

Antimicrobial Activity of Nitroaromatic Derivatives

Subjects: **Chemistry, Medicinal**

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Searching for new and efficient pharmaceuticals is a constant struggle for medicinal chemists. New substances are needed in order to treat different pathologies affecting the health of humans and animals, and these new compounds should be safe, effective and have the fewest side effects possible. Some functional groups are known for having biological activity; in this matter, the nitro group (NO_2) is an efficient scaffold when synthesizing new bioactive molecules. Nitro compounds display a wide spectrum of activities that include antineoplastic, antibiotic, antihypertensive, antiparasitic, tranquilizers and even herbicides, among others.

antimicrobial

Antibacterial

Antitubercular

Antifungal

Nitroaromatic compounds

1. Introduction

Pharmaceuticals are chemical substances able to cause a local or systemic action in humans and animals. A specific chemical structure is fundamental regarding its activity since the molecule relates to specific targets due to several interactions between the pharmaceutical itself and receptors, enzymes or channels. After absorption, pharmaceuticals may undergo some structural changes with the consecutive change in activity, which can increase, decrease or even change. Since the discovery of chloramphenicol in 1947, nitro containing cycles and heterocycles have been extensively investigated due to their antibacterial activity; however, nitro containing molecules exhibit a wide variety of biological activities that are attractive to medicinal chemists, for example, some are antineoplastic, antibiotic, antihypertensive, antiparasitic agents, tranquilizers and even herbicides, among many others.^{[1][2][3][4][5][6][7]} The nitro group (NO_2) is a functional group formed by one nitrogen atom linked to two oxygens, it is a particularly electron-withdrawing moiety since the N has no lone pair, hence it bears a positive charge (**Figure 1**).^[8] The electron-withdrawing effect is easily observed in aromatic rings **1** due to resonance with the nitro group, deactivating certain positions and causing changes in the polarity of molecules, which in some cases favors interaction with nucleophilic sites of protein structures such as enzymes, causing inhibition. The nitro group not only works as a pharmacophore but also as a toxicophore, making it even more interesting for medicinal chemists. In most cases, the nitro group is present in a specific structure but it is not entirely related to the activity; however, it affects pharmacokinetics. The whole activity regarding the nitro group directly (whether beneficial or toxic) depends entirely on the reduction of the nitro itself, accepting up to six electrons in order to form the amine derivative. This reduction occurs through enzymatic reactions using NADH or NADPH as reducing agents. During the reduction of the NO_2 , some nitroso and hydroxylamine intermediates are formed and react with biomolecules producing undesired toxic and mutagenic effects. Although reduction of the nitro group itself is toxic to humans, in

some cases this might be seen as the desired effect for designing and synthesizing new antiparasitic drugs. In some other cases (most of them) the activity of the corresponding molecule is “affected” just by the presence of the NO_2 and its electron-withdrawing properties, polarity, or stereochemistry.[\[9\]](#)[\[10\]](#)[\[11\]](#)[\[12\]](#)[\[13\]](#)[\[14\]](#)[\[15\]](#)[\[16\]](#)[\[17\]](#)[\[18\]](#)[\[19\]](#)

