopiperidine analogues, have been found to be the strongest acting opioids known so far, reaching 100 to 10.000 times the analgesic potency of morphine. For this reason, fentanyl and analogues have found more restricted clinical use than their 4,5-oxymorphinan counterparts. In rats, fentanyl has a median lethal dose (LD50) of 3.1 mg per kg, while on monkeys it was found to be 0.03 mg/kg. A median effective dose (ED_{50}) of 0.08 mg/kg was found in mice, compared to 15 mg/kg of morphine, in a modified Haffner's method study, making it at least 100 times stronger than morphine. (GARDOCKI; YELNOSKY, 1964) These important qualities of

fentanyl may be attributed to its molecular features, and the structure-activity relationship of fentanyl and its analogues have been extensively studied since their invention. (BAGLEY et al., 1991; CASY et al., 1969; KUDZMA et al., 1995; VUCKOVIC et al., 2009; YADAV et al., 2010)

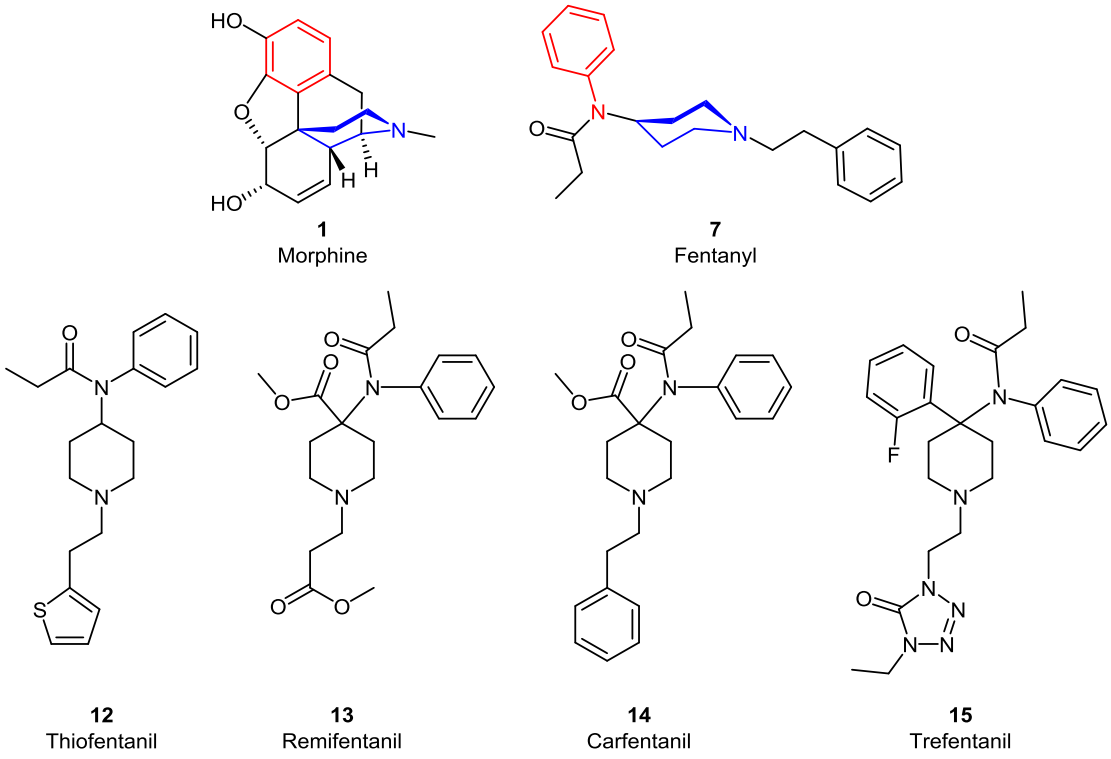


Figure 6. The structure of Fentanyl in relation to Morphine and analogues.

As expected, fentanyl preserves some structural similarities with morphine, and it is reasonable to expect that it would keep important pharmacophores of the original opiate. In summary, some of the most significant structural features responsible for fentanyl's high potency as an anesthetic have been propose to be: (COMETTA-MORINI; MAGUIRE; LOEW, 1992)

- A viable chair conformation of the piperidine ring.

-An amine group able to be protonated in physiological conditions for interaction with a negatively charged receptor site.

-A hydrogen bond accepting polar function, such as the *N*-carbonyl group.

