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Pharmaceuticals based on the Pyrrole Nucleus

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Main Scope: Organic Chemistry

Secondary scopes: Pharmaceutical chemistry and Biochemistry

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Resumen

El pirrol es un compuesto heterocíclico común con una química única. Se encuentra en una multitud de estructuras, y el alcance de su potencial en el campo terapéutico todavía está por verse. La comprensión de esta estructura nos ayuda en el desarrollo de nuevas síntesis y moléculas basadas en el pirrol. Las estructuras más reconocidas del pirrol se revisan de acuerdo a su eficacia farmacológica. En este trabajo, primero se profundiza lo que distingue al pirrol de otras moléculas aromáticas y cómo su estructura química afecta a las reacciones que puedan ocurrir. Esto se podrá aplicar a las reacciones de substitución del pirrol; estas se muestran de forma dinámica para entender los diferentes tipos de reacciones disponibles. Desde aquí se exploran varios métodos de síntesis del pirrol, desarrollando algunos de los más comúnmente utilizados: síntesis de Knorr, síntesis de Paal-Knorr, síntesis de Hantzsch y reacción de Barton-Zard. Finalmente, esta información se aplica para desarrollar la síntesis de tres productos farmacéuticos bien conocidos que contienen pirrol.

Abstract

Pyrrole is a common heterocyclic compound with a unique chemistry. It is found in a multitude of structures, and the scope of its potential is still to be seen. Understanding this structure aids us in developing new syntheses and molecules based around pyrrole. Common pyrrole structures are revised to view which is their most frequent use. In this work, we first delve into what differentiates pyrrole from other aromatic molecules and how its chemical structure affects the reactions that can take place. This knowledge can then be applied to common pyrrole substitution reactions; these are shown in a dynamic form so as to understand the different types of reactions available. From here exploring various pyrrole synthesis methods, further developing some of the most commonly used: Knorr pyrrole synthesis, Paal- Knorr synthesis, Hantzsch synthesis and Barton-Zard reaction. Finally, this information converges into understanding the synthesis of three well-known pyrrole-containing pharmaceutical products.

SCOPE DISCUSSION

The aim of this dissertation is not only to create a work based on the principal subject area but to also apply knowledge from other areas of study and integrate them to create a well-rounded analysis of the subject.

In this work the principal area of study is organic chemistry, pyrrole is one of the most common nuclei in organic chemistry and so without understanding its structure, chemistry and reactivity we cannot develop its synthesis. A secondary area of study is pharmaceutical chemistry which together with organic chemistry allows for the development and understanding of the syntheses involved in poly substituted pyrroles, which can then be applied to the synthesis of current pyrrole-containing pharmaceuticals. The other subject area applied is biochemistry, since this work is regarding pharmaceuticals based on the pyrrole nucleus it is not only important to understand their synthesis but also the use of these pharmaceuticals in humans. The pyrrole nucleus is often found in natural products therefore it is important to recognise how metabolic pathways are used to create these structures since this can help us develop synthetic pathways.

1. INTRODUCTION

With numerous new pharmaceuticals coming onto the market yearly, it is ever more challenging to discover successful, economically viable molecules. One such way of identifying these potentially useful molecules is by examining the pharmacophores of other natural products or successful drugs, to try and expand on their structure and to identify efficient ways to synthesise them.

One such molecule is pyrrole, a common chemical structure which stands out due to its repeated occurrence in natural and synthetic products as well as its particular chemistry. To be able to fully comprehend the scope of pyrrole it is essential that we first understand its unique structure and how this affects its synthesis. Following on from this we can explore common syntheses and how these are applied in well-known pharmaceutical products. Understanding these processes will allow us to be able to apply these methods to future endeavours, such as new chemical entities.

2. OBJECTIVES

This work aims to integrate the information acquired throughout the pharmacy degree to be able to apply it to a bibliographic research project.

Specifically, this work aims to:

- Develop an understanding of the presence of pyrrole in natural and synthetic molecules
- Contextualise the structure, chemistry and reactivity of pyrroles to apply it to current examples of pyrrole-containing molecules
- Create familiarity with these processes to be able to apply the knowledge to new chemical entities

3. MATERIALS AND METHODS

This work is bibliographic and based on research found through literature regarding the topic of pyrroles. Firstly, a rough outline of the basis of the text was developed to structure the work. Based on this initial outline several sources were consulted. There is a wealth of information available regarding the chemistry of pyrrole since this entity has been known and researched for decades and so some of the information may be from older sources. *Heterocyclic chemistry* by J.A. Joule and K. Mills was of great use in this work as a starting point to understand the basic chemistry of pyrrole. From there SciFinder® was used to understand specific reactions further. Review articles of the current synthesis of pyrrole were consulted to have a further understanding of the scope of the syntheses available. From there three molecules were chosen to research their synthesis further. These molecules were chosen due to their variety of therapeutic use and effectivity in treatment; it was essential that the molecules chosen were both commercialised and successful. When researching these pharmaceutical entities, SciFinder® was once again used, referencing either academic articles or patents. Priority was given to industrial methods of synthesis rather than academia. PubMed® was a valuable resource when researching the use of these pharmaceuticals.

Throughout this work primary, secondary and tertiary sources have been used, with keywords including pyrrole, pharmaceuticals, and names of specific reactions and products. Oftentimes the search was dependent on the section that was being developed. When researching the sections pertaining to the structure, chemistry and synthesis of pyrrole, secondary sources were predominantly used, most notably books on the subject of heterocyclic chemistry. As for the section on common examples of pyrrole products, primary sources were favoured.

An important aspect of this body of work was the depiction of reactions related to pyrrole, for this ChemDraw® was used, offered by CRAI (Universitat de Barcelona). Part of the aim of this project was for it to be easily understandable for any person who has a foundational understanding of chemistry. Therefore, all diagrams are designed to be dynamic and easily understood. All drawings are my own.

4. RESULTS AND DISCUSSION

4.1. Overview

One interesting structure identified throughout nature and in a very diverse range of pharmaceuticals is pyrrole (Figure 1). This heterocyclic five-membered ring containing nitrogen has a molecular weight of 67.091 mg/ml, is less dense than water (0.968) and has no formal charge. It is a colourless liquid at room temperature though quickly turns brownish in contact with air, and it has a significant irritant odour and taste. Its boiling point is 129-131℃, when heated it emits toxic fumes. Its freezing point is -24℃. It is almost insoluble in water and dilute alkali solution, though soluble in alcohol, dilute acids, ether, and most organic chemicals.[1]

67.091 mg/ml
p 0.968
B.P. 129 ºC
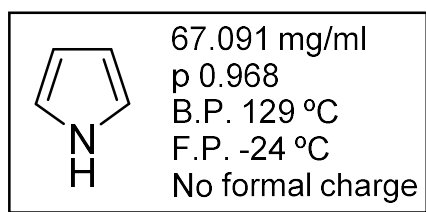F.P. -24 ºC
No formal charge

Figure 1: Pyrrole

It is a naturally occurring product present in bone oil and coal tar - where it was first detected in 1834 by F. F. Runge. It is most notably found in porphyrins. Though they are not found naturally on their own, they are always part of a larger structure. Its name comes from the Greek *pyrrhos*, meaning red or fiery.[2] This name likely derives from its reaction with hydrochloric acid, where when moistened with said acid it readily polymerises into dark red resin trimer,[2] this reaction can be used to identify it.

4.2. Pyrrole containing products

Pyrrole is found in numerous natural and synthetic products, one of the most common structures is tetrapyrrole, four pyrroles joined together to create a scaffold often with a metallic ion in its centre. These structures are based on porphyrin which is synthesised through the condensation of four methanol or amine-substituted pyrroles. These create a ring structure which is subsequently reduced to give porphyrin.

The starting reactant is 5-aminolevulinic acid, following a Knorr type reaction this molecule is cyclized, this produces porphobilinogen which is the pyrrole base for the structure. Four porphobilinogen are assembled to give a macro scaffold which, via specific enzymatic pathways, will go on to give different products depending on the porphyrin structure required (Scheme 1).[3]

From this structure Heme b (Scheme 1), found in oxygen transport proteins,[4] is produced in humans as well as other species. Factor 430 (Scheme 1) is also derived from this structure; it is the prosthetic group of the enzyme methyl-coenzyme M reductase,[5] found in only some Archaea and thought to be involved in reverse methanogenesis. It is also the scaffold for chlorophyll a[4] (Scheme 1), a green pigment found in plants, algae and bacteria which is crucial for photosynthesis. Other notable products are bilirubin, a degradation product of heme, and cobalamin, an essential vitamin required for DNA synthesis, metabolism as well as other vital processes in the human body.
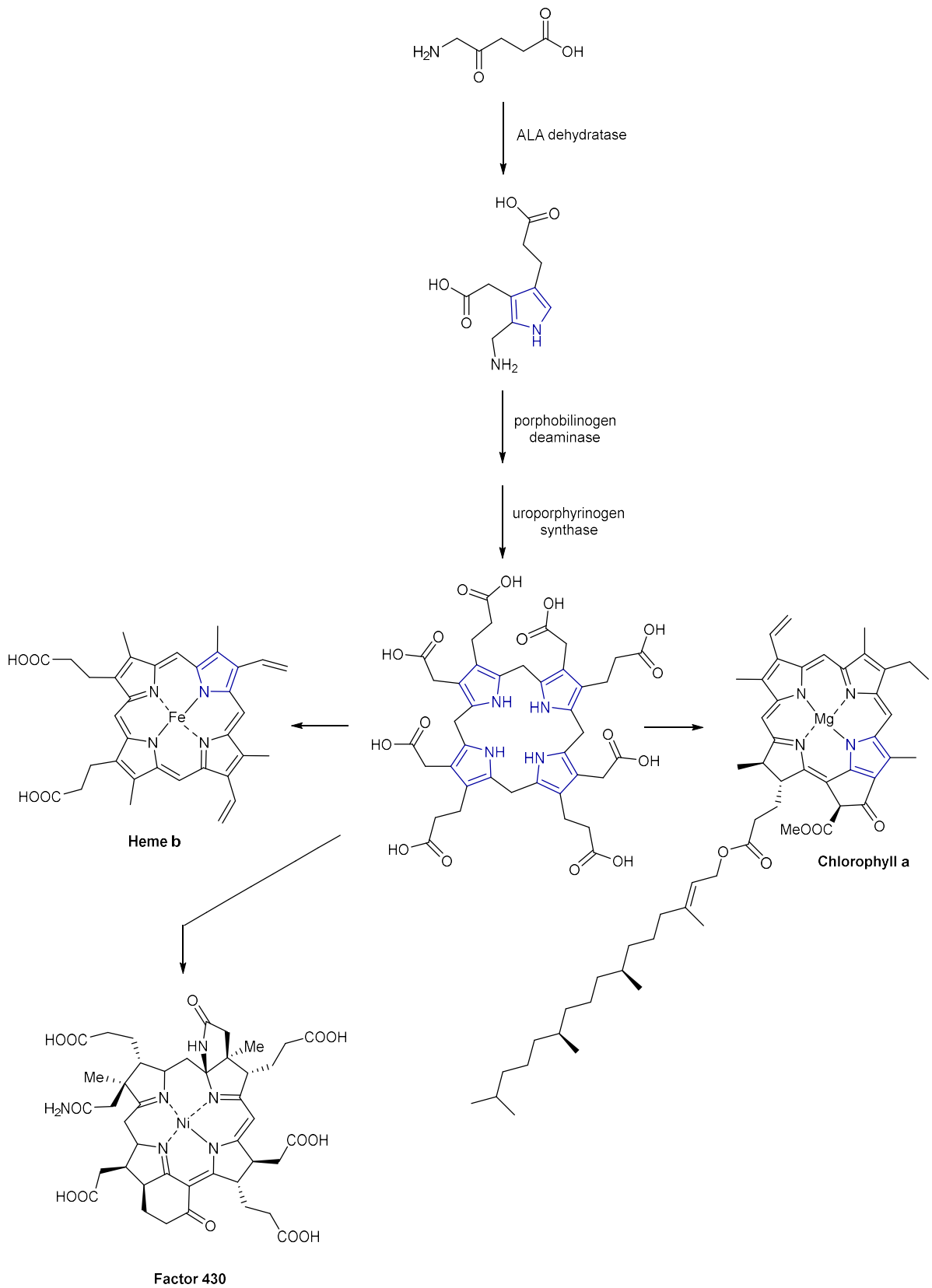
Scheme 1: Generalized biosynthesis of tetrapyrroles