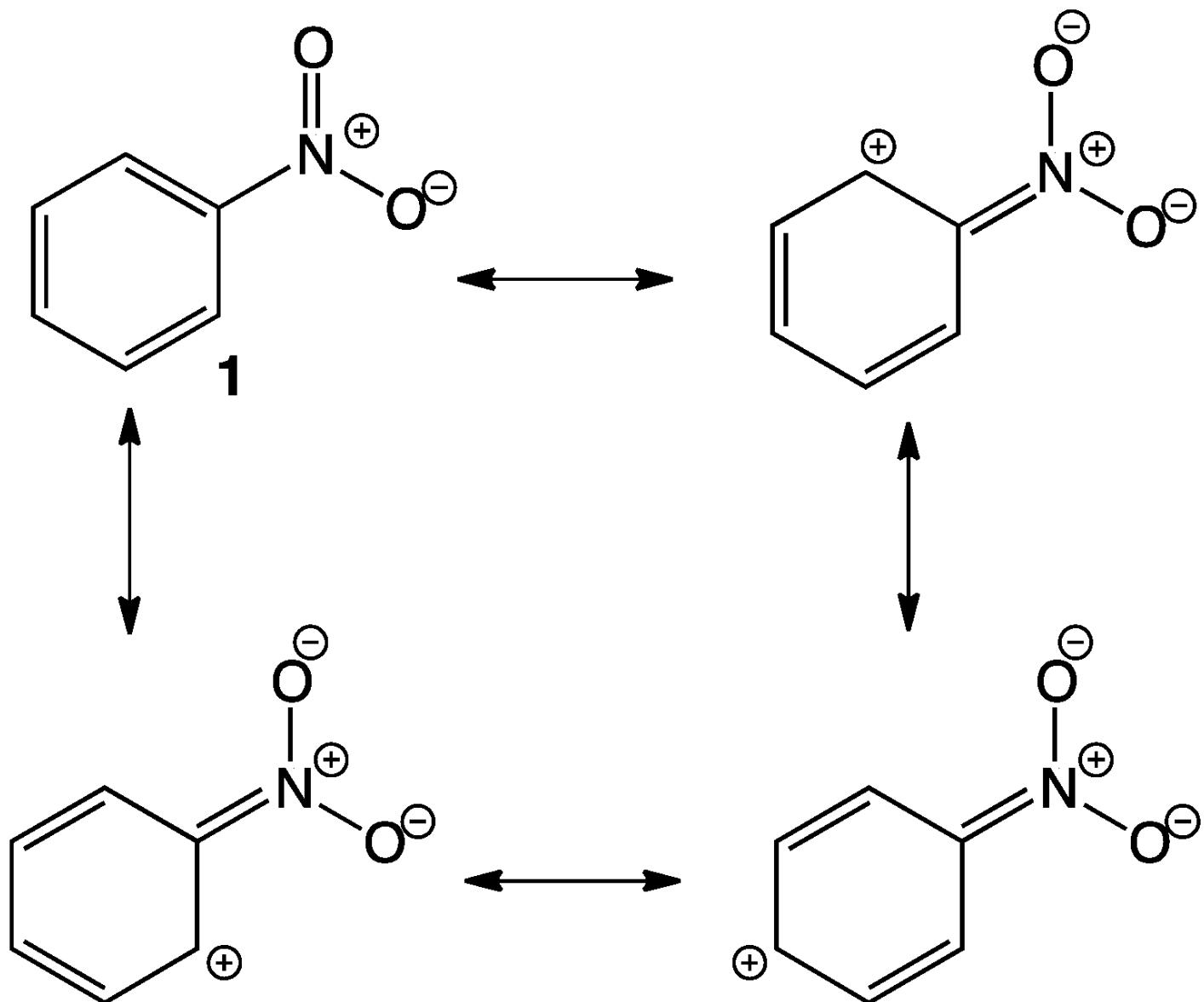


Figure 1. Resonance structures in nitrobenzene.

2. Antimicrobial Activity

Nitro-containing molecules are some of the first lines of treatment for common infections caused by several microorganisms. Metronidazole, chloramphenicol and other nitro derivatives display antimicrobial activity by different mechanisms. One of the most accepted and general models states that when nitro compounds are reduced, they produce toxic intermediates (such as nitroso and superoxide species), then, the reduced nitro species bind covalently to DNA resulting in nuclear damage and cell death.[\[20\]](#) Some examples of molecules that required activation in order to be antimicrobial agents are 5-nitroimidazole derivatives. These compounds undergo

intercellular reduction giving rise to a nitro anion radical (NO_2^-) of short life but a crucial step in the mechanism of action of nitroimidazoles. 5-nitroimidazole is a significant moiety in medicinal chemistry since it is present in commercial drugs such as miconazole, ketoconazole and metronidazole among others.^{[13][21]}

2.1. Antibacterial

The antibacterial activity of nitro-containing molecules is one of the widest effects observed, not only in human or veterinary pharmaceuticals but also in the manufacturing of new materials with antimicrobial properties.^[22] Metronidazole is one of the primary pharmaceuticals employed in the treatment of *H. pylori*, and it contains the moiety 5-nitroimidazole. Unfortunately, it has lost efficiency as this microorganism is developing resistance against traditional treatments. For this reason, several 5-nitroimidazole derivatives have been developed throughout the years in order to overcome this problem, the imidazole base structure is known for having activity against *H. pylori* as it can be found already existing pharmaceuticals such as metronidazole (Figure 2).^[23]

