Mini-review: Advances in the synthesis and biological activity of benzofuroxan and furoxan derivatives

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Benzofuroxan and furoxan derivatives are heterocyclic compounds well known for their ability to act as nitric oxide (NO) donors. Due to their NO-releasing properties, these compounds have attracted considerable attention for their antimicrobial, antiviral, and antitumor activities. Their potential use in treating cardiovascular, gastrointestinal, and neurodegenerative disorders further underscores their pharmacological relevance. Given the increasing research interest in these compounds, there is a need to consolidate recent findings related to their chemical properties and biological potential. This mini-review aims to provide an up-to-date overview of the synthetic strategies and bioactivities of benzofuroxan and furoxan derivatives. Rather than focusing on ring synthesis, this review highlights the reactivity of side-chain functional groups and the design of hybrid molecules. Representative examples of drug-like compounds are discussed, along with their biological profiles. The review also explores emerging directions in the development of novel NO donors based on these frameworks with improved pharmaceutical efficacy and controlled NO release.

Keywords: benzofuroxan; furoxan; NO donor; heterocyclic compounds; hybrid compounds; antibacterial properties; antiviral and antitumor drugs.

Қысқаша шолу: Бензофуроксан және фуроксан туындыларының синтезі және биологиялық белсенділігіндегі жетістіктер

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Бензофуроксан мен фуроксан туындылары азот тотығының (NO) донорлары ретінде белгілі гетероциклді қосылыстар болып табылады. NO бөлу қабілетінің арқасында бұл қосылыстар антимикробтық, вирусқа және ісікке қарсы белсенділіктерімен ғылыми қызығушылық тудырып отыр. Сонымен қатар, оларды жүрек-қан тамырлары, асқазан-ішек және нейродегенеративті ауруларды емдеуде қолдану мүмкіндігі олардың фармакологиялық маңыздылығын арттыра түсуде. Бұл қосылыстарға қатысты зерттеулер санының артуы олардың химиялық қасиеттері мен биологиялық әлеуетіне байланысты соңғы ғылыми жетістіктерді жүйелеуді қажет етеді. Осы қысқаша шолудың мақсаты – бензофуроксан мен фуроксан туындыларының синтезі мен биологиялық белсенділігіне қатысты заманауи деректерді жинақтап ұсыну. Шолу бензол сақинасын құруға емес, бүйірлік тізбектердегі функционалдық топтардың реакциялық қабілетіне және гибридті молекулаларды жобалауға баса назар аударады. Дәрілік заттарға ұқсас қосылыстардың мысалдары мен олардың биологиялық қасиеттері келтірілген. Сонымен қатар, бұл шолу осы гетероциклдерді күрделі молекулалық құрылымдарға енгізу және тиімді әрі бақыланатын NO бөле алатын жаңа донорларды әзірлеу бағытындағы ғылыми ізденістерді сипаттайды.

Түйін сөздер: бензофуроксан; фуроксан; NO донор; гетероциклді қосылыстар; гибридті қосылыстар; антибактериалды қасиет; вирусқа және ісікке қарсы препараттар

Краткий обзор: Достижения в синтезе и биологической активности бензофуроксана и производных фуроксана

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Бензофуроксан и производные фуроксана представляют собой гетероциклические соединения, хорошо известные своей способностью действовать как доноры оксида азота (NO). Благодаря свойству высвобождать NO, эти соединения привлекли значительное внимание как агенты с антимикробной, противовирусной и противоопухолевой активностью. Их потенциальное применение в лечении сердечно-сосудистых, желудочно-кишечных и нейродегенеративных заболеваний подчёркивает их фармакологическую значимость. С учётом растущего научного интереса к этим соединениям возникает необходимость в систематизации последних данных об их химических свойствах и биологическом потенциале. Целью настоящего мини-обзора является представление актуальной информации о стратегиях синтеза и биологической активности производных бензофуроксана и фуроксана. В обзоре акцент сделан не на синтезе кольцевых структур, а на реакционной способности функциональных групп боковых цепей и создании гибридных молекул. Рассматриваются примеры лекарственно-перспективных соединений и их биологический профиль. Также рассматриваются перспективы разработки новых доноров NO с улучшенными фармацевтическими характеристиками и контролируемым высвобождением NO.

Ключевые слова: бензофуроксан; фуроксан; донор NO; гетероциклические соединения; гибридные соединения; антибактериальные свойства; противовирусные и противоопухолевые препараты.

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Review

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1. Introduction

The exploration of new classes of biologically active compounds and the development of innovative synthetic methods are critical and valuabla endeavours in the field of organic chemistry. N-oxide heterocyclic compounds are emerging as promising platforms for the development of novel pharmacological treatments against diseases such as tuberculosis, malaria and neglected tropical diseases such as leishmania amazonensis. Notable antimicrobial agents, including minoxidil, acipimox, chlordiazepoxide and quinoxidine, as well as veterinary antimicrobials such as quindoxin and carbadox, all incorporate an n-oxide fragment in their molecular architecture.

The diverse biological activities of n-oxide heterocycles can be attributed to their ability to releasa nitric oxide (NO) under physiological conditions. The seminal work of nobel laureates R.F. Furchgott, L.J. Ignarro and F. Murad highlighted NO as a key regulator of cellular metabolism, with significant effects on various physiological processes in mammals [1].