Pyrrole is also present in many marine organism metabolites (Figure 2*a*); such examples are Storniamide A which is an inhibitor of multidrug resistance, a phenomenon where a cell is inherently resistant to commonly used drugs, complicating the patient's treatment. Marinopyrrole A is useful against methicillin-resistant Staphylococcus aureus strains. Halitulin is a cytotoxic natural product isolated from a marine sponge (*Haliclona tulearensis*).[6] These substances can potentially lead to useful therapeutic molecules.

Lead products for new drugs are usually derived either from natural products with interesting therapeutic properties - as above - or de-novo, where newly synthesised molecules are tested to determine if they have any therapeutic properties. One example is BM 212 (Figure 2*a*), a promising lead product with anti-bacterial and anti-fungal properties.

Also shown are several commercially available drugs used to treat a variety of diagnostics (Figure 2*b*). Atorvastatin is frequently used to lower cholesterol levels, and one of the world's most successful drugs. Sunitinib is a neoplastic drug used to treat renal cell carcinoma and gastrointestinal stromal tumour. Ketorolac and Tolmetin are anti-inflammatory drugs; the former is used for acute moderate to severe pain with analgesic effects similar to those shown by opioids. The latter, Tolmetin, can be used long-term for acute flare-ups of rheumatoid arthritis and osteoarthritis,[7] and to treat pain associated with these conditions. Both these anti-inflammatory drugs are COX inhibitors, which are involved in prostaglandin formation.

Finally, in Figure 2c optoelectrical materials are also shown, pyrrole has been a source of much attention for material scientists. BODIPY dyes are chemically inert and fluorescent, with great potential use in imaging. Electrochromic conductive polymers can be formed with a pyrrole scaffold giving a stable conducting material.
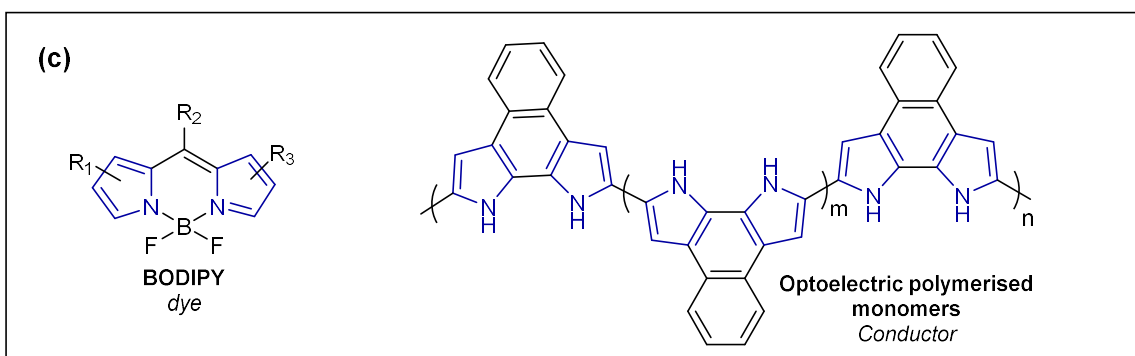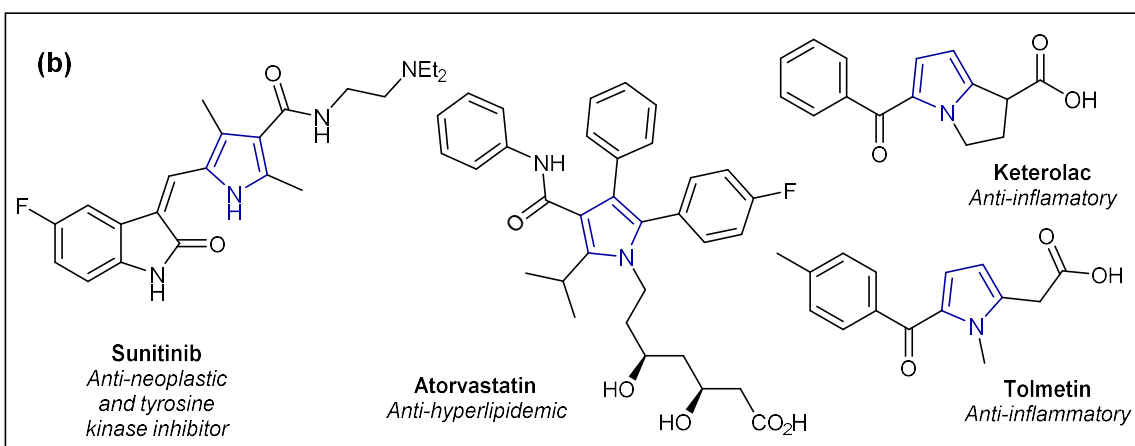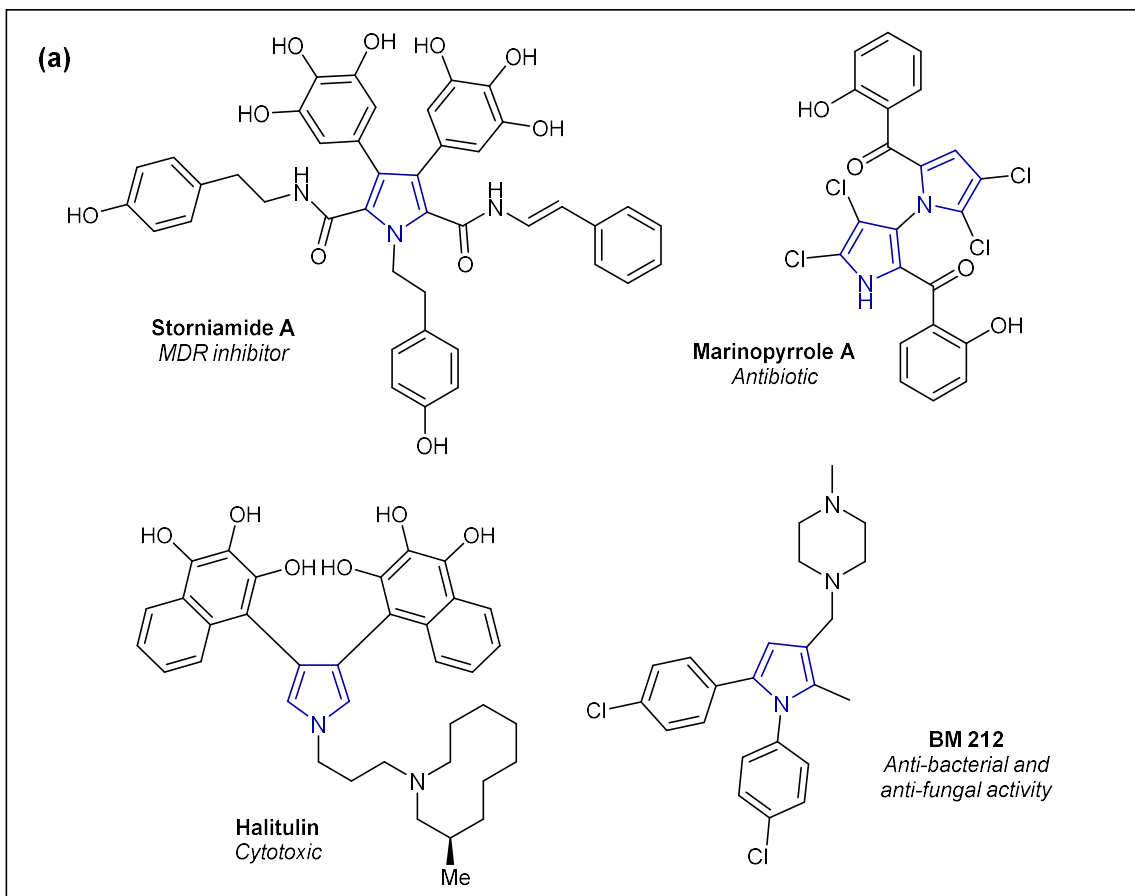
(a)

Storniamide A
MDR inhibitor

Marinopyrrole A
Antibiotic

Halitulin
Cytotoxic

BM 212
Anti-bacterial and anti-fungal activity

(b)

Sunitinib
Anti-neoplastic and tyrosine kinase inhibitor

Atorvastatin
Anti-hyperlipidemic

Keterolac
Anti-inflamatory

Tolmetin
Anti-inflammatory

(c)

BODIPY
dye

Optoelectric polymerised monomers
Conductor

Figure 2: Examples of pyrrole-containing product. (a) Natural products (b) Pharmaceuticals (c) Optoelectrical materials

4.3.   Structure of Pyrrole

Pyrroles have unique chemistry since the nitrogen atom within the pyrrole molecule is sp^2 hybridised, its unshared electron pair occupies *p*-orbitals. Consequently, pyrrole's electron cloud consists of overlapping *p*-orbitals (Figure 3).[2] It is important to recognise that the nitrogen lone pair in pyrrole forms part of this conjugated system; hence it has aromatic character.
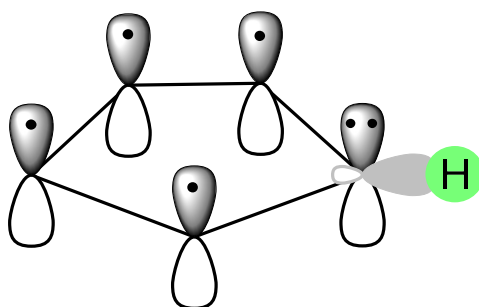

Figure 3: Pyrrole orbital structure

Their aromaticity is not particularly stable, and therefore they react far more rapidly than even electron-rich aromatic rings with substances like air, or acid.[8] This electron structure also means that pyrrole, unlike other amines, is a weak base since its lone pair of electrons is not readily available. They can react with both nucleophiles and electrophiles. The most nucleophilic site is on hydrogen, though an electron-withdrawing group is required for the reaction to take place. Electrophilic attack occurs at C_2 since this is the site of most electron density. The electron-rich nature of pyrroles has a profound effect on ring substituents since they react far more rapidly than other normal arenes.

