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Revisiting Nitroaromatic Drugs: Mechanisms of Bioactivation, Metabolism and Toxicity and Methods to Synthesize Nitroaromatic Fragments

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Nitroaromatic drugs represent an important class of therapeutic agents, endowed with different pharmacological properties such as antibacterial, antiprotozoal, anti-Parkinson, anticancer, etc. However, the nitroheterocycle and nitroarene fragments are considered potentially toxic, with reports of mutagenicity and genotoxicity. The bioreduction process of the nitro group plays a central role in the antimicrobial and toxicological mechanism of action of nitroaromatic drugs. This article will review the nitroaromatic drugs approved by the Food and Drug Administration (FDA) in the last 30 years, the mechanisms of bioactivation, metabolism and toxicity and, finally, it will revisit the main methodologies for obtaining the nitroaromatic fragment from aromatic nitration reaction and oxidation of arylamines and/or heteroarylamines.

Keywords: nitroarene, nitroheterocycle, FDA, bioreduction, aromatic nitration reaction, aryl/heteroarylamine oxidation

1. Introduction

The nitro substituent (R–NO_2) is a functional group widely used in the design and synthesis of bioactive compounds. It is characterized by the presence of a tetravalent nitrogen, with zero formal charge, linked through a single bond to an alkyl or aryl group, a double bond to an oxygen atom and another single bond to a second oxygen atom. This ends in a positive charge centered on the nitrogen atom (N) and a negative charge centered on the oxygen atom (O). Therefore, NO_2 is a particularly electron-withdrawing group since the N has no lone pair (Figure 1). The nitro group properties are associated with its high electron-withdrawing ability, by means of both resonance and inductive effect. The substituent effect of the nitro group may be well described using either traditional Hammett substituent constants (NO_2 σ_p = +0.78 and σ_m = +0.71) or characteristics based on quantum chemistry. Aromatic compounds substituted with nitro group are substrate to nucleophilic aromatic substitution. They are usually divided into two subclasses: nitroarenes and nitroheterocycles. From the medicinal chemistry point of view, the electron-withdrawing ability, polarity, size, facility to form hydrogen bonds and redox properties of nitro group linked to an aromatic fragment have an impact on its polarity, aqueous solubility, receptor binding affinity, cellular uptake, bioavailability, and toxicity.[2-6] In fact, the introduction of the nitro group as a substituent on a benzene ring (**1**-**2**; Figure 1) or on heterocycle rings (**3**-**7**; Figure 2) results in an increase in lipophilicity, polarizability, dipole moment, area and volume and a decrease in lowest unoccupied molecular orbital (LUMO) energy. Although nitroaromatics have various industrial claims, such as explosives, herbicides, pesticides, dyes, and medicines, it is in the pharmaceutical sector that the main examples of biological applications for this class of chemical compounds are found.[5]

In this review article we will look at drugs whose structure contains the nitroaromatic fragment, focusing on

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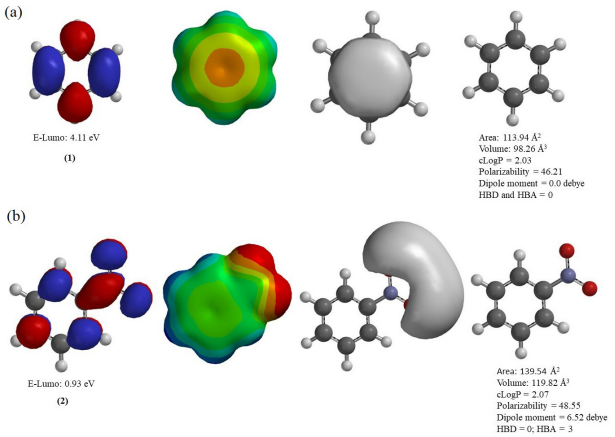


Figure 1. The benzene (**1**) and nitrobenzene (**2**) were drawn in the Spartan 14 program[1] and the equilibrium geometry was calculated with Hartree-Fock 3-21G. The electrostatic potential map, lowest unoccupied molecular orbital (LUMO) and potential surfaces was determined. Comparative area, volume, cLogP, polarizability, dipole moment, number of hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) was calculated to each fragment, as well as their E-LUMO. From left to right is shown the LUMO surface, electrostatic potential map, potential surface, and physicochemical properties. (a) Benzene; (b) nitrobenzene.

those approved by Food and Drug Administration (FDA) in the last 30 years. The mechanisms of bioactivation, metabolism and toxicity of these nitroheterocycle and nitroarene bioactive compounds will be discussed and the main methodologies for nitroaromatic fragments obtainment, based on aromatic nitration reaction and oxidation of arylamines and/or heteroarylamines, will be reviewed.

2. Nitroaromatic as Drugs

As anticipated during the Introduction section, the differences in electronic density induced by the nitro group attached to an aromatic ring provide favorable conditions for the interaction of nitroaromatics with biological receptors, specifically proteins, nucleic acids, and enzymes present in living systems. This interaction may induce intended or unintended biological alterations, achieved through mechanisms such as nucleophilic addition, electron transfer involving oxidation and reduction, or molecular complexation,[7] that justify the long-lasting utilization of nitro group-containing pharmaceuticals for anti-inflammatory,[8] anti-parasitic,[9] anti-tumor,[10] and antibacterial[11] activities.

To gain a broad overview of the drugs approved for use in humans that contain nitroaromatics in their structures, a thematic search was conducted on online and free database platforms, namely DrugBank[12] and ChEMBL.[13] For both databases, the search was performed using the chemical structure drawing tool Marvin Js.[14] In this tool, the nitro group was drawn in isolation to encompass both nitroaryls and nitroheteroaryls, excluding structures where this

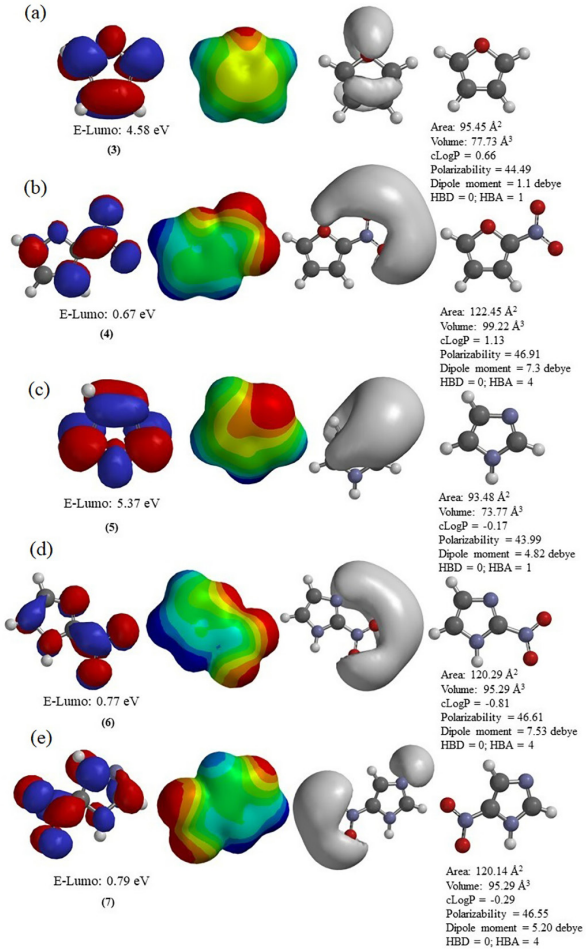


Figure 2. The fragments 3-7 were drawn in the Spartan 14 program[1] and the equilibrium geometry was calculated with Hartree-Fock 3-21G. The electrostatic potential map, lowest unoccupied molecular orbital (LUMO) and potential surfaces was determined. Comparative area, volume, cLogP, polarizability, dipole moment, number of hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) was calculated to each fragment, as well as their E-LUMO. From left to right is shown the LUMO surface, electrostatic potential map, potential surface, and physicochemical properties. (a) Furan (**3**); (b) nitrofuran (**4**); (c) imidazole (**5**); (d) 2-nitroimidazole (**6**); (e) 5-nitroimidazole (**7**).

moiety was not directly linked to the aromatic ring. On all platforms, the search utilized the "substructure filter" to identify molecules containing the drawn structure. Specifically, within the "DrugBank" database, the search was restricted to approved drugs or those that were withdrawn from the market. Conversely, for the ChEMBL database, the search focused on approved substances. As an additional source of information, a third database (named Cortellis)[15] was used. The results of these searches revealed that of the thirty-four nitroaromatic drugs approved until 2023 and shown in the timeline diagrammed in Figure 3, twelve are nitroheterocycles (**8**, **10**, **12**, **13**, **32**-**34**, **36**-**39**, **41**) and twenty-two are nitroarenes (**9**, **11**, **14**-**31**, **35**, **40**). Among the nitroheterocycles, with one exception (i.e., azathioprine), all the others have been approved as

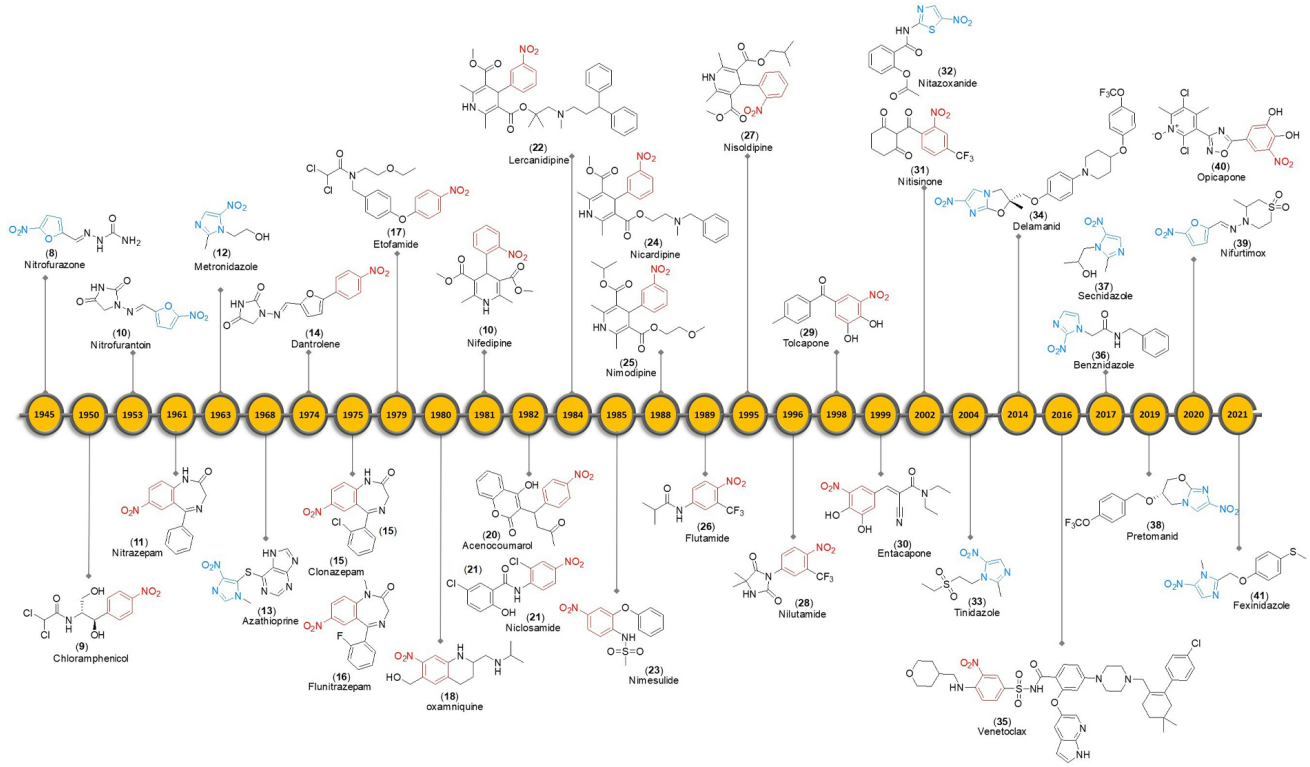


Figure 3. Timeline showing the nitroaromatic drugs approved until 2023.

antimicrobials, particularly as antibacterial and antiparasitic drugs. They are mainly from the class of nitrofurans, nitroimidazoles and more recently nitrothiazole.

The nitrofurazone (**8**) or nitrofural (a nitrofuran derivative), approved in 1945, was the first nitroaromatic to be marketed as a drug. It is a topical anti-infective agent, effective against several Gram-positive and Gram-negative microorganisms (such as staphylococci, streptococci, dysentery bacillus, colon bacillus, paratyphoid bacillus, etc.).[16] Although nitrofurazone has been used in the treatment of trypanosomiasis by oral administration, it has been withdrawn by FDA in 1991, due to concerns regarding its carcinogenicity. Its use for medical purposes is now limited to topical use as antimicrobial for dermatologic application with warnings about the possibility of hypersensitivity reactions.[16]

The second oldest nitroheterocycle drug in history is metronidazole (**12**), approved by FDA in 1963. It is a 5-nitroimidazole derivative indicated to treat anaerobic bacterial and parasitic infections, and use continues for trichomoniasis, amebiasis, giardiasis and vaginosis. The risks associated with metronidazole include a low risk of carcinogenicity, and that prolonged use is linked with neurological disturbances due to neurotoxicity.[17-19]

Considering the last 30 years as a time window, the FDA has approved eight nitroheterocycles (**32**-**34**, **36**-**39** and **41**) and seven nitroaromatics as drugs (**27**-**31**, **35** and **40**) (Figure 4), which shows that despite the challenge of understanding and discriminating the pharmacophoric and toxicophoric role of the nitro group, nitroaromatic continue to arouse interest and constitute an important molecular fragment to be explored in bioactive compounds.[20-22] The history and the pharmacological properties of those fifteen nitroaromatics will be revised, along with an example of synthetic route used to obtain each one.

2.1. Nifurtimox

Although approved by the FDA in August 2020 for the treatment of Chagas disease, the trypanocide properties of nifurtimox (**39**), a nitrofuran derivative developed, have been known and used in medicine since the 1960s. In fact, nifurtimox was first administered to adults with Chagas disease in 1965, a time when the drug approval process was simpler and several preclinical and early clinical development studies were not performed that are now conducted routinely. The drug displays activity against both African and American trypanosomiasis. It is the agent most used for treatment of acute infections with *Trypanosoma cruzi*, for which it is about 80% effective. However, the efficacy of nifurtimox for the chronic forms of Chagas disease appears to be more geographically variable. It is well absorbed following oral administration, reaching maximum concentrations in 3-4 h and with an elimination half-life of only 3 h. Like

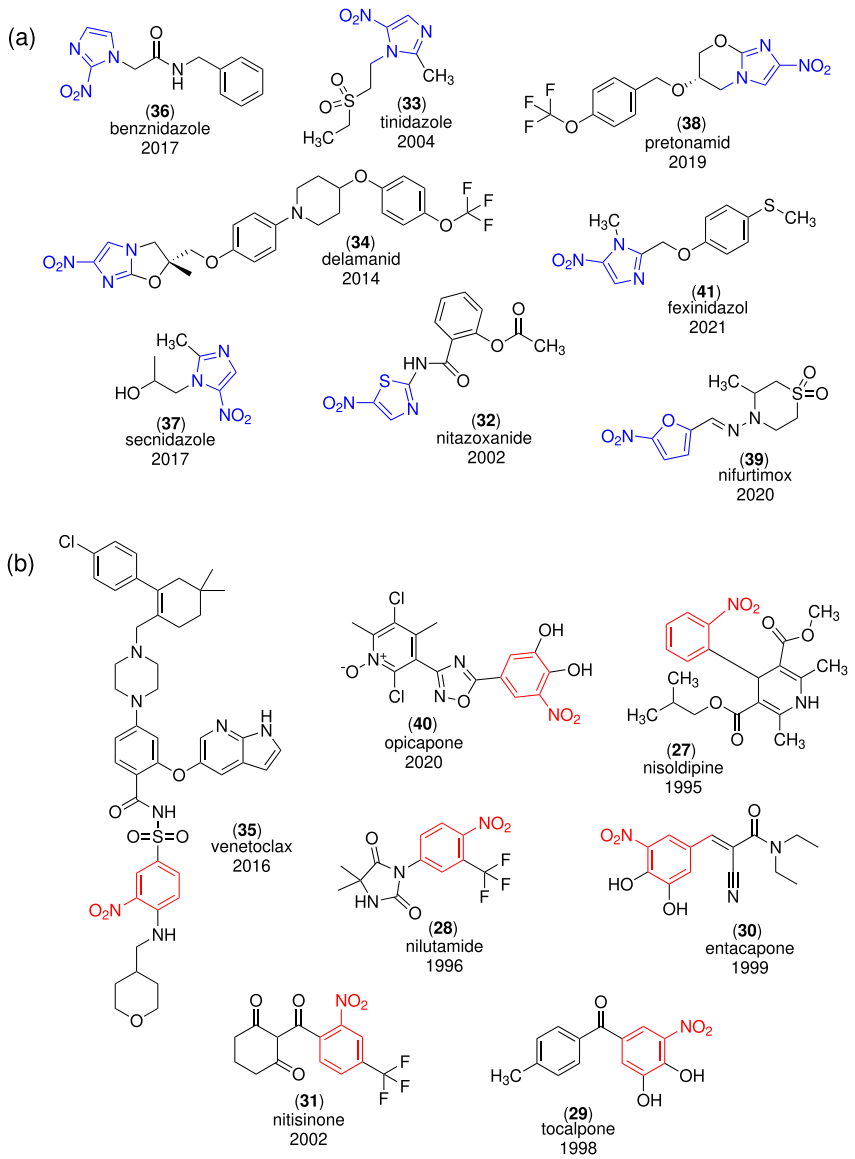


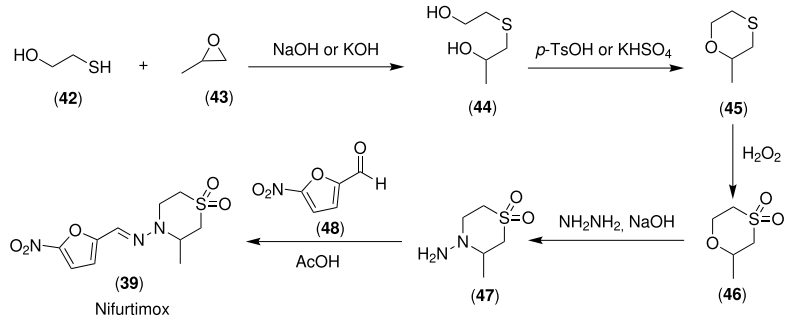
Figure 4. Nitroaromatic drugs approved by FDA in the past 30 years. (a) Nitroheterocycle drugs; (b) nitroarene drugs.

other nitrofurans, nifurtimox mechanism of action involves various reduction and oxidation reactions of its nitro group, leading to the production by parasite enzymes of a variety of reactive oxygen species that react with cellular macromolecules and are lethal to the parasite. In addition, nifurtimox leads to the inactivation of trypanothione reductase of *T. cruzi*, a key enzyme in the antioxidant metabolism of the parasite, although it is a stronger inhibitor of glutathione reductase (inhibitory constant (Ki) = 40 μM) than of trypanothione reductase (half-maximal inhibitory concentration (IC_{50}) = 200 μM).[23-26] The mechanism of action of nifurtimox and other prodrugs of the nitrofuran class has been extensively studied and will be further discussed in this review.