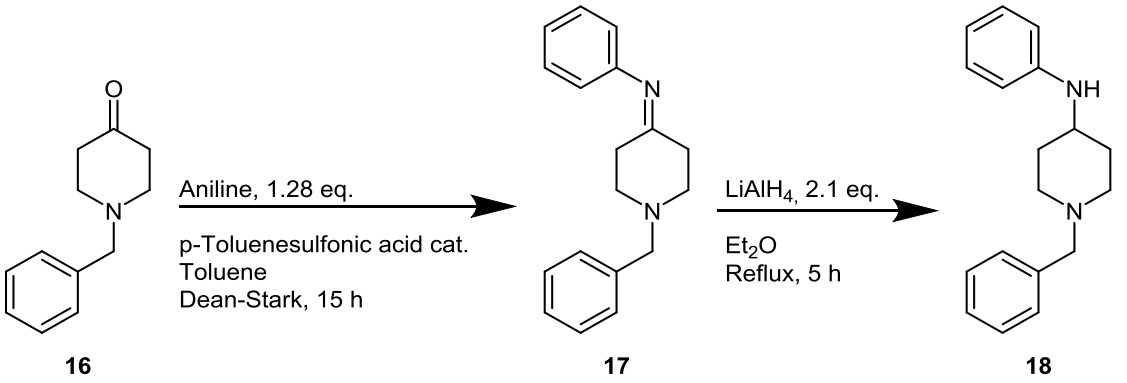
-Two aromatic rings able to form lipophilic and electronic interactions with the receptor.

Indeed, some fentanyl analogues were found to be even more potent than fentanyl itself, and all share these traits, as well as introduce some moieties that are able to further increment their interaction with **μ** receptors (MAGUIRE et al., 1992). Their enhanced anesthetic potency, however, is accompanied by likewise higher respiratory depression. Carfentanil (figure 6, structure **14**) is a modification of the basic fentanyl structure including a carbomethoxy ester in the position 4 of the central piperidine ring, functioning as an additional polar moiety for interaction with μ receptors. This analogue was found to be 10,000 times more potent than morphine, rendering its clinical use virtually impossible, as a reliable therapeutic margin for humans is mostly unlikely. Carfentanil, then, has been limited for veterinary use on large animals. (ZAWILSKA et al., 2021) Like fentanyl, however, carfentanil been found its way among illegally manufactured fentanyl analogues that are frequently detected by authorities as a component or contaminant of street drugs worldwide.

A fentanyl analogue that also deserves significant attention is remifentanil (figure 6, structure **13**). Unlike carfentanil, remifentanil holds an equivalent potency to that of fentanyl. Nevertheless, it is a particularly interesting variation of the basic structure of carfentanil where its *N*-alkylaryl tail is substituted by an *N*-methylpropionate. This modification, devised by Feldman et al. from Glaxo inc., rendered the molecule highly susceptible to hydrolysis by non-specific blood esterases. While fentanyl, carfentanil and the other phenylpiperidines are mostly inactivated by oxidation/*N*-dealkylation by liver CYP3A4 complexes, remifentanil is rapidly broken down in the bloodstream, affording remifentanil acid, which holds 0.005 to 0.01% of the original potency of remifentanil, (BÜRKLE; DUNBAR; VAN AKEN, 1996) making it a strong but very short-lived opioid anesthetic. Currently, ANVISA has granted registry licenses for remifentanil hydrochloride to numerous manufacturers, being utilized in perioperative general anesthesia, as well in assisting sedation of patients going through tracheal intubation that requires mechanical ventilation.