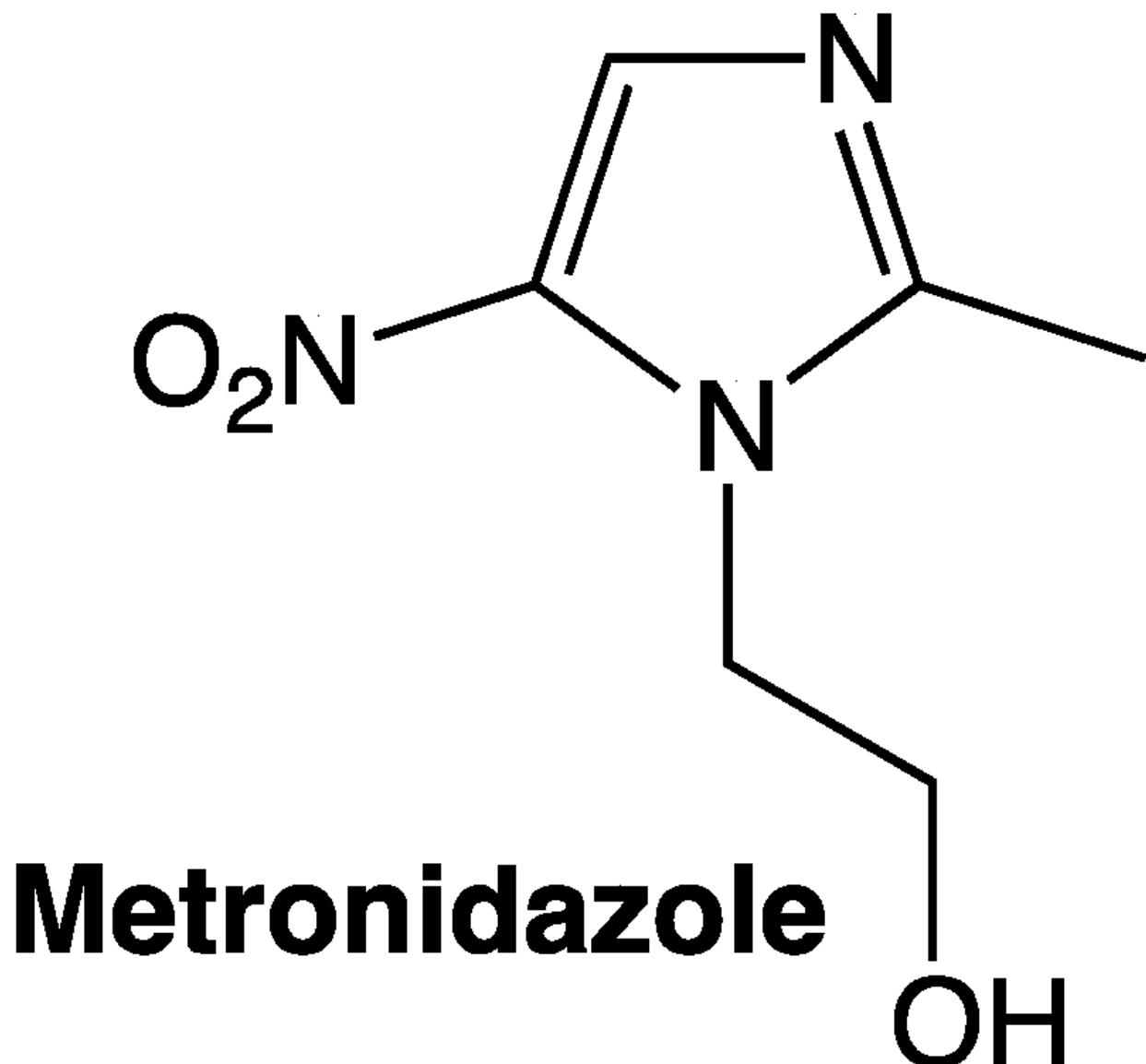


Figure 2. Metronidazole as a 5-nitroimidazole.

Many existing drugs have some degree of nitration in their structures, for example, chloramphenicol or nitrofurantoin. These well-known substances are of common use and will continue so for a while; however, there are many other compounds being developed and tested for their antimicrobial properties. Such is the case of a series of nitrated pyrrolomycins that proved to be efficient against Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*) bacteria.^[24] Pyrrolomycins are halogenated organic compounds isolated from *Actinosporangium* and *Streptomyces* species that show a variety of biological activities such as neuro and immune-modulatory, antiproliferative, insecticidal and antimicrobial. This latter property is attributed to a protonophoric effect of pyrrolomycins, which is the ability of some molecules to translocate protons from one side to another of biological membranes. Even though pyrrolomycins are potential candidates for developing new antibacterial pharmaceuticals, they are also toxic compounds due to the halogens present in their structure (Cl or Br).^[25] By chemically modifying the structure of some pyrrolomycins, researchers are able to obtain new compounds with enhanced antimicrobial activity and low toxicity. One of these modifications includes a nitration step on the pyrrole ring **3a-d**, which is easily achieved through an electrophilic aromatic substitution reaction (**Figure 3**). The C2 position in the pyrrole ring is favored for electrophilic substitution, however, when C2 has either Br or Cl, C1 becomes particularly activated for an electrophilic attack due to the halogen lone pair. The bromine-substituted compound **4c** showed the best yield compared to Cl derivatives **4b** and **4d**, indicating a stronger activation by Br. Experimental results also indicated that the presence of nitro groups (especially in the C2 and C4 positions) in the pyrrole ring enhanced the antibacterial activity **4b** (20 μ M against *S. aureus*) and **4d** (30 μ M against *P. aeruginosa*). Researchers propose not only a protonophoric effect, but also improved lipophilicity and hence a better interaction with membranes.^[24]