Nifurtimox is synthesized as depicted in Scheme 1. In the first step, the 2-hydroxyethyl 2-hydroxypropyl sulfide (**44**) is produced when 2-mercaptoethanol (**42**) reacts with propylene oxide (**43**) in the presence of NaOH or KOH in EtOH at 100 °C. In the next step, an acid-catalyzed intramolecular cyclization results in the formation of intermediate **45**. After oxidation of **45** with H_2O_2 in AcOH the 2-methyl-1, 4-tetrahydro-thioxane-4,4-dioxide (**46**) is formed and then treated with hydrazine in the presence or absence of NaOH in H_2O to furnish the key intermediate **47**. Ultimately, nifurtimox (**39**) is produced by condensation of derivative **47** with 5-nitrofurfural (**48**) in the presence of AcOH in EtOH.[27]

2.2. Benznidazole

Benznidazole (**36**) is a 2-nitroimidazole prodrug that came into medical use in 1971, as an antiprotozoal

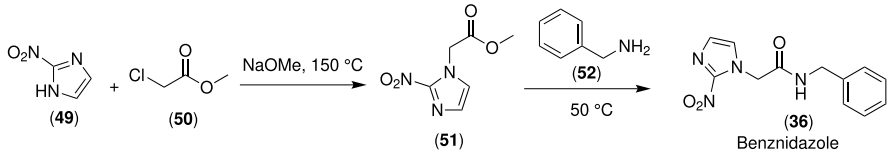


Scheme 1. Synthesis of nifurtimox.[27]

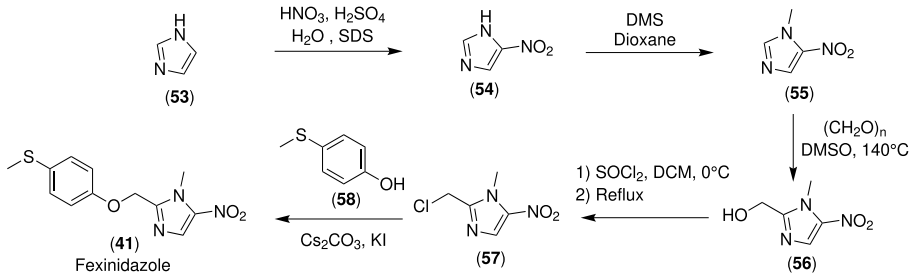
indicated for the treatment of Chagas disease and American trypanosomiasis. But, only in 2017 it was approved by FDA for use in children ages 2 to 12 years old with Chagas disease. It exerts trypanocidal activity after activation to produce reactive metabolites. In *T. cruzi*, it is enzymatically activated by trypanosomal type I nitroreductases (NTR), a class of oxygen-insensitive enzymes present in several protozoan parasites, for which there is no mammalian homologue. Its bioactivation mechanism will be discussed later in comparison with nifurtimox and other nitroaromatics. Benznidazole is the only drug available for the etiological treatment of Chagas disease in Brazil. Its toxicity and limited effectiveness in the chronic phase of the disease are issues that must be overcome. Following oral administration, benznidazole is readily absorbed, with peak plasma concentrations achieved in 3-4 h. It is extensively metabolized, with only 5% of the dose excreted unchanged in the urine, with an elimination half-life of approximately 12 h.[6,28-30] As depicted in Scheme 2, the synthesis of benznidazole begins with *N*-alkylation of 2-nitroimidazole (**49**) with methyl chloroacetate (**50**), in the presence of NaOMe in MeOH/dimethylformamide (DMF) at 150 °C, yielding the methyl 2-(2-nitroimidazolyl) acetate (**51**). Then, this intermediate is condensed with benzylamine (**52**) in MeOH at 50 °C to yield the desired benznidazole (**36**).[31]

2.3. Fexinidazole

Fexinidazole (**41**) is a 5-nitroimidazole derivative first described in 1978 as a broad-spectrum antimicrobial agent. Its development as a pharmaceutical was ceased in the 1980s, due to concerns about toxicity and lack of commercial viability. In 2000's, as part of an innovative partnership between Drugs for Neglected Diseases initiative (DNDi), fexinidazole was studied as a likely clinical candidate to treat Human African Trypanosomiasis (HAT) or sleeping sickness. The results of the clinical trials were conducted in partnership with the National Sleeping Sickness Programs of the Democratic Republic of Congo (DRC) and Central African Republic (CAR). In November 2018, the European Medicines Agency (EMA) adopted a positive opinion of fexinidazole for the treatment of both first- and second-stage HAT in adults and children aged ≥ 6 years and weighing ≥ 20 kg.[7] Seven months later, fexinidazole was added to the World Health Organization (WHO) Essential Medicines Lists for children and adults. In 2021, FDA approved fexinidazole as the first all-oral treatment for both stages of the *Trypanosoma brucei gambiense* form of sleeping sickness. After oral administration, fexinidazole is well absorbed and metabolized by cytochrome P450 (CYP450) and flavin mononucleotide (FMN) enzymes to two main metabolites: fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2), the latter being eliminated more slowly. Both metabolites had potent trypanocidal activity against all *T. brucei* sub-species and strains, being M2 slightly more potent than the parent compound (**41**). The higher and more sustainable concentrations of M2 in the brain, compared to that reported for the parent drug, support the hypothesis that this metabolite is the most likely responsible for the efficacy of fexinidazole.[30,32,33] Fexinidazole could be synthesized (Scheme 3) by the methodology described by McInturff *et al.*,[34] that begins with sodium dodecyl sulfate (SDS) acting as a catalyst, for imidazole (**53**) get nitrated to generate the nitro-substituted product (**54**).



Scheme 2. Synthesis of benznidazole.[31]



Scheme 3. Synthesis of fexinidazole.[34]

After *N*-methylating with dimethyl sulfate (DMS), the intermediate **55** was produced. This intermediate underwent a polyformaldehyde-participated substitution process, yielding benzyl-like-alcohol **56** in two steps. The treatment of **56** with thionyl chloride produced the chlorination product **57**, which was subsequently substituted with 4-(methylthio)phenol (**58**) to produce the fexinidazole (**41**).

2.4. Tinidazole

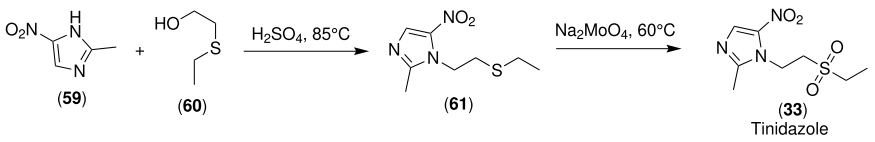
Tinidazole (**33**) is a second-generation of 5-nitroimidazoles with an antiprotozoal and antibacterial effects. Structurally similar to metronidazole, it displays an antiprotozoal and antibacterial actions similar to the latter, but exhibiting a longer half-life (allowing for a shorter course of therapy) and fewer side effects than metronidazole. Although tinidazole has been available outside the United States for more than 25 years, only in 2004 it was approved by FDA for the treatment of trichomoniasis, giardiasis, amebiasis, and bacterial vaginosis in nonpregnant women. It has become the drug of choice in the US for giardiasis due to its efficacy, tolerability, and convenience (a single oral dose is recommended). As other nitroheterocyclic drugs, tinidazole is considered a prodrug which mechanism of bioactivation is dependent of the nitro reduction to toxic free radical intermediates by low redox potential reactions present only in the anaerobic target microbes. The radicals that result from nitro drug reduction form covalently bonded adducts on microbial target molecules, leading to their inactivation.[35-37]

The synthesis pathway of tinidazole (**33**) is shown in Scheme 4 and it is carried out in two steps. First, the 2-[2-(ethylsulfanyl)ethyl]-2-methyl-5-nitroimidazole (**61**) is obtained by condensation of 2-methyl-5-nitroimidazole (**59**) with 2-(ethylsulfanyl)ethan-1-ol (**60**) in the presence of H_2SO_4 in AcOH at 85 °C. Then, the key intermediate **61** is oxidized with Na_2MoO_4 in H_2O at 60 °C to produce the target drug tinidazole (**33**).[38]

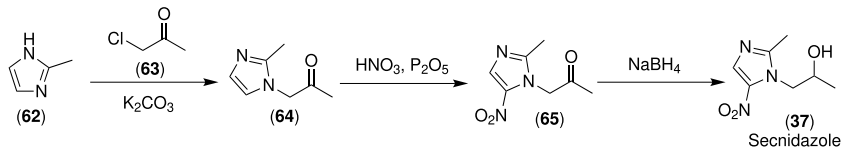
2.5. Secnidazole

Secnidazole (**37**) is a second-generation of 5-nitroimidazole antimicrobial agent, primarily used in the treatment of amoebiasis. It was first described in the 1960s, Newark, NJ, USA. It is structurally related to metronidazole and tinidazole and containing a hydroxypropyl functionality at position C1 of imidazole ring. Although it was already used as a drug in Europe, Asia, South America, and Africa for decades, it was only in 2017 that FDA approved secnidazole for the treatment of bacterial vaginosis and trichomoniasis caused by *Trichomonas vaginalis* in 12 years old and older patients. It is an orally available prodrug that unlike metronidazole, has not been linked to serum enzyme elevations during therapy or to cases of clinically apparent acute liver injury. Its mechanism of action involves intracellular activation by bacterial or parasitic enzymes to a radical anion, which damages large protein molecules and DNA (deoxyribonucleic acid).[39-41]

Secnidazole could be synthesized as shown in the Scheme 5. The intermediate (2-methylimidazol-1-yl) acetone (**64**) is produced when the 2-methylimidazole (**62**) reacts with chloroacetone (**63**) using K_2CO_3 in refluxing acetone. This ketone intermediate (**64**) is nitrated with HNO_3 and P_2O_5, yielding the nitro compound **65**. In the last synthethic step, the intermediate **65** is reduced in room temperature methanol using $NaBH_4$, producing the racemic secnidazole (**37**).[42]



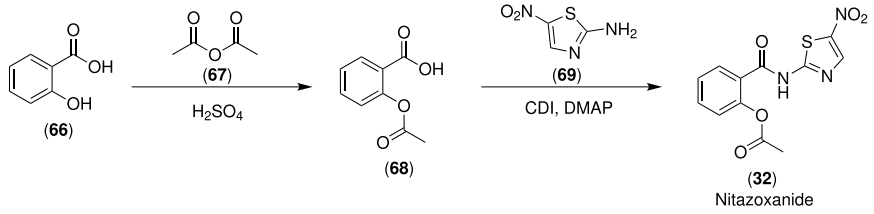
Scheme 4. Synthesis of tinidazole.[38]



Scheme 5. Synthesis of secnidazole.[42]

2.6. Nitazoxanide

Nitazoxanide (**32**) is the only nitroaromatic drug containing the nucleus 5-nitrothiazole. It is originally discovered in 1975 at the Pasteur Institute by Jean-François Rossignol, and it was initially developed as a veterinary anthelminthic with activity against intestinal nematodes, cestodes, and liver trematodes. In humans, nitazoxanide has been used worldwide mainly in Latin America as an anthelminthic drug since 1996. However, only in 2002 it received the approval of FDA for being used to treat diarrhea caused by *Cryptosporidium* species and *Giardia intestinalis* in pediatric patients (1-11 years of age). Two years later, it was approved for treatment of diarrhea caused by *G. intestinalis* in adults, being the first new drug approved for treatment of giardia infection in > 40 years. Since then, it has been studied as part of various drug repositioning projects, which has led to the identification of its broad-spectrum of antiviral activity. Nitazoxanide is metabolized in plasma by esterase to form the des-acetyl active metabolite tizoxanide. The antiprotozoal activity of nitazoxanide and its active metabolite is believed to be due to interference with the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential to anaerobic energy metabolism, while their antiviral action is associated to their ability to inhibit replication of a broad range of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses.[43-46] Nitazoxanide can be easily synthesized in two linear steps, starting by the acetylation of salicylic acid (**66**) with acetic anhydride (**67**) in the presence of H_2SO_4 to provide the acetylsalicylic acid (**68**). Then, the intermediate **68** is coupled with the 2-amino-5-nitrothiazole in the presence of carbonyldiimidazole (CDI) and 4-dimethylaminopyridine (DMAP) in tetrahydrofuran (THF), to produce nitazoxanide (**32**) (Scheme 6).[47]



Scheme 6. Synthesis of nitazoxanide.[47]

2.7. Pretomanid

Pretomanid (**38**) is a nitroimidazopyran derivative first identified in 2000. Nine years later, it was designated as an 'orphan medicine' and approved by EMA for treating adults with drug-resistant tuberculosis (TB) in Europe. It represents the newest classes (nitroimidazooxazines) of drugs approved for TB treatment. It requires metabolic activation by *Mycobacterium* for antibacterial activity and it exhibited bactericidal activity against both replicating and static *M. tuberculosis*. Its mechanism of action is not fully understood. The most accepted proposals include its ability to inhibit the synthesis of protein and cell wall lipid by interfering with the production of one of the cell wall components and its ability to trigger the production of reactive nitrogen species that are toxic for the bacteria. In 2019, the FDA also approved pretomanid, as part of a multi-drug regimen for treating a limited and specific population of adult patients with extensively drug resistant, treatment-intolerant, or nonresponsive multidrug resistant pulmonary tuberculosis.[11,48]

Pretomanid is a chiral drug that is obtained in 5 synthetic steps (Scheme 7). First, the starting material 2,4-dinitroimidazole (**70**) is condensation-bonded to silyl-protected (*S*)-glycidol (**71**), yielding *N*-substituted imidazole (**72**). Then, the hydroxyl group of the intermediate **72** is protected as the tetrahydropyranyl ether (**73**), using pyridinium tosylate (PPTs) and dihydropyran (DHP) in the presence of dichloromethane as solvent. Tetrabutylammonium fluoride (Bu_4NF) was used to desilylate (**73**), and the nitro group was simultaneously displaced to produce the pyranoimidazole derivative **74**. Then, the alcohol **75** was produced by hydrolyzing **74** in an acidic solution to remove the tetrahydropyranyl group. Pretonamid (**38**) was finally obtained by condensation of **75** with 4-(trifluoromethoxy)benzyl bromide (**76**) under Williamson's ether synthesis conditions (Scheme 7).[49]

2.8. Delamanid

Delamanid (**34**) is considered a first-in-class bicyclic nitroimidazole, developed in the early 1990s, as part of its TB drug development program. Its first global approval for the treatment of multi-drug resistant (MDR)-TB took place in 2014 by the EMA. Like pretomanid, delamanid is a prodrug which mechanism of action involves the reduction of the nitro group and may involve the release of free radicals such as nitric oxide (NO). It also inhibits the production of mycolic acid which makes delamanid more effective in treating mycobacterial infection, since mycolic acids are only found in the cell walls of mycobacteria.[50-53]

Delamanid is a chiral drug that can be synthesized as exemplified in Scheme 8. First, the beta-methylallyl alcohol (**77**) is sharply asymmetrically epoxidized with cumene hydroperoxide (CMNOOH) in the presence of titanium isopropoxide ((i-PrO)$_4$Ti) and (*R*,*R*)-diethyl tartrate ((+)-DET) in toluene. This yields 2(*S*)-methylglycidyl alcohol (**78**), which is then condensed with 4-bromophenol (**79**) in the presence of NaOH to yield 3-(4-bromophenoxy)-2(*R*)-methylpropane-1,2-diol (**80**). Buchwald-Hartwig reaction is performed to produce the tertiary amine (**82**) by combining aryl bromide (**80**) with 4-[4-(trifluoromethoxy)phenoxy]piperidine (**81**) in the presence of $Pd_2(dba)_3$, sodium *tert*-butoxide (*t*-BuONa) and *t*-Bu XPhos in toluene. The oxirane (**83**) is produced by activating the main hydroxyl group in diol **82** with methanesulfonyl chloride (MsCl) in the presence of Et_3N in EtOAc, then cyclizing the resulting hydroxy mesylate (**83**) in MeOH using K_2CO_3 to generate the epoxide **84**. Ultimately, the reaction between the epoxide **84** with 2-chloro-4-nitroimidazole (**85**) at 100 °C in *t*-BuOAc with NaOAc provides the delamanid (**34**) (Scheme 8).[54]

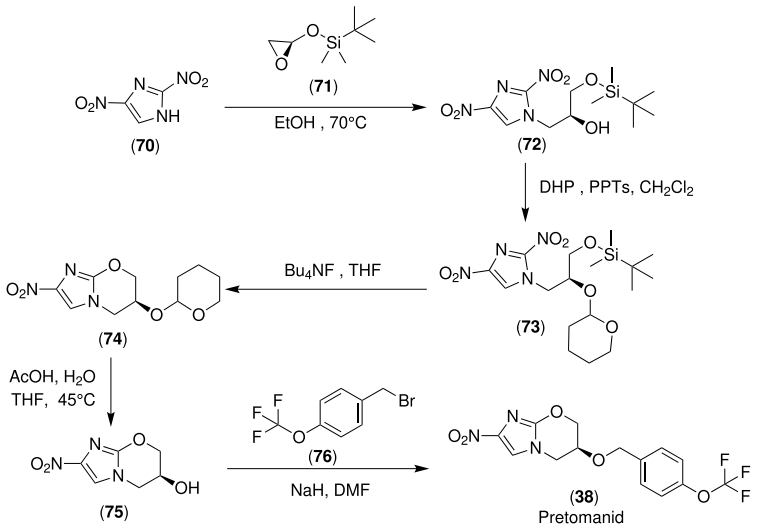
2.9. Nisoldipine

Nisoldipine (**27**) is a nitroarene derivative which belongs to the 1,4-dihydropyridine class of bioactive compounds, first described in the literature in 1972. Unlike the nitroheterocycle drugs, it is effective and well tolerated as long-term treatment, and the nitro group does not participate in its mechanism of action. Nisoldipine was negative when tested in a battery of genotoxicity assays including the Ames test and the Chinese hamster ovary/hypoxanthine-quanine phosphoribosyl transferase (CHO/HGRPT) assay for mutagenicity and the *in vivo* mouse micronucleus test and *in vitro* CHO cell test for clastogenicity. It was granted FDA approval in 1995 to the treatment of hypertension.[55,56]

