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The Role of Nitro Groups in Pharmaceuticals: Effects and Interactions with Biological Systems

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Abstract

The nitro group (–NO_2) is a popular chemical function in drug design because its characteristic properties affect the pharmacokinetics, pharmacodynamics and thus the efficacy of pharmaceutical agents. This mini-review examines the role of nitro groups in drug molecules, focusing on the part of nitro group work in the structure of a drug molecule, their mode of action and biological interactions. To date, even from drug discovery on a nonclinical level, the inclusivity of nitros (nitro groups) remains in another word stage as an invaluable target for its therapeutic promise but repulsion toxicity too.

Keywords: *Nitro groups, Drug design, Pharmacokinetics, Pharmacodynamics*

1. Introduction

Nitro groups (-NO_2) have long been incorporated into drug design due to their unique chemical properties (Nepali *et al.*, 2019). In addition, nitro compounds facilitate interesting C–C bond-forming reactions. Thus, transforming the nitro group into other functional groups is as well an important step for the synthesis of pharmaceutically relevant compounds (Nishiwaki, 2020; Sukhorukov, 2020). These functional groups can influence the pharmacokinetics, pharmacodynamics, and toxicological profiles of medications (Paoli-Lombardo *et al.*, 2022). Although the nitro group has long been used in therapeutics it is associated with a number of toxicity issues (Olender *et al.*, 2018) and as such might be classified as either a structural alert or toxicophore (Kovacic and Somanathan, 2014; Patterson and Wyllie, 2014; Noriega *et al.*, 2022). The majority of compounds that include nitro might potentially be mutagenic and produce methaemoglobinemia (Smith, 2011; Gooch *et al.*, 2017; Nepali *et al.*, 2019). Yet the question of whether there is any real evidence for drugs containing nitro groups to be hazardous or not remains somewhat equivocal. The current mini review explores

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the importance of nitro groups in drug molecules, their impact on therapeutic action, and the biological interactions that result from their presence.

2. Structural Characteristics of Nitro Groups in Drug Design

Nitro groups are characterized by their electron-withdrawing nature, which can affect the electronic distribution in drug molecules (Figure 1), moderately polar substituent (Hansch *et al.*, 1973).

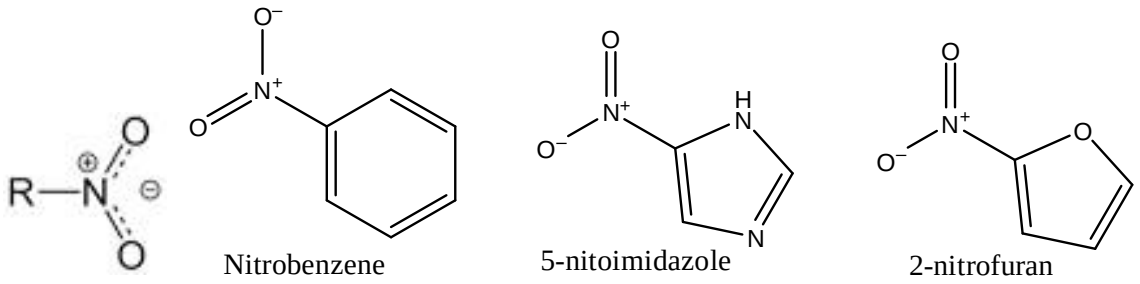

Figure 1: The General Valence-Bond Structures of the Nitro Containing Compounds, and Three Nitroaromatics

This can lead to increased stability, enhanced solubility, or improved receptor binding affinity (Meanwell, 2011; Patrick, 2017; Nepali *et al.*, 2019). Moreover, due to its simplicity in going through reduction (redox biochemistry) (Rice *et al.*, 2021) at the molecular level, where subsequent bond-cleavage events can produce highly reactive, confined, and electrophilic sites (Sharma *et al.*, 2019) the nitro group is essential for bioactive substances (Pal and Bandyopadhyay, 2012; Patterson and Fairlamb, 2019; Xavier *et al.*, 2021). Some notable drugs that contain nitro groups include nitrofurantoin (Figure 2, used for the treatment of uncomplicated lower urinary tract infections (Squadrito and del Portal, 2024)) and nitroglycerin, each showcasing different mechanisms of action.