1.3. Synthesis of fentanyl and fentanyl analogues by Janssen.

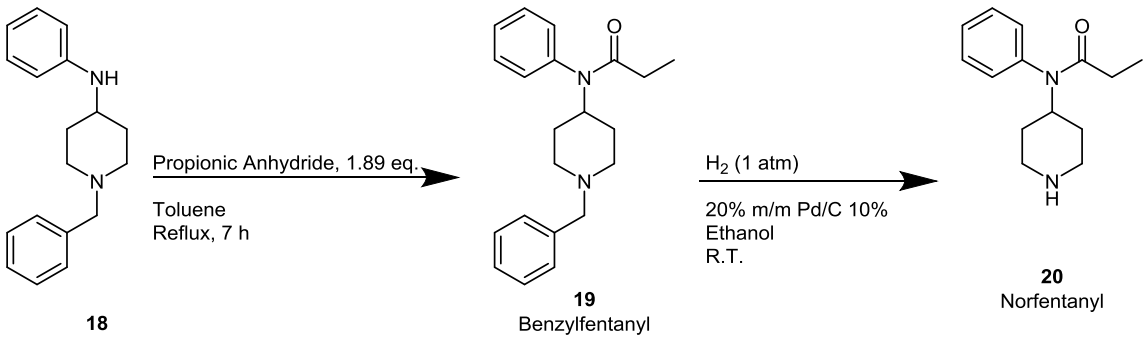
The first synthesis of fentanyl and many of its analogues, as realized by Paul Janssen in 1959 and registered in US patent N° 3141823, began with the preparation of imine **17**, formed from the 1-benzyl-4-piperidone **16** and aniline (scheme 1), followed by its reduction to the anilino piperidine **18** with use of $LiAlH_4$. (JANSSEN; GARDOCKI, 1964)



16 **17** **18**

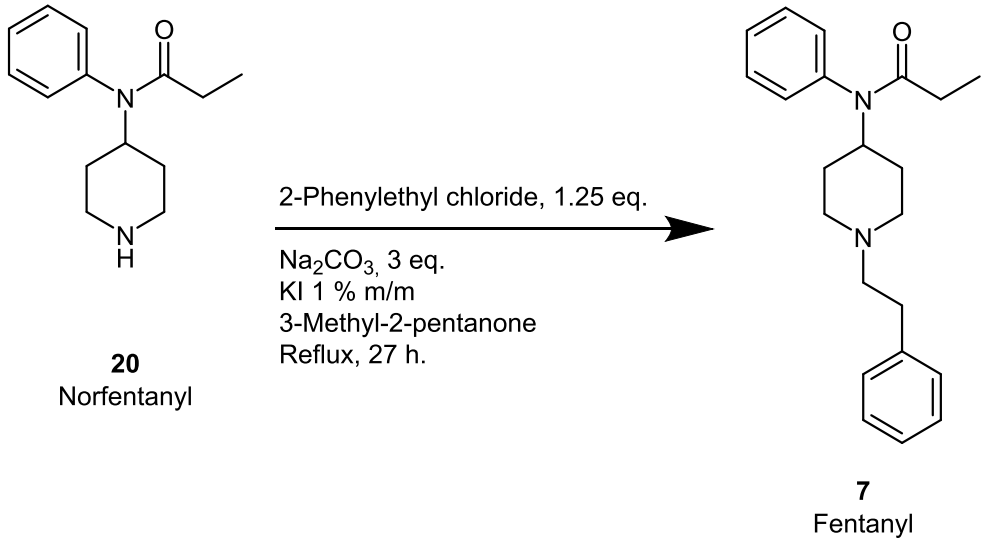
Scheme 1. First two steps in the preparation of fentanyl (Janssen et al. 1959).

Then, **18** was treated with propionyl anhydride to form propionalinide **19** (also called benzylfentanyl) (scheme 2, structure **19**). Then, a palladium-catalyzed reductive deprotection of the *N*-benzyl moiety afforded the intermediate **20** (norfentanyl), which was then *N*-alkylated with 2-ethylphenyl chloride furnishing fentanyl **7** (scheme 3).



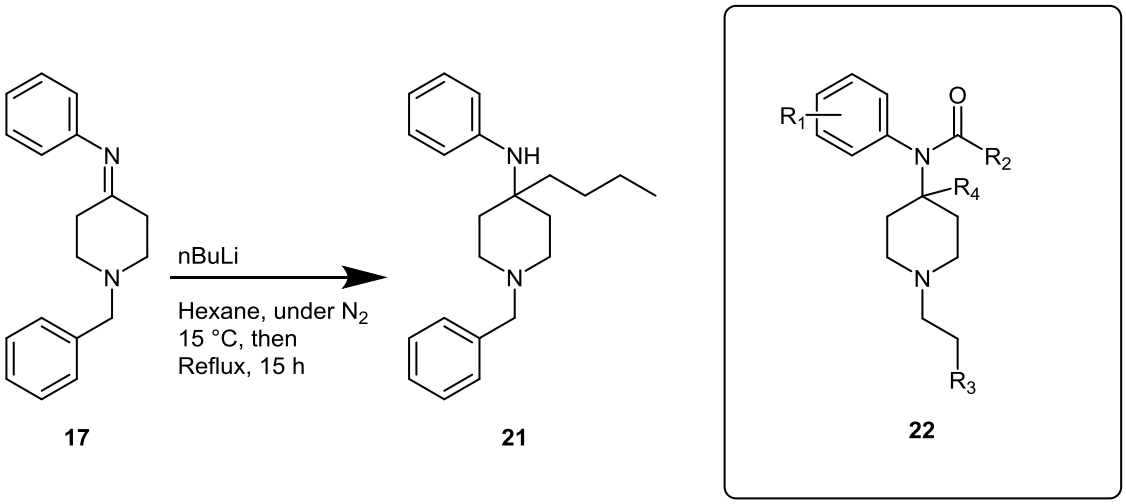
18 **19** Benzylfentanyl **20** Norfentanyl