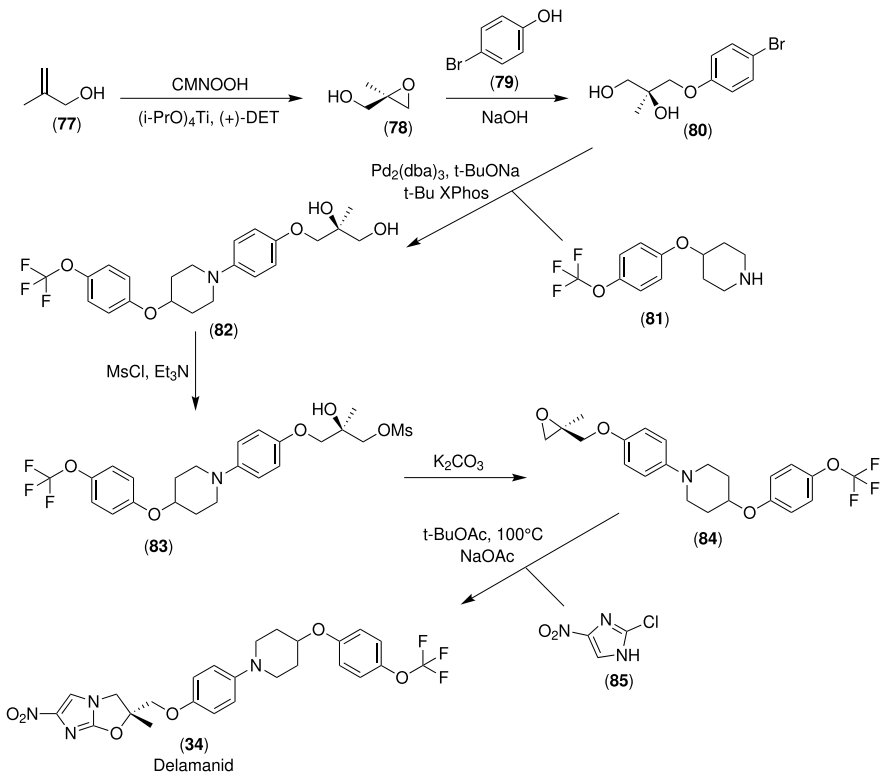
Scheme 9 shows a synthetic route for obtaining nisoldipine. The proposal synthesis starts with the condensation of diketene (**86**) with 1-methoxy-2-methylpropane (**87**) in the presence of $MeNH_2$ to yield isobutyl acetoacetate (**88**). This intermediate is treated with NH_3 in *i*-PrOH to produce isobutyl 3-aminocrotonoate (**89**). When 2-nitrobenzaldehyde (**90**) and methyl acetoacetate (**91**) are combined in *n*-hexane with *n*-Bu_2NH and AcOH, the methyl 2-(2-nitrobenzylidene)-3-oxobutyrate (**92**) is produced. This intermediate (**92**) is then cyclized with isobutyl 3-aminocrotonoate (**89**) in *i*-PrOH to produce nisoldipine (**27**) (Scheme 9).[57]

2.10. Nilutamide

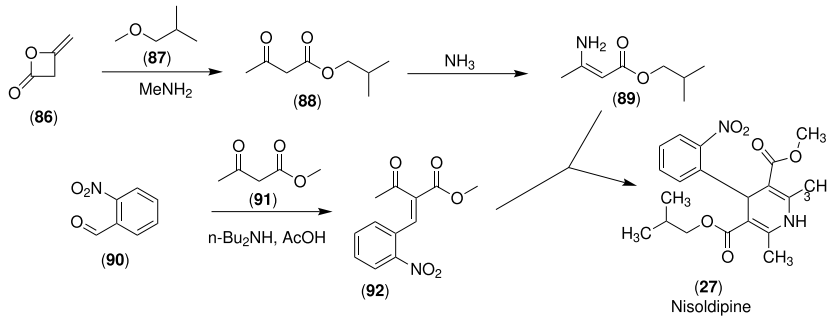
Nilutamide (**28**) is an androgen receptor antagonist that competitively inhibits the effects of testosterone by



Scheme 7. Synthesis of pretomanid.[49]



Scheme 8. Synthesis of delamanid.[54]

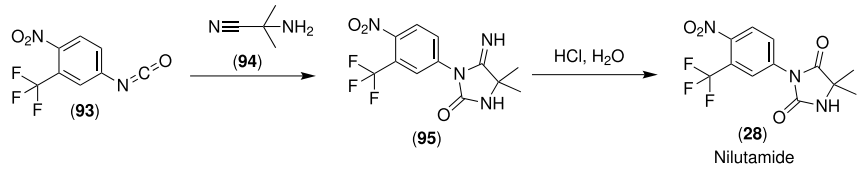


Scheme 9. Synthesis of nisoldipine.[57]

interacting with the androgen receptor. It is a nitroarene derivative developed by a French pharmaceutical company. It was first described in 1977 and first introduced for medical use in 1987 in France. However, only in 1996 the nilutamide was approved by FDA in combination with surgical castration for the treatment of stage D2 metastatic carcinoma of the prostate. Like nisoldipine, its biological effect is independent of nitro reduction.[58] One of the synthetic pathways proposed for nilutamide synthesis is depicted in Scheme 10. The key intermediate 1-(3'-trifluoromethyl-4'-nitrophenyl)-4,4-dimethyl-5-imino-2-imidazolidinone (**95**) is obtained by condensing 3-trifluoromethyl-4-nitrophenylisocyanate (**93**) with 2-amino-2-cyanopropane (**94**). This intermediate is heated, cooled and then put into water while suspended in aqueous hydrochloric acid to get the desired product, nilutamide (**28**).[59]

2.11. Tolcapone

Tolcapone (**29**) is another interesting nitroarene approved by the FDA in last 30 years. This 5-nitrobenzophenone derivative is the only one nitroaromatics drugs selected in this time window approved for the treatment of a central nervous system (CNS) disease. It was developed as a central and peripheral selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT). In 1997, tolcapone was introduced into the European market to treat Parkinson's disease (PD) patients with motor fluctuations, after its approval by EMA. The following year, it also received marketing approval from the FDA. Risk of potentially fatal acute fulminant hepatic failure led to the suspension of tolcapone's marketing authorization in 1998 in Europe and Canada. In USA, the FDA issued



Scheme 10. Synthesis of nilutamide.[59]

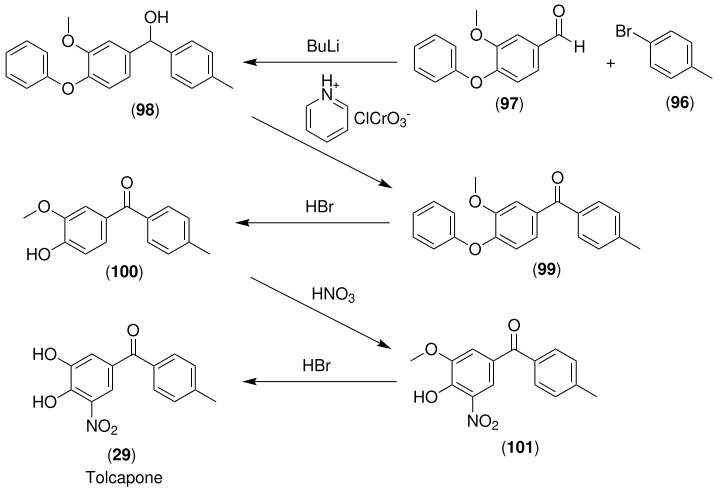
a black box warning for tolcapone and label revisions that aimed to regulate the monitoring of those prescribed tolcapone for Parkinson's disease. In 2009, EMA renewed the authorization for tolcapone commercialization in Europe with special warnings and precautions for use.[60,61]

Tolcapone can be synthesized in five linear steps as demonstrated in Scheme 11. The initial intermediate 4-(benzyloxy)-3-methoxy-4'-methylbenzhydrol (**98**) is produced by adding 4-bromotoluene (**96**) to 4-(benzyloxy)-3-methoxybenzaldehyde (**97**) in THF at –78 °C, when butyllithium (BuLi) is present. Oxidation of **98** in CH_2Cl_2 with pyridinium chlorochromate results in the obtainment of 4-(benzyloxy)-3-methoxy-4'-methylbenzophenone (**99**). The debenzylation of the intermediate **99** is carried out in acetic acid with 30% aqueous hydrobromic acid to furnish the 4-hydroxy-3-methoxy-4'-methylbenzophenone (**100**). A regioselective nitration of intermediate **100** is performed using 65% aqueous nitric acid in acetic acid to yield the 4-hydroxy-3-methoxy-4'-methyl-5-nitrobenzophenone (**101**). Then, tolcapone (**29**) is produced by demethylation of the methoxy group in **101** using 30% aqueous hydrobromic acid in boiling acetic acid.[62]

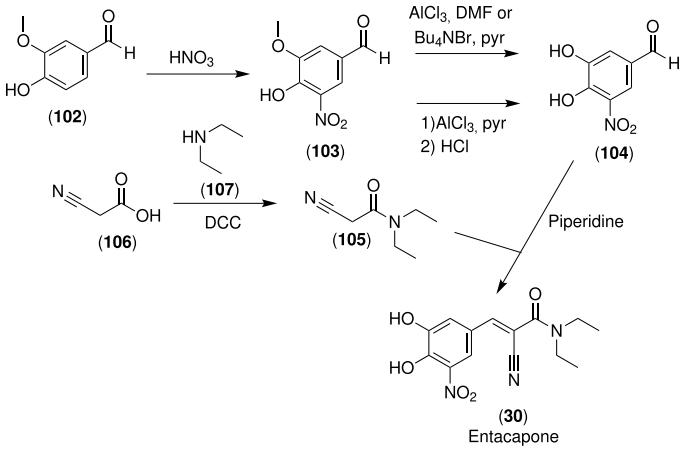
2.12. Entacapone

Entacapone (**30**) is another nitro catechol similar to tolcapone. Due to its poor lipophilicity and unlike tolcapone it does not penetrate the blood-brain barrier (BBB) to any significant extent, being a peripheral selective and reversible inhibitor of catechol-*O*-methyl transferase (COMT). Therefore, it is believed that its biological effect stems from its ability to alter the plasma pharmacokinetics of levodopa. Into biophase, it undergoes isomerization for conversion from *trans* isomer to *cis* isomer form of the propenamide moiety. Both isomers are mainly metabolized by glucuronidation. The glucuronides account for 95% of all urinary metabolites (70% as parent and 25% as *cis* isomer glucuronides). The glucuronide conjugates of *cis* isomer are inactive, while the *trans* are active. Entacapone was first approved by EMA in 1998, then approved by FDA in 1999 to be used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. No evidence of significant liver toxicity with entacapone has been reported.[63,64]

The synthesis pathway for entacapone obtention is summarized in Scheme 12. The first intermediate, the 5-nitrovanillin (**103**), is obtained by vanillin (**102**) nitrating in the presence of HNO_3 in AcOH. Then, compound **103** is demethylated at 55 °C using $AlCl_3$ in pyridine, optionally with DMF in CH_2Cl_2 or pyridine and Bu_4NBr in CH_2Cl_2, to produce 3,4-dihydroxy-5-nitrobenzaldehyde (**104**). **104** could also be prepared from **103** by its treatment with $AlCl_3$ in the presence of pyridine in chlorobenzene followed by it hydrolysis with HCl. Entacapone (**30**) is produced by the Knoevenagel condensation of aldehyde **104** with



Scheme 11. Synthesis of tolcapone.[62]



Scheme 12. Synthesis of entacapone.[65]

2-cyano-*N*,*N*-diethylacetamide (**105**) (which is prepared by condensation of *N*,*N*-diethylamine (**107**) with cyanoacetic acid (**106**) in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC)) in the presence of piperidine.[65]

2.13. Nitisinone

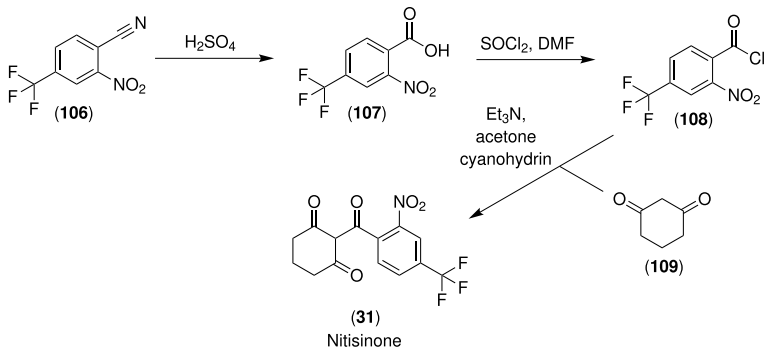
Nitisinone (**31**) is a nitroarene derivative obtained from natural source. It is a triketone herbicide derived from leptospermone produced by the bottlebrush plant. It was first discovered in 1982. This compound is a potent reversible tight-binding inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase, involved in the catabolism of the amino acid tyrosine. The elucidation of its mechanism of action has led to the proposal to use it to treat rare hereditary disorders of tyrosine catabolism. In 2002, the FDA first approved nitisinone as an orphan drug for managing and treating hereditary tyrosinemia type 1 (HT-1). In 2005, the EMA authorized nitisinone medical use in the European Union.[66-68]

Synthetically, nitisinone can be obtained from a linear three-step synthesis, as shown in Scheme 13. The starting material 2-nitro-4-(trifluoromethyl)benzonitrile (**106**) is hydrolyzed using H_2SO_4 at 123 °C to yield the carboxylic acid intermediate (**107**). By an interconversion of functional groups, the carboxylic acid is converted to acyl chloride (**108**), using $SOCl_2$ and DMF at 80 °C. This key intermediate is condensed with 1,3-cyclohexanedione (**109**) using Et_3N as base or, alternatively, acetone and cyanohydrin in CH_2Cl_2, to furnish nitisinone (**31**).[69]

2.14. Opicapone

Opicapone (**40**) is a third generation of COMT inhibitors structurally analogous to tolcapone and endocapone, sharing the presence of the nitro-catechol subunit. It was developed in Portugal and approved by EMA in 2016 and by FDA in 2020 as an add-on treatment for patients with Parkinson's disease. Its potency is like that of tolcapone. However, due to the high binding affinity and a slow dissociation rate of the opicapone-COMT-complex, it only needs to be taken once daily and it provides long-lasting COMT-inhibition (> 24 h). Opicapone does not exhibit liver toxicity.[70-73]

Opicapone can be obtained by the synthesis route shown in the Scheme 14. Vanillic acid (**110**) is regioselectively nitrated with HNO_3 in AcOH to produce 4-hydroxy-3-methoxy-5-nitrobenzoic acid (**111**). An alternative

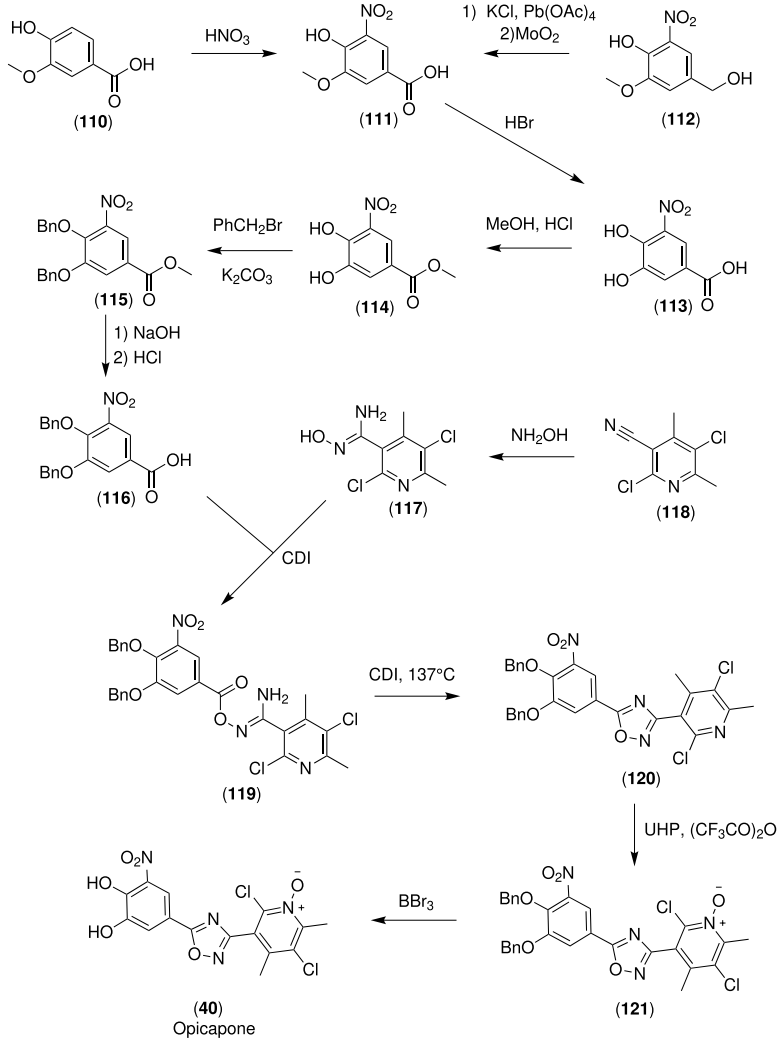


Scheme 13. Synthesis of nitisinone.[69]

method involves treating 4-(hydroxymethyl)-2-methoxy-6-nitrophenol (**112**) with KCl and $Pb(OAc)_4$, then oxidizing the resultant acid (**111**) in AcOH at 120 °C. Demethylating the acid with HBr in AcOH produces catechol (**113**). Methyl 3,4-dihydroxy-5-nitrobenzoate (**114**) is produced by esterifying carboxylic acid (**113**) with MeOH in the presence of HCl. The diol groups of this product are then benzylated using $PhCH_2Br$ in the presence of K_2CO_3 in acetonitrile at 100 °C, yielding methyl 3,4-bis(benzyloxy)-5-nitrobenzoate (**115**). The equivalent carboxylic acid (**116**) is obtained by saponification of methyl ester (**115**) with NaOH in $MeOH/H_2O$ at 60 °C, followed by acidification with HCl. **116** is coupled with 2,5-dichloro-*N*'-hydroxy-4,6-dimethylpyridine-3-carboximidamide (**117**) in the presence of CDI in DMF to yield the intermediate **119**. The intermediate **117** is prepared by reacting 2,5-dichloro-4,6-dimethylnicotinonitrile (**118**) with NH_2OH in refluxing EtOH. Oxadiazole **120** is produced by cyclizing intermediate **119** in DMF at 135 °C when CDI is present. Pyridium oxide derivative **121** is produced by *N*-oxidation of pyridine derivative **120** with urea hydrogen peroxide (UHP) in the presence of $(CF_3CO)_2O$ in CH_2Cl_2. Finally, the debenzylation of **121** with BBr_3 in CH_2Cl_2 at –78 °C results in the obtainment of opicapone (**40**).[74]