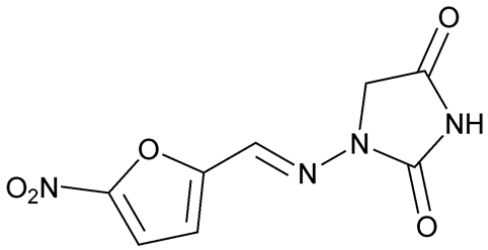

Figure 2: Structural Formula of Nitrofurantoin

Nitro containing bioactive compounds are also naturally occurring. As an antibacterial agent effective against both Gram-positive and Gram-negative bacteria, chloramphenicol (Figure 3) a naturally nitro aromatic

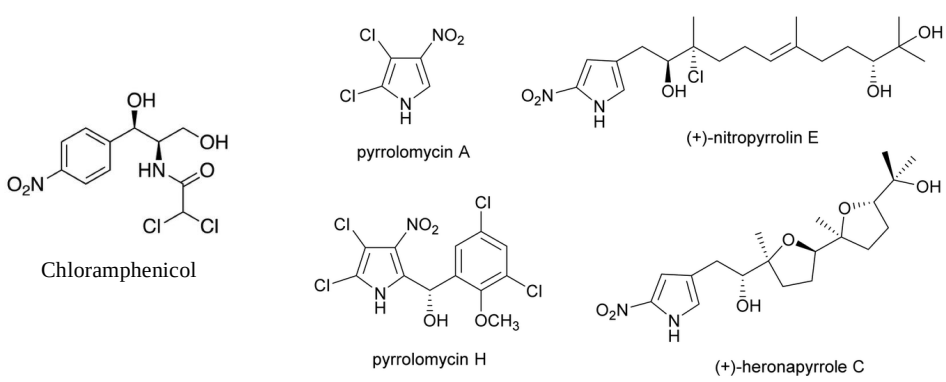

Figure 3: Chemical Structures of Some Nitro Natural Bioactive Products

chemical that was identified from the culture of the soil Gram-positive bacterium *Streptomyces venezuelae*. The pyrrolomycins (Figure 3) family are another natural potent antibiotics compounds (Parry *et al.*, 2010; Ding *et al.*, 2016; K *et al.*, 2019).

3. Mechanisms of Action in Biological Systems

Once administered, drugs with nitro groups often undergo metabolic reduction to yield reactive intermediates, including free radicals and Reactive Oxygen Species (ROS) (Penning *et al.*, 2022). Nitro aromatic compounds have the potential to function as prodrugs of Reactive Nitrogen Species (RNS), namely different nitrogen oxides, due to their bio reductive metabolism (Whitmore and Varghese, 1986; Rice *et al.*, 2021; Penning *et al.*, 2022). Moreover, these intermediates can either contribute to the therapeutic action, as in the case of antibiotics, or induce cytotoxicity, as seen in certain anticancer drugs. Nitroreductase and nitro aromatic prodrug systems are potentially active against hypoxic cancers (Kim *et al.*, 2018). The reduction process is typically mediated by enzymatic systems such as cytochrome P450. It has been demonstrated that nitro-aromatic chemical metabolites bind covalently to DNA (Smith, 2011).