Scheme 2. Third and fourth steps in the preparation of fentanyl (Janssen et al).



Scheme 3. Last step in the preparation of fentanyl **7** (Janssen et al).

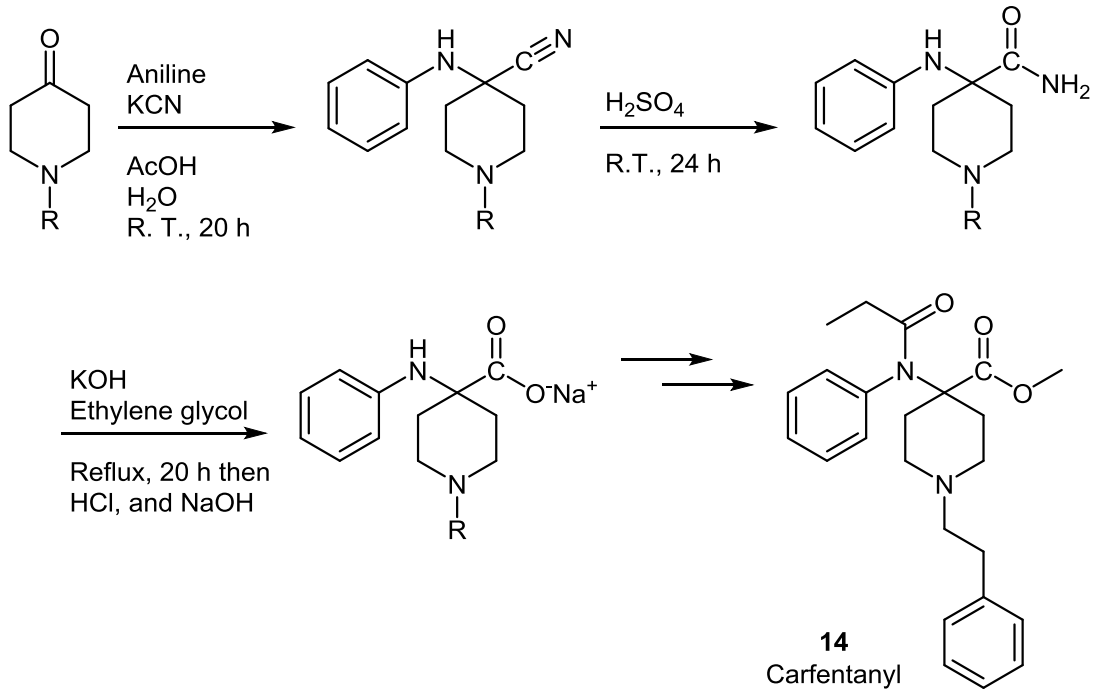
In the preparation of 4-disubstituted analogues, the imine **17** was also utilized as a substrate for addition by n-butyllithium, furnishing 1-benzyl-4-butyl-anilinopiperidine **21**.



Scheme 4. Left, reaction of imine **17** with organometallic reagents in the preparation of 4-disubstituted fentanyl analogues. Right, analogues of structure type **22**.