Pyrrole is electrically different from its carbon-based counterpart due to the presence of nitrogen. Where cyclopentadiene anion has five equivalent contributing structures, in which each carbon is equivalent and so carries one-fifth of the negative charge (Figure 4).
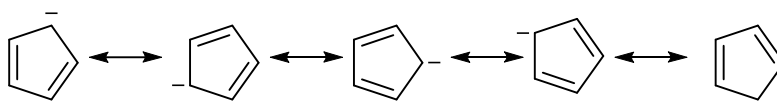

Figure 4: Cyclopentadiene anion resonance

In pyrrole the structure is electrically neutral because of the higher nuclear charge on nitrogen, this means that it does not have five equivalent mesomeric forms: one of its forms has no charge separation, and the other two pairs are equivalent forms in which there is charge separation (Figure 5).[8]

These forms do not contribute equally with the importance being **a > c+e > b+d**.

This produces a notable electron density drift away from the nitrogen towards the ring carbons and is responsible for the dipole moment of the molecule, which overpowers over the inductive effect of nitrogen.[2]
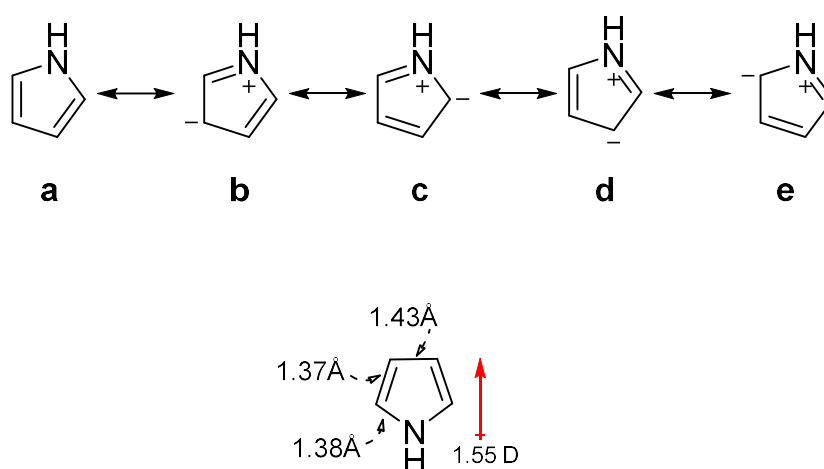

Figure 5: Pyrrole resonance and how it affects bond length and the dipole moment

Pyrrole is referred to as electron rich due to said electronic drift; away from nitrogen and towards the ring carbons. This is due to the mesomeric effect (contribution of the various mesomeric forms shown above), which places partial negative charges on carbon, overpowering the inductive effect of nitrogen to create a dipole directed away from the nitrogen. A consequence of this dipole is that the 3,4 C-C bond is considerably longer (1.43Å) - though still shorter than a single bond - than its counterparts (Figure 5).

4.4. Pyrrole Chemistry

It is essential to comprehend pyrrole's set of reaction mechanisms since they differ from that of benzene. Understanding this chemistry allows us to develop appropriate synthetic routes for more complex products based around the pyrrole scaffold.

Pyrroles are resistant to nucleophilic attack though are very susceptible to electrophilic reactions due to their 'π-excessive' structure. As mentioned previously, they readily polymerise in the presence of a strong acid, meaning that typical aromatic substitution reactions cannot be used. Though, polymerisation can be avoided by the addition of an electron withdrawing group.[8]

Halogenation

Attempts to halogenate pyrroles often result in tetrahalo-pyrroles (Scheme 2, Method B) since pyrroles readily react with halogens, and the fully substituted product is very stable. Under controlled conditions, mono-substitution of pyrrole can take place[8] (Scheme 2, Method A). As with other electrophilic additions, halogenation occurs at the C_2 position, though if a large group is added to the nitrogen (such as TIPS - triisopropylsilyl) halogenation can occur at the C_3 position. This can be a useful method for further functionalization of the less reactive 3-position.

Nitration

Pyrroles can be nitrated by reacting with acetyl nitrate at low temperatures, predominantly giving 2-nitropyrrole[9] (Scheme 2, Method C). The reaction can be directed towards a 3-nitropyrrole by adding a large substituent to the nitrogen (such as triisopropylsilyl), which can be easily removed with TBAF (tetrabutylammonium chloride) (Scheme 2, Method D).

Acylation

The Vilsmeier reaction was developed to carry out acylation without the need of a strong acid, as in Fridel-Crafts. It uses an N,N-dialkyl-chloromethyleneiminium cation, with selectivity for the α position.[2] An iminium salt is formed, which is then hydrolysed to give an aldehyde (Scheme 2, Method F). Again, if a large substituent is added to the nitrogen, the reaction will lose its selectivity and take place on the β position.

Alkylation

Alkylation cannot be carried out by a simple alkyl halide. An acidic catalyst is used – ensuring it does not cause pyrrole to polymerise – together with an alkene carrying an electron-withdrawing group (Scheme 2, Method E). It can be used to incorporate single or double bonds.

N-methylation

Side chains can easily be added to the nitrogen atom in pyrrole by using a halogenated reactant and a catalyst. Shown is the introduction of a simple alkyl group (Scheme 2, Method G). This reaction is not only useful for introducing substituents, but also for protecting the nitrogen on pyrrole. By adding a phenyl substituent we can maintain pyrrole's aromaticity while avoiding any reaction on nitrogen. This reaction is also used when introducing TIPS, a group which due to its volume allows the α-selective reactions to take place on beta.

Reactions with nucleophilic reagents

Pyrroles only react by substitution with nucleophilic reagents when there is a leaving group present on one (or more) of the carbons. An example of this is shown, where the nitrogen has been protected, and there is a nitro group present on both α positions of the pyrrole. In such cases, pyrrole can react with a nucleophilic reagent (Scheme 2, Method H).
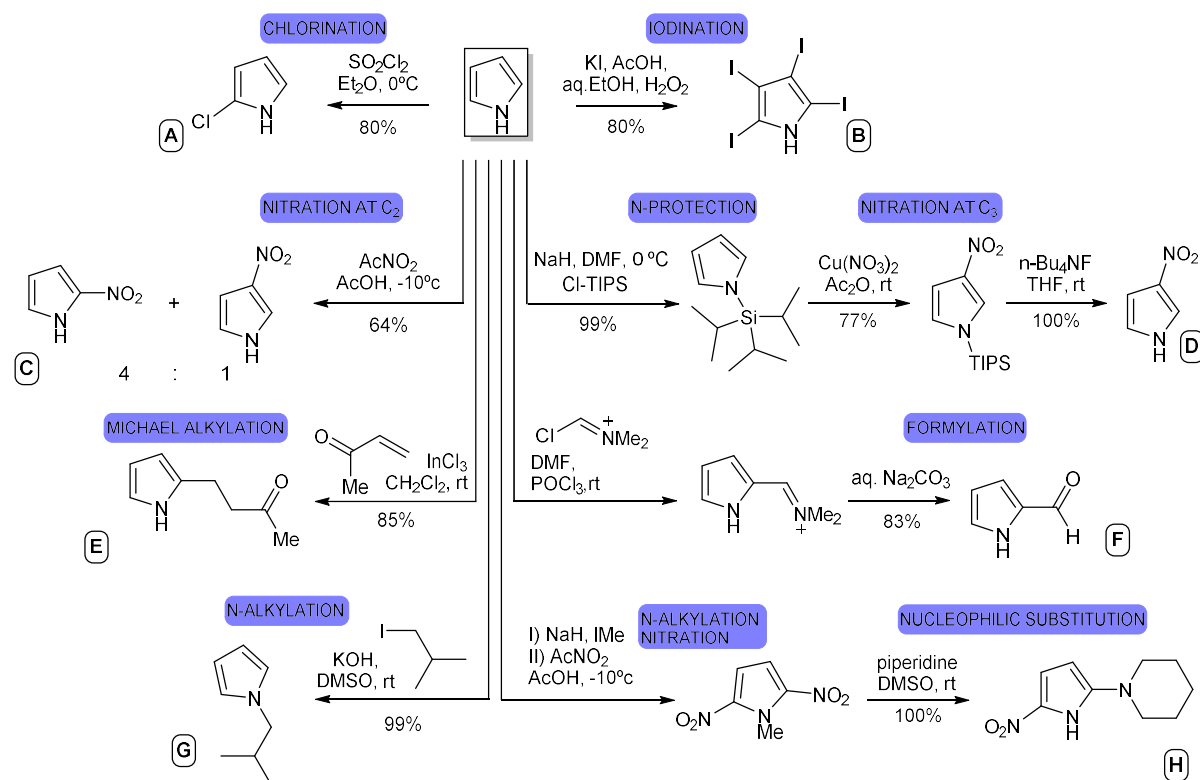
Scheme 2: Common pyrrole substitution reactions