2.15. Venetoclax

Venetoclax (**35**) is a nitroarene derivative considered an innovative drug to treat advanced forms of leukemia. It was developed based on a landmark discovery made in the 1980s, that the dysfunction of apoptosis due to a protein called B-cell lymphoma-2 (BCL-2) overexpression is one of the hallmarks in most B-cell malignancies. The collaboration produced the BCL-2-selective drug venetoclax, approved by FDA (in 2016) for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Venetoclax (ABT-199) is a successful example of the application of the



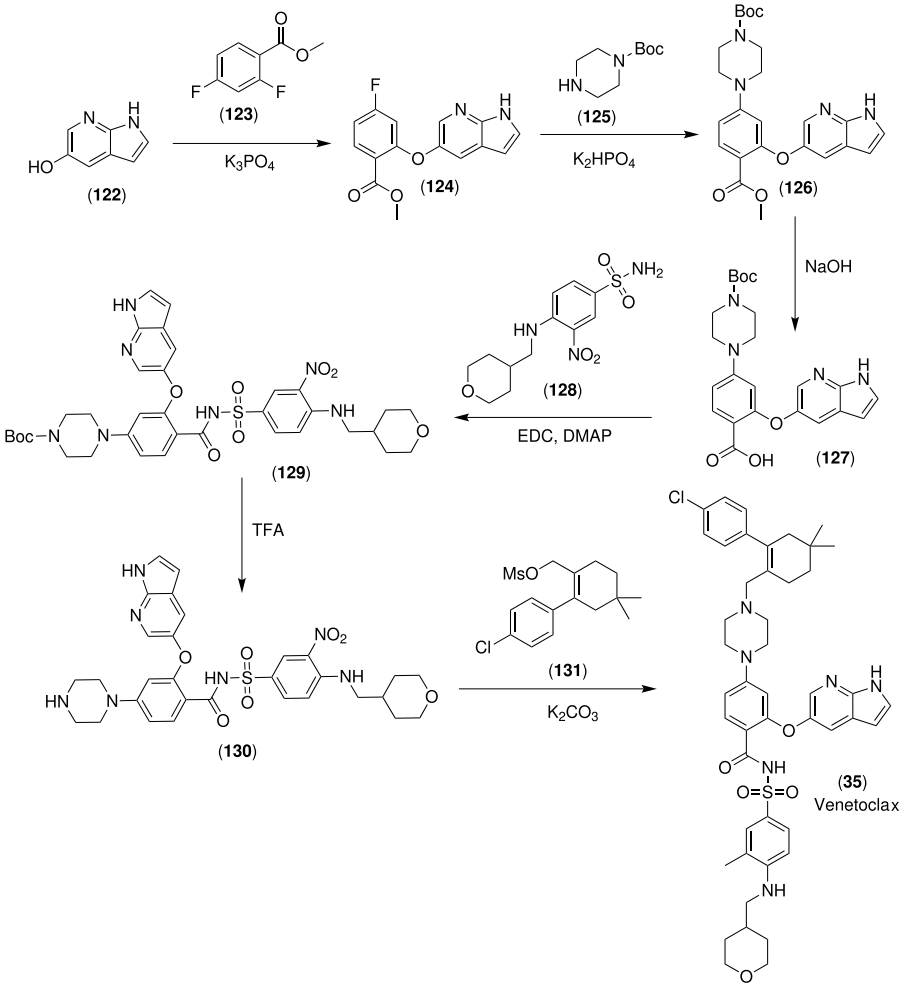
Scheme 14. Synthesis of opicapone.[74]

fragment-based drug discovery (FBDD), being the second fragment-based drug approved.[75-78]

A convergent large-scale synthesis for venetoclax was described by Ku *et al*.[79] in 2019. As exemplified in Scheme 15, the first intermediate (**124**) is obtained by condensing the 5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**122**) with methyl 2,4-difluorobenzoate (**123**) in diethyl glycol dimethyl ether at 110 °C, in the presence of K_3PO_4. Then, **124** is coupled with *N*-Boc-piperazine (**125**) in dimethyl sulfoxide (DMSO) at 120 °C with K_2HPO_4 to produce the intermediate **126**. This intermediate is hydrolyzed with aqueous NaOH in THF at 65 °C to produce the carboxylic acid **127**. Intermediate **127** and sulfonamide **128** are coupled in the presence of EDC and DMAP in CH_2Cl_2 to produce compound **129**, which is then *N*-deprotected in CH_2Cl_2 using trifluoroacetic acid (TFA) to produce free amine **130**. The last step in the synthesis of venetoclax (**35**) is based on the nucleophilic substitution reaction between the piperazine present in **130** and the mesylate group of **131** (Scheme 15).[79]

3. Mechanism of Bioactivation and Metabolism of Nitroaromatics

Drugs containing the nitroheterocycle framework, such as the nitrofuran and nitroimidazole antimicrobials, are considered prodrugs. They must undergo enzyme-mediated activation within the pathogen to have cytotoxic effects, which are mainly catalyzed by nitroreductases (NTRs). Based on oxygen sensitivity, NTRs are divided into two groups. Type I NTRs contain FMN as a cofactor, and they mediate a two-electron reduction of the nitro group to generate a nitroso intermediate (**133**) that rapidly undergoes reduction to a hydroxylamine derivative (**134**), which can then be processed further to generate either the amine (**135**) or nitrenium cations (**138**) that promote DNA damage (Figure 5a). The complete reduction of a nitroaromatic to the corresponding aniline is considered a complex process since it requires the sequential delivery of three hydride equivalents. Because reduction by type I NTRs do not involve oxygen and does not result in the production of reactive oxygen species, this activity is said to be "oxygen-



Scheme 15. Synthesis of venetoclax.[79]

insensitive." Type I NTR is largely restricted to bacteria and absent from most eukaryotes. However, Wilkinson *et al.*[80] have demonstrated that trypanosomes express a type I NTR and a reduction in the level of its activity plays a major role in trypanosomes resistance to nitroheterocycle drugs. Therefore, it is now clear that trypanosomes activate nitroheterocycle drugs using a mitochondrially targeted oxygen-insensitive type I NTR, leading to the formation of cytotoxic reduction products. Type II NTRs are ubiquitous oxygen sensitive flavin adenine dinucleotide (FAD)- or FMN-containing enzymes that mediate a one electron reduction of the nitro-group yielding an unstable nitro-anion free radical (**139**). The latter undergoes spontaneous re-oxidation by O_2 producing superoxide (which accounts for the oxygen-sensitivity of these enzymes), with the subsequent regeneration of the parent nitro-compound (**132**) (Figure 5b).[80-82]

Anaerobic intestinal bacteria in the lower gastrointestinal tract are also rich in nitroreductase enzymes. Chloramphenicol (**9**), a natural nitroarene isolated from the culture of the soil Gram-positive bacterium *Streptomyces venezuelae* as an antibacterial agent, is metabolized by nitro-reduction to an amine metabolite in bacteria and in several tissues (Figure 6). Therefore, nitroreduction by intestinal bacteria has been implicated in modulating the efficacy and/or toxicity of some nitroaromatic drugs. Clonazepam (**15**) is a sedative-hypnotic drugs that are widely used to treat sleeping disorders and relieve anxiety-related symptoms. It is a member of nitrobenzodiazepines, such as nitrazepan (**11**), that is considered safe at therapeutic doses, but adverse effects such as reproductive and hepatic toxicities have been described associated with an accidental or intentional overdose. These toxic effects have been suggested to be due, at least in part, to the formation of the nitroreduction metabolites (Figure 6). Moreover, the nitroreduction by gut bacteria is suggested to be a primary determinant for nitrazepam-induced teratogenicity. Reductase activity is also found in the microsomal fraction and in the cytosol of the hepatocyte. In fact, in humans, xanthine oxidase and microsomal nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome P450 reductase have been also identified as enzymes involved in nitroreduction. However, its contribution to total amounts of amino metabolites produced *in vivo* appears to be minimal. Recently, Penning *et al.*[83] have reviewed the main reductive enzymes found in mammalian cells that are capable of nitroreduction, such as P450 oxidoreductase (POR),

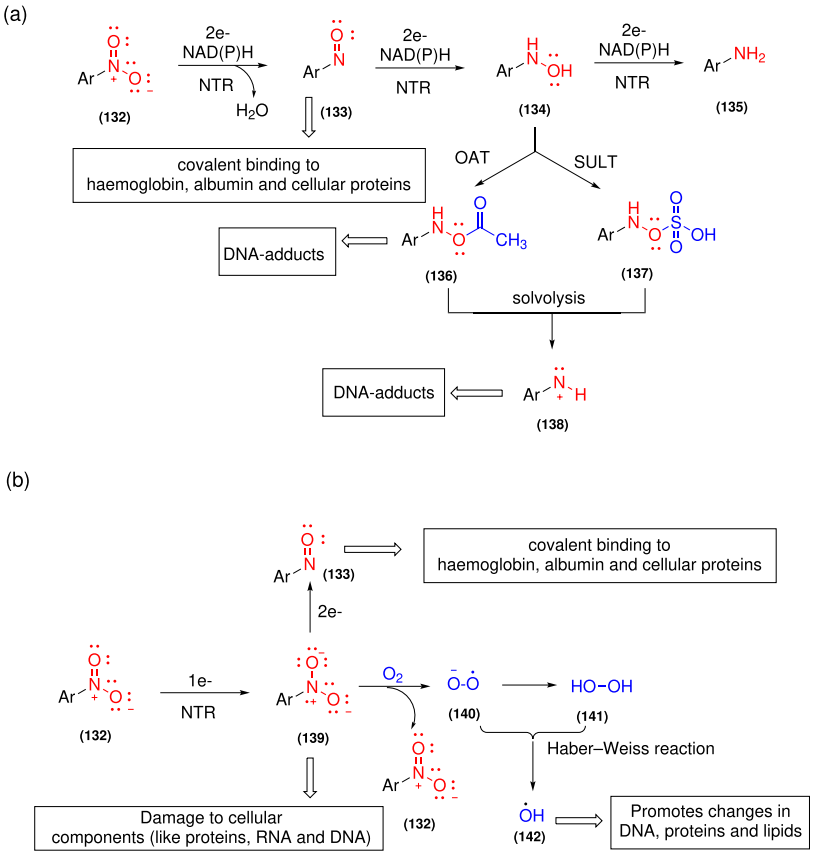


Figure 5. Bioreduction of the nitro group by nitroreductases (NTR) or others flavoenzymes and/or their physiological redox partners (i.e., metalloproteins) and their involvement with antimicrobial activity and toxicity. (a) Two-electron nitroreduction; (b) one-electron nitroreduction.

adrenodoxin reductase, aldehyde oxidase, aldo-keto reductases and so on.[5,84-89]

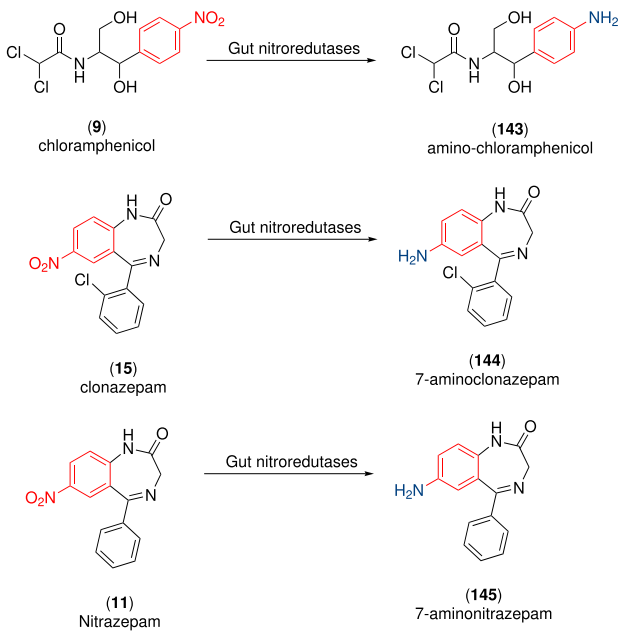


Figure 6. Gut bacterial nitroreduction of chloramphenicol, clonazepam and nitrazepam.

In this context, the presence of the nitro group introduced to a phenyl or heterocycle ring, giving rise to the respective nitroarene and nitroheterocycle, brings the possibility of using the nitroreduction process as a mechanism for prodrugs bioactivation, guiding selectivity towards the species that specifically or selectively expresses a particular nitroreductase, providing a mechanism of selective cytotoxic action. However, as we have seen, several reductases involved in the metabolism of xenobiotics in mammals recognize nitroheterocycles and nitroarenes as substrates. As a result, they metabolize these fragments into metabolites that are potentially toxic to mammalian cells and tissues, calling into question the principle of selective toxicity initially expected.

Although the bioreductive mechanisms leading to activation of nitro compounds and their conversion to cytotoxic and potential mutagenic and genotoxic metabolites are known and shared between compounds containing the nitroheterocycle and nitroarene fragments, the generation of reactive species between them may be different. This is due to the influence of bioreduction on the other fragments that make up the structure of a given drug. This can be easily visualized by comparing the bioactivation mechanism of nifurtimox and benznidazole (Figure 7).

Activation of nifurtimox occurs by a type I NTR, under aerobic conditions, via a two-electron reduction pathway. So, the formation of the nitroso (**146**), hydroxylamine (**147**) and nitrenium ion (**150**) are expected. Nevertheless, an unsaturated open chain nitrile (**151**) is generated *in vitro* through the incubation of nifurtimox with *T. brucei* (Tb) NTR or *T. cruzi* (Tc)NTR (Figure 7). This product is generated from the hydroxylamine (**147**) by the loss of a water molecule followed by the opening of the furan ring. The conjugated double bond could be reduced to produce a saturated open-chain nitrile (**152**). Hall *et al.*[82] have demonstrated that the nitrile product (**151**) generated from nifurtimox is toxic to bloodstream-form trypanosomes, displaying an IC_{50} value comparable with that of the parent compound, while the saturated analogue (**152**) was inactive. This implies that the NTR-dependent synthesis of the unsaturated open-chain nitrile may be the causative factor in cell death following nifurtimox treatment. Notably, *in vitro*, the unsaturated open-chain nitrile exhibits equipotent properties against both *T. brucei* and mammalian cells, nonetheless, nifurtimox itself exhibits a tenfold increase in potency against *T. brucei*, aligning with the theory that the selective bioactivation by the parasite contributes to selectivity. The mechanism through which unsaturated open-chain nitrile induces cell death remains uncertain. But this nitrile contains a Michael's acceptor, a chemical entity recognized for its reactivity with sulfhydryl groups in proteins or other biomolecules.[90] Consequently, it is hypothesized that the unsaturated open-chain nitrile irreversibly obstructs one or more crucial proteins by covalently binding to accessible and/or active cysteine residue(s), ultimately leading to cell death.[82,91]

TcNTR and TbNTR are also enzymes that mediate the bioactivation of benznidazole (**36**). Like nifurtimox, upon incubation with recombinant NTR and NADH (nicotinamide adenine dinucleotide (NAD) + hydrogen (H)), the nitro group of benznidazole undergoes two consecutive two-electron reductions, resulting in the formation of a hydroxylamine intermediate (**154**). This intermediate was identified through liquid chromatography-mass spectrometry (LC-MS).[81] In contrast to nifurtimox, the reduced benznidazole does not undergo a ring-opening reaction. Instead, the hydroxylamine (**154**) undergoes a series of non-enzymatic processes, leading to the formation of 4,5-dihydroxyimidazole (**157**) (Figure 7b).[92,93] Notably, LC-MS analysis of the reaction mixture detected both *cis* and *trans* isomers of this diol.[81] The equilibrium existence of these dihydro-dihydroxyimidazoles (**157**) with glyoxal (**159**) and a substituted guanidine product (**158**) in aqueous solution is documented (Figure 7b).[94] The highly toxic and reactive dialdehyde **159** is known to chemically modify proteins, lipids, and nucleotides.[95] It is postulated that the anti-trypanosomal activity of benznidazole is in part attributed to the synthesis of glyoxal. Supporting this

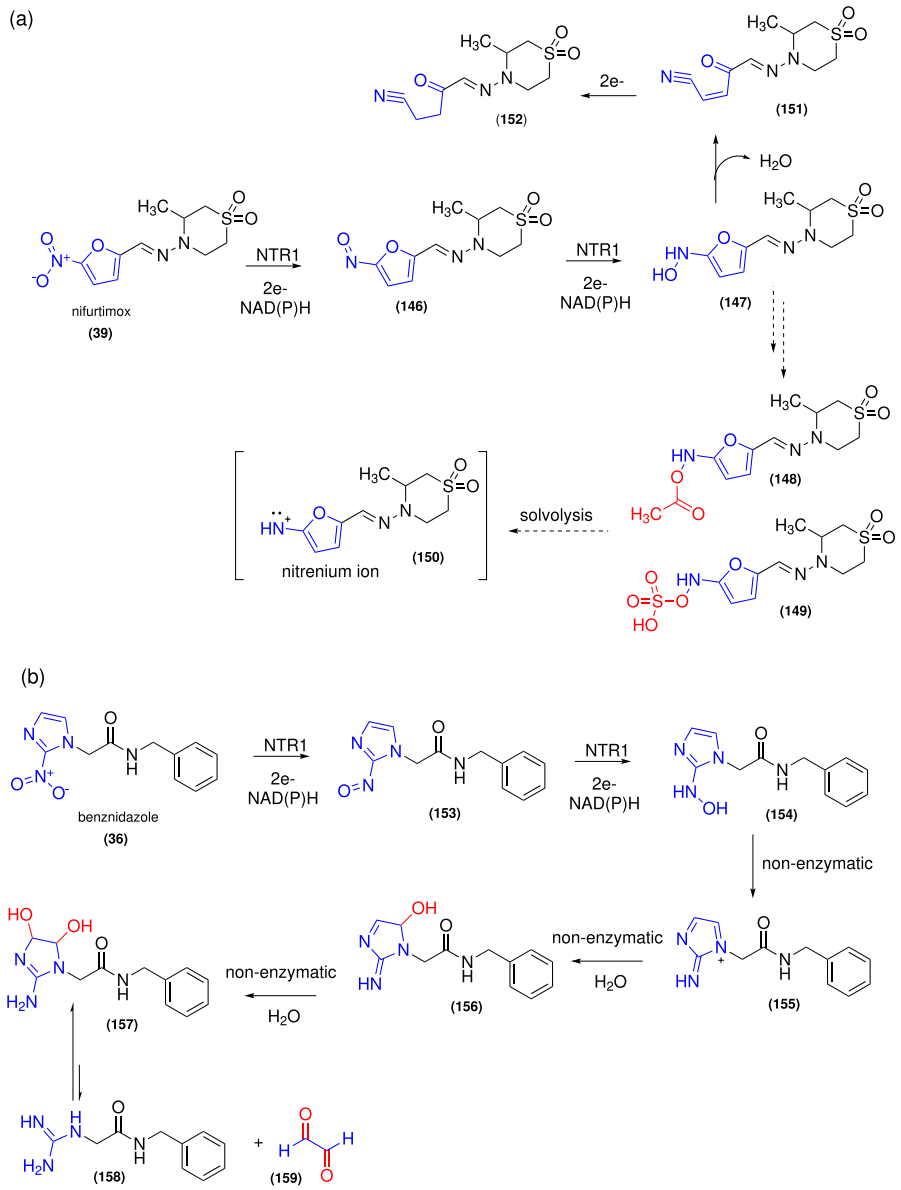


Figure 7. Proposed mechanism of bioactivation of the prodrugs nifurtimox (a) and benznidazole (b).

hypothesis, evidence suggests the formation of guanosine-glyoxal adduct when guanosine is introduced into the reaction mixture.[81] However, the synthesis of glyoxal from dihydro-dihydroxy imidazoles occurs at a notably sluggish pace.[94] Consequently, it raises doubts that the synthesis of glyoxal is the exclusive cytotoxic process.