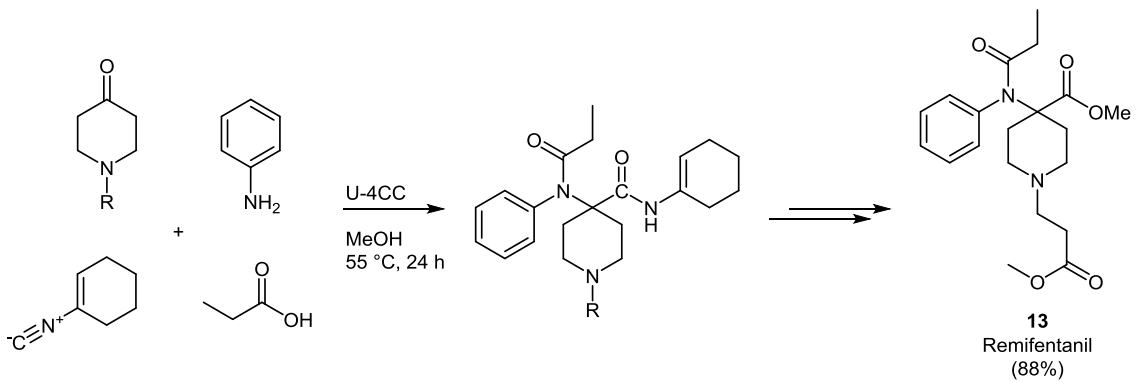
As discussed earlier, fentanyl analogues containing an additional substitution at the 4 position of the piperidine ring comprise a class of piperidine opioids of particular interest, since some 4-acyl-4-anilido piperidines, i.e. carfentanil and remifentanil, have been found to be hundreds of times more potent than fentanyl itself. The preparation of this variant of molecules have

been proposed by Janssen et al by means of the reaction of piperidone similar to **16** with aniline in the presence of alkali cyanides in a Strecker type multicomponent reaction (JANSSEN; VAN DAELE, 1979) (scheme 5).



Scheme 5. Preparation of 4-acyl-4-4-anilidopiperidine analogues (Janssen et al).

The formation of this 4-substituted nucleus has been accomplished through a novel strategy as reported by Laconde, Deprez et al., where the reaction of piperidone of type **16** reacts in a one-pot fashion with aniline, propionic acid and a isocyanide species, in a form of Ugi 4-component condensation. This strategy was successful in the preparation of carfentanil, as well as remifentanil (MALAQUIN et al., 2010) (scheme 6)



Scheme 6. Ugi 4-CC reaction in the preparation of remifentanil.

Thus, utilizing the piperidone **16** as starting material, chemists have been resorting to a varied set of reactions to furnish many of the first fentanyl analogues, e.g. replacing the aniline in the formation of the imine **17** for functionalized aromatic amines (anisidines, toluidines), substituting the acylating agent (propionic to acetic anhydride), or the alkylating reagent at the final step (e.g. other aryl-alkyl halides). All these synthetic alternatives account for structures of type **22** (scheme 4) that could be furnished with the same piperidone **16**, attesting to the importance and versatility of this building block in the preparation of anilidopiperidine opioids.

1.4. Continuous flow processes in organic chemistry and API production.

For decades, continuous processes have been a mainstay for industries such as in petrochemical and food manufacture. In pharmaceuticals and fine chemistry, however, mass production had been most exclusively done by batch processes. In batch operations, the preparation of compounds is accomplished in various chemical reaction steps, and in the process, each reaction step is accompanied of several segmented operation units (such as reactor loading, mixing, heating, separation, extraction, purification, etc.) (SHARRATT, 1997). Therefore, the mass batch production of a desired compound may become increasingly costly and cumbersome the more reaction steps are involved in its preparation. As the volume of batch reactors increases, as a response to manufacturers demand for higher product throughput, there are increased hazards, especially when dealing with potentially toxic reagents, runaway reactions, unstable reactants and others. Hoping to tackle these and other limitations related to batch reactions, both industries and researchers have increased efforts in the development of continuous flow processes.

Figure 7. Our own Flow Asia system (Syrris) comprised of syringe pumps (left) and column heater with an exposed Pd/C-filled packed bed reactor (right).

In a continuous flow setting, neat or solution reagents are continuously pumped through low diameter-tubing, are mixed together and pass through a temperature-controlled reaction zone, where the reaction mixture can absorb energy (e.g. heat, light, ultrasound). With the continuous pumping, after a period of time, the reaction mixture will leave the reactor, and can be collected at the end of the setup for further processing. This would the basic arrangement of a continuous setting, but continuous processes allow for a great diversity of techniques to be employed in organic synthesis, such as consecutive in-line reactions (BRITTON; RASTON, 2017; JIAO et al., 2021), real-time reaction monitoring (DE SOUZA et al., 2018; SAGMEISTER et al., 2019; WILES; WATTS, 2009) and automation of reaction optimizations (BREEN et al., 2021; SCHWEIDTMANN et al., 2018), to name a few.