4.5. Methods for the synthesis of pyrroles

A vital part of developing pyrrole-based pharmaceuticals is their synthesis, particularly how to synthesise polysubstituted pyrroles. As we have previously seen, the range of reactions that pyrroles can undergo is limited, so it is often beneficial to incorporate substituents during the synthesis of pyrrole. Figure 6 shows an overview of common pyrrole retrosynthesis, each is a pathway to obtaining polysubstituted pyrroles.
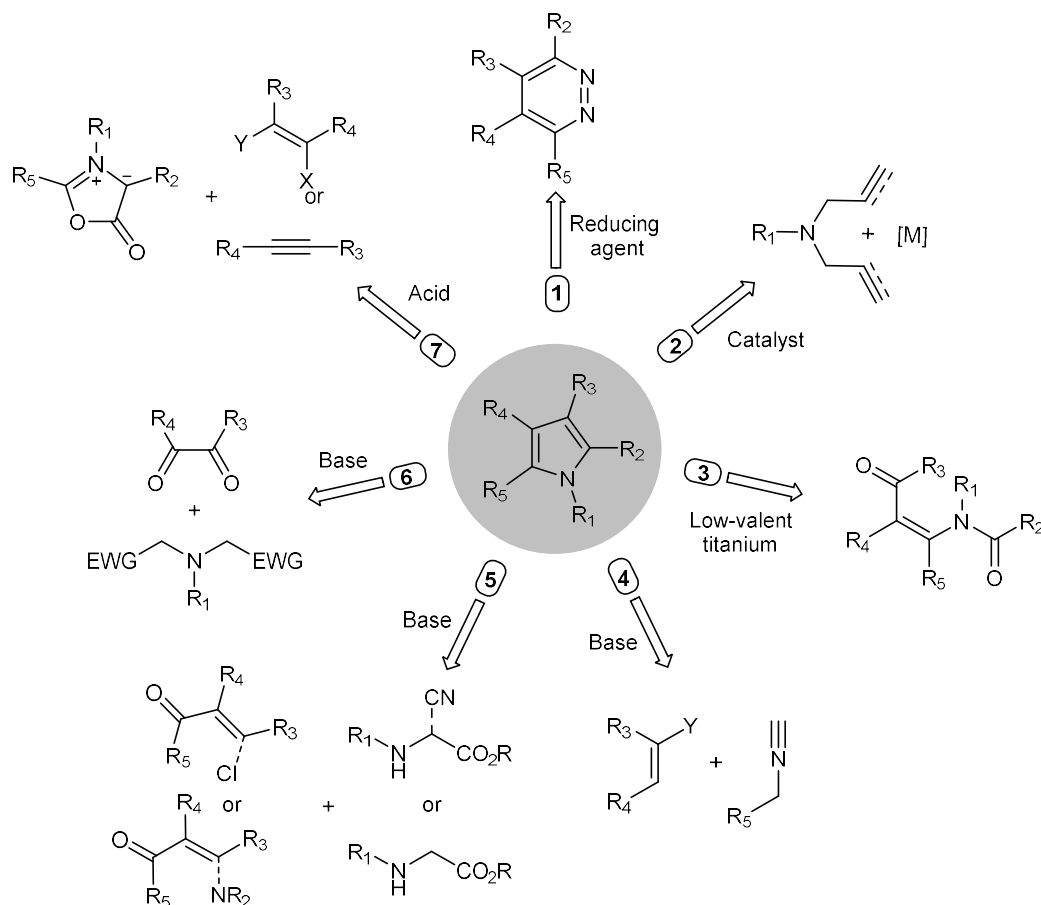

Figure 6: Common retrosynthesis of pyrrole

Figure 6, method 1 is a reductive ring contraction;[10] this is carried out through either chemical or electrochemical reduction. It is essential that pyridazine is substituted, preferably with electron withdrawing groups. Figure 6, method 2 shows a catalyst-led ring closure, the metal involved can be Pd, Ru or Ir.[11] Figure 6, method 3 is a McMurry-type coupling,[12] using low-valent titanium, the carbonyls are reduced to alkenes. All substituents must be hydrogen or carbon-based, except R_2 where an amine or ether is also possible. Figure 6, method 4 depicts two possibilities; the first van Leusen synthesis[13] where R_5 is Tos (a toluenesulfonyl group), and Y is hydrogen.[13] A later development of this reaction is Barton-Zard,[14] where R_5 is any substituent and Y is a nitro group. Figure 6, method 5 is a converging coupling[15] of an enone and a secondary amide. Figure 6, method 6 depicts a Hinsberg type reaction,[16] under basic conditions, pentasubstituted symmetrical pyrroles are formed. Figure 6, method 7 is based on the cycloaddition of münchones[17] (1,3-oxazolium-5-ones) to alkenes or alkynes.

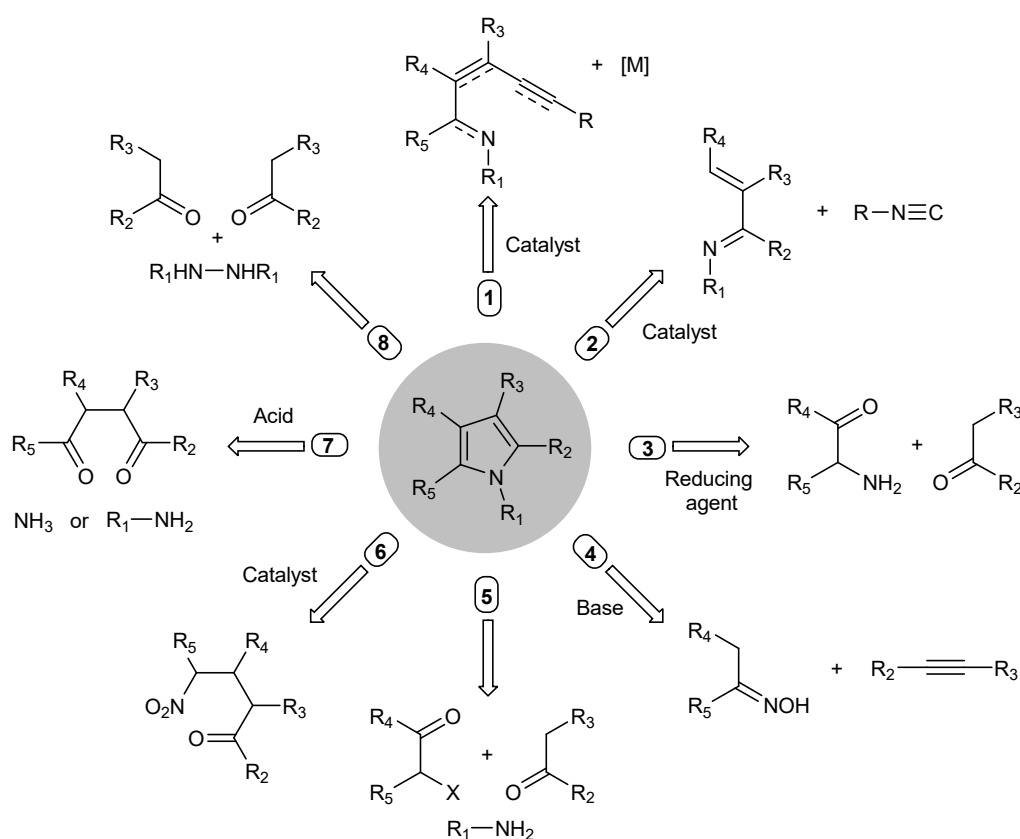Figure 7 shows the synthesis of pyrroles based on 1,4-dicarbonyl.

Figure 7: Retrosynthesis of pyrrole based on 1,4-dicarbonyl

In Figure 7, method 1 we see how various combinations of double or triple bonds can easily be converted into pyrrole using a metallic catalyst,[18] such metals include Au, Pd, Ir, or Cr. Figure 7, method 2 is the addition of isocyanide to 1-azabutene[19] and requires $AlCl_3$, this reaction is useful when forming 2-aminopyrroles. Figure 7, method 3 shows Knorr pyrrole synthesis,[20] a method commonly used; it consists of the condensation of α-aminoketone with a ketone. Trofimov pyrrole synthesis[21] is shown in Figure 7, method 4, this synthesis has the same disconnection as Knorr but instead uses ketoximes and alkynes to give 4,5-substituted pyrrole, in the presence of a strong base. Figure 7, method 5 is Hantzsch pyrrole synthesis[22] and it is the condensation of α-haloketones or aldehydes with β-ketoesters. Figure 7, method 6 is the nitro Michael approach.[23] Though typically used to form indoles, this method has been used to produce polysubstituted pyrroles. It involves intramolecular cyclization of γ-nitroketones. Paal-Knorr,[24,25] shown in Figure 7, method 7, involves an acid-catalysed condensation of ammonia or a primary amine with 1,4-dicarbonyl compounds, this is the parent compound for all the reactions shown in Figure 7. Finally, Figure 7, method 8 shows the Piloty-Robinson synthesis[26] where two equivalents of a ketone or aldehyde are reacted with hydrazine, producing a symmetrical polysubstituted pyrrole, where R_2 and R_3 are the same as R_5 and R_4 respectively.