4. Nitroaromatic Toxicity

In the literature, the distinction between the toxicophoric potential of nitro compounds linked to aromatic heterocycles and nitroarenes is not yet fully elucidated. As depicted in Figure 5a, the bioreduction of nitro group involves the formation of reactive metabolites such as nitro radical-anion (**132**), nitroso derivative (**133**) and hydroxylamine (**134**), which may contribute to toxicity. While hydroxylamines (**134**) are often responsible for methemoglobinemia, the mutagenic and carcinogenic activity may be due to the combination of nitro radical-anion (**132**), nitroso derivatives (**133**) and the phase II metabolites of hydroxylamine (**136** and **137**) with cellular macromolecules. The attempt to bioinactivate hydroxylamine results in the acetylation of its hydroxyl by *O*-acetyltransferase and its sulfation mediated by sulfotransferases. These conjugated metabolites, having a good leaving group, can undergo solvolysis and generate a highly electrophilic and reactive arylnitrenium ion (**138**), capable of forming covalent adducts with several biological nucleophiles as glutathione, DNA, cell proteins, etc. The nitrenium

or carbene tautomeric ion can be also generated directly from hydroxylamine, due to its protonation followed by water loss, in biological conditions where the pH of the biophase is more acidic.[96] Notably, the arylnitrenium ion is known to be a DNA alkylator, associated with reports of mutagenesis and genotoxicity. DNA can be acetylated by the metabolite **136** (Figure 5a), contributing to the mutagenicity and genotoxicity of nitroaromatic-dependent metabolism. Arylamines (**135**), the final metabolites of the bioreduction of nitroaromatics, are also considered to be toxophores, given their oxidation, catalyzed by enzymes of the cytochrome P450 family, into hydroxylamine and nitroso derivatives. As early as 1974, Wang *et al*.[97] have demonstrated that rat liver cytosol and microsomes were able to catalyze the nitroreduction of *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA), a potent carcinogen for the mouse, rat, hamster and dog, to furnish a metabolite capable of binding to cellular proteins.[83,97-99]

The nitroaromatic bioreduction by a single-electron transfer leads to the formation of the nitro anion radical (**139**) and its subsequent conversion to the nitroso compound (**133**) (Figure 5b), which can be further reduced to form the corresponding hydroxylamine and thus generate the same potentially toxic, species-dependent, metabolites shown in Figure 5a. On the other hand, nitro anion radical (**139**) can react with molecular oxygen to generate superoxide anion (**140**), regenerating the nitroaromatic compound (**132**). Therefore, the bioreduction of nitroaromatic, mainly in aerobic condition results in the formation of reactive oxygen species that induce cellular oxidative stress and ultimately lead to cell death (Figure 5b).[100]

In 2003, Katritzky *et al*.[101] reported a quantitative structure-activity relationship (QSAR) study on nitrobenzene toxicity. Hydrophobicity and the electron affinity seem to be the two most important contributing factor to the nitro group reduction. The first contributes to control transport to the action site, and the second being responsible for the intrinsic reactivity property of the nitro group.[21,101] The intrinsic reactivity property of the nitro group (i.e., intrinsic redox properties) can be correlated to its reduction potential, that is the tendency of a specie to gain electrons and get reduced. Nitroaromatic compounds with reduction potentials higher than –330 mV is believed to be too easily reduced, while reduction potentials below –450 mV is indicative of a lower tendency to get reduced.[5,85,102-104]

Considering that toxicity and therapeutic action of nitroaromatic drugs may involve similar initial steps, based on a single- or two-electron reduction in nitro group, catalyzed by several flavoenzymes and/or their physiological redox partners (i.e., metalloproteins), present in different species, such as bacteria, protozoa, fungi and mammals, to design new nitroaromatic that can be able to have selectivity or ideal intrinsic redox properties for a desired nitroreductase, in theory, would be an efficient strategy for discriminating between pharmacological and toxicological effects of this important class of bioactive compounds.

5. Synthesis of Nitroaromatic Framework

Nitroaromatics play an important role as building blocks and synthetic intermediates. They are a basis for the preparation of many medicines, agricultural chemicals, dyes, and explosives.[5,6,105-107] Therefore, the number of published articles reporting more efficient and practical methods for their preparation is increasing.[106-117]

A nitroaromatic fragment is usually synthesized using two main synthetic strategies: electrophilic aromatic substitution and functional group interconversion (based on the oxidation of aryl/or heteroarylamines). This article reviews the main methods of aromatic nitration reaction and oxidation of aryl/or heteroarylamines.

5.1. Aromatic nitration reaction

Aromatic nitration reaction occurs via Ar-S_E mechanism. Several reagent systems are useful for aromatic nitration reaction. The major factor in the choice of reagent is the reactivity of the ring to be nitrated. The conventional method employs the use nitric acid as a reagent and solvent of the reaction. The NO_2^+ cation (nitronium ion **162**) is a better electrophile than the HNO_3 (**160**) molecule. It is formed by the elimination of a water molecule in $H_2NO_3^+$ (**161**), in the presence of concentrated sulfuric acid and when concentrated nitric acid is used (Figure 8). The nitration reaction will depend on the reactivity of the aromatic ring, the more activated (richer in electrons) the more feasible the reaction. The concentration of NO_2^+ (**162**) is higher in acid sulfuric acid as solvent than in nitric acid (Figure 8). This methodology is useful for the nitration of aromatic compounds with deactivating groups. However, it can also be used in aromatic system substituted by an amino unit. It can be explained by the fact that in very acidic reaction medium the amine group will be protonated and, therefore, acting as electron-withdrawing group.[109] These conventional methods suffer from large amounts of waste acids and difficulty of regiocontrol.[107,108] As a result, several new methodologies were studied in last 30 years and will briefly be introduced.

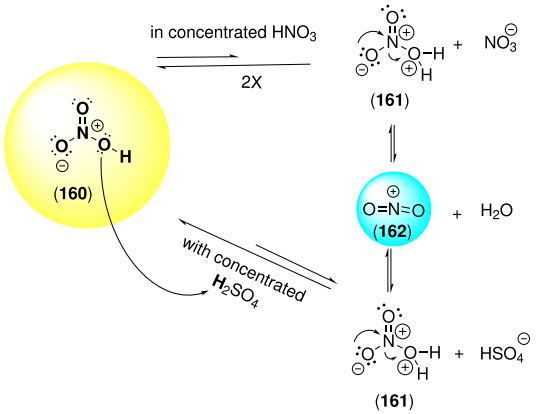
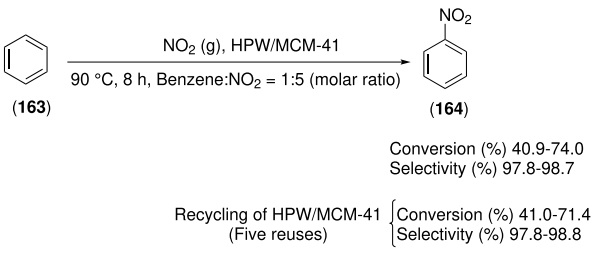


Figure 8. Reactive electrophiles in the nitration of aromatic compounds with nitric acids with different concentrations and with H_2SO_4/HNO_3.[109]

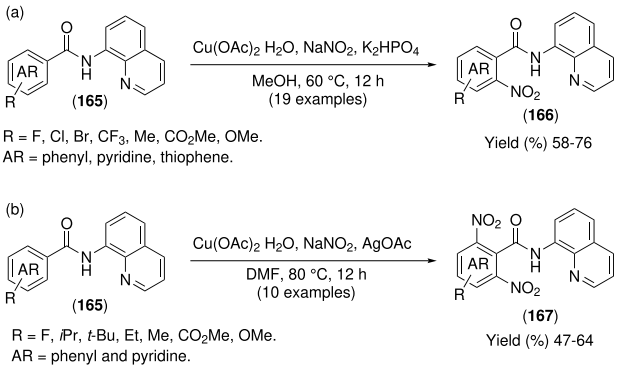
5.1.1. Recent methodologies for nitration of aromatic and heteroaromatic nitro compounds

You *et al.*[118] have reported the selective nitration of benzene using the HPW/MCM-41 catalyst. The authors studied several reaction conditions using $NO_{2(g)}$ as a nitrating agent and observed the synergistic effects of the catalyst obtained by impregnating the phosphotungstic acid ($H_3PW_{12}O_{40}$, HPW) in MCM-41 (mobil composition of matter No. 41), a solid mesoporous material composed of silicate and aluminosilicate, over the nitration reaction, obtaining the best results when 50% of HPW/MCM-41 was used, in a time of 6 h and a molar ratio of NO_2 = 1:5 (molar ratio), at 90 °C. However, to industrial applications the authors point out that there is still a need to study the stability of HPW/MCM-41 (Scheme 16). Likewise, the authors compared the efficiency of the reaction in the presence of different percentages of HPW acid in MCM-41 and other catalysts purchased commercially under the same conditions, such as SiO_2, SBA-15 (Santa Barbara amorphous-15), $H_3PMo_{12}O_{40}$ (phosphomolybdic acid, HPMo), ammonium phosphotungstate (AMPW) and ammonium phosphomolybdate (AMPMo). The authors carried out five consecutive catalyst recyclings, adding 0.02 g of HPW to maintain the amount of acid in the catalytic system, as observed in Scheme 16, the loss in efficiency is low.



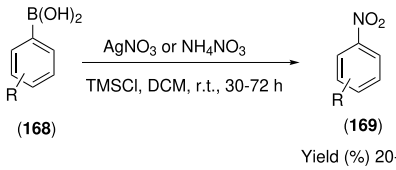
Scheme 16. Nitration reaction of benzene with NO_2 over HPW/MCM-41.[118]

Liu *et al.*[119] have studied the use of $NaNO_2$ as a nitrating agent catalyzed by copper salts. The role of several bases (NaOAc, K_2CO_3, KOAc, K_3PO_4, KH_2PO_4, K_2PO_4, Ag_2CO_3, AgOAc), different copper salts ($Cu(OAc)_2.H_2O$, $Cu(OAc)_2$, $CuBr_2$, $CuCl_2$, CuI) and solvents (MeOH, toluene, dioxane, CH_3CN, DMF, THF) were studied. The products obtained showed a critical dependence on the directing group present in 8-aminoquinoline. It was observed that the proportions of mono- or di-nitrated products (Schemes 17a and 17b, respectively) can be modulated by changing the reaction conditions.



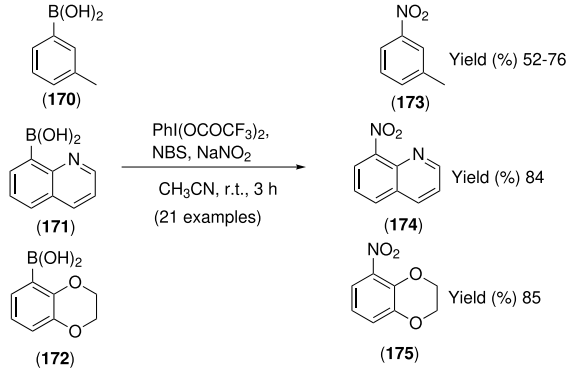
Scheme 17. Copper-mediated mononitration (a) and dinitration (b) of carboxylic acid derivatives.[119]

One of the first reports on the use of nitrate salts for the aromatic nitration of boronic acids derivatives was made by Prakash *et al.*[120] The authors proposed the use of mixtures of trimethylsilyl chloride (TMSCl) and nitrate salts for the *ipso* oxidative nitration of boronic acids (Scheme 18). They studied several salts, among which are $AgNO_3$, NH_4NO_3, $NaNO_3$, KNO_3, $Ba(NO_3)_2$, $Fe(NO_3)_3$, observing yields ≥ 95%, with the exceptions of $Ba(NO_3)_2$ where no product was obtained, and $Fe(NO_3)_3$ where was obtained in 40% of yield. In addition to the nitrated derivative, the mixture of TMSCl and nitrate salts (providing the aryl *ipso* product) can also produce chlorine-substituted derivative in approximately 2-10%. To overcome such issue, the authors suggest the use of silver salts, since they can induce the precipitation of the chloride ion as AgCl. The authors also evaluated the influence of different solvents (CH_2Cl_2, $CHCl_3$, CCl_4, $ClCH_2CH_2Cl$ and CH_3CN) on the efficiency of the reaction, with dichloromethane being considered the best solvent.



Scheme 18. *ipso*-Nitration of arylboronic acids.[120] DCM: dichloromethane; TMSCl: trimethylsilyl chloride; r.t.: room temperature.

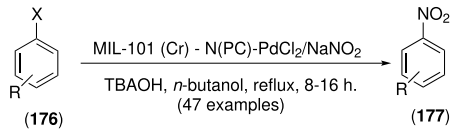
Chatterjee *et al.*[121] have described a methodology for nitrating the benzene ring under mild conditions free of transition metals. The methodology involves radical oxidative *ipso* nitration of functionalized organoboronic acids, with groups, aryl alkyl, halide, nitro, aldehyde, keto and nitrile, methoxy, as well as heteroarylboronic acids containing N, O and S. They investigated the *in situ* formation of $\bullet NO_2$ radical from the combination of [bis-(trifluoroacetoxy)]iodobenzene (PIFA), in the presence of *N*-bromosuccinimide (NBS) and sodium nitrite (Scheme 19). They have shown that under this methodology, regioselectivity can be achieved, obtaining the nitro derivatives from phenylboronic acids, in yields of 52-76%, in the presence of NBS and PIFA and acetonitrile (ACN) as solvent in 3 h of reaction, without the need for anhydrous conditions.



Scheme 19. *ipso*-Nitration of arylboronic acids.[121] NBS: *N*-bromosuccinimide; PIFA: $PhI(OCOCF_3)_2$; r.t.: room temperature.

Several works are found in the literature with variations in *ipso* nitration methodologies using boronic acids, as the one described by Murray *et al.*[122] The authors use fuming nitric acid as a nitrating agent, of some boronic acid derivatives to yield the correspondent nitro derivatives in 79-96%. They also studied the *ipso* reaction mechanism and concluded that the reaction order for HNO_3 is > 2 and indicate that $\bullet NO_2$ corresponds to the active species. The authors also report that they observed an unusual autocatalytic kinetics that results in a terminal exotherm from decomposition of HNO_3 excess.

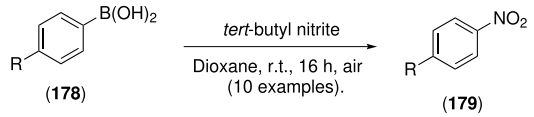
The work described by Sepehrmansourie *et al.*[123] extended the application of the *ipso*-nitration reaction to a wide range of structures, totaling 47 examples. The authors use $NaNO_2$ to carry out the nitration of boronic acids, aryl halides, aryl trifluoromethanesulfonate and aryl chloride derivatives, in the presence of a catalytic amount of palladium (Pd) embedded into MIL-101(Cr)-NH_2 (as a porous metalorganic framework) to generate a catalyst that they call "MIL -101(Cr)-N(PC)-$PdCl_2$" (Scheme 20). The authors verified the chemoselectivity of the *ipso*-nitration reaction, concluding that reactivity occurs in the following order Ar-W, where W = $B(OH)_2$ > OTf > halogens (I > Br > Cl) > COCl. The authors tested the interconversion of carboxylic groups, via the formation of acyl chlorides and hydroxyl groups via the formation of triflates, to nitro groups, with conversions reaching 80-88% (Scheme 20).



X = $B(OH)_2$, R = OMe, CHO, COMe, Br, NO_2, OH, NH_2. yield 65-89%
X = COCl, R = H, Me, OMe, NH_2, OH, NH_2, CHO. yield 72-86%
X = Otf, R = H, Me, OMe, NH_2, OH, NH_2, CHO. yield 80-88%
X = I, Cl, Br, R = H, Me, OMe, NH_2, OH, NH_2, CHO. yield 22-91%

Scheme 20. Preparation of nitro compounds via an ipso-nitration reaction using MIL-101(Cr)-N(PC)-$PdCl_2$/$NaNO_2$.[123]

Wu *et al.*[124] have proposed a modification in the methodology inicially described by Prakash *et al.*[120] (Scheme 21). The change was based on the replacement of the salt with *tert*-butyl nitrite. Further, they evaluated the influence of several solvents, including dioxane, toluene, heptane, 1,2-dimethoxy ethane, acetonitrile, ethanol, *n*BuOH and dioxane (Scheme 21). A better yield (88%) was observed when dioxane was used, at a temperature of 80 °C, in the presence of 10 mmol of *tert*-butyl nitrite in 16 h of reaction. A decrease in the amount of nitrite from 10 mmol to 6 mmol was also explored, however, there was a 15% loss in yield. The decrease in temperature from 80 to 50 °C brought a drop in conversion from 88 to 36%. For derivatives of boronic acids that have electron-withdrawing groups such as *p*-Br and *p*-COH, it was necessary to add 1 equivalent of boric acid as an additive, due to the need for additional activation of the alkyl nitrite. They concluded that this methodology cannot be applied to boronic acids with hydroxy groups or vinyl groups. Pyridinyl- and quinolinylboronic acids give deborylation products.