In order to graphically convey continuous flow setups, schematic diagrams are drawn with representations of all elemental parts that compose them (e.g. reactors, pumps, mixers, valves, etc.). Flow symbols and elements utilized in this thesis are listed in the List of Symbols and Units part (page VII).

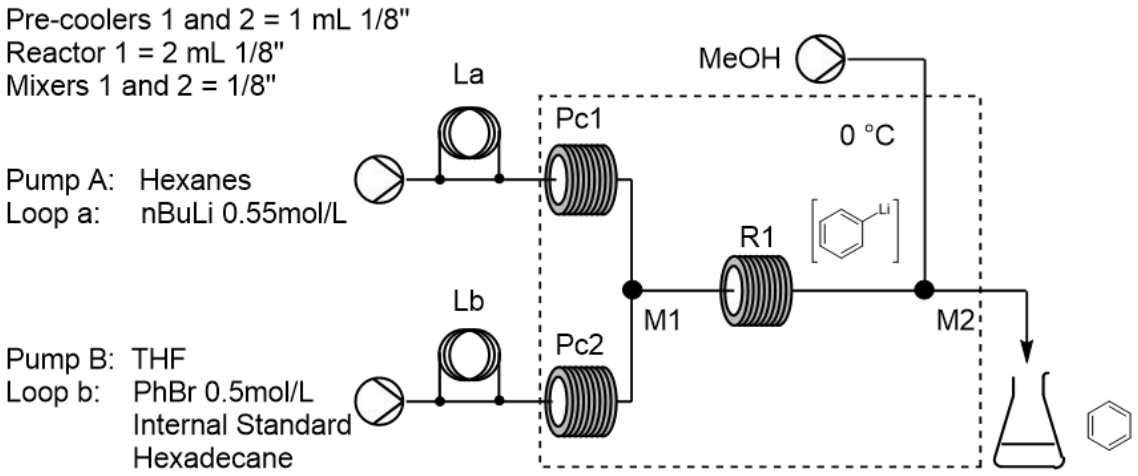


Figure 8. Top, an assembly for the evaluation of metal-halogen exchange of aryl-halides (as PhBr) and nBuLi in continuous flow. Bottom, the schematic diagram of the reaction.

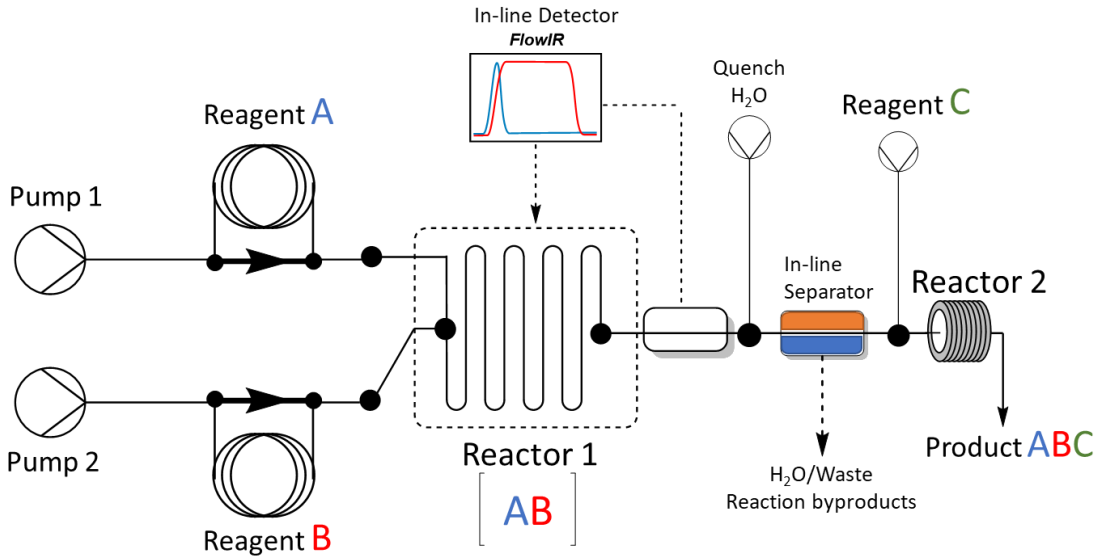


Figure 9. A schematic example of a continous flow setting, showing advanced techniques such as in-line separators, real-time Infra-Red analysis, consecutive reaction steps.