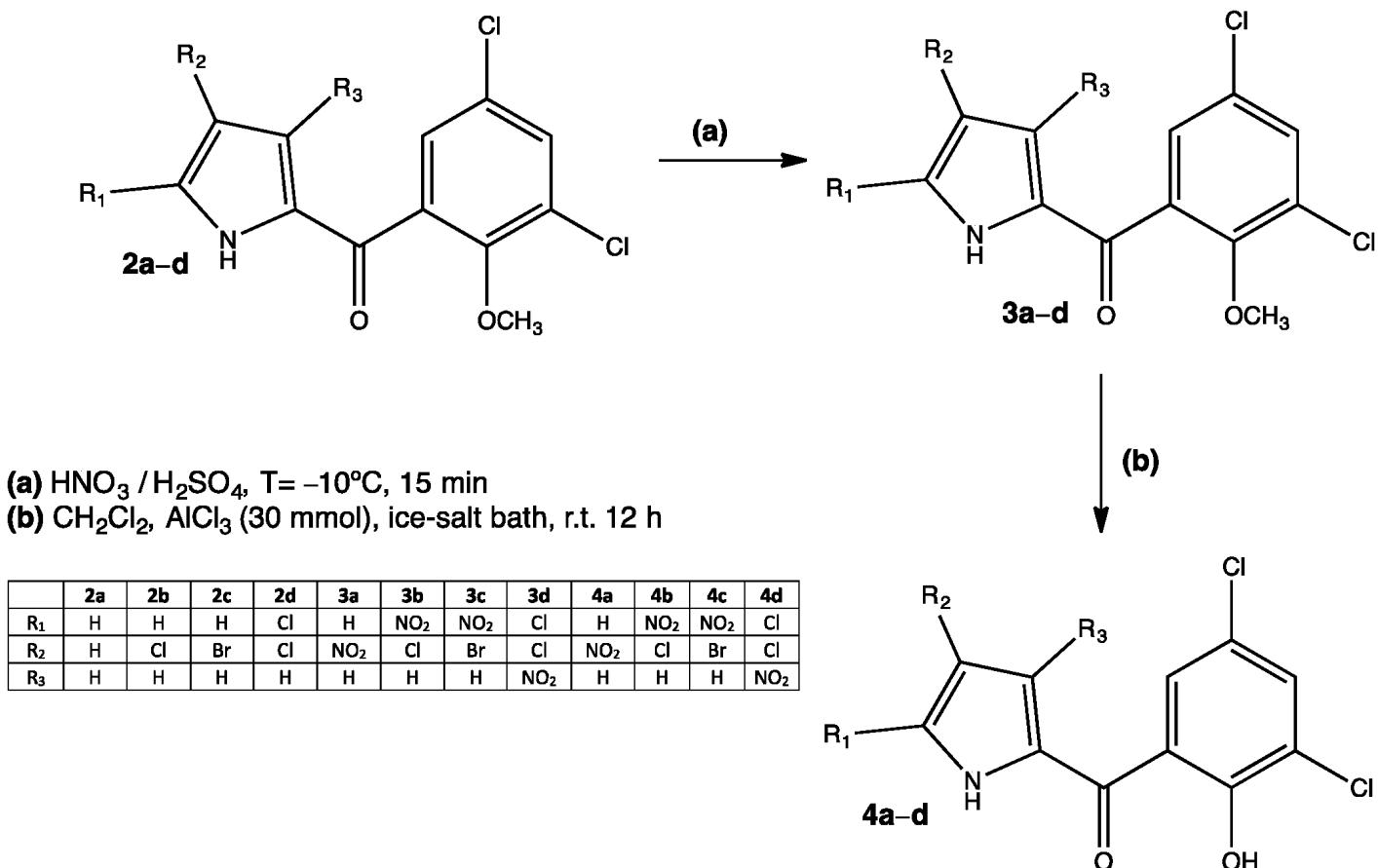


Figure 3. Nitrated pyrrolomycins with potential antibacterial activity.^[24]

For many years, the coordination chemistry of transition metals was not considered an important part of medicinal chemistry. However, in recent years, metal complexes with Schiff bases as ligands have gained attention due to their wide potential biological activity. A series of 4-nitro-1,2-phenylenediamine metal complexes were synthesized and tested against Gram-positive microorganisms (*Streptococcus mutans* and *Staphylococcus aureus*) Gram-negative (*Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*) and the fungus *Candida albicans*. A total of nine new compounds were obtained but only the Zn(II) complex **5** showed significant activity against *Streptococcus mutans* (Figure 4). Antibacterial activity was reported as the inhibition zone diameter, with 40.7 mm being the inhibition obtained with the Zn(II) complex. The rest of the compounds with other metals such as Co(II), Cr(III), Fe(III) and Ni(II) showed little or no activity at all.^[26] Even when these results might seem discouraging, these kinds of compounds represent new synthetic methods to be addressed in future research or metal complexes with biological activity.