A particularly noteworthy class of cyclic compounds containing an N-oxide fragment capable of NO release is the 1,2,5-oxadiazole-2-oxide, commonly known as furoxan [2]. Furoxans exhibit a remarkable array of chemical properties, including tautomerism, ease of ring opening, and reactivity with both electrophiles and nucleophiles. These attributes have positioned furoxans as intriguing candidates for various applications due to their demonstrated capabilities as NO donors, as well as their antitumour, cardiotropic, antibacterial and antiparasitic properties. In addition, the cytotoxic effects of furoxans may be partly related to oxidative stress.

Among the furoxans, benzofuroxans stand out due to their unique properties. The introduction of different substituents on the aromatic ring can significantly influence their physicochemical characteristics, enhancing their ability to penetrate lipid membranes and consequently altering their biological activity. This potential for modification paves the way for further research and development in the field, highlighting the importance of ongoing investigations into N-oxide heterocycles and their applications in medicine.

In recent decades, there has been a significant increase in patents related to the use of benzofuroxan as thiol-dependent NO-donors. Unlike other NO-donors, furoxan uniquely releases nitrogen (II) oxide molecules gradually, which can enhance their biological effectiveness. The mechanism involving the attack of the thiolate anion on the c-3 and/or c-4 atom of the furoxan ring with ring opening and subsequent release of no-from furoxans, as noted in the review by V.G. Granik and N.B. Grigorev [3].

A considerable amount of research has been dedicated to advancing the fields of medicine and furoxan chemistry, particularly in the synthesis of bifunctional compounds. These innovative compounds integrate furoxan fragments with various pharmacological groups, creating hybrid molecules that possess both pharmacological activities and NO-donor properties. Such hybrid compounds often demonstrate a broader range of pharmacological effects while exhibiting lower toxicity compared to single-pharmacological-group compounds, paving the way for more effective therapeutic options.

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As nitric oxide (NO) donors, furoxans and benzofuroxans are widely utilized in various fields. NO donor agents play a crucial role in pharmaceutical chemistry, particularly as antiviral and antitumor agents, in the treatment of antibiotic-resistant bacteria and biofilm infections, as well as in cancer chemoprevention and chemotherapy. As demonstrated in the extant literature, these substances have been shown to contribute to memory formation in the central nervous system [4]. Furthermore, they have been demonstrated to be significant in the therapeutic management of diabetes and neovascularization. Benzofuroxans' ability to introduce pharmacophore groups into their structures, along with the potential to synthesize heterocyclic compounds with NO donor properties, positions them as valuable compounds for creating multifunctional therapeutic agents.

Benzofuroxan derivatives show significant activity against various forms of *Leishmania amazonensis*, being more effective than amphotericin B and pentamidine by a factor of three. Benzofuroxans also exhibit high fungicidal activity against phytopathogenic fungi, such as *Rhizoctonia solani* and *Fusarium graminearum*. Additionally, they are used as aldose reductase inhibitors, making them promising for treating cardiovascular complications associated with type 5 diabetes. Hybrid compounds containing both benzofuroxan and fluoroquinoline fragments demonstrate superior antibacterial activity compared to the original fluoroquinolines.

Benzofuroxans are also employed as synthetic precursors for obtaining new biologically active compounds, such as quinoxaline dioxide and benzimidazoles. The introduction of various substituents into the benzofuroxan ring significantly influences their chemical reactivity and biological activity.

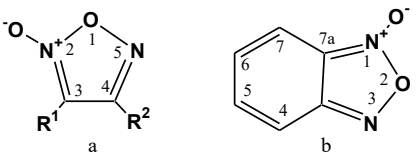
This mini-review examines the scientific literature published in Russian and English over the last few years concerning heterocyclic compounds synthesized based on benzofuroxan. It focuses on their potential as biologically active substances in medical chemistry. The importance of this research lies in expanding the knowledge of benzofuroxan and furoxans as a promising class of compounds for drug development. The results can contribute significantly to the development of medicinal chemistry, organic synthesis, and new treatment methods for severe diseases.

2. Main part

2.1 Chemical structure and synthesis methods of Benzofuroxans

Furoxan is the common name for 1,2,5-oxadiazole-2-oxide (Scheme 1a). It is characterized by an oxygen atom outside the ring attached to the nitrogen atom's electron lone pair, making the furoxan ring asymmetric. The oxygen atom located outside the ring structure is indicated as position 1, whereas the nitrogen atom, which is bonded to an oxygen atom, occupies position 2 [5]. The other atoms in the molecular framework are numbered sequentially as positions 3, 4, and 5. Notably, derivatives of Furoxan (Scheme 1a) and Benzofuroxans (Scheme 1b) have undergone extensive investigation in the field of medicinal chemistry [6]. These compounds are of significant interest due to their diverse biological activities and potential applications in drug development, thus underscoring the importance of their structural elucidation and analysis.

Benzofuroxan is the common name for benzo[1,2-*c*] [1,3,6] oxadiazole-1-oxide [1] (Scheme 1b), where the oxygen atom outside the ring makes the benzofuroxan ring asymmetric, leading to the existence of two regioisomers when the substituents R^1 and R^2 are different [7].