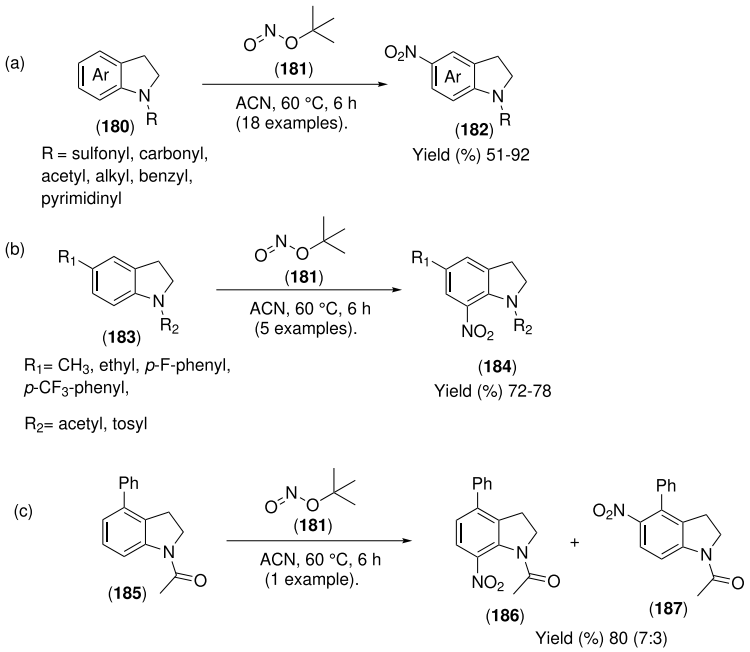


R_1=H, CH_3, OCH_3, Br, F, O-phenyl, COH. Yield (%) 22-87

Scheme 21. *ipso*-Nitration of arylboronic acids.[124]

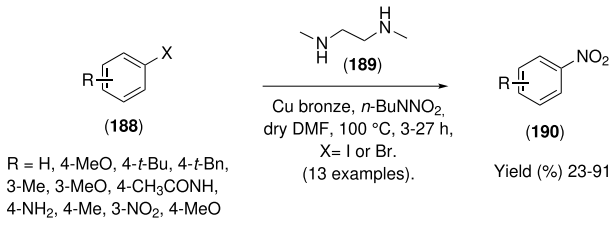
Other more recent work using *tert*-butyl nitrite was described by Sau *et al.*[125] They investigated the influence of different solvents, reaction time and temperature on mono-nitration at C-7 or C-5 of a diversity of indolines substrates, getting 100% of selectivity (Scheme 22).

The transformation of aryl iodides into nitro-compounds was studied by Saito and Koizumi.[126] The authors used CuI



Scheme 22. Mono-nitration of indolines under mild condition. (a) C-5 nitration with 100% selectivity; (b) in C-7 with 100% selectivity and (c) mixture of C-5 and C-7 nitrations.[125]

and metallic alloys of Cu and bronze, in the presence of several ligands from the amine family, aliphatic, aromatic and cyclic, in the presence of any of the salts: KNO_2, $NaNO_2$ or n-Bu_4HNO_2, whether or not containing 18-crown-6 as an additive in the presence of DMF or dry DMSO as solvent to convert aryl iodides into nitro-compounds in moderate yields (Scheme 23). The best results were obtained for substrates 4-*t*-Bu-iodobenzene and 4-OMe-iodobenzene treated with the Cu bronze alloy (5 mol%), the ligand dimethylenediamine ($CH_3N(C_2H_4)_2NCH_3$) (10 mol%), in the presence of n-Bu_4NNO_2 (1.2 equiv) in dry DMF at 100 °C for a period of 21-27 h.

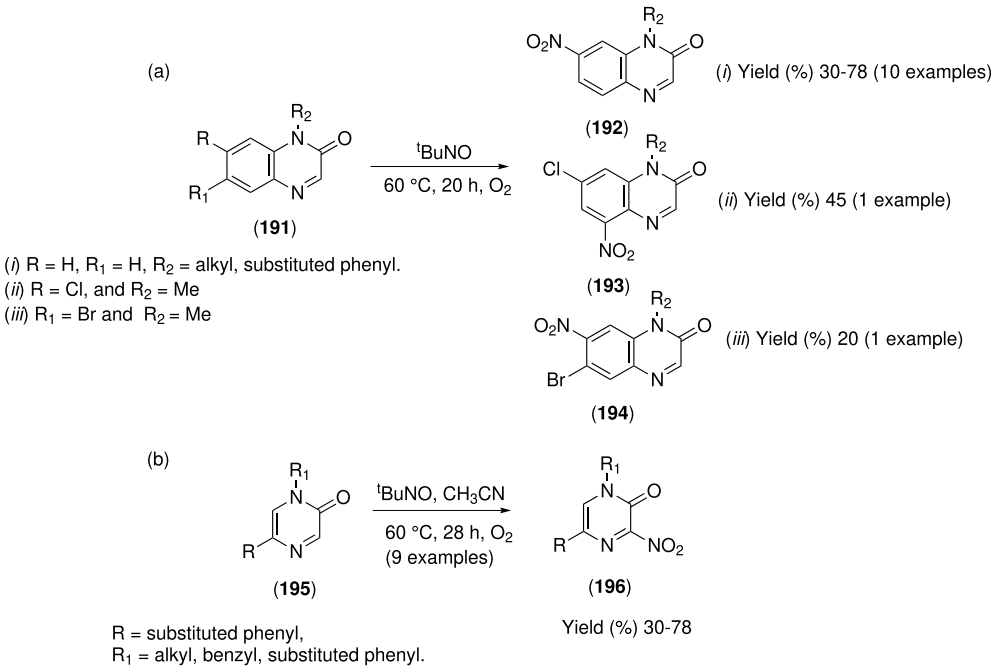


Scheme 23. Nitration of haloarenes catalyzed by Cu-bronze.[126]

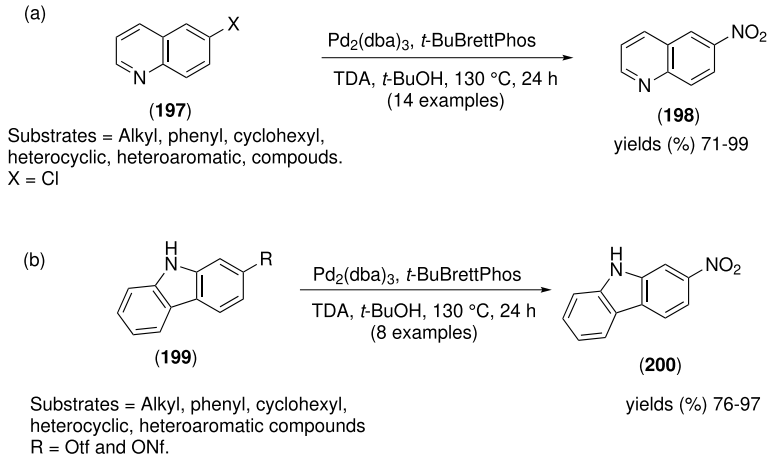
Among the methodologies using *t*-butyl nitrite as a nitrating agent the one described by Moon *et al.*[127] deserves to be highlighted. The authors studied the selective nitration of quinoxalinones and pyrazinones in the presence of *t*-butyl nitrite (Scheme 24). The reactions were carried out using a quinoxalinone: *t*-butyl nitrite ratio of 0.2 mmol:0.6 mmol, in the presence of CH_3CN as solvent, under an O_2 atmosphere at 60 °C for 20 h, to produce the desired product in 20-78% (Scheme 24a). The nitration of 5-aryl-pyrazin-2-ones was carried out using 0.2 mmol (*t*-butyl nitrite):1.0 mmol (substrate), in CH_3CN under an O_2 atmosphere at 60 °C for 28 h, with a yield of 30-78% (Scheme 24b). The authors carried out subsequent scale-up tests, on the gram scale, obtaining yields of 68% for quinoxalinone and 65% pyrazin-2-ones, demonstrating that the methodology can be reproducible and robust.

Fors and Buchwald[128] have described an efficient procedure for converting aryl chlorides, triflates and nonaflates to nitroaromatic compounds, using palladium as a catalyst and biarylphosphine ligands. The best condition was obtained when aryl chlorides (Scheme 25a) and triflates/nonaflates (Scheme 25b) were subjected to the following reaction conditions: 0.5-2.5 mol% ($Pd_2(dba)_3$, 1.2 mol% of *t*-BuBrettPhos ligand, in the presence of 5-6 mol% of tris(3,6-dioxaheptyl)amine (TDA), *t*-BuOH, at a temperature of 130 °C, in a time of 24 h, with yields of 71-99% (Scheme 25).

Rajanna *et al.*[129] have studied the nitration reaction of phenols with various metallic nitrates, such as $Zn(NO_3)_2$, $Cu(NO_3)_2$, $Ni(NO_3)_2$, $Zr(NO_3)_2$, $Cr(NO_3)_2$, $Cd(NO_3)_2$, $Co(NO_3)_2$ and $AgNO_3$, in the presence of several polyethylene glycols (PEGs, such as PEG-200, PEG-300, PEG-400, PEG-600, PEG-4000 and PEG-6000). The best yields were achieved using PEG-400 and $Zn(NO_3)_2$. The authors compared the influence of ultrasonic-assisted organic synthesis (USAOS) and microwave-assisted synthesis (MWAS) in relation to conventional heating methods (70-90% yield, 24 h of reaction and 90 °C). Increases of 3-7% were observed for the use of USAOS



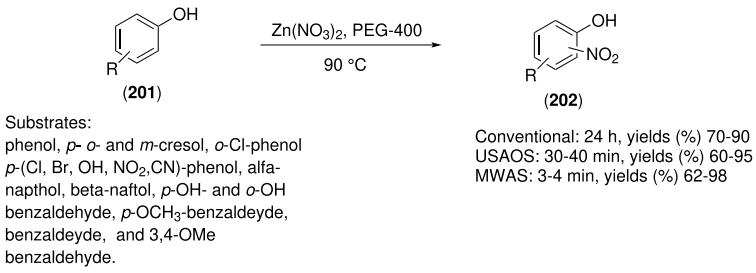
Scheme 24. Nitration of quinoxalinones (a) and 5-aryl pyrazin-2-ones (b).[127]



Scheme 25. Conversion of aryl chlorides (a), aryl triflates and nonaflates (b) to nitroaromatics.[128]

(40-45 min of reaction) and 8-12% (3-5 min reaction) in yield using MW when compared to conventional (Scheme 26).

Sun *et al.*[130] have proposed a phenol nitration protocol using metalloporphyrins in the presence of peroxynitrite ($ONOO^-$), which could be prepared by H_2O_2 and $NaNO_2$. Authors demonstrated that metalloporphyrins may have the potential to catalyze nitration reaction in the metalloporphyrins/H_2O_2/NO_2^- system or FeTSPP/H_2O_2/NO_2^- system. They described the preparation of several metalloporphyrins, based on the reaction



Scheme 26. Nitration of aromatic compounds (phenols) using $Zn(NO_3)_2$ in PEG-400.[129]

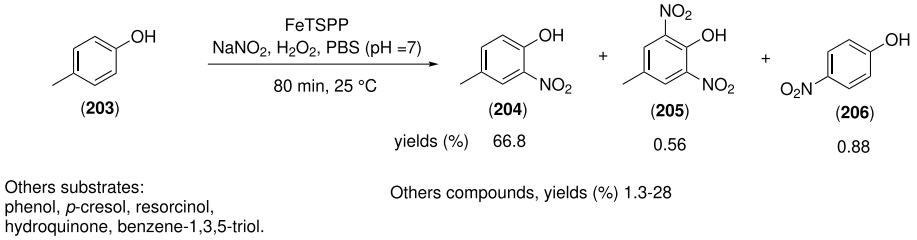
of porphyrins and $FeCl_3$, $CoCl_2$, $MnCl_2$, $CuCl_2$ or $Zn(OAc)_2$. The metalloporphyrins/H_2O_2/NO_2^- system showed the formation of traces of products, while the FeTSPP/H_2O_2/NO_2^- system proved to be more efficient, reaching yields of approximately 0.56-66.8%. Further, the authors compared the iron porphyrins FeTSPP system with the nitration capacity of several enzymes *in vitro*, such as horse radish peroxidase and laccase. They demonstrated a better yield for the nitration catalyzed by FeTSPP than the one performed by the selected enzymes (Scheme 27).

You *et al.*[131] have studied the nitration of naphthalene and 1-nitronaphthalene with nitrogen dioxide without the use of nitric acid/sulfuric acid or nitric acid, in the presence of cold liquid nitrogen dioxide ($NO_{2(l)}$) and catalyst in a sealed autoclave. The authors evaluated the influence of temperature (50 to 150 °C) on the selectivity of the reaction, observing that an increase in temperature leads to an increase in the conversion of 1-nitronaphthalene from 3.6 to 41.5%, high temperatures accelerate the formation of trinitration products. The best temperature and molar ratio of 1-nitronaphthalene to NO_2 to obtain the dinitrated derivatives was 100 °C and 1:2 in a reaction time of 3 h. The nitration reaction of 1-nitronafthalene in the presence of $Ni(CH_3COO)_24H_2O$ under optimized conditions led to the best results with 33.10 conversion and 34.10, 19.30 and 23.56% selectivity for 1,5-dinitronaphthalene (1,5-DNN), 1,4-dinitronaphthalene (1,4-DNN), 1,3-dinitronaphthalene (1,3-DNN), respectively (Scheme 28).

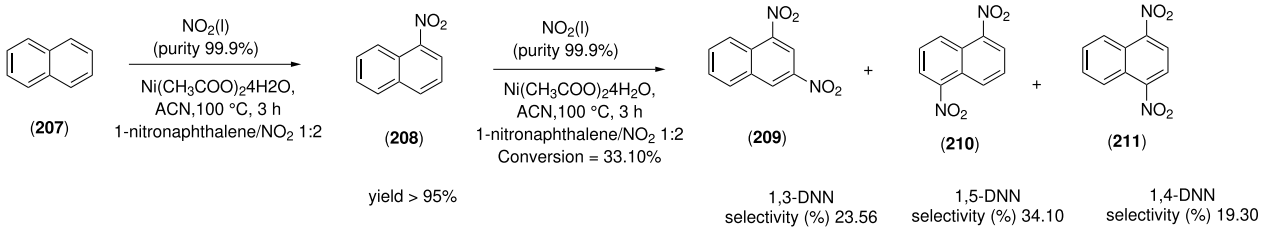
A radical nitration methodology, under mild conditions, using isoamyl nitrite in dichloromethane at room temperature, was described by Deng *et al.*[132] The authors applied the method to the nitration of norcorrole and evaluated the time and selectivity of nitration. After 1 h of reaction, the mononitration product was obtained selectively in 80% yield. Within 2 h, isomers with dinitration products were obtained. At times of 3 and 5 h, tri-nitration and tetra-nitration products were obtained in yields of 50 and 52%, respectively (Scheme 29). The data reveal the time dependence of the nitration regioselectivity.

Dhokale and Mhaske[133] developed a nitration method from *o*-silylaryl-triflates and $NaNO_2$. The authors carried out the procedures in the range of 50-500 mg, the reaction occurs in the presence of a source of fluoride ion which can be: CsF, KF, TBAF or CsF, in the presence or absence of additives such as 18-crown-6, H_2O, or mixtures of additives with $Mg(OtBu)_2$ or $Cu(OTf)_2$ in a time of 1-24 h at 0 °C or room temperature. Yields depend on the substituent on the phenyl ring and vary between 30-63% for the compounds studied. The authors also carried out some tests for a multicomponent reaction, employing *o*-silylaryl-triflates, in the presence of aromatic and aliphatic aldehydes, with the aim of providing methodologies for the preparation of carbinols, obtaining yields of 26 to 60% (Scheme 30).