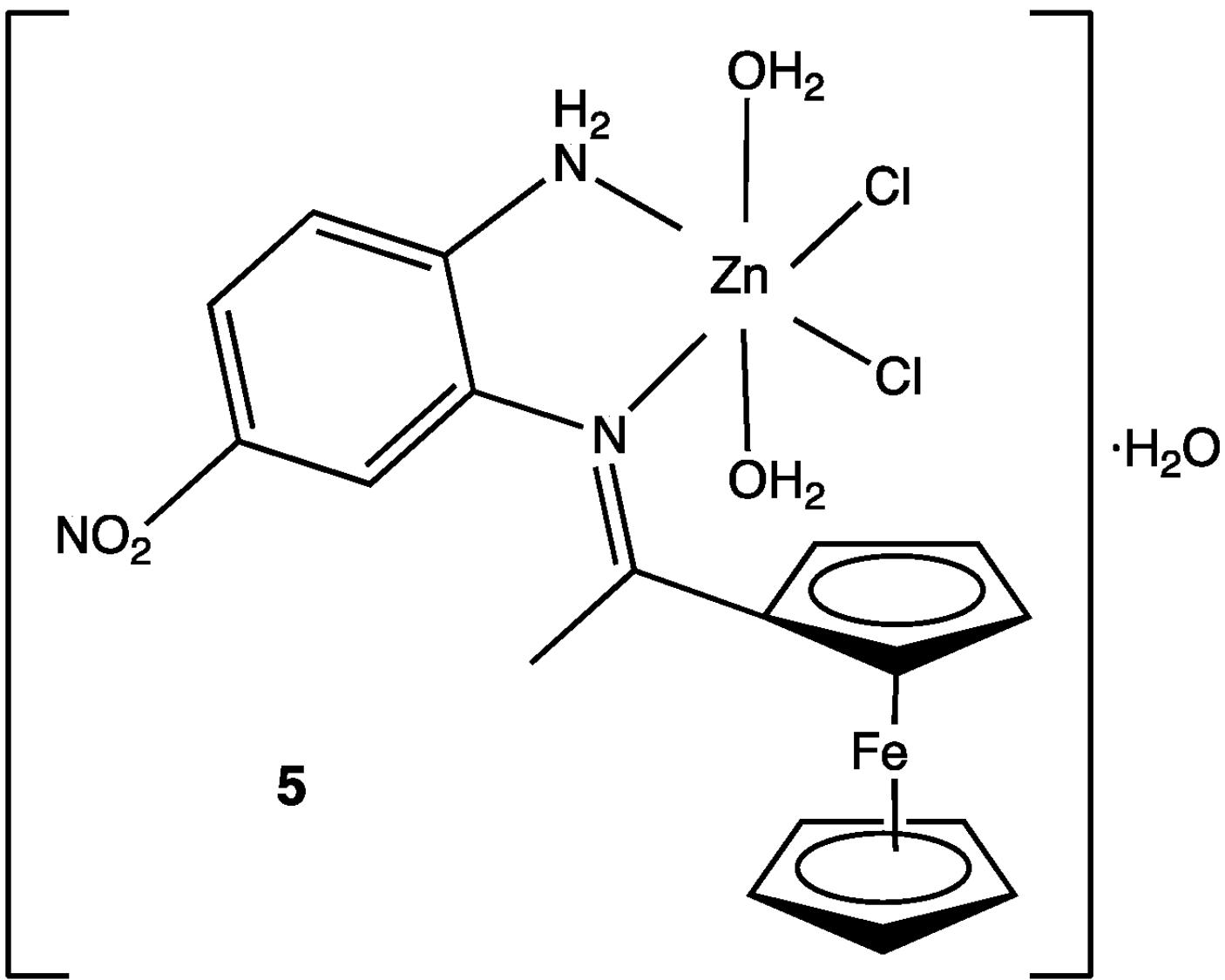


Figure 4. Structure of the Zn(II) complex against *Streptococcus mutans*.^[26]

There is an increasing interest in developing new antimicrobial agents not only because of the growing resistance to antibiotics but also because of the risk of nosocomial infections (infectious diseases acquired within a hospital). In some regions, these types of infections could reach up to 40% of hospitalized patients. Gram-positive bacteria are responsible for more than 90% of nosocomial infections, and *Staphylococcus aureus* is one of the pathogens listed as a priority for research and development according to the World Health Organization (WHO). In this context, researchers synthesized several nitro derivatives through an oxa-Michael-aldol condensation reaction and tested their potential antimicrobial activity against *Staphylococcus aureus* and *Candida* sp., two main microorganisms involved in frequent nosocomial infections (Figure 5). Experimental results indicated that nitro derivatives with some degree of halogenation **9b–9d** had the best results with minimum inhibitory concentration (MIC) in the range of 15.6–62.5 µg/mL for *S. aureus* and minimum fungicidal concentration (MFC) 15–500 62.5 µg/mL in the case of *Candida*.^[27]

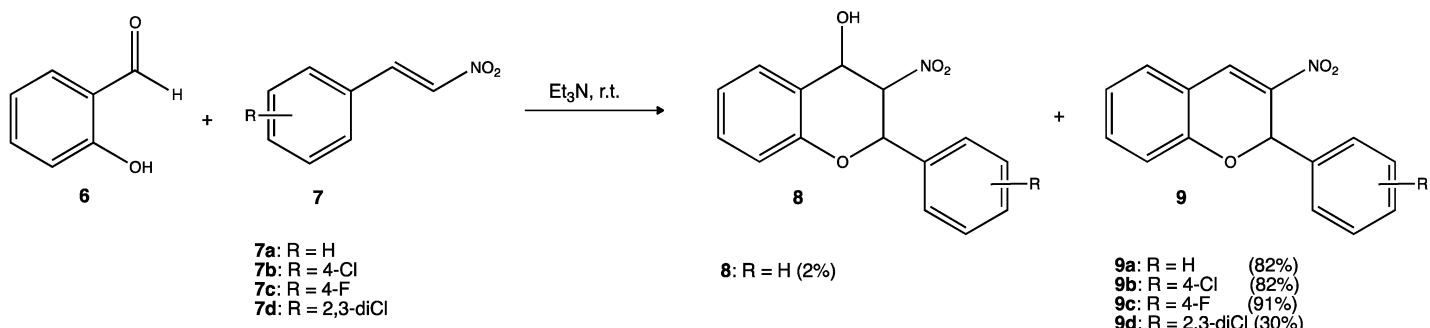


Figure 5. Nitroderivatives containing one F and/or two Cl atoms showed the best activity against *S. aureus* (15.6–62.5 µg/mL) and *Candida* sp. (15–500 62.5 µg/mL), respectively.^[27]

Pseudomonas aeruginosa is another type of bacteria responsible for nosocomial infections, so it has become important to develop new antibiotics able to inhibit the growth or kill Gram-negative organisms as well. In this matter, heterocycles such as benzothiazoles show antibacterial activity, especially the ones containing the nitro functional group. In a study, several nitrated benzothiazoles were obtained through nitroanilines and KSCN under relatively mild conditions. A total of nine compounds were tested against *P. aeruginosa* but only three showed significant activity **10–12** (Figure 6), becoming pharmaceutical targets for future research as lead compounds. Inhibition was compared with procaine penicillin obtaining similar inhibition.^[28]