Scheme 1 – Chemical structure of furoxan (a) and benzofuroxan (b) [7,8]

The position of the N-oxide fragment is indicated as 1-N or N1-oxide in the case of Benzofuroxan. The numbering of atoms in the heterocyclic ring system follows Scheme 1 [7,8].

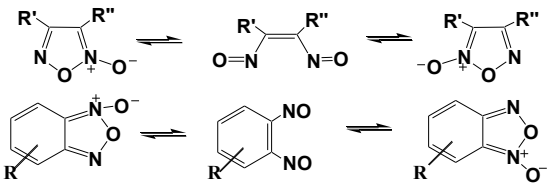
The functional group of N-oxide is formed by the attachment of an oxygen atom to the nitrogen atom's electron lone pair, which makes this group neutral, although nitrogen and oxygen carry formal positive and negative charges.

The furoxan ring is an aromatic system with 6 π-electrons, but due to the presence of heteroatom-heteroatom bonds, the aromatic stabilization energy is relatively low. Furoxan, depending on the nature of the substituents, is stable in both oxygen and water and can be purified by silica gel chromatography. Many low molecular weight furoxans are solids at room temperature, making their molecular structure reliably determined by single-crystal X-ray analysis. Furoxans with normal carbon substituents show chemical shifts in the ^{13}C NMR spectrum around 115 And 160 ppm for C3 And C4 carbons, respectively. It is evident that the elevated magnetic field resonance associated with carbon atom C3, in comparison to carbon atom C4, is unequivocally attributable to mesomeric electron donation of the oxygen atom located outside the ring to adjacent carbon atom C3 [2]. This significant difference in chemical behavior is pivotal for accurately determining isomeric structures. By examining these resonance variations, researchers can precisely uncover the electronic environments of the atoms within the molecule, which is essential for clarifying the compound's molecular architecture and reactivity. Such understanding is crucial in medicinal chemistry, where elucidating the impact of structural modifications on biological activity is paramount for drug development and optimization.

Almost all furoxan regioisomers are stable at ambient temperature, but most furoxans tend to isomerize at temperatures above 100°C. This thermal isomerization has

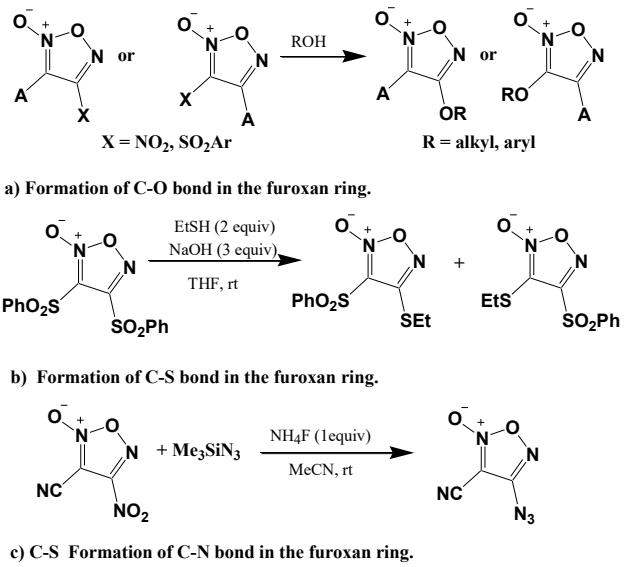
been proposed to proceed via dinitrosoalkenes as intermediates [9]. Professor Alberto Gasco's extensive research [5,10] demonstrated the varying NO production capacities of different regioisomeric furoxans with N-oxide groups in different positions. Furoxan isomers can easily interconvert via a dinitrosoethylene intermediate upon heating or photochemical irradiation, leading to the development of new NO-donor drugs targeted to show different properties based on the isomeric structure of furoxan [11].

Tautomerism associated with 1,2-dinitroso intermediates in furoxans and benzofuroxan derivatives demonstrates significant energetic variations, which are profoundly influenced by the chemical character and positional arrangements of attached functional groups. This influence is particularly marked when the subject under discussion pertains to benzofuroxans [12]. These variations are further impacted by solvent interactions and the specific temperature conditions utilized during the reactions [12]. Furoxans, with their more complex electronic structures, necessitate a greater input of energy for interconversion, while benzofuroxans achieve a rapid equilibrium state at ambient conditions, reflecting their lower activation energy barriers. Consequently, the energy needed for interconversion in furoxans is substantially elevated and is intricately linked to the distinctive properties of substituents R1 and R2, which can significantly influence the overall stability of the tautomers. Rauhut et al. have provided compelling evidence that, in the context of benzofuroxans, the dinitrobenzene interim is effectively stabilized by strong aromaticity derived from the formation of a quinonoid six-membered ring, which substantially contributes to the stability of the interim [12]. In contrast, this stabilising effect does not extend to the energy requirements for isomerisation in furoxans. This finding indicates a fundamental difference in their reactivity profiles and the underlying mechanisms governing their behaviour (Scheme 2) [13].