Knorr pyrrole synthesis

Initially reported in the late 1800s this widely used reaction consists of the condensation of an α-aminocarbonyl with a ketone or ketoester[20] (Scheme 3), this second component must possess a methylene group alpha to a carbonyl. A reducing agent, such as Zinc-acetic acid, is required. One issue with this method is the α-aminocarbonyl tendency to self-condensate, a way of avoiding this is by preparing them in the presence of the second component, often using the relevant oxime. Several variations of this mechanism have been developed to improve on issues associated with it such as, its lack of regioselectivity with unsymmetrical beta-diketones, often symmetrical beta-diketones are used.
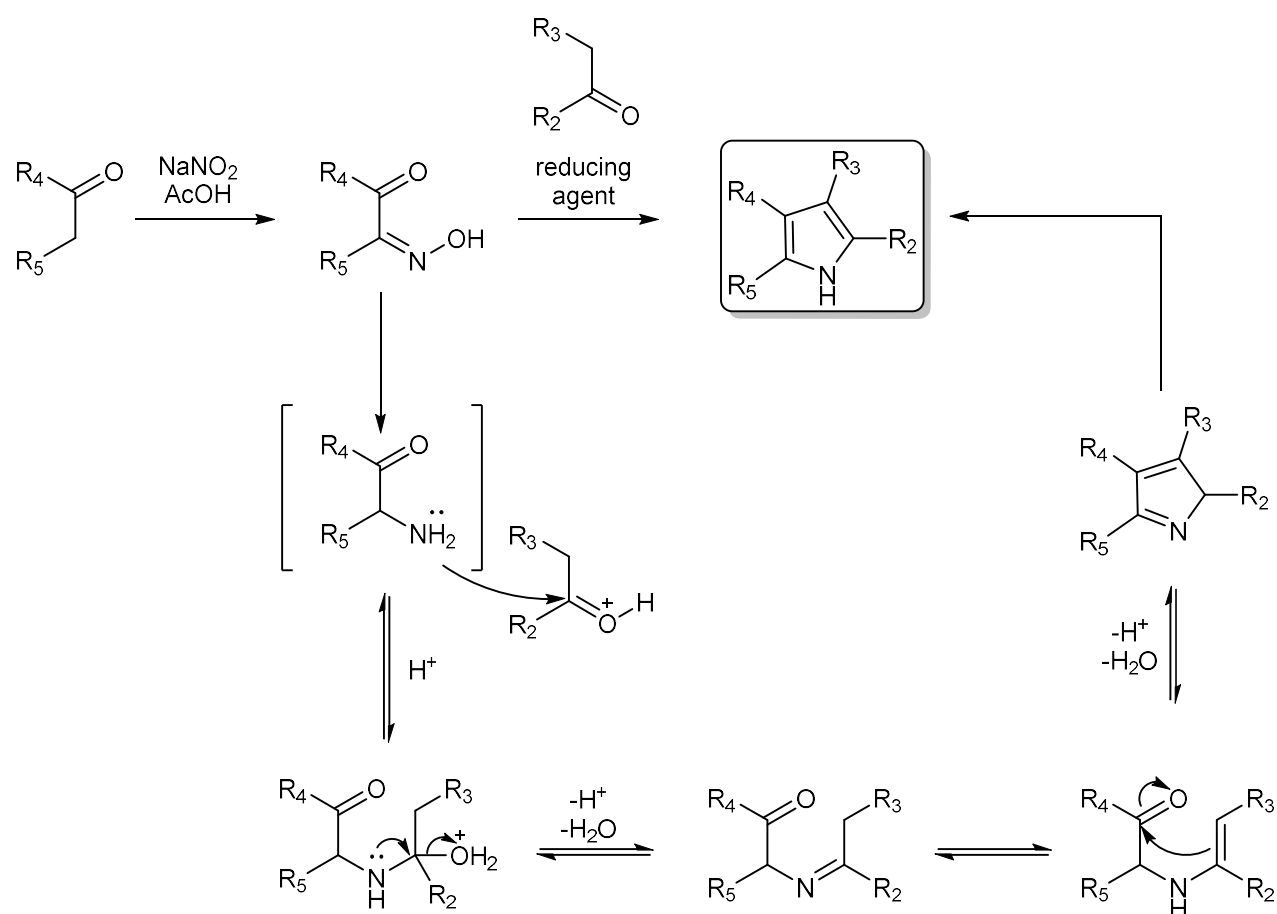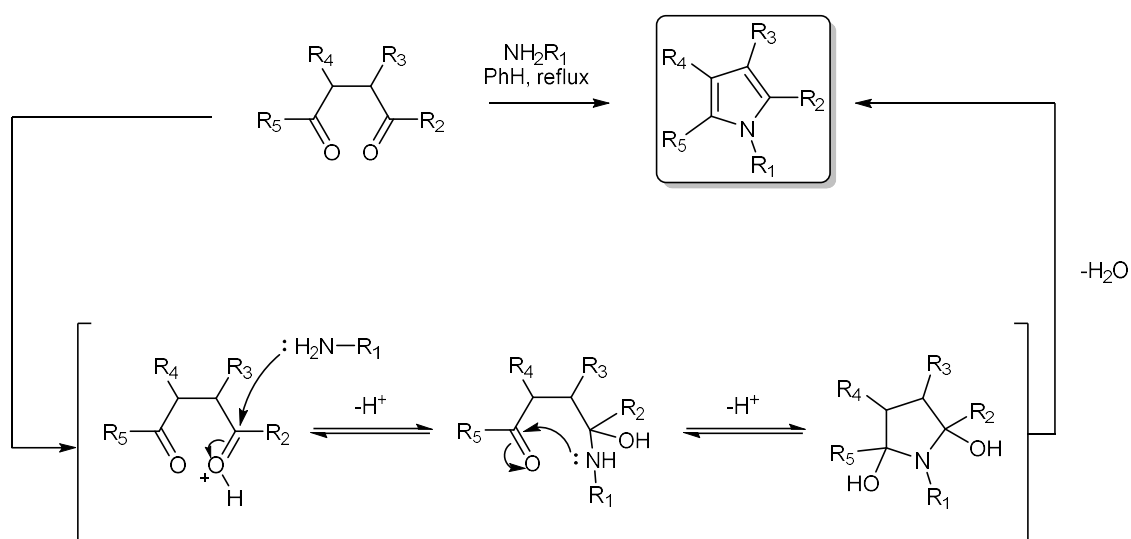

Scheme 3: Knorr pyrrole synthesis

R_4 must be an alkyl or aryl, and R_5 can be H, aryl or carboxylic acid. R_3 must be an electron withdrawing group (such as an ester), and R_2 may be H, alkyl, aryl or CO_2R.[15] The initial carbonyl is reacted with a nitro group to give an oxime; this is to introduce nitrogen, while also avoiding self-condensation. The oxime is reduced to give the initial α-aminoketone. The amine attacks the carbonyl on the second component, condensing to give an imine. The imine tautomerizes to an enamine, which is then cyclized, and water eliminated. Finally, the electron structure is rearranged so that the aromaticity of pyrrole is established.

Paal Knorr Synthesis

This synthesis involves the reaction of ammonia or a primary amine with a 1,4-dicarbonyl compound, via an acid catalysed condensation.[24,25] It yields a polysubstituted pyrrole. The method was initially reported in 1884 though its mechanism was not understood until the 1990s.[27] There have been several variations to this synthesis, improving its speed and regioselectivity. An alternative to using ammonia is hexamethyldisilane on alumina, or ammonia can be produced in-situ using magnesium nitride in methanol.


Scheme 4: Paal-Knorr synthesis

This reaction allows the substitution of the nitrogen in pyrrole, in the R_1 position either an alcohol or any carbon-based substituent can be introduced. If ammonium hydroxide is used, an N-unsubstituted pyrrole will be produced. As for the other R groups, R_2 and R_5 must be either hydrogen or carbon-based, whereas R_3 and R4 can be either of these as well as a carboxylic acid derivative. The amine attacks one of the carbonyls, this product then undergoes dehydration which gives the polysubstituted pyrrole.

Hantzsch pyrrole synthesis

This method allows the synthesis of an ester-substituted pyrrole.[22] Initially, it was reported that this was the only substitution that could take place, but it has been demonstrated that through this method R_4 and R_5 can also be added. In this scheme, an equimolar mixture of a β-ketoester (or β-diketone) and an α-haloketone or aldehyde are refluxed in the presence of aqueous ammonia. The ester is converted into an enamine, which then reacts with the ketone.

An amine can be used instead of ammonia, to give an N-substituted pyrrole but this produces a very low yield, and so it is not frequently used.
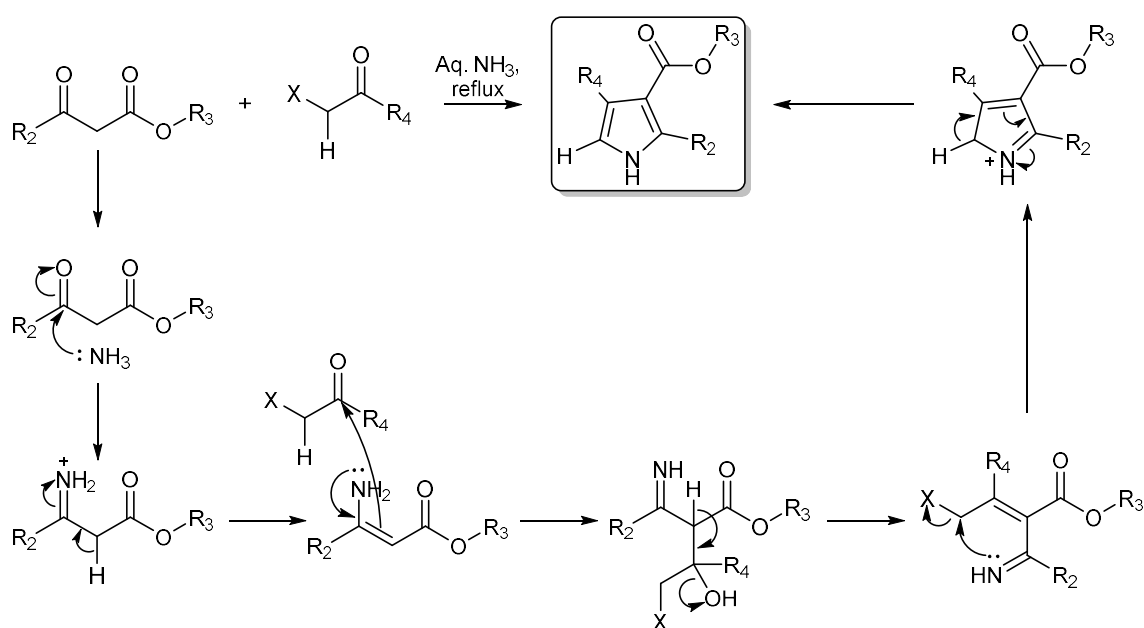

Scheme 5: Hantzsch synthesis

The amine (NH_4) attacks the β-carbon of the ketoester, forming an enamine. The enamine then attacks the carbonyl of the second component. The loss of water produces an imine, this undergoes an intramolecular nucleophilic attack, removing the halogen and closing the ring. There is a rearrangement of electrons, finally yielding the substituted pyrrole.

Barton-Zard Reaction

This route leads to a polysubstituted pyrrole with a ketone on C_2. It is an expansion on the van Leusen synthesis. It comprises of the reaction of a nitroalkene with an α-isocyanoacetate ester under basic conditions.[14] The non-nucleophilic base involved can be KOtBu, DBU or guanidine bases. The nitro group activates alkenes, leading them towards Michael addition and making them good leaving groups.
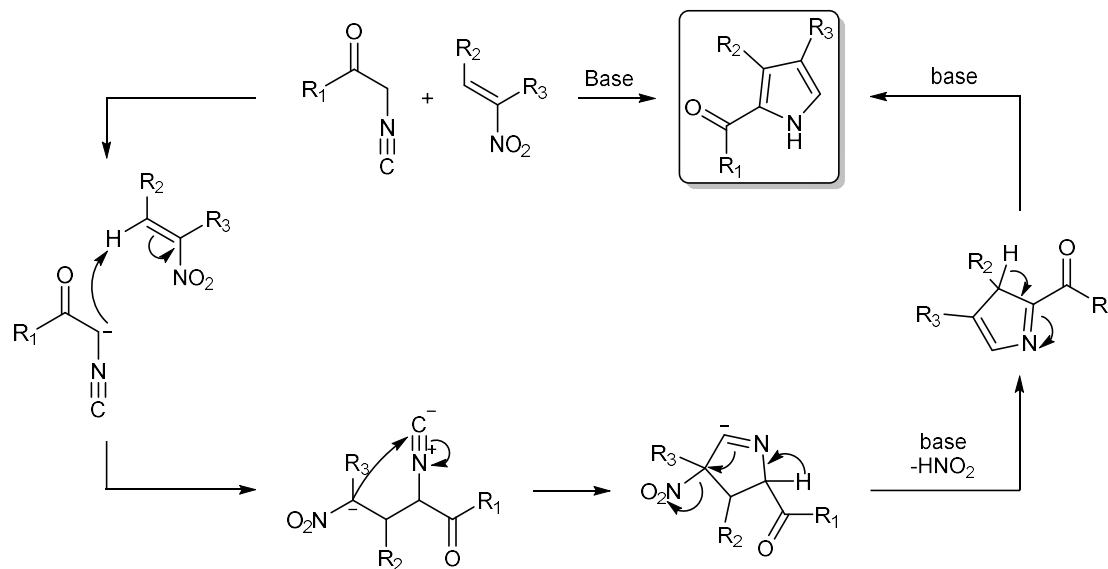
Scheme 6: Barton-Zard Reaction

The reaction is divided into five steps; first, the α-isocyanoacetate is enolised, which allows the Michael-type addition of the nitroalkene. Next, there is an intramolecular cyclization, with the base catalysing the elimination of the nitro group. Then there is a rearrangement of electrons, finally yielding the aromatic substituted pyrrole.