Furthermore, there are some aspects intrinsic to any continuous flow setting that makes them interesting for chemists even in their most basic form. Flow reactors consist basically of narrow channels, comprised of chemically resistant tubing (e.g. stainless steel or polymers, with polytetrafluoroethylene being the preferred option for its flexibility and chemical/mechanical resistances). These channels provide an increased surface area available in the reaction zone for heat exchange, allowing for the fast, controlled heating (or cooling) of the reaction mixture, diminishing undesired hotspots or overheating. This fast flow and fast temperature control have allowed, for example, researchers to *trap* very transient chemical species that would otherwise decompose in a batch reactor or be converted do undesired byproducts, in what has been called Flash Chemistry, accentuating the possibility of greater chemo- and regioselectivity in organometallic reactions (NOËL; SU; HESSEL, 2016; PETERSEN; BECKER; KNOCHEL, 2014; YOSHIDA; TAKAHASHI; NAGAKI, 2013).

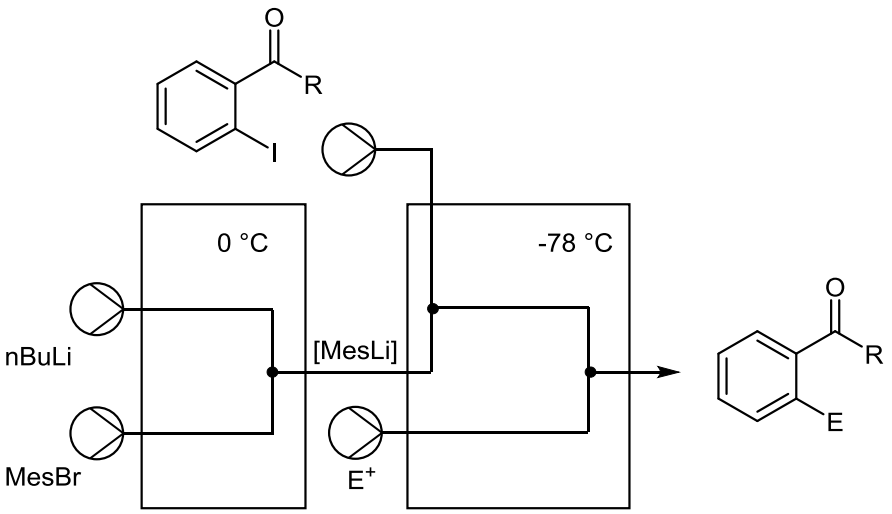
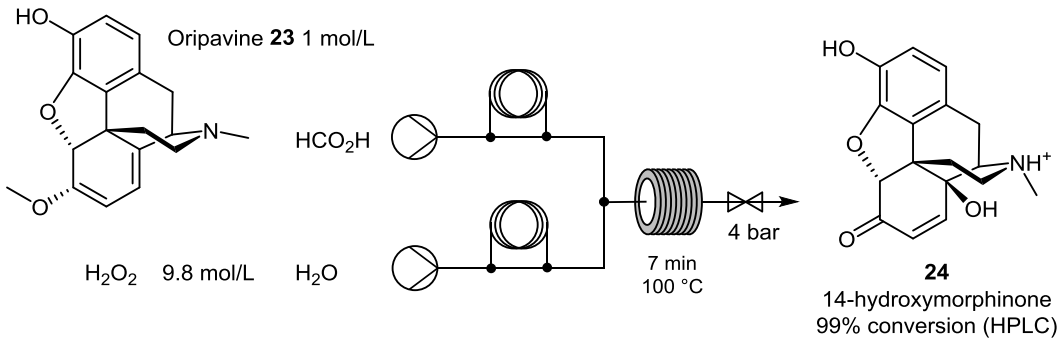


Figure 10. Generation of aryllithium species in "flash-chem" flow as described by Yoshida et al.