Scheme 2 – Isomerization mechanism of the furoxan cycle [13]

Due to weak aromaticity and the presence of numerous heteroatom-heteroatom bonds, furoxans are prone to ring cleavage under various reaction conditions. Therefore, the primary strategy for furoxan synthesis is the introduction of the necessary substituents into the precursor before forming the furoxan ring. The formation of C–O [14], C–S [2], C–N [15], and carbon-halogen bonds [6] in the furoxan ring is documented in the literature (Scheme 3).



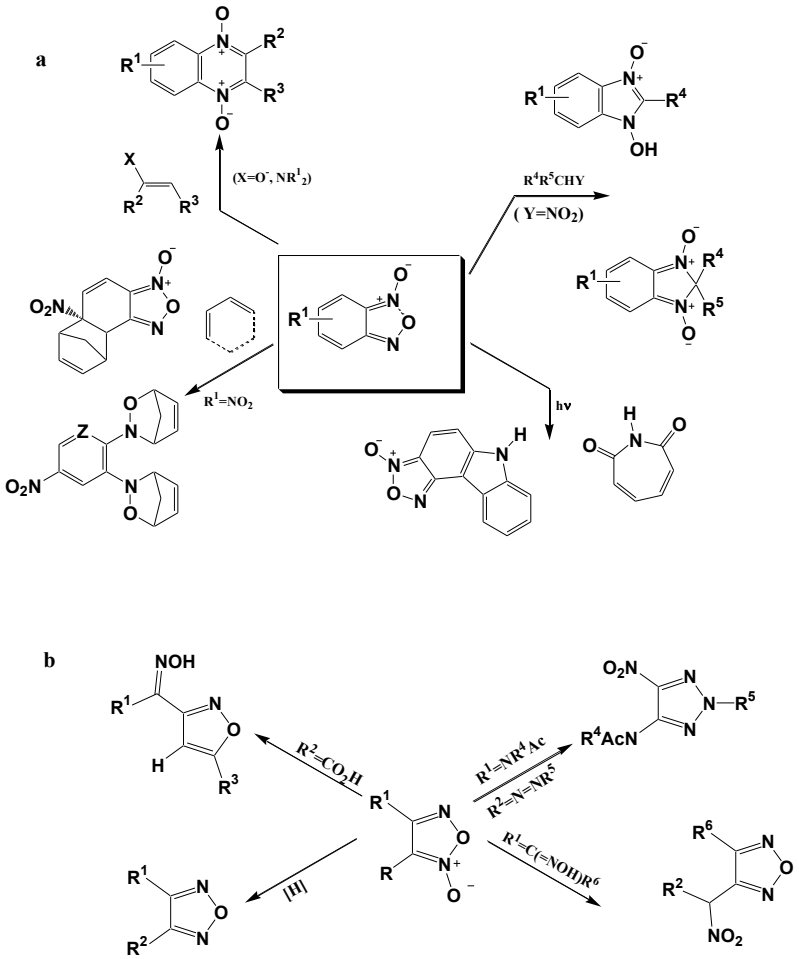
Scheme 3 – Formation of a) C–O [14], b) C–S [2], and c) C–N [15] bonds in the furoxan ring

As synthetic methods continue to evolve, research into the applications of furans and benzofurans is gaining valuable momentum (Scheme 4) [12]. These compounds serve as versatile intermediates in the synthesis of furazan derivatives, particularly 1,2,5-oxadiazoles, and nitrile oxides. Their utility extends to various heterocyclic rearrangement processes and numerous chemical transformations involving heterocyclic compounds. Additionally, benzofuran derivatives are frequently used as synthetic intermediates, as evidenced by a wealth of supporting literature.

This system demonstrates a notable level of reactivity towards a range of electron-rich compounds, including enamines and enolates. Sebban et al. [16] emphasizes the capacity of this system to react with a variety of these substrates, facilitating the formation of heterocyclic compounds that exhibit diverse biochemical properties [12]. This finding provides new opportunities for research and development. Furthermore, J.C.Halle [16] emphasises the pivotal role of nitrobenzofuroxan analogues in Diels-Alder reactions, functioning as carbodienophiles, heterodienophiles and heterodienes.

Furthermore, the irradiation of benzofuroxans enhances the synthesis of numerous heterocyclic compounds, including among others 1H-azepine-2,7-dione and 6H-furazan[3,4-C] carbazole-3-oxide [12,17], thereby contributing to the expansion of synthetic methodologies and the development of novel chemical entities. This ongoing research contributes not only to the enrichment of the field of synthetic chemistry but also has the potential to drive innovative solutions in various applications.

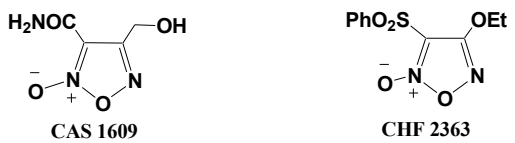
Benzofuroxans have emerged as some of the most promising nitric oxide (NO) donor agents in the field of medicinal chemistry due chiefly to the occurrence of the $N^{+}\rightarrow O^{-}$ functional group in benzofuroxans' chemical constituents [4,20]. Extensive



Scheme 4 – Main reactions characteristic of a) benzofuroxans and b) furoxans [12,18,19]

research has highlighted the capability of benzofuroxans to effectively release NO under non-pathological conditions, thereby promoting the production of a range of reactive nitrogen species within biological systems. These reactive species play crucial roles in various physiological processes, such as vasodilation and neurotransmission [12].