4.6. Pyrrole containing medicinal compounds

Atorvastatin

Atorvastatin (Figure 8) is an inhibitor of HMG CoA reductase, an enzyme involved in the synthesis of cholesterol in mammals. The inhibition of this enzyme leads to a reduction in total cholesterol levels and therefore is useful in the prevention of heart disease. Atorvastatin is part of a much larger groups of statins – all inhibitors of HMG CoA reductase – though they all have very different chemical structures, their commonality being an opened-lactone (shown in blue). Within this group of statins, atorvastatin is the most prescribed due to its lower incidence of serious side-effects.[28]

- Antihyperlipidemic
- HMG CoA reductase inhibitor
- Statin
- Commercialised in 1996
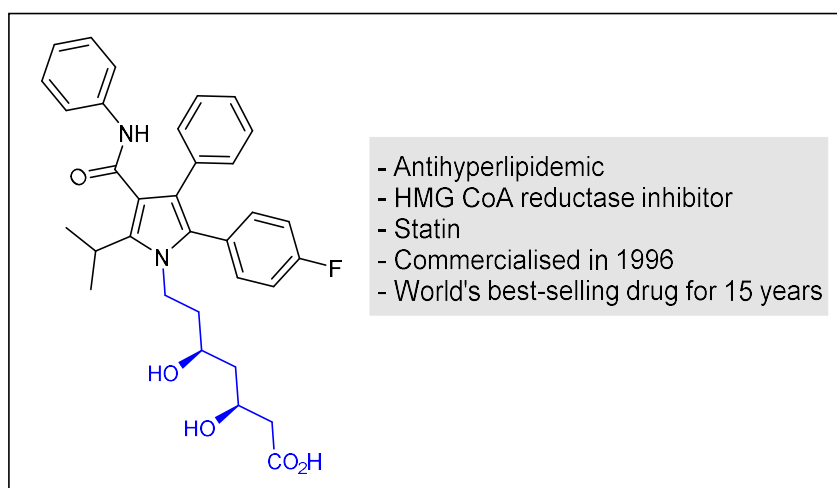- World's best-selling drug for 15 years

Figure 8: Atorvastatin   Figure 9: Compactin
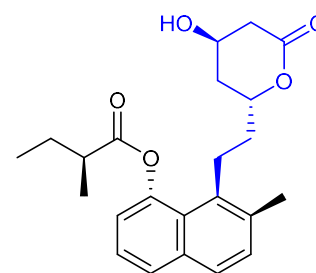
Atorvastatin was first commercialised as Lipitor® by Pfizer in 1996. From its release till the end of its patent, Lipitor® broke records by becoming the world's bestselling pharmaceutical of all time, amassing roughly $125 billion in sales over almost 15 years.

The drug is based on a fungal metabolite named compactin (Figure 9). The potential use of this metabolite was known as the first statin was already on the way to market. With structure-activity studies, the Warner-Lambert company found that 3- and 4- substituted pyrroles had an increased potency compared to classical 2- and 5- substituted pyrroles.[29] The only structure that is conserved from the original lead molecule is the lactone (shown in blue). Within statins, there are several heterocycles, but atorvastatin is the only to contain a pyrrole structure.

Substituted pyrrole rings by $ZnCl_2$-catalysed condensation reactions were limited when trying to synthesise more complex structures such as atorvastatin. Through several trials, it was

found that creating the central pyrrole scaffold then adding the necessary side chain was the most effective synthesis.

Initially, a [3 + 2] cycloaddition of an acetylene component with an amino acid was tested, but this led to an undesired isomer, with the undesired regioisomer being the favoured product (4:1) causing a very low yield. However, by carrying out the analogous reaction and starting with a fluoride substituted phenyl (Scheme 7), instead of an iso-butyl group on the amine structure, led to a completely regiospecific product, though it still gave a moderate yield.[30]
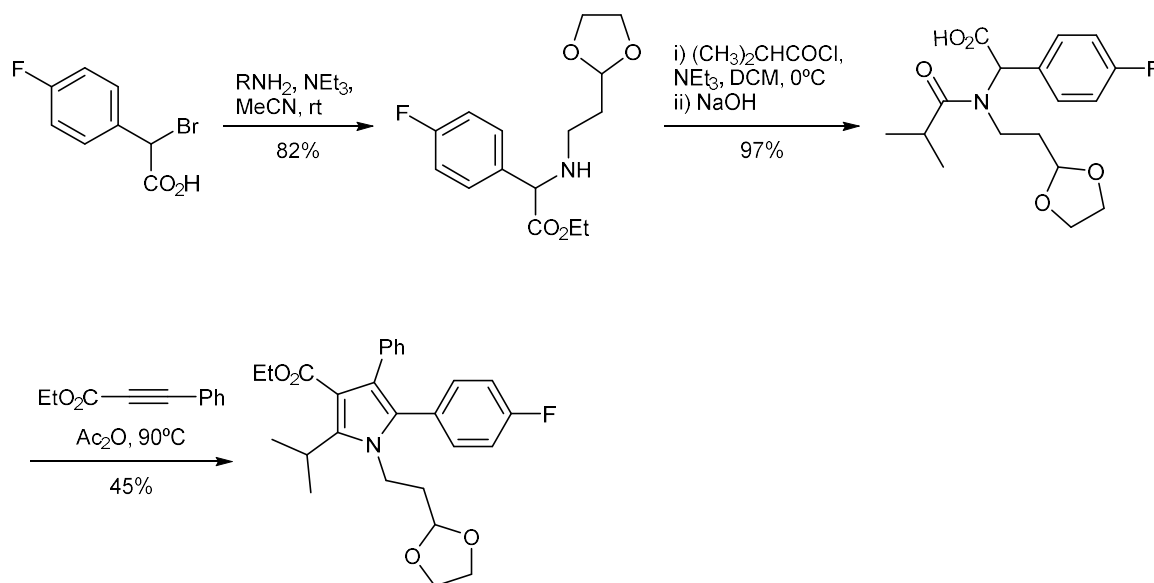

Scheme 7: Synthesis of pyrrole nucleus via [3+2] cycloaddition

By modifying the last step to create a münchone, it was easier to establish the desired regiospecific structure so that a side chain could be synthesised and added. By adding nitrogen, the pyrrole base becomes complete, even though it still produces a low yield[30] (Scheme 8).
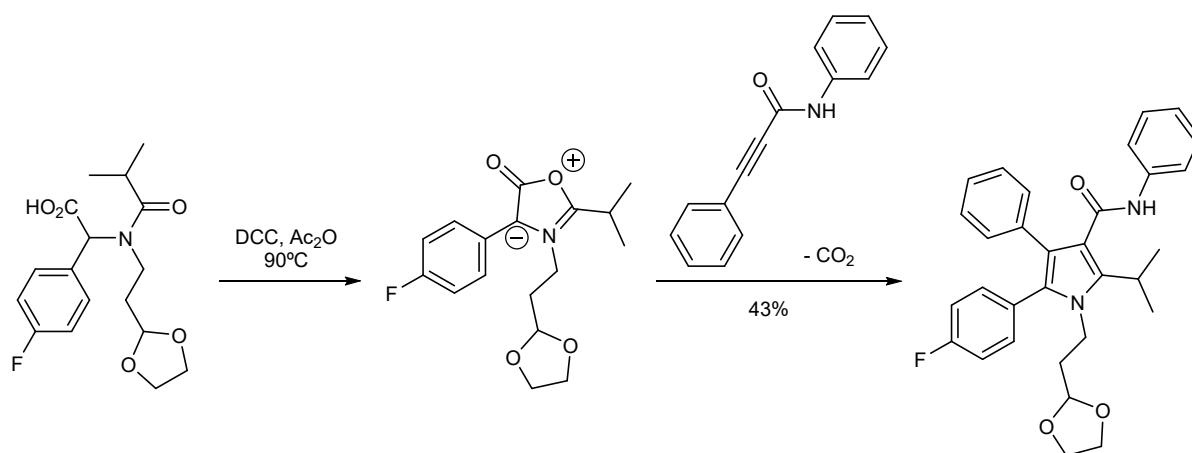