While dealing with very transient reactants, their fast generation and consumption allowed by flow chemistry was exploited by researchers to harness the oxidizing power of highly unstable high-concentrate performic acid in the preparation of the opiate derivative 14-hydroximorphinone **24** from oripavine 23, which is a precursor to important *N*-alkylated **μ** receptor antagonists and other derivatives (MATA; CANTILLO; KAPPE, 2017). The low volume/high surface area characteristic of flow conditions allowed the group to generate and consume the highly explosive performic acid in temperatures that surpassed the safety limits associated with batch conditions (DALLINGER; GUTMANN; KAPPE, 2020) (scheme 7).



Scheme 7. Flow setup for the hydroxilation of opivarine **23** in the preparation of 14-hydroxymorphinone **24**.

The capacity of flow chemistry methods to provide extreme reaction conditions (i.e. temperature and pressure) that would otherwise be

unsafe/unreachable in batch reactions have heralded continuous flow as a great opportunity to explore novel process windows in organic synthesis. (HESSEL, 2009; HESSEL et al., 2013; MOMO et al., 2015) Definitely, continuous flow is now an additional instrument for chemists exploring such extreme reaction conditions, along with microwave-heating, for example. In fact, high temperature, high pressure reactions that have been carried out in pressurized sealed microwave vials have been successfully carried out in continuous flow settings. Microwave assisted reactions has then become a tool when screening for extreme reaction conditions applicable in a continuous flow setup, what has been called ‘’microwave-to-flow’’ approach (GLASNOV; KAPPE, 2011). The intent, here, would be to search for reaction conditions in a microwave-assisted, reduced scale setting, that could be transposed to a more easily-scalable setting in a flow setup.

Figure 11. 2, 10 and 30 mL microwave reaction vials provided by Anton Paar.

The volume limitations of ordinary benchtop and microwave-assisted reactions can be addressed in continuous flow as well, where intensification of product throughput is realized with significant more ease in flow in a ‘’scale-out’’ approach, in contrast with the non-trivial difficulties (and hazards) associated with the scale-up of batch operations that inexorably requires greater reactor dimensions (GUTMANN; CANTILLO; KAPPE, 2015). Scaled-up flow chemistry operations, nonetheless, are not without its own set of issues and challenges, but these are being extensively addressed (DONG et al., 2021; HONE; KAPPE, 2021).

2. Overall aims and objectives.

2.1. Aims

This thesis comprises the development and adaptation of continuous flow methodologies in the preparation of fentanyl, of some precursors common to the 4-anilidopiperidine synthetic opioids.

2.2. Objectives

-To investigate the preparation of the 1-benzyl-4-piperidone, an important precursor of 4-anilidopiperidine opioids, in continuous flow.

-To develop new methodologies in the preparation the synthetic opioid fentanyl, in continuous flow.

-To develop new, or adapt known, methodologies utilized in the synthesis of fentanyl derivates, in continuous flow.

3. General Conclusions

In this thesis, we have shown the successful multi-step preparation of fentanyl from simple commercially available starting material by means of continuous flow techniques. These techniques and methods were developed by means of adaptation of classical reactions first investigated with a “microwave to flow- approach”, in order to optimize reaction conditions before translation to continuous flow settings.

First, the preparation of 1-benzyl-4-piperidone, an important and highly versatile starting compound, was investigated. Its precursors were successfully prepared under flow conditions with excellent results. The last step in the preparation of the piperidone, a decarboxylation reaction, was accomplished in batch. A continuous setting capable of this key decarboxylation step, however, is yet to be determined.

In the first step of the preparation route of fentanyl, an innovative strategy was developed in continuous flow: the direct reductive amination reaction utilizing a highly versatile and mild amino-borane reducing reagent, PICB, was investigated with great results under continuous flow.

The acylating step in the preparation of the benzylfentanyl intermediate was effectively achieved under continuous flow after investigation of reaction conditions under batch. Excellent conversion rates were observed and precipitate formation, critically detrimental to flow settings, was successfully avoided.

The reductive deprotection step in the preparation of norfentanyl from benzylfentanyl was successfully achieved in flow through a catalytic hydrogen transfer strategy. A packed bed reactor was utilized as support for the heterogeneous catalyst and it was shown to be very effective, while important aspects and limitations of this type of reaction explored.

Finally, fentanyl was prepared in a last *N*-alkylation reaction that was successfully achieved under continuous conditions, by means of an heterogenous liquid-liquid slug-flow regime, a strategy that was replicated with

great outcomes in the preparation of the important fentanyl analogue, remifentanil.