4. Therapeutic Uses of Nitro Group-Containing Drugs

Many nitro drugs (Figure 4) are used in the treatment of infections (Olender *et al.*, 2018; Noriega *et al.*, 2022), insomnia, and Parkinson's disease (Mattila and Larni, 1980; Truong, 2009). For instance, nitroimidazoles (e.g., metronidazole) are efficient for different anaerobic bacterial infections (Tally *et al.*, 1981), trichomoniasis, giardiasis, and amoebiasis (Pal *et al.*, 2009). Moreover, for cardiovascular diseases, nitroglycerin is commonly used for angina pectoris, aka angina (Divakaran and Loscalzo, 2017). Nitazoxanide is approved for giardiasis and cryptosporidiosis (Hemphill *et al.*, 2006).

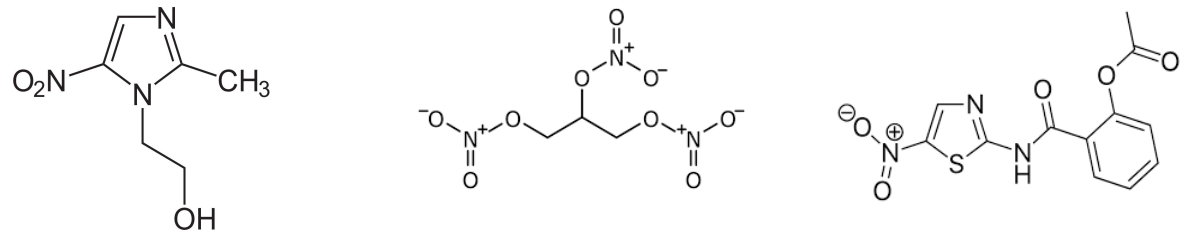

Figure 4: Chemical Structures of Some Nitro Containing Drugs

The nitro group enhances the drug's ability to target specific pathogens or organs, often through selective toxicity (Edwards, 1993) or vasodilatory effects through the release of nitric oxide (Fung, 1983).

5. Toxicity and Side Effects Associated with Nitro Drugs

Despite their therapeutic potential, nitro-containing drugs can also present toxicity risks (Li *et al.*, 2020). For example, nitro aromatic compounds are known to induce oxidative stress and, in some cases, trigger mutagenic or carcinogenic effects due to DNA damage (Purohit and Basu, 2000; Orsière *et al.*, 2003; Rafii *et al.*, 2005; Kovacic and Somanathan, 2014; Kannigadu and N'Da, 2020). The generation of ROS is a double-edged sword, offering both therapeutic benefits and the potential for harmful side effects (Wallace, 1997; Wang *et al.*, 2021; Mendes *et al.*, 2022; Zhao *et al.*, 2023; Zhu *et al.*, 2023). As a result, when there are appropriate substitutes, certain nitro medications are avoided; for instance, other antibiotics are favored over chloramphenicol (Feder *et al.*, 1981).

6. Metabolic Pathways and Detoxification

The metabolism of nitro drugs (Figure 5) is a critical factor in determining their biological activity and toxicity. To exhibit biological activity, reductive bio activation is necessary, and nitroreductases (NTR) of type I or type II are responsible for this reduction. Thus, the NTR enzymes that reduce nitro groups to amines or