Among the most notable NO donors identified are compounds CAS 1609 and CHF 2363 (Scheme 5) [4], both of which were elucidated in the intermediate years of the 1990s [4]. These compounds have demonstrated powerful vasodilatory effects, facilitating the relaxation of vascular smooth muscle and thus aiding in the management of conditions related to blood flow. Additionally, their anti-aggregatory properties contribute to the inhibition of platelet aggregation, which can be beneficial in preventing thrombotic events.



Scheme 5 – Structure of CAS 1609 and CHF 2363 [4]

The findings emphasize the substantial therapeutic potential of benzofuroxans, particularly in the modulation of vascular function and the treatment of various cardiovascular disorders. The ongoing exploration of their mechanisms of action continues to reveal insights that could lead to new treatment strategies aimed at enhancing overall vascular health and addressing related pathologies.

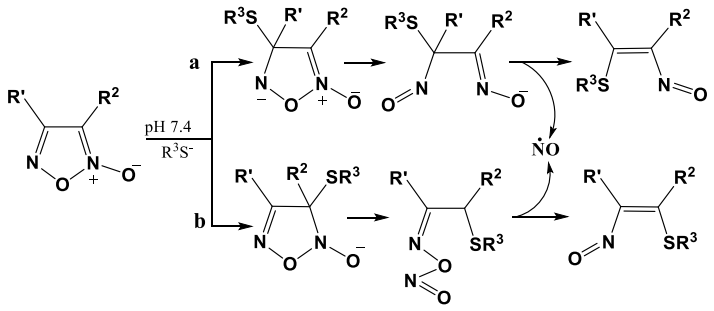
With regard to the subject of nitric oxide (NO) donors, CAS 1609 [4] is a highly effective compound that has been shown to enhance cyclic guanosine monophosphate (cGMP) [4] levels in rodent models of hypertension. It has been demonstrated that this compound can effectively reduce blood pressure and left atrial inferior pressure, even at conservative doses [4]. Following this discovery, L.L. Fershtat and colleagues elucidated the anti-aggregatory activity of CAS 1609 against ADP, adrenaline, and partially collagen-induced aggregation, highlighting its therapeutic potential in managing cardiovascular conditions

[21]. Likewise, CHF 2363 exhibits promising cardiorespiratory benefits, demonstrating substantial NO emission alongside notable anti-aggregatory and vasodilatory effects [22]. It is important to note, however, that CAS 1609 [4] shows limited cellular toxicity and damage at very low concentrations (1 millimole) while the hydrophilic version CHF 2363 [4] shows comparable effects only at significantly elevated concentrations (5 moles). This discrepancy highlights the need to understand the NO donor capabilities of various furoxans, especially in relation to those without such capabilities, as well as the impact of NO-scavenging agents like oxygenated hemoglobin in mitigating these effects.

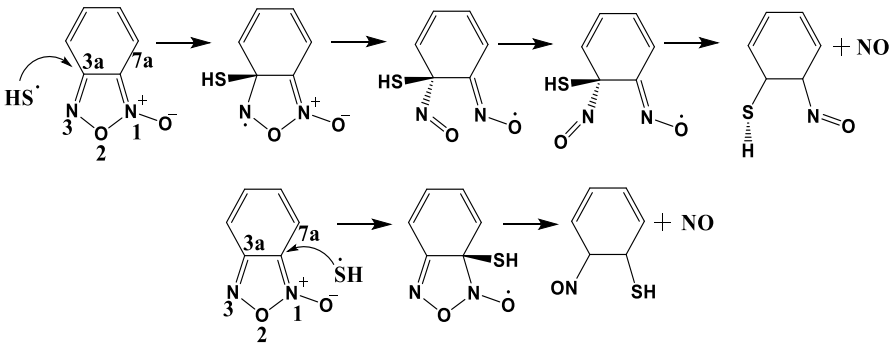
The thiol-dependent process underlying NO emission in furoxans is broadly recognized, yet there are critical aspects of that release pathway that require further investigation. The furoxan cycle is highly electrophilic due to the electron-withdrawing nature of its ring, meaning that it can interact with nucleophilic substances. This leads to two main pathways for NO release from furoxans, both of which involve the interaction of thiolate anions from cysteine with either the third or forth carbon atom within the furoxan frame (Scheme 6) [21]. This exploration into the mechanisms of action will enhance our understanding of the therapeutic potential of these compounds in clinical use.

It has been established that both pathways, designated as a and b, contribute to the degradation of the furoxan ring, while concomitantly facilitating the release of nitric oxide (NO). Recent investigations [24] have indicated that, in certain instances, the approach of the anionic thiolate moiety to the 3-carbon part in the furoxan structure is associated with increased reactivity. The reaction involving 4-nitrofurans and thiolate anions is a well-documented process, involving the replacement of the nitro group by a sulfonylfuroxan compound [4]. This phenomenon is likely due to the high reactivity of thiolate anions with electrophilic centers, which leads to unique chemical transformations within 4-nitrofuroxan molecules.