Scheme 8: Addition of sidechain after [3+2] synthesis

A few years after the initial patent, a second patent was issued to synthesise the pyrrole scaffold using a different approach (Scheme 9). This new method is based on the Paal–Knorr synthesis previously mentioned, first, the substituted 1,4-diketone is set up through condensation and alfa-substitution. Following on from this a substituted amine is introduced, and the remainder of the scaffold constructed. Lastly, the structure is refluxed with toluene under mildly acidic conditions where the pyrrole is formed with a much more desirable yield.
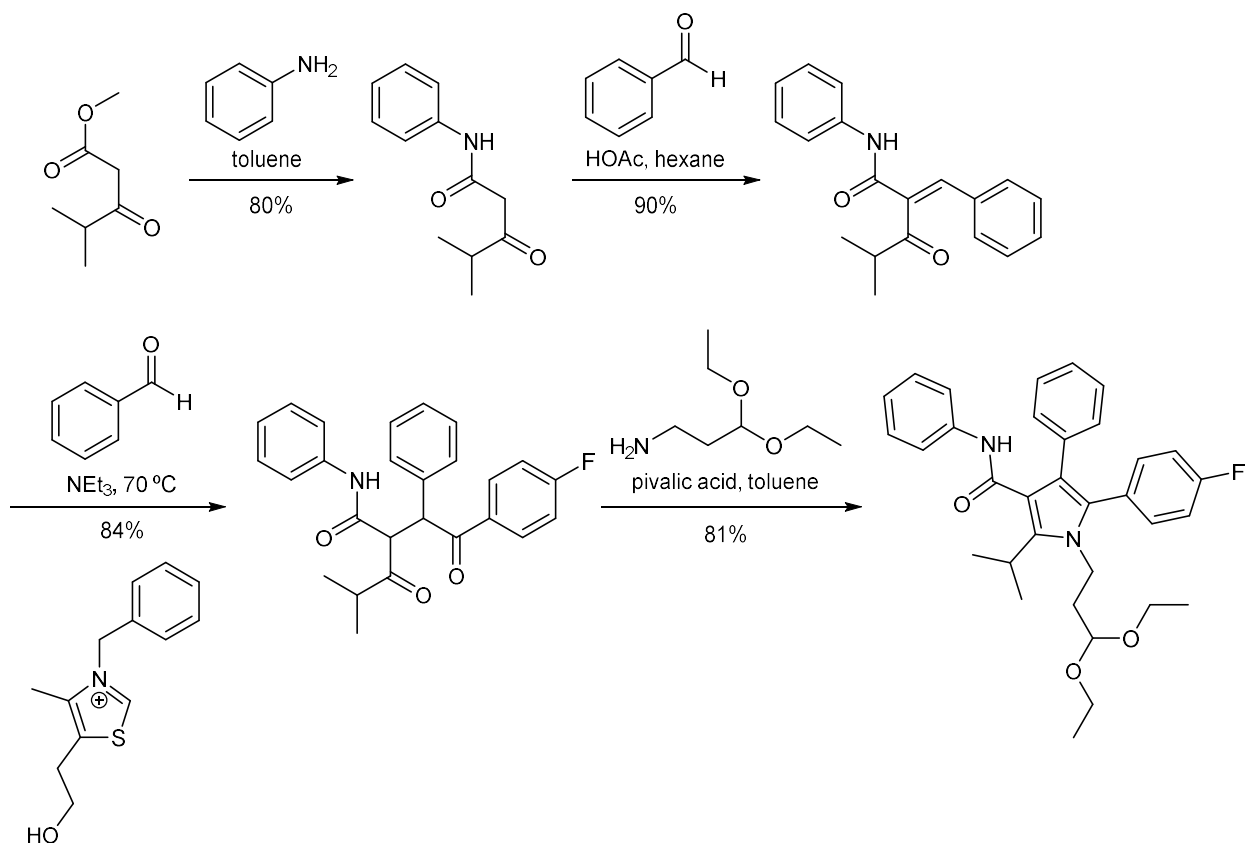
Scheme 9: Actual synthesis of atorvastatin

To further improve the yield the last step was altered so that the side chain can be added (Scheme 10). The side chain is synthesised via fermentation since this gives the required stereochemistry. Once the final structure is obtained the acetal is cleaved to give two alcohols, the tert-butyl chain is removed, and the calcium salt is formed.
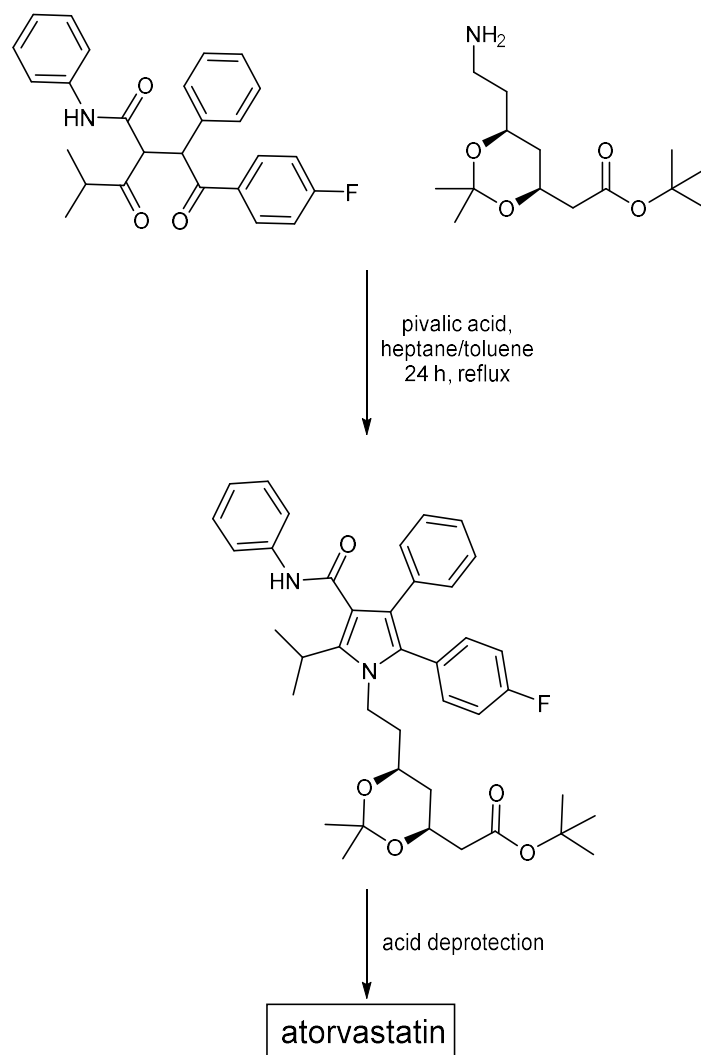
Scheme 10: Synthesis of atorvastatin via Paal-Knorr

Sunitinib

Sunitinib (Figure 10), commercialised as Sutent®, is a multi-targeted tyrosine kinase (RTK) inhibitor used for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumour (GIST);[31] it is considered a second-line treatment.

- Antineoplastic
- Tyrosine kinase inhibitor
- Second-line treatment
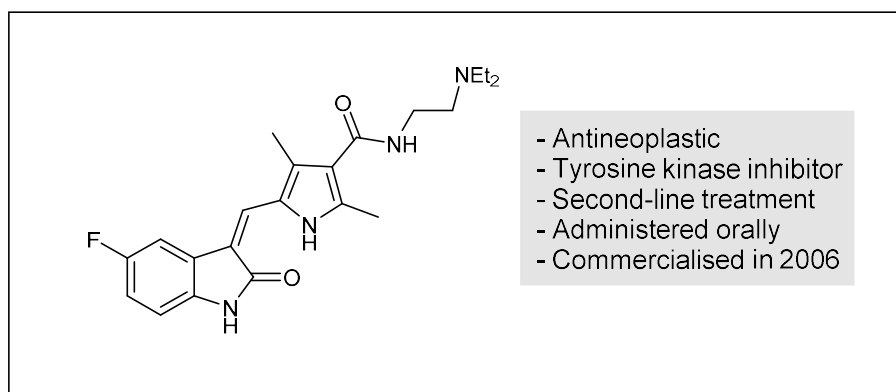- Administered orally
- Commercialised in 2006

Figure 10: Sunitinib

Tyrosine-kinase receptors are high-affinity cell surface receptors found throughout the human body. This includes platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs) the inhibition of these targets reduces tumour vascularisation, resulting in apoptosis and so tumour shrinkage.[31] Since sunitinib produces tumour shrinkage it is useful in increasing life expectancy though it is not able to eliminate the tumour - hence it is not a cure. One of the advantages of sunitinib is its route of administration since it is an oral drug; it can increase the quality of life as it does not require hospitalisation for its administration. Since it is multi-targeted with low specificity it is associated with many side effects, though these are considered to be manageable.[32]

Sunitinib consists of a complex pyrrole-substituted 2-indolinone core. It is synthesised by nitrosation of tert-butyl acetoacetate, producing an oxime which is then reduced by zinc to give an unstable aminoketone intermediate, which allows for a Knorr pyrrole synthesis. An imine is produced, tautomerized and consequently cyclized to produce the substituted pyrrole scaffold. The tert-butyl ester is then removed to yield the fully elaborated pyrrole aldehyde. From here an aldol condensation between the pyrrole scaffold and a 2-indolinone fragment is carried out. Lastly, ester hydrolysis and amide formation complete the synthesis (Scheme 11).[30]
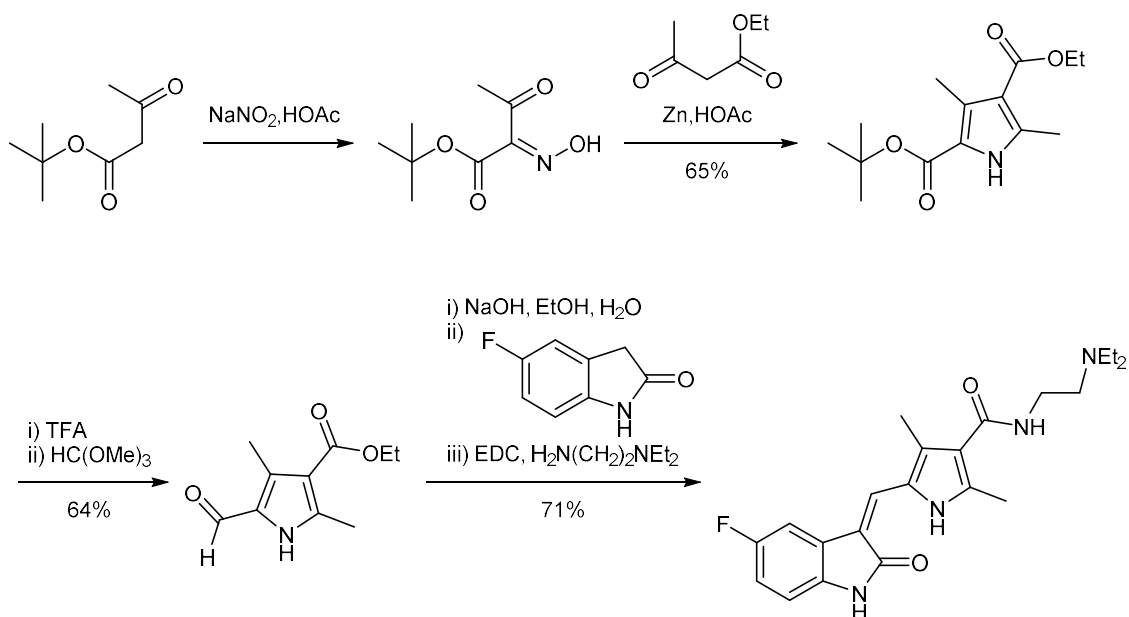
Scheme 11: Synthesis of sunitinib