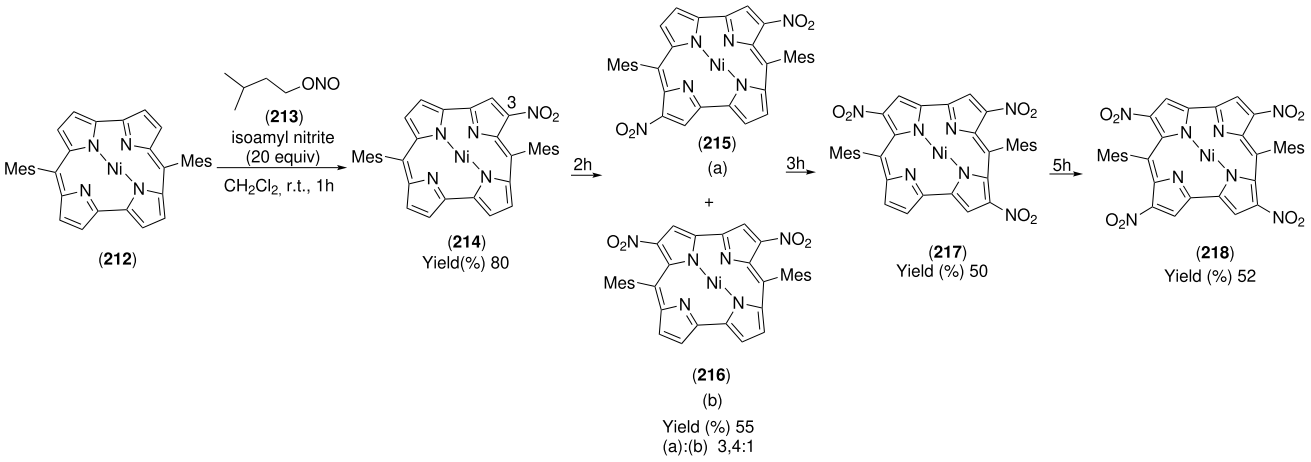
Katritzky *et al.*[134] and Duddu *et al.*[135] reported extensive studies applying mixtures of HNO_3/H_2SO_4 and some additives to carry out the nitration of 1-methyl-1*H*-imidazole and other heterocycles (pyrazole, imidazole, 3-methylisoxazole, isothiazole, thiazole, 4-methylthiazole and 3,5-dimethylthiazole). Katritzky *et al.*[134] have found in their research that pyrazole, imidazole and isoxazole undergo nitration as quickly as nitrobenzene, while thiazole and isothiazole react less easily, approximately the same as *m*-dinitrobenzene, and oxadiazole, thiadiazole, triazole, etc., with great difficulty. Strong electron-donating substituents favor the occurrence of substitution, but the reaction conditions required for nitration are more



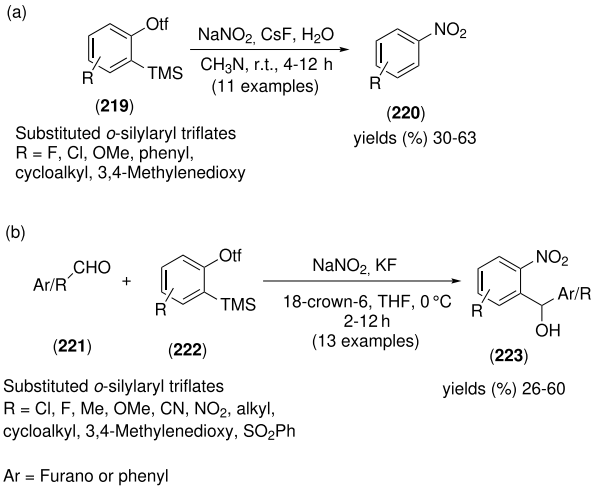
Scheme 27. Nitration of aromatic compounds (phenols) using FeTSPP/H_2O_2/NO_2^- system in phosphate sodium buffer (PBS) (pH = 7).[130]



Scheme 28. Regioselective synthesis of dinitronaphthalene from 1-nitronaphthalene with nitrogen dioxide as nitrating reagent.[131]



Scheme 29. Nitration of the norcorrole ring with isoamyl nitrite.[132]



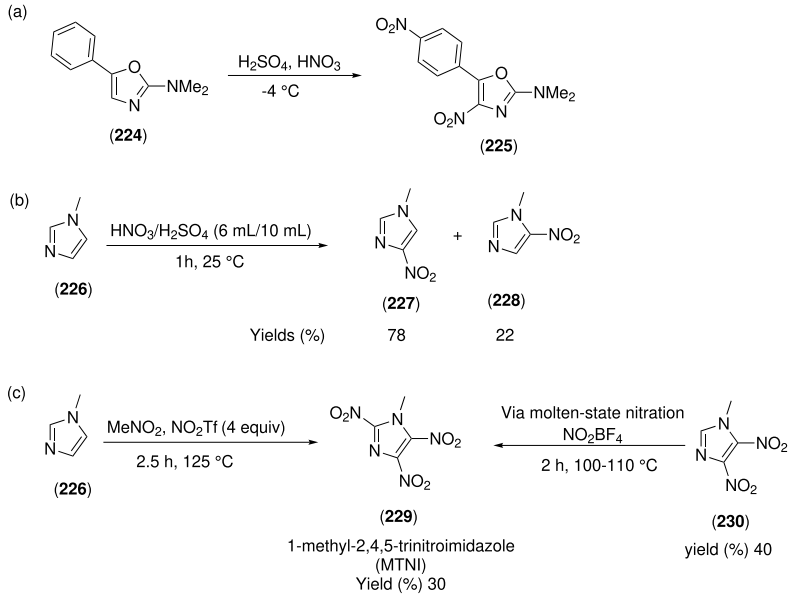
Scheme 30. (a) Nitration of *o*-silylaryl triflates by sodium nitrite; (b) multicomponent reaction (MCR): preparation of carabinol *o*-nitroderivatives from aldehydes and o-silylaryl triflates.[133]

vigorous than for benzene and milder than for pyridine. Thus, based on the results, nitration in the oxazole ring is rare, and so the derivative shown in Scheme 31a is an interesting example where nitration was possible under the conditions indicated, unfortunately the authors do not report the yield obtained. It is important to note that the work by Duddu *et al.*[135] focused especially on obtaining 1-methyl-2,4,5-trinitroimidazole (MTNI), testing different conditions with variations in time, nitration agent and reaction time. Among the best conditions obtained was the use of a mixture of 6 mL of HNO_3 and 10 mL of H_2SO_4 at 25 °C, for the nitration of 1-methyl-1*H*-imidazole, which led to the formation of 1-methyl-4-nitro-1*H*-imidazole in 78% after 1 h of reaction (**227**, Scheme 31b), increasing the temperature led to the formation of a mixture of di- and trinitrated products. The reaction in the presence of 4 equivalents of nitronium trifluoromethanesulfonate ($NO_2.CF_3SO_3$) and $MeNO_2$ and gradually heated to 125 °C for 2.5 h, led selectively to obtaining MTNI (**229**, Scheme 31c), while the reaction via a nitration route in the molten state in the presence of NO_2BF_4 at a temperature of 100-110 °C and 2 h, led to 40% of MTNI (**229**, Scheme 31c), these being the best results obtained.

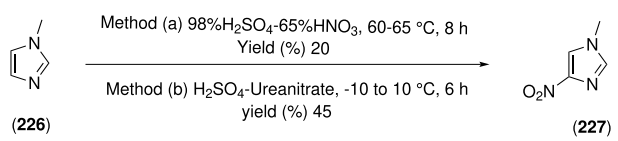
An adjustment to the temperature and reaction conditions employed by Katritzky *et al.*[134] in 2010 and by Duddu *et al.*[135] in 2011, was proposed by Shahid *et al.*[136] in 2016. The authors have demonstrated that temperature is an essential parameter for selectivity, reporting a yield of 20% for the regioisomer 1-methyl-4-nitro-1*H*-imidazole, in a reaction at 65 °C/8 h, using a mixture of 98% H_2SO_4 (non-fuming) and 65% HNO_3. In another reaction, the authors tested urea nitrate/non-fuming conc. H_2SO_4 (98%) at low temperatures, –10 to 10 °C, and selectively obtained in 45% of yield the regioisomer 1-methyl-4-nitro-1*H*-imidazole (Scheme 32).

Matsumoto *et al.*[137] described a methodology to be applied in the nitration of anisole and cresol derivatives, for various substrates substituted in the phenyl group, such as: by 1,4-dimethoxy-, 1,2-dimethoxy-, 1,3-dimethoxy-, 1,3,5-dimethoxy- and 4-methyl-, and substituted in the naphthalene group, such as: 1-methoxy-, 2-methoxy- and 3,3-dimethyl-. This methodology was based on the use of $Mg(NO_3)_2$, as a nitrating agent, impregnated in silica gel. The process was carried on solid state and proved to be efficient, providing mononitration products, based on the targeting of substituents on the ring, with yields of 9-82% of isolated product, as an example shown in the nitration of 2-methoxynaphthalene in Scheme 33a. The authors observed the formation of different products when using *p*-cresol and 2-naphthol, in the presence of $Mg(NO_3)_2$, resulting in 2-nitro-*p*-cresol and 4-tolylnitrate in the first case and naphthalene-2-ylnitrate in the second case, where nitration occurred in the hydroxyl group (Scheme 33b).

Zhou *et al.*[138] have carried out selective nitration



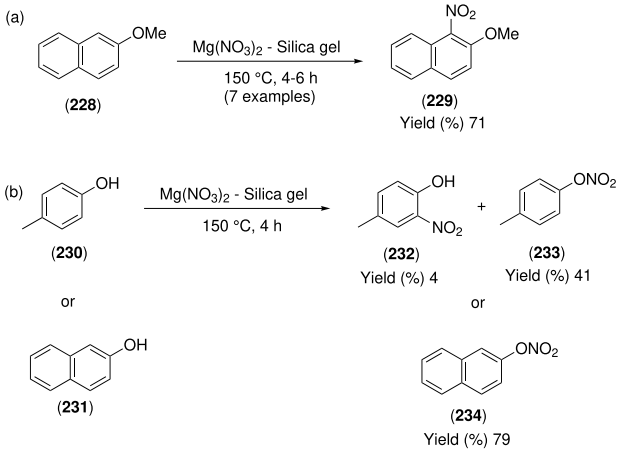
Scheme 31. Nitration of oxazoles (a) and imidazoles (b and c).[134,135]



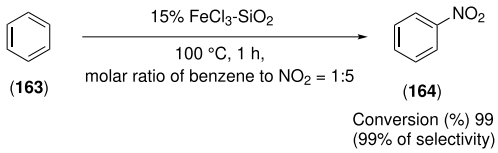
Scheme 32. Synthesis of 1-methyl-4-nitro-1*H*-imidazole.[136]

studies of benzene, using a highly efficient catalyst, mesoporous silica-immobilized $FeCl_3$ ($FeCl_3$-SiO_2) and $NO_{2(g)}$ (purity > 99.9%). The authors prepared the catalyst impregnating the SiO_2 with different amounts of $FeCl_3$. The catalysts were named based on their percentage of $FeCl_3$: 5% $FeCl_3$-SiO_2, 15% $FeCl_3$-SiO_2 and 25% $FeCl_3$-SiO_2. The authors carried out a comparative analysis with other catalysts, to demonstrate the efficiency of the prepared catalyst. When comparing the results obtained from homogeneous catalysis ($FeCl_3$) and heterogeneous catalysis (15% $FeCl_2$-SiO_2), a gain of 5.8% in conversion was observed for the latter. Additionally, a study of the variables that influence the reaction was carried out, evaluating the temperature, molar ratio of benzene and $NO_{2(g)}$ and amount of catalyst, with the best results being obtained with a molar ratio of benzene and $NO_{2(g)}$ of 1:5, a temperature of 100 °C and a reaction time of 1 h (Scheme 34).

Saha *et al.*[139] have reported the preparation of nitrosyl complex of cobalt porphyrin [(Cl_4TPP)-Co(NO)] which in the presence of CH_2Cl_2/CH_3CN and H_2O_2 can generate *in situ* the Co-nitrite complex [(Cl_4TPP)Co(NO_2)] that was used in the nitration of 2,4-ditertiarybutylphenol to obtain 2,4-di-*tert*-butyl-6-nitrophenol, in 50% yield (Scheme 35). The authors do not cite further examples but assume that the mentioned nitration reaction occurs via the formation of the corresponding Co-peroxynitrite intermediate.

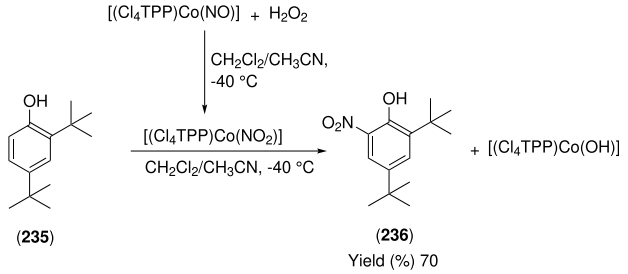


Scheme 33. Products of solid-phase nitration. Anisoles (a) and phenols (b).[137]

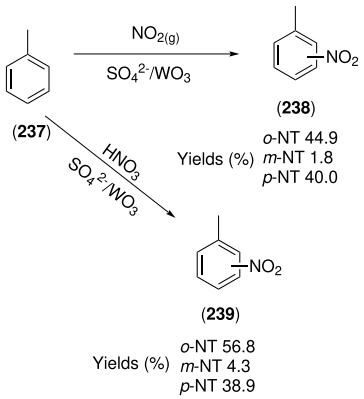


Scheme 34. Benzene nitration with 15% $FeCl_3$-SiO_2.[138]

A selective nitration of toluene was described by Jiao *et al.*[140] Authors demonstrated that using $NO_{2(g)}$ (purity, 99.9%) as a nitrating agent and SO_4^{2-}/WO_3 as substituents for traditional HNO_3 and H_2SO_4, under mild reaction conditions the selective nitration of toluene was achieved (Scheme 36). The methodology with NO_2 showed moderate results, with yields of approximately 44.9% for *o*-nitrotoluene (*o*-NT) and 40.0% for *p*-NT, forming approximately 1.8% of *m*-NT products, maintaining conversion in cycles of 80-100%, with selectivity of 87%, for mononitration derivatives, even after 5 recycling,



Scheme 35. Nitration of 2,4-ditertiarybutylphenol from the Co-nitrite complex $[(Cl_4TPP)Co(NO_2)]$.[139]



Scheme 36. Nitration of toluene with NO_2 and HNO_3 over sulfated SO_4^{2-}/WO_3 catalyst.[140]

thus demonstrating that this type of process can be more environmentally acceptable. For the reaction with SO_4^{2-}/WO_3 and HNO_3, the yield was 56.8% for *o*-NT, 4.3 for *m*-NT and 38.9% for *p*-NT, however, the conversion drops from 100%, in the second cycle to 63% and in the fifth to 22%, showing the advantage of the process with NO_2.

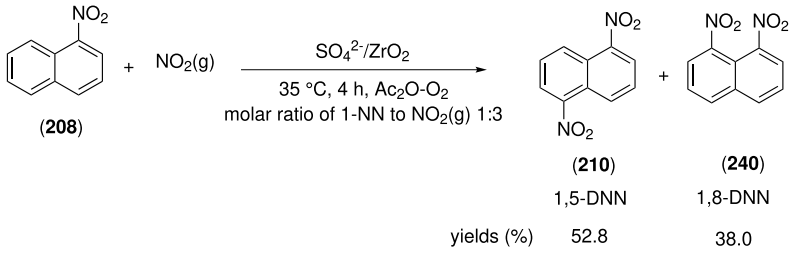
Yan *et al.*[141] have carried out a similar methodology using $NO_{2(g)}$ as a nitrating agent, but changing the support WO_3 for ZrO_2 and in the presence of $O_{2(g)}$ and acetic anhydride to study the nitration of 1-nitronaphthalene to 1,5-dinitronaphthalene. The methodology showed similar yield and selectivity to that of toluene nitration, even considering the difference in substrates and second nitration in naphthalene ring. The best results allowed a conversion of 90.8%, with 52.8% being 1.5-DNN and 38.0% being 1.8-DNN (Scheme 37).

Several authors have explored the use of solid catalysts in the nitration reaction, such as copper-cobalt with a synergistic effect on Cu^{I}-$xCo_xFe_2O_4$ spinel ferrite,[142] zeolites,[143,144] catalysts supported on SiO_2, such as: MoO_3/SiO_2,[145] WO_3/SiO_2,[146] WO_3-TiO_2/SiO_2,[147] H_2SO_4/SiO_2,[148] $H_3PO_4/MoO_3/SiO_2$,[149] or on other supports, such as: sulfated zirconia,[141,150] sulfated titania,[151] sulfated SnO_2,[152] heteropolyacid,[153] super-acidic metal oxides[154] and Fe(III) pillared acid activated montmorillonite.[144]

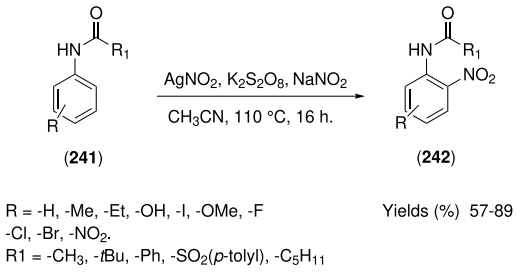
Kianmehr and Nasab[155] have studied extensively the nitration of anilides catalyzed by $AgNO_2$ and palladium catalysts, including $Pd(OAc)_2$ and $PdCl_2$ and compared them with the results previously described in the literature.[141,156-159] The reaction was tested in the presence of several oxidants, such as $K_2S_2O_8$, $(NH_4)S_2O_8$, NaS_2O_8, *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), $Cu(OAc)_2.H_2O$ and CuO and several solvents, including the most used acetonitrile. The work describes the methodology applied to 20 examples, at temperatures of 90-110 °C. The authors demonstrated the applicability of the methodology to various substrates, revealing that the method is tolerant to functional groups that increase and decrease the electron density of the aromatic ring (Scheme 38).

Deng *et al.*[160] have described methodology to aromatic nitration of toluene using alumina supported on silica $AlCl_3$-SiO_2. The authors prepared different catalysts with different concentrations of alumina, 10% $AlCl_3$-SiO_2, 15% $AlCl_3$-SiO_2 and 20% $AlCl_3$-SiO_2 (wt.%), respectively. Then, they tested their catalytic activity in the presence of $NO_{2(g)}$ (wt.% > 99.9). The best reaction condition (at 35 °C) allowed obtaining 100% selective mononitrotoluene, with a yield of 65.7% and a proportion of 45.4% *p*-NT, 50.3% *o*-NT and 4.3% from *m*-NT. The 10% $AlCl_3$-SiO_2 catalyst was recycled and reused 5 times, maintaining catalytic activity (Scheme 39).

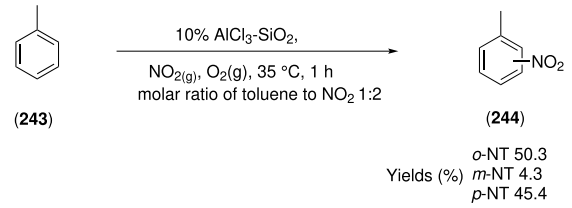
Lowe[161] describes in his work the nitration of naphthyridines, indicating that the nitration reaction takes place when donor groups are in the 2- and/or 4-positions and occurs more easily when there are donor substituents in both positions. Thus, the nitration reaction of 1,7-naphthyridine-4(l*H*)-one produces the derivative 3-nitro-1,7-naphthyridin-4(1*H*)-one (Scheme 40a) and the nitration of 4-hydroxy-l,7-naphthyridin-2-one



Scheme 37. Catalytic nitration of 1-nitronaphthalene (1-NN) with $NO_2(g)$ over SZr catalyst promoted by $O_2(g)$ and acetic anhydride.[141]

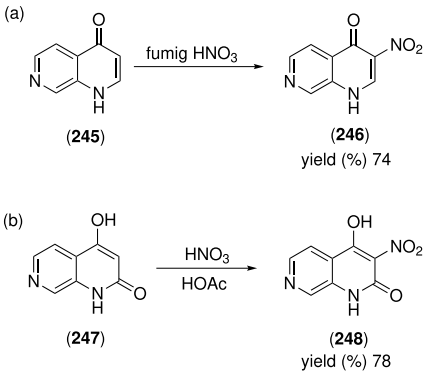


Scheme 38. Silver-catalyzed regioselective *ortho*-nitration of anilides.[155]



Scheme 39. Catalytic nitration of toluene over immobilized $AlCl_3$-SiO_2.[160]

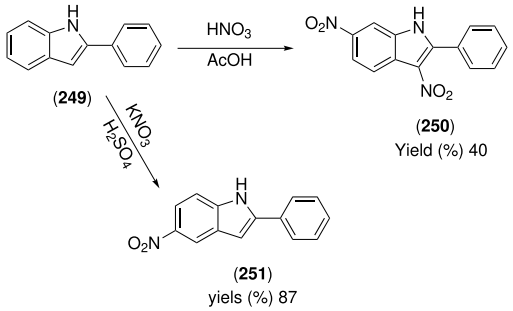
produces 4-hydroxy-3-nitro-1,7-naphthyridin-2(1*H*)-one (Scheme 40b), while when there are other activated positions, the substitution will depend on the reaction conditions (H_2SO_4/HNO_3 or HNO_3/Ac_2O).



Scheme 40. Catalytic nitration of naphthyridine (a) and naphthyridinone (b).[161]

Hurst[162] describes numerous methodologies for nitrating heterocyclic compounds, including the preparation of derivatives containing the nitro group from indoles, such as 2-phenyl-1*H*-indole, which has different reactivities based on the reagents used for nitration, thus, in the presence of nitric acid and acetic acid, 3,6-dinitro-2-phenyl-1*H*-indole is obtained in 40% yield, whereas in the presence of nitrate salts and sulfuric acid, 5-nitro-2-phenyl-1*H*-indole is obtained in 87% yield (Scheme 41).

Calvo *et al.*[163] carried out an in-depth study of the direct nitration of many aryl derivatives, including heterocycles, to obtain nitroarenes and nitroheteroarenes by reaction with the nitration reagent (**253**), which was found to be stable on the bench, cheap, easy to synthesize and recyclable. The saccharin derivative has a simple



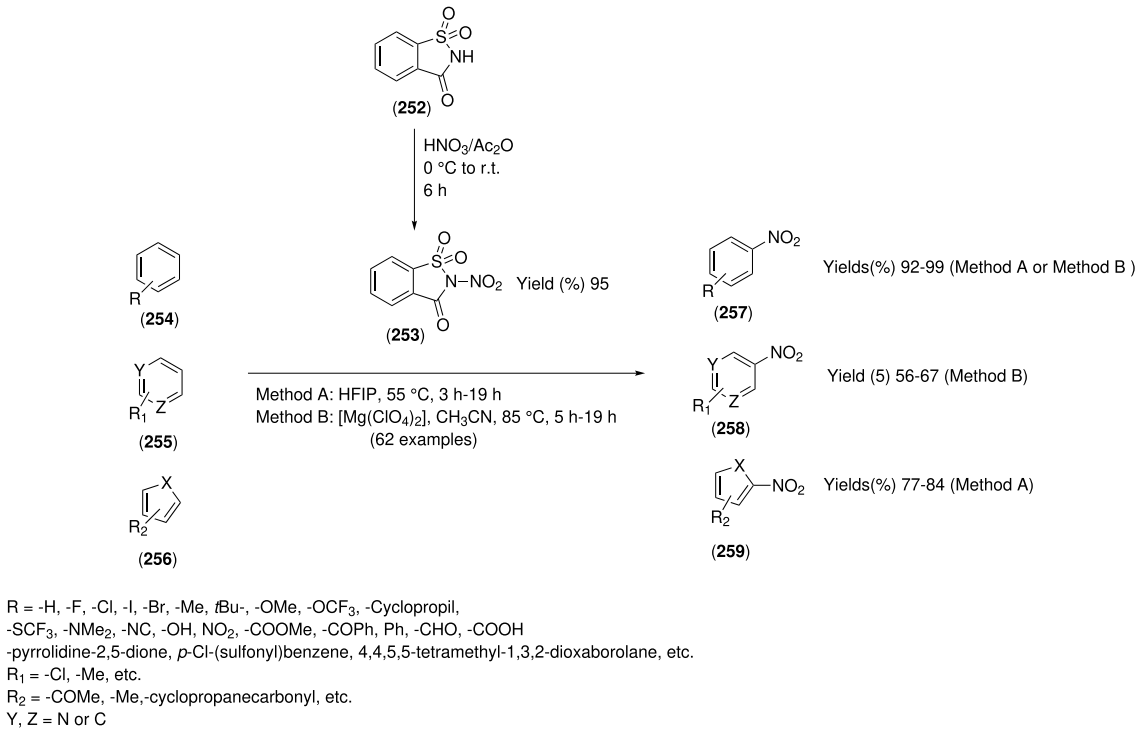
Scheme 41. Catalytic nitration of 2-phenyl-1*H*-indole in the presence of HNO_3/AcOH and KNO_3/H_2SO_4.[162]

procedure for obtaining it, as shown in the Scheme 42. The authors describe the reagent as a controllable source of nitronium ions, an important feature for the nitration of arenes and heteroarenes, which favors tolerance with different functional groups. This is briefly illustrated in Scheme 42. The protocol developed by the authors is acid-free. It can be carried out in two ways with different proportions of reagents depending on the substrate used. In the first method A, the nitration agent (**253**) is used in the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at a temperature of 55 °C. In the second protocol method B, the nitration agent (**253**) is used in the presence of magnesium perchlorate ($Mg(ClO_4)_2$) at 85 °C (Scheme 42).

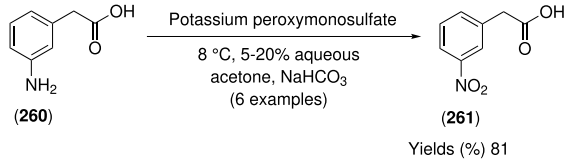
5.2. Recent methodologies for oxidation of aryl/or heteroarylamines to obtain the nitroaryl/or nitroheteroaryl derivatives

Other methodologies used at industrial level to obtain nitroaromatic compounds are the direct oxidation of aryl/or heteroarylamines. Therefore, there are several oxidizing agents reported in the literature. Among them, potassium peroxymonosulfate - oxone (O_3) was used by Webb and Seneviratne[164] to convert anilines substituted with aliphatic carboxylic acids and alcohols to the correspondent nitroaromatic derivatives (Scheme 43). The reaction was carried out under mild conditions for several substrates, such as 4-aminobenzoic acid, 4-aminophenethyl alcohol, 4-aminophenylacetic acid, 4-(4-aminophenyl) butyric acid and 5-aminosalicyclic acid, with yields ranging between 73-84%.

Dewkar *et al.*[165] evaluated the catalytic activity of the heterogeneous catalyst Ti superoxide, prepared by the action of 50% H_2O_2 on $Ti(OR)_4$ in anhydrous MeOH at 25 °C, in the selective oxidation of arylamines to nitrobenzene, and of aliphatic amines to oximes and ketones (Scheme 44). It was observed that the selectivity of the reaction is dependent on the molar ratio of H_2O_2/amine, with the best results being obtained in the proportion 6/1, as shown for 4-methylaniline, which provides 4-methylnitrobenzene



Scheme 42. Electrophilic nitration of arenes and five- and six-membered heteroarenes using *N*-nitrosaccharin.[163]

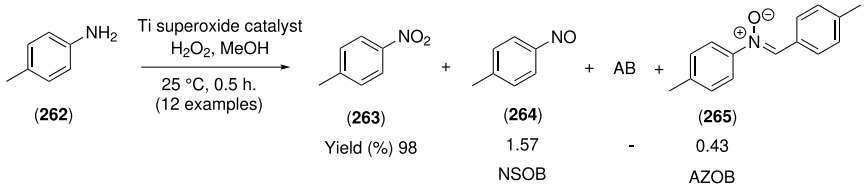


Scheme 43. Oxidation of aromatic amines with potassium peroxymonosulfate - oxone (O_3) in aqueous acetone.[164]

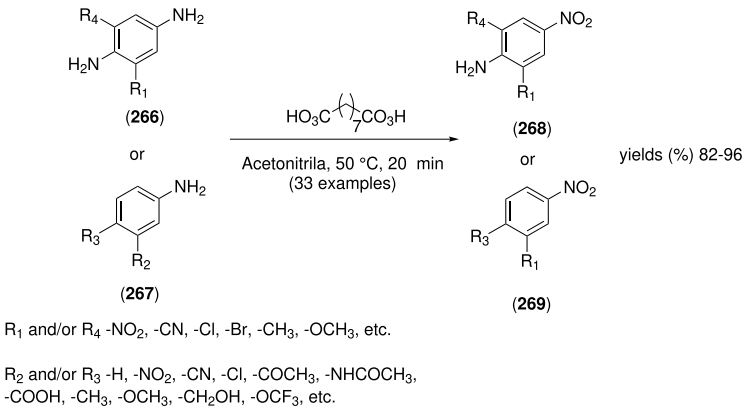
in 98% yield. Other by-products were obtained in proportions that are dependent on the substrate type, these being nitrosobenzene (NSOB), azobenzene (AB) and azoxybenzene (AZOB) (Scheme 44).

Patil and Shankarling[166] studied the regio- and chemoselective oxidation of arylamines to the corresponding arylnitro derivatives using nonanebis(peroxoic acid) ($HO_2OC(CH_2)_7CO_2OH$). The authors observed that the reaction involves hydrogen bonding in the *ortho* positions of the ring, with the reaction being effective when the groups –H, $–NH_2$, $–NHCH_3$, –OH, $–NHCOCH_3$ and –NHPh are present in this position and null when groups without hydrogens are substituted in the *ortho* position (such as: $–NO_2$, –CN, –Cl, $–CH_3$, $–OCH_3$, $–N(CH_3)_2$). The authors also studied the effects of different solvents, concluding that acetonitrile is the most suitable, allowing conversions of 100% of nitro compounds, in a time of 20 min (Scheme 45).

Ravi *et al.*[167] have reported the selective oxidation of several aromatic amines into the respective nitro compounds, using a mixture of formic acid (HCOOH) in hydrogen peroxide (aqueous solution, H_2O_2) at a temperature of 35 °C. The authors evaluated the effect of several surfactants on the dispersion of organic compounds, which improved the selectivity, with the best results being observed when cetyltrimethylammonium bromide (CTAB) was used, obtaining 85% of selectivity for the formation of nitrobenzene. According to the authors, CTAB can stabilize the nitrous oxide intermediate and prevent the further addition of aniline to form by-products. The effect of H_2O_2 concentration and aniline/H_2O_2 molar ratio in the reaction medium was also studied. They observed that the increase in H_2O_2 concentration leads to the increase in the conversion rate and selectivity. In the same way the increase in molar ratio of aniline/H_2O_2 led to the increasing in the

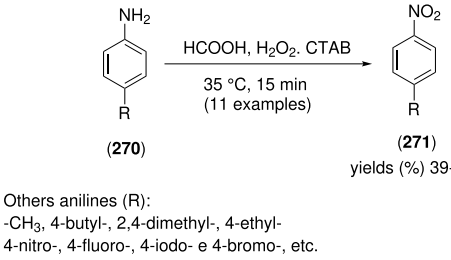


Scheme 44. Oxidation of amines with Ti superoxide as catalyst.[165]



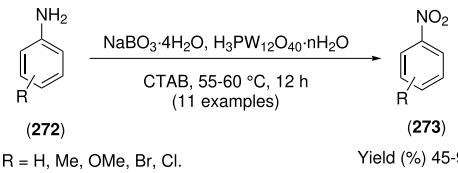
Scheme 45. Selective oxidation of various aromatic and diamines with peroxoic acid.[166]

selectivity of nitro-derivatives formation, the best condition being 1:6 (Scheme 46).



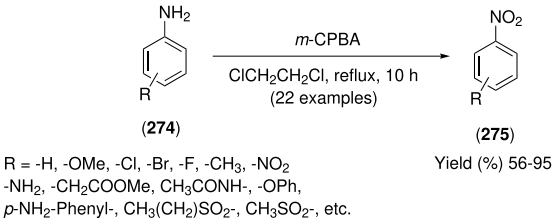
Scheme 46. Selective oxidation of aromatic amines with $HCOOH/H_2O_2$.[167]

The catalytic force of sodium perborate ($NaBO_3{\cdot}4H_2O$, SPB) in water, CTAB and tungstophosphoric acid ($H_3PW_{12}O_{40}{\cdot}nH_2O$) in the oxidation of anilines substituted by electron-donating groups was studied by Firouzabadi and Amani.[168] The authors have demonstrated the efficiency of the proposed method, being the best results obtained at a temperature of 50-60 °C. They suggested that the presence of CTAB increases chemoselectivity, favoring the formation of nitroarene derivatives (Scheme 47).



Scheme 47. Oxidation of anilines in the presence of $H_3PW_{12}O_{40}{\cdot}nH_2O$/ $NaBO_3{\cdot}4H_2O$.[168]

Arylamines can also be oxidized using *meta*-chloroperoxybenzoic acid (*m*-CPBA), as described by Liu *et al.*[169] The authors studied the oxidation of several aromatic amines with *m*-CPBA in the presence of different solvents, identifying the 1,2-dichloroethane as the best one. They also demonstrated that the oxidation methodology is well tolerated in the presence of several substituents on the aryl group (Scheme 48).

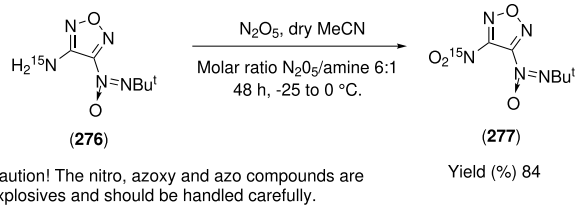


Scheme 48. Oxidation of anilines in the presence of *m*-CPBA.[169]

More recently, Capperucci and Tanini[170] have published an excellent review work, describing multiple methodologies for the oxidation of arylamines to their respective nitrocompounds. The main oxidizing systems used in this interconversion of functional groups (Ar-NH_2 → $ArNO_2$) include: peroxyacids such as *m*-CPBA, *m*-CPBA/$[bmim]_3[PW_{12}O_{40}]$), nonanebis, TBHP/CuAlPO-5, TBHP/chromium silicalite-2 (CrS-2), TBHP/dirhodium caprolactamate ($Rh_2(cap)_4$), TBHP/manganese(III) tetraaryl porphyrins and TBHP/$Zr(OtBu)_4$; and oxidation with hydrogen peroxide, such as $H_2O_2/CaWO_4$, $H_2O_2/K_7[PMo_2W_9O_{39}]{\cdot}19H_2O$, H_2O_2/K_2CO_3.

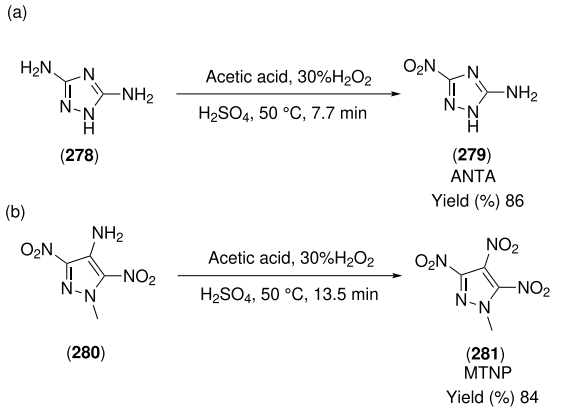
Several other catalysts have already been described and applied to the transformation of arylamines into arylnitro derivatives. These include the use of methylrhenium trioxide,[171] peroxomonosulphate (PMS) in phthalate buffers[172] and peroxodiferric complex.[173]

Churakov *et al.*[174] studied the transformation of the amino group to the nitro group in heterocycles, using dinitrogen pentoxide (N_2O_5) as the oxidizing agent. The authors identified that the oxidation reaction goes through several intermediate transformations: amine-nitramine-nitroso-nitro compound. To prove their hypothesis, they carried out the reaction with ^{15}N-labeled intermediates, as shown in Scheme 49, thus verifying, through experimental evidence, that this methodology leads to an oxidation product and not a substitution product.



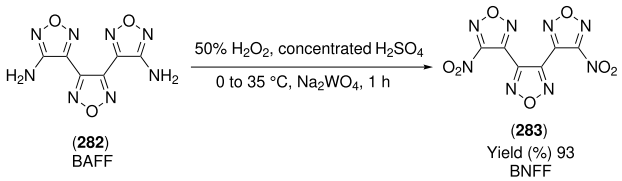
Scheme 49. Oxidation of heterocyclic amines to nitro compounds using N_2O_5.[174]

Although, in theory, there is the possibility of synthesizing nitroheterocycles from the oxidation of heteroarylamines, this method is very little explored in the literature. In the last thirty years, it has not been possible to find any significant examples of the application of this approach. However, it is worth mentioning the work of Wu *et al.*[175] that described a facile and sustainable approach for continuous-flow oxidation of amines based on nitrogen-rich heterocycles. The authors have demonstrated the utility of the proposed approach in the synthesis of 5-amino-3-nitro-1,2,4-triazole (ANTA) (Scheme 50a) and 1-methyl-3,4,5-trinitropyrazole (MTNP) on a multigram scale (Scheme 50b).



Scheme 50. Synthesis of 5-amino-3-nitro-1,2,4-triazole (ANTA) (a) and 1-methyl-3,4,5-trinitropyrazole (MTNP) (b) on a multigram scale.[175]

Another recent example includes the oxidation of the fragment bis(aminofurazano)furazan (BAFF) into its corresponding bis(nitrofurazano)furazan (BNFF), using a mixture of 50% H_2O_2 and concentrated H_2SO_4, as described by Tang *et al.*,[176] Feng *et al.*[177] and Zhang *et al.*[178] (Scheme 51).



Scheme 51. Synthesis of bis(nitrofurazano)furazan (BNFF) using a mixture of 50% H_2O_2 and concentrated H_2SO_4.[176-178]

6. Concluding Remarks

Throughout this review article, we hope to have shown, through the examples selected, the historical importance of nitroaromatics as drugs introduced as therapeutic options in the context of western medicine. The duality of nitro as a pharmacophoric and toxicophoric group has for many years held back the discovery of new drugs containing this structural subunit. The recent FDA approvals in essence have not changed this scenario, as they only represent the authorization to market nitroaromatic drugs discovered, for the most part, in the second half of the 20th century.

While the nitroheterocycles discussed in this review are prodrugs, whose bioactivation mechanism depends exclusively on the nitroreduction step catalyzed by bacterial and protozoan nitroreductases, nitroarene drugs often have their biological response independent of the presence of the nitro group. However, nitro group is still categorized as a structural alert or a toxicophore due to toxicity issues, which are related to the reduction of the nitro group to electrophilic species capable of interacting with biological nucleophiles, causing a series of damages to cellular proteins and genetic material. As such species can be formed by the action of mammalian enzymes, normally associated with the metabolism of xenobiotics in humans, eliminating the toxic and accumulative effects of nitro-derivatives is a task to be overcome.

Nitroaromatic compounds are mostly synthesized using electrophilic aromatic substitution reactions (known as nitration) and various aromatic nitration methods have been reviewed in this work. Although nitroaromatics can be obtained from the interconversion of functional groups, using the oxidation of anilines and heteroarylamines, this method has little practical application when compared to the nitration approach.

Acknowledgments

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