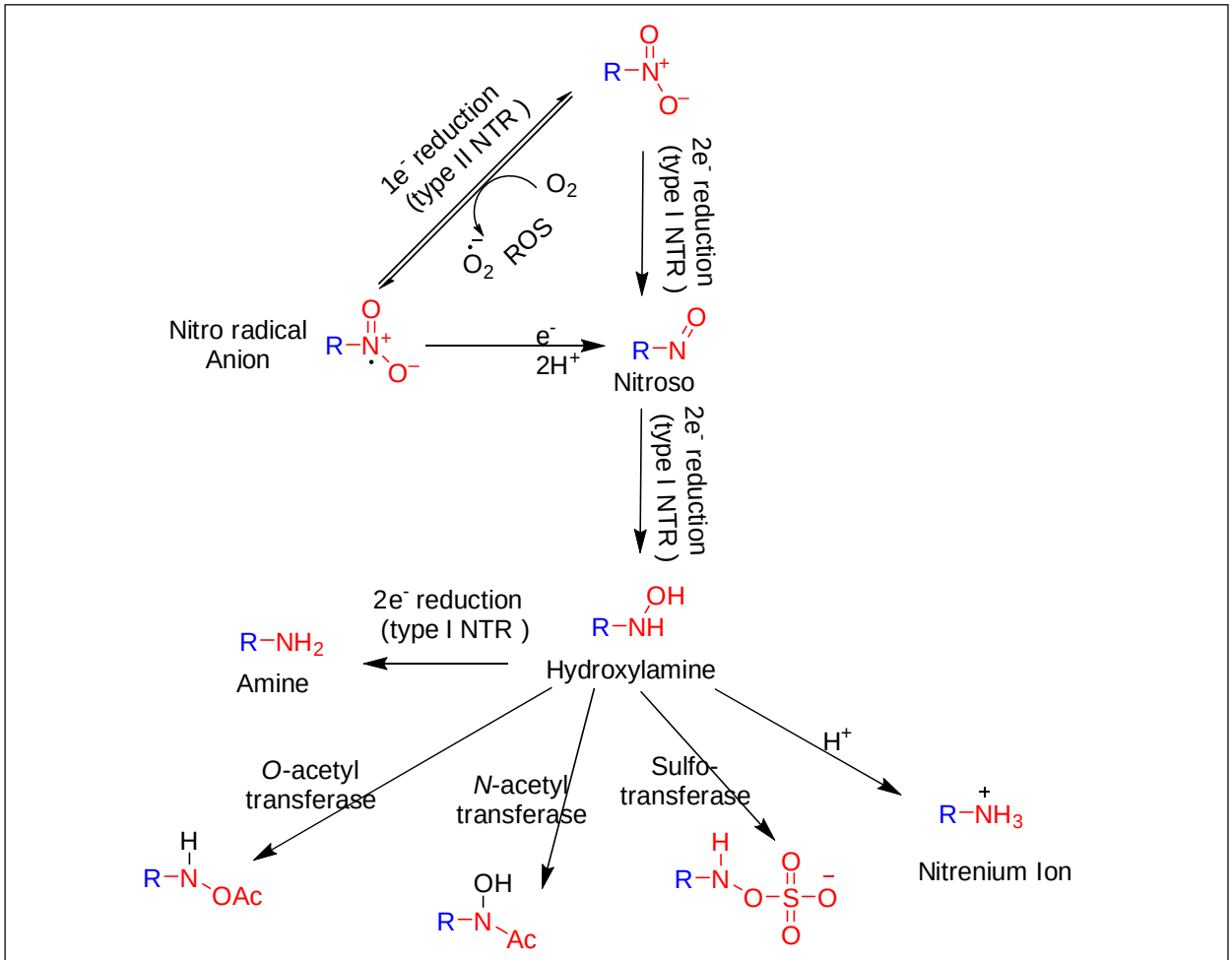

Figure 5: General Reduction Mechanism of Nitroaromatic Compounds

hydroxylamines, play a central role in modulating drug action (Rauth *et al.*, 1998; Miller *et al.*, 2018; Nepali *et al.*, 2019; Gallardo-Garrido *et al.*, 2020).

Nitroreductases exist in all other phyla, in mammalian cells, and in the gut microbiome (Roldán *et al.*, 2008; Bartel *et al.*, 2009). Detoxification pathways often involve conjugation reactions, but excessive production of reactive intermediates can overwhelm cellular defenses, leading to adverse effects (Guengerich, 2008; *Casarett & Doull's Toxicology*, 2018).

7. Conclusion

As one of the best example of substances having double-sword nature, medicinal chemists can point nitro containing drugs without any doubt. Nitro groups are valuable in the development of a wide range of pharmaceutical agents, providing both therapeutic benefits and challenges in terms of toxicity and metabolic stability. Further research is needed to optimize the balance between efficacy and safety, ensuring that nitro drugs remain an essential part of modern medicine.

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