An alternative synthesis proposed by Pfizer, which produces a higher yield, is shown below. It introduces the amide side chain earlier since it is based on the starting reactant of the synthesis. Said reactant is a substituted oxetane, with a carbonyl and an alkene group. This is reacted with N,N-diethylethane-1,2-diamine, resulting in a β-ketoamide. The pyrrole is then formed, again using the Knorr synthesis as seen in Scheme 12. Deprotection and decarboxylation of the remaining tert-butyl ester produce the desired pyrrole intermediate, which using Vilsmeier reagent undergoes a formal acylation. This intermediate is immediately reacted with a 2-indolinone fragment[30] (same reactant as seen above) to give sunitinib.
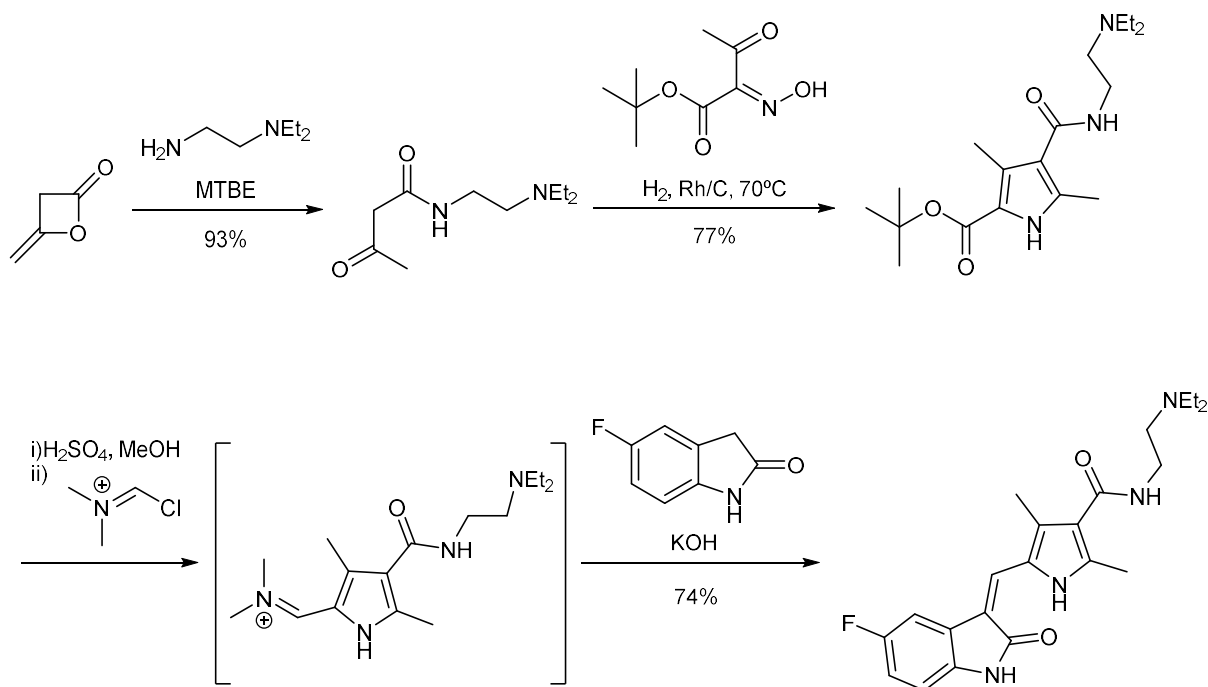
Scheme 12: Alternative synthesis of sunitinib

Ketorolac

Ketorolac (Figure 11) is a short term NSAID (a non-steroidal anti-inflammatory drug) and is usually not prescribed for longer than five days. It is mostly used for its analgesic effect, treating acute moderate to severe pain. Its analgesic potency is similar to that of opioids though does not cause respiratory problems; therefore it is useful in neonatal pain control.[33] The biological activity of ketorolac tromethamine is associated with the S-form. It is an inhibitor of both cyclooxygenase-1 (COX-1) and cyclooxygenase 2 (COX-2).[34]

- Non-steroidal anti-inflammatory
- Strong analgesic effect
- Systemic, nasal or opthalmic
- One of the first intravenous NSAID
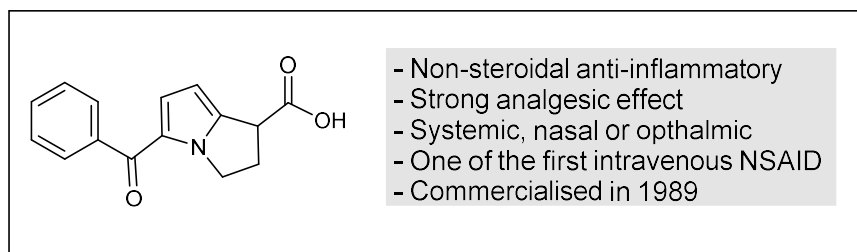- Commercialised in 1989

Figure 11: Ketorolac

As well as being a systemic analgesic it is also used in ophthalmology, aiding to maintain mydriasis so that cataract surgery can be carried out. It can also be used for pain associated with corneal abrasions.[35]

Ketorolac can only be used for short periods due to its increased risk of causing kidney damage.[34] In high-risk patients, this drug should be avoided (such as patients over 65 years old).

Unlike other pyrroles we have seen, ketorolac is a much simpler molecule with fewer substitutions meaning that more traditional methods of synthesis can be used. It is crucial that the benzoyl group be introduced towards the end of the sequence to prevent electrophilic reactions to the C_4 position of the pyrrole. The carboxylic acid will also need to be protected since it is very reactive.

The sequence below is an example of the reaction which is described in the original patent of ketorolac, assigned to Syntex (USA) Inc.[36]

In this the starting reactant is pyrrole (Scheme 13), this is converted to a pyrrole Grignard reagent using an alkyl-magnesium halide. The resulting reactant is combined, in excess, with a dihalobutanamide, this is a simple substitution reaction. The resulting product, pyrrolylbutanamide, is then cyclized with a quaternary amine salt catalyst and is obtained by crystallisation with water. A modified Vilsmeier-Haack arylation is carried out, enabling the addition of the second benzene. This product is obtained by acidification. Finally, the ketorolac amide is hydrolysed to ketorolac and isolated by acidification.[36]
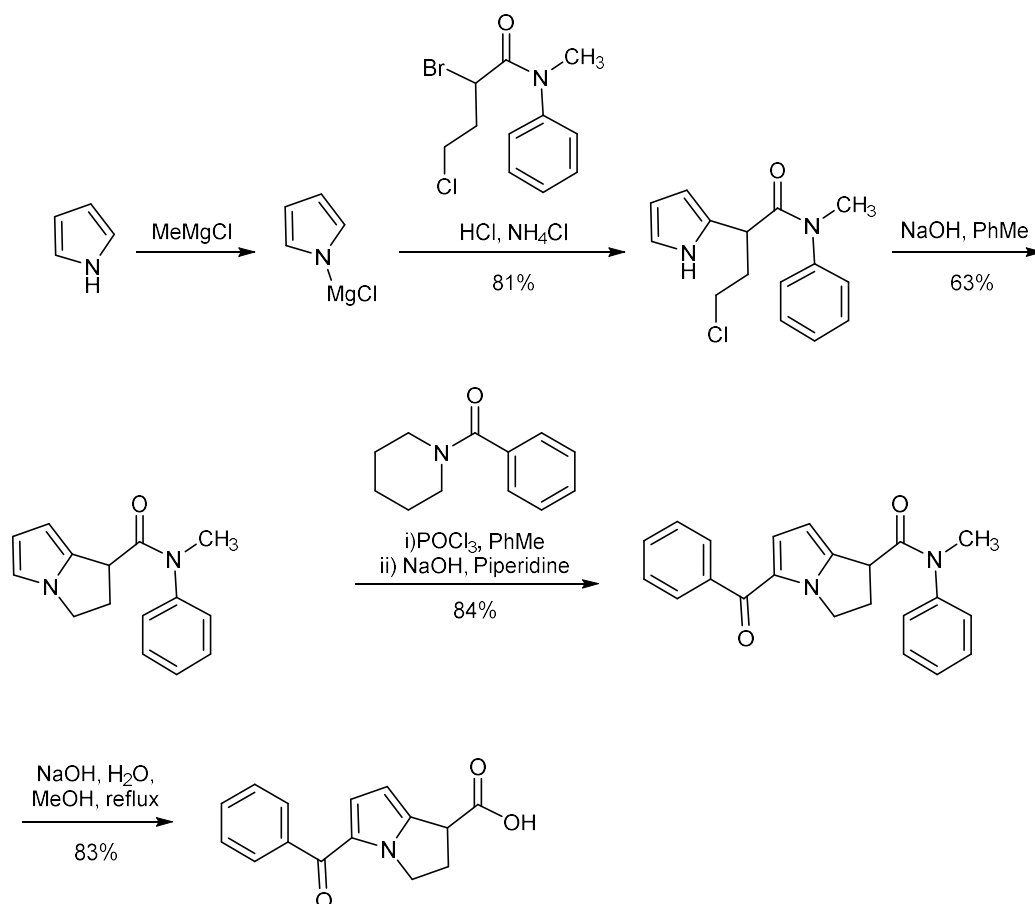
Scheme 13: Synthesis of ketorolac

The dihalobutanamide side chain is available commercially or can be incorporated as a previous step to the synthesis of ketorolac. An N-alkyl-arylamine is treated with a 2-bromo-4-chlorobutanoyl bromide in the presence of a tertiary amine base and an organic solvent (Scheme 14). It is then isolated and used in the previous reaction, with or without further purification.[36]
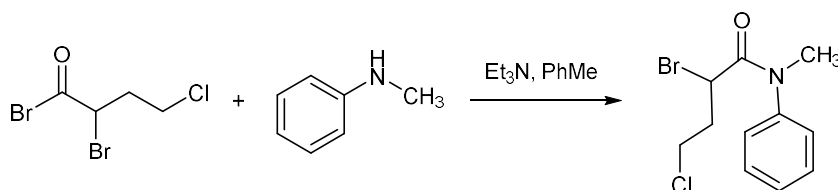
Scheme 14: Synthesis of ketorolac side chain

5. CONCLUSION

The pyrrole ring system is a key feature in many products, ranging from anti-hyperlipidemic pharmaceuticals, to basic biochemical structures for photosynthesis, to fluorescent dyes, to marine life metabolites. The diversity of these properties shows such a wide range that pyrrole is an attractive structure when developing new chemical entities.

In this work an overview of key components of pyrrole structure, chemistry and synthesis have been highlighted and discussed. From this work a basis is built to be able to apply said methods to new compounds and be able to effectively synthesise pyrrole.

The application of key chemistry components has been highlighted in the context of the synthesis of three important pharmaceutical products. Firstly, atorvastatin, a very profitable drug whose synthesis is based on the Paal-Knorr mechanism. Sunitinib, an effective neoplastic drug following the Knorr synthesis. Finally, ketorolac a potent analgesic which is synthesised following basic substitution methods to create a molecule of much greater complexity.

From this work, we can ascertain not only pyrrole's chemistry and reactions but also the importance of thoroughly understanding the structures uses before being able to apply it to new chemical entities.

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