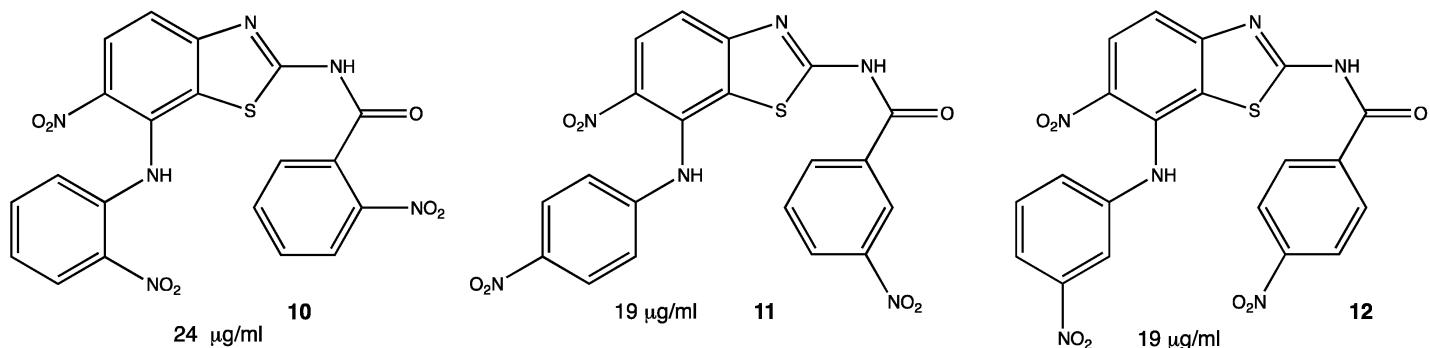
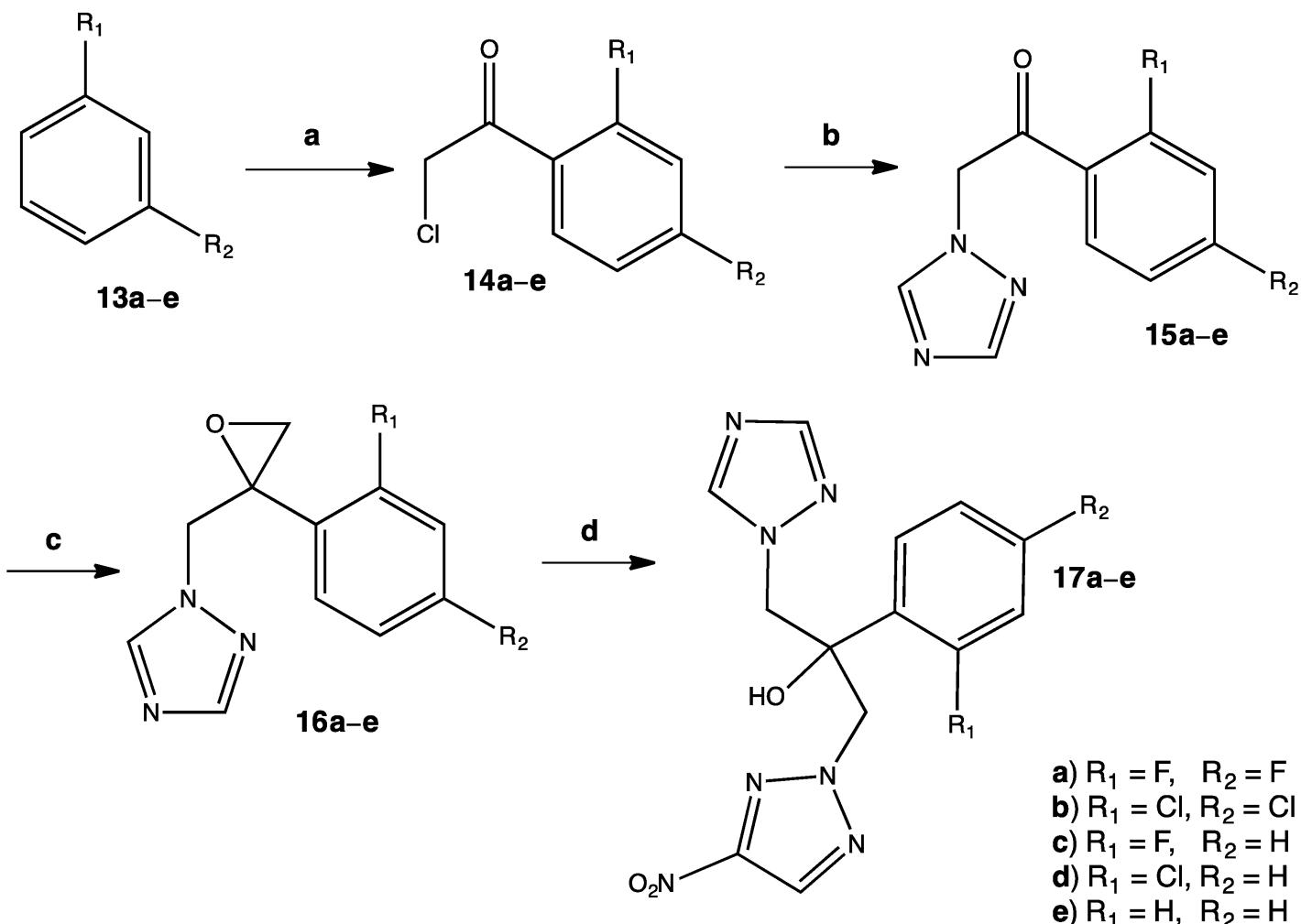


Figure 6. Benzothiazole derivatives against *P. aeruginosa*.^[28]

2.2. Antifungal

Nowadays, fungi resistance is becoming a topic of discussion among medicinal chemists. There are some species resistant to classical treatments such as fluconazole (including *C. krusei*, and *C. albicans*), so new molecules are needed in order to limit this growing clinical problem. One of the best methods to obtain new molecules with a desired and specific activity is from already existing molecules that show this particular activity. In this way, researchers are able to obtain new substances by synthesizing derivatives from a parent compound. By these means, a series of fluconazole derivatives **17a–e** were prepared to have a piperazine or nitrotriazole moiety in their structure (Figure 7).^[29]