Furthermore, recent biochemical studies have demonstrated a strong correlation with the calculated activation characteristics of various reactions, thereby reinforcing the robustness of our understanding in this domain. O.N. Burov and his colleagues have proposed two potential radical mechanisms for the release of NO from benzofuroxan [25]. The first of these mechanisms involves a four-stage process in which the thiyl radical attacks the C(3) atom, overcoming a maximum energy barrier of 20.2 kcal/mol [25. This pathway ultimately results in the formation of nitrosothiophenol, indicating a promising approach for further exploration of this reaction. Furthermore, the attack by the thiyl radical on the C(7a) atom of benzofuroxan is kinetically more favorable [26]. The generation of nitrogen oxide (II) occurs in two distinct stages, and the activation barriers for these processes are comparatively lower [26]. This enhanced understanding of the reactivity of benzofuroxans and their potential applications in therapeutic settings is a significant advancement in the field [26].

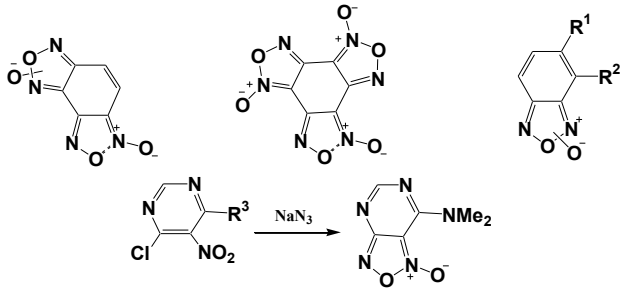


Scheme 6 – Mechanism of NO release from furoxans [18,21,23]



Scheme 7 – Mechanism of NO-release from benzofuroxan [26]

Within the domain of organic synthesis, the employment of sulfonylfuranoic derivatives as reagents is a pervasive practice, with the aim of synthesizing functional compounds and biosynthetically active substances [4]. Medana C. and her team conducted studies involving benzotrifuronic and benzofuronic derivatives (Scheme 8) [7], and their subsequent findings confirmed the involvement of N-oxide in the vasodilation process [7].



Scheme 8 – Benzofuroxans as NO-donor agents [7,26]

A methodology for targeted diazotation was formulated with the objective of facilitating the acquisition of readily available 4-aminofurans. This approach relies on the utilisation of NOBF4 which functions as a relatively benign source of nitrosation [4,27]. This method is of significance in that it leads to a notable increase in the availability of fluorochloridum compounds, which can be efficiently purified. In their solid state, these salts exhibit heightened susceptibility to azo linkage with reducing agents such as reducing arenes or CH-acids.In certain instances, NaNO2 has additionally been employed for diazotation, with the resultant arylazofurans demonstrating the capacity to undergo photocomputation. In the presence of visible light, electron isomerisation of the N=N) [28] bond to form stable Z-arylalazofurans) [28] occurs under ambient conditions (Scheme 9) [28].

It is evident that a significant proportion of photochemical reactions of this nature follow a similar mechanism. In such reactions, the E/Z ratio [2] is contingent upon the substituents present within the furoxan ring and the N=N bond.UV light has been observed to induce a gradual conversion back to the initial E-arylalazofurans. It is noteworthy that the release of N-isomers is relatively limited (N-isomers released: <10%), whereas the presence of adducts of E- and Z-isomers results in a considerably higher level of N-isomer. release (33-52%), which exceeds the standard of CAS 1609 [4,27]. The phototherapeutic property of furoxan-based molecular switches is a highly effective result of their ability to undergo this transformation and become visible light.

2.2 Benzofuroxans' biological activity and prospects for application

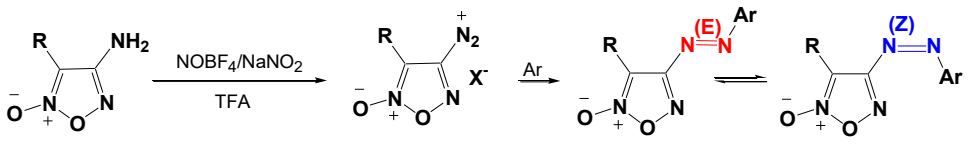
In the current era, organic chemists specializing in organic synthesis are placing considerable emphasis on the development of hydroid drugs. These innovative compounds seek to integrate a nitric oxide (NO) donating furoxan group [24] with well-established pharmacophores or promising agents connected through meticulously selected binder molecules [24]. This constructive approach aims to harness the advantages inherent in both elements, thereby enhancing therapeutic efficacy while concomitantly minimizing adverse effects. Consequently, this paves the way for more effective treatment options.

Given their current potential as NO donors and their ability to produce reactive nitrogen species in biological systems, benzofuroxans have attracted considerable interest from organic chemists for the synthesis of multifunctional compounds.

The development of multifunctional drugs is currently a rapidly advancing direction in medicinal chemistry. Such biologically active substances can exert a complex influence on multiple mechanisms of pathological processes simultaneously and interact with several targets, which generally significantly enhances their effectiveness and expands their pharmacological potential, while also reducing undesirable side effects.

Multifunctional drug compounds can provide targeted delivery. For example, the low bacteriostatic activity of sulfanilic acid is due to its poor permeability through cell membranes, which is based on its high hydrophilicity. The introduction of lipophilic fragments into sulfanilic acid enhances its antibacterial activity. Hybrid structures based on sulfanilic acid and pyridoxine exhibit high antibacterial activity [29].