(a) AlCl_3 , 1,2-dichloroethane, chloroacetyl chloride, 25–30 °C;

(b) 1H-1,2,4-triazole, NaHCO_3 , toluene, reflux;

(c) trimethylsulfoxonium iodide, NaOH , tetraethylammonium bromide, toluene, 60 °C;

(d) EtOH , Et_3N , 3-nitro-1,2,4 triazol, 80 °C;

Figure 7. The presence of a nitrotriazole moiety in the fluconazole derivatives enhances antifungal properties.^[29]

The nitrotriazole derivatives were obtained through a four-step synthesis under relatively mild conditions. Although reflux was employed, there was no need for temperatures higher than 80 °C. Yields varied from a range of 30% to 56%, but considering the products the results were satisfactory. The best antifungal properties were observed among the molecules baring halogens in the benzene ring, especially Cl. Halogens tend to make compounds more lipophilic and at the same time more polar, improving their pharmacokinetics. It is noteworthy that the nitrotriazole derivative showed better activity against *C. krusei* (MIC = 1 μM for 17b) compared to the fluconazole standard. The mechanism of action of these fluconazole derivatives involves the inhibition of the 14 α -demethylase, an enzyme necessary for the synthesis of ergosterol in fungi.^[30] Such antifungal activity observed in the nitro compounds is attributed to an efficient electrostatic interaction between the NO_2 and the Fe(II) in the heme group of 14 α -demethylase, triggering a strong inhibition of the enzyme. Docking studies were performed in order to complement experimental results.^[29]

2.3. Antitubercular

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, and it is an issue of growing concern for global health because of concomitant infections with HIV. *M. tuberculosis* has developed resistance to traditional treatments, so it has become imperative to find new substances able to kill or inhibit the growth of this pathogen. Regiments for treatment against TB are long (up to 18 months in the case of multi-resistant bacteria) due to its slow bacterial growth, so it is imperative to develop new drugs targeting different metabolic stages. Some lead compounds have been found such as 5-nitrophenanthroline **18** with an MIC value of 0.78 μ M against *M. tuberculosis*;^[31] researchers found that the presence of the NO_2 group in the C5 was essential for antitubercular activity (**Figure 8**). They replaced it with other withdrawing groups, such as cyano, bromo or chloro, and observed ten times less activity with these substituents; furthermore, they also concluded that the NO_2 moiety modulates intracellular mechanisms involved in killing bacteria.^[31]