Research on the synthesis and biological activity of multifunctional compounds based on various drugs containing NO-donating organic nitrates is rapidly advancing [30]. For example, "hybrid" compounds based on aspirin and organic nitrates retain the anti-inflammatory and antithrombotic (anti-aggregation) activities characteristic of aspirin, while also possessing the gastroprotective properties of nitric oxide. In addition, these compounds reduce the known aspirin's side effects as an increased risk of gastrointestinal disorders [30].



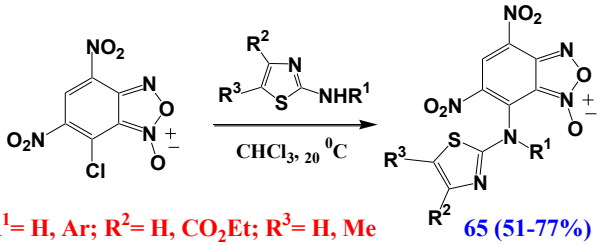
Scheme 9 – Synthesis and photoisomerization of arylazofuroxans [28]

Benzofuroxan is regarded to be an optimal foundation for the development of novel biosynthetically reactive molecules [26], with the N-releasing capability of the benzoyl group representing a particularly fruitful research trajectory. The present study investigates benzofuraxan motifs, with a view to ascertaining their potential as multifunctional compounds [26]. The subject of this study has been described in literature for a period of time exceeding 60 years. For example, the chemical properties and synthesis of benzofuroxans and furoxans have been published in the works of Gasco A., Boulton A.J. [14], and Katritzky A.R. [31]. The pharmacological properties and biochemical activity of benzofuroxans have been studied since 1981. In that year, Ghosh R., Turney B., and Whitehouse M. [32] published the first comprehensive article on the biochemical activity of benzofuroxans.

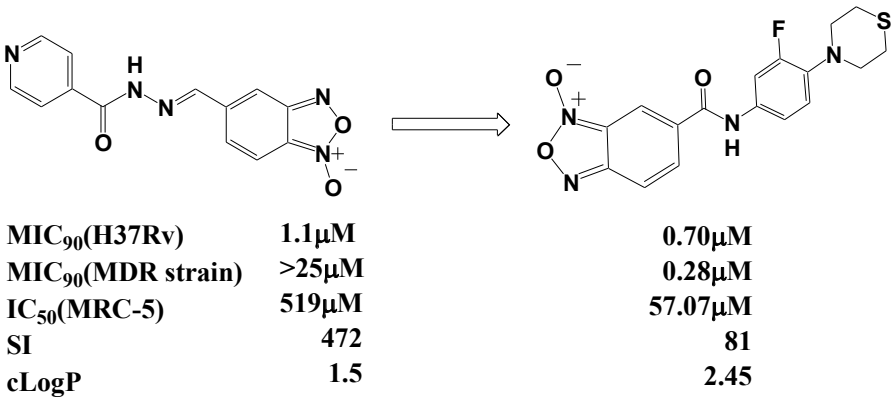
In the last decade, a large number of benzofuroxan derivatives, showing a wide range of biological activities including antibacterial, antifungal, antileukemic, acaricidal, and immunosuppressive properties, have been studied and described. The chemistry of benzofuroxans is notable for the ease with which they can be incorporated into the frameworks of a variety of medically significant substances [2]. The rhombohedral groups are responsible for the manifestation of physiological activity, while the furoxan remains unaltered. Evidently, the group is responsible for the occurrence of biological activity, whilst preserving the furoxan. In addition, it has been demonstrated that the group is able to obtain a wide range of different classes of heterocyclic compounds, which contain N-donors [2]. This determines great prospects for their use in the targeted synthesis of compounds with useful properties.

In recent years, several innovative approaches have been developed for the functionalization of pharmacologically active benzofuroxans. For instance, the combination of benzofuroxan carboxylic acid with drug-designing amines has led to the creation of a range of biologically active amides. Notably, the thiomorpholine derivatives of these amides have demonstrated remarkable antibacterial activity against *Mycobacterium tuberculosis* strains that are resistant to conventional drugs [33]. This progress underscores the significant potential of benzofuroxan-based compounds in addressing critical challenges in the field of antimicrobial therapy. The research by Fernandes G.F.S. and colleagues falls short in providing thorough *in vivo* studies, detailed toxicity assessments, clear mechanistic explanations, and pharmacokinetic evaluations, which hinders the practical application of benzofuroxan derivatives as viable treatments for multidrug-resistant *Mycobacterium tuberculosis* [33].

Three- and tetracyclic ring systems containing nitrofuroxanquinoline have demonstrated remarkably elevated nitric oxide (NO)-donating capacity, thus establishing them as highly promising candidates for further drug development [34]. Benzofuroxans that incorporate supplemental free-electron-pair acceptor groups are recognized as super-electrophiles, facilitating the rapid and efficient attachment of various pharmacophore fragments [35]. In recent years, there has been extensive research on the reactivities of 4,6-dichloro-5-nitrobenzofuroxan [35] with both heteroaromatic amines and homomeric amines [35]. The super-electrophilic properties of benzofuroxan have been harnessed in the synthesis of a series of promising anticancer agents featuring 2-amino thiazoles, which show potential in therapeutic applications.



Scheme 11 – Synthesis of hybrid compounds based on benzofuroxan and 2-aminothiazole [23,35,36]



Scheme 10 – Benzofuroxan derivatives with anti-*M*-tuberculosis activity [33]

As demonstrated in the extant literature, the substrate toxicity of the primary compound with a 4-methoxybenzyl substituent is associated with the induction of the early stage of programmed cell death in M-HELa cells [37]. As demonstrated in Figure 30, at concentrations ranging from 50 to 100 M, a proportion of 10.7-17.3% [37] of the cells exhibited characteristics of the cell cycle [37].

It has been demonstrated that a number of alternate furoxan compounds also manifest a broad spectrum of biomedical characteristics, as illustrated by the identification of 3-cyano- and 3-nitro-4-phenylfuroxan as anti-aggregatory agents [38]. Furthermore, the compound in particular has been shown to inhibit the growth of *Pseudomonas aeruginosa* (PAO1) [38] and to hinder the formulation of PAO1 biofilms [39]. Moreover, hybrid compounds of furoxans and perrithinides have been exhibited to display microbicidal qualities, as evidenced by their ability to impede the formation of *Staphylococcus aureus* and *Escherichia coli* biofilms [40]. The main compound, PGR150 (3-methylfurane-4-carbonylhydride) [40], is being explored as a potential candidate for new analgesics to effectively treat severe diabetic neuropathy, with the administration of the drug known as RG150 [41] having been demonstrated to result in a significant reduction in the mechanical load on the rato model of noxious diabetic nerve pain [41].

The investigation revealed that the PRG150 exhibited both metabotropic resonance and bio-distribution within the somatosensory system [41] when utilising carbon-11 and nitrogen-13 nuclear magnetic resonance-labelled compounds [42]. The use of carbon-11 and nitrogen-13 nuclear magnetic resonance-labelled phosphorus emission tomography has been demonstrated to show higher uptake of the nitrogen-13 isotope in the dorsal neural tube compared to carbon-11. This finding suggests a pivotal function for NO release in the nociceptive neurotransmission process, which contributes to the analgesic effect of PPG150 [43]. Subsequent studies have corroborated the role of Nogo in the treatment of severe diabetic neuropathy, as well as the effect of PPG150 on forskolin-based studies. Furthermore, the adenosine monophosphate (AMP) has been demonstrated to modulate the opioid receptor signal in both in vitro and in vivo experiments [44].

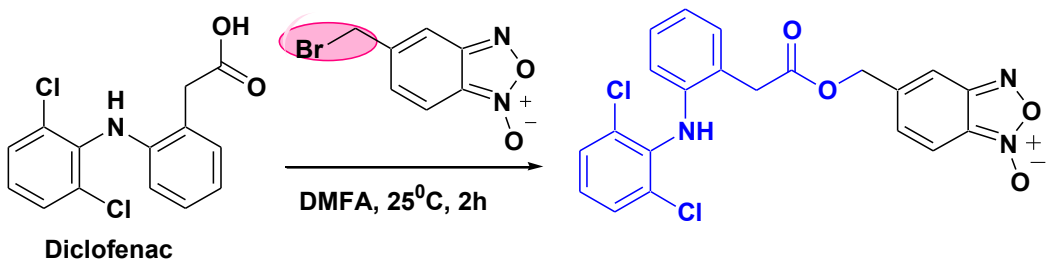
Notwithstanding, the initial constituents of said compounds were synthesised at the terminus of the despite the initial members of these communities being sunthesiazed towards the close of the 19th century [45], the exploration of novel benzofuroxan derivatives persists. Researchers from the university of Illinois, such as Thatcher J., showed that benzofuroxans act as thiol-bioactivated NO mimetics, exhibiting biological activity through NO release [45]. Using the benzofuroxan fragment as a basis, new non-steroidal anti-inflammatory drugs were developed from diclofenac (Scheme 12) [46]. A common negative side effect of nsaids as gastrointestinal toxicity, was reduced by incorporating benzofuroxan into the structure while maintaining the biological activity of diclofenac [46].

Recent advancements in the fields of pharmaceutical science and the study of benzofuroxan moieties [47] have led to the development of hybrid compounds [47], which combine benzofuroxan fragments with diverse pharmaceutical groups within a single molecule [48]. These bivalent drugs interact with a pharmacophore group and the NO-donor sarcosine of benzofuroxan chromane, typically [47]. The former exhibits a more extensive pharmacologic spectrum and reduced toxicity in comparison to the latter, which consists of a single farmacorhe unit.

The scope of NO-donating “hybrid” substances [47] has been expanded to encompass anti-inflammatory properties, in the context of procterial and pharmacological interventions for the treatment of numerous pathologies, including heart diseases, motility disorders of the gastrointestinal tract, and migraines [47]. Robotic interventions are also employed in the treatment of carcinomas, Parkinson’s disease, high blood pressure, and a range of other conditions [38,49–51].

Benzofuroxan compounds represent a pivotal class of hydrophobic, thiol-dependent N-oxide donors [52]. After the identification of NO as a pivotal intraspecies modulator within metabolic networks, the elevated NO-releasing