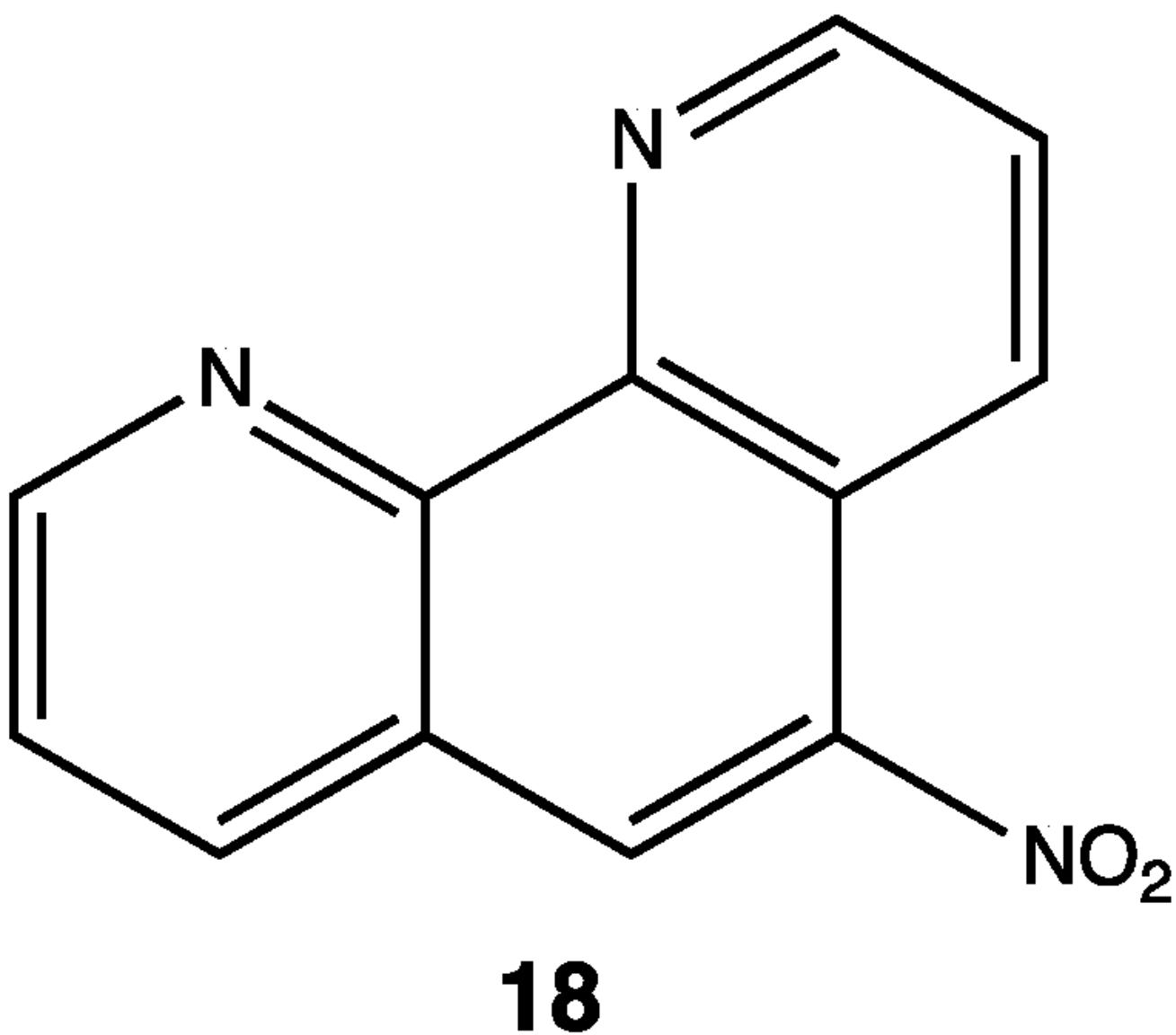


Figure 8. 5-nitro-1,10-phenanthroline compounds tested against *Mycobacterium tuberculosis*.^[31]

Some nitro-containing molecules such as 5-nitroimidazooxazine and 5-nitro-imidazooxazole are currently studied in clinical trials in the US.^[32] However, there have to be more options available for the treatment of tuberculosis. A promising group of molecules with antitubercular activity is nitrotriazoles; in particular, 3-nitro-1,2,4-triazole-based derivatives **19–23** (Figure 9). It was reported that these classes of compounds inhibit *M. tuberculosis* in the range of 3–50 μ M. Compared to other effective and still used antitubercular agents such as isoniazid, the MICs (minimum inhibitory concentration) observed in nitrotriazoles are not so far from this reference; they are 0.3 μ M for isoniazid and 3.0 μ M for the most active nitrotriazole. These molecules are effective, but they still need to be further investigated in order to obtain new nitrotriazole derivatives that can compete with lead compounds such as isoniazid or rifampicin.^{[33][34]}

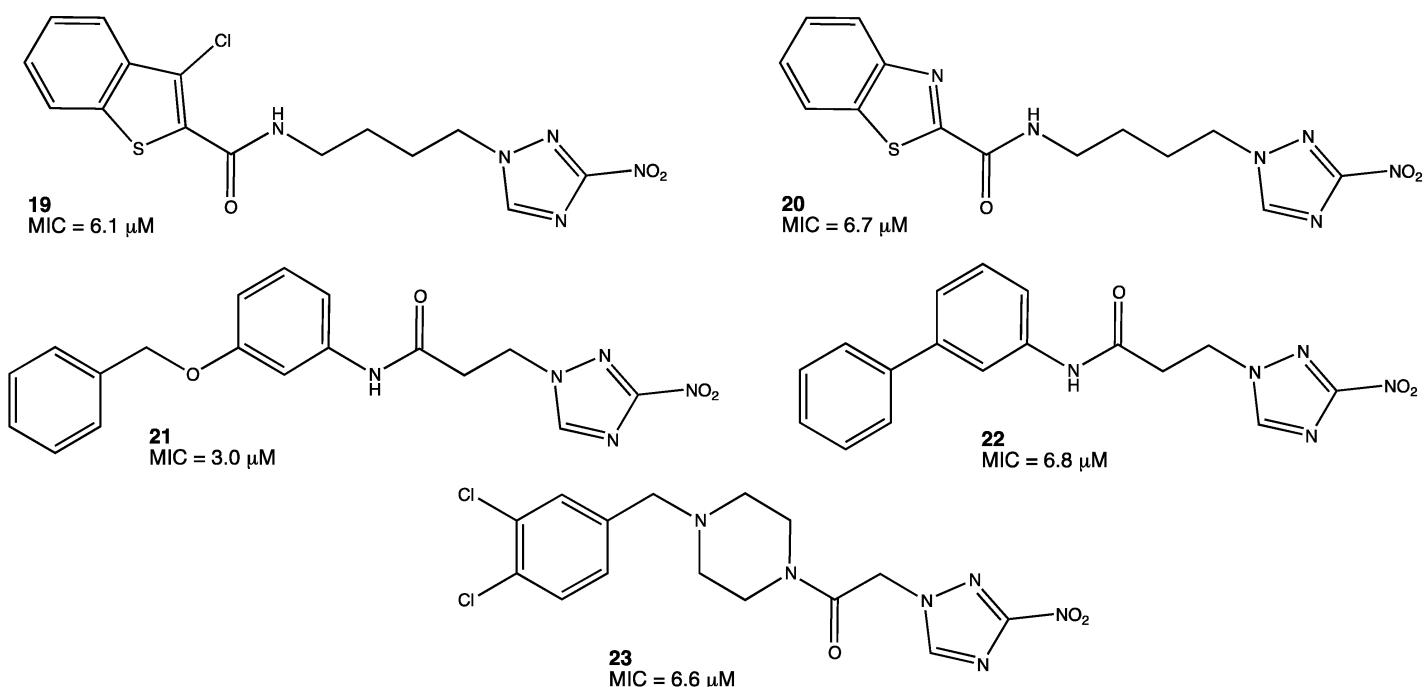


Figure 9. Nitrotriazole derivatives with antitubercular activity.^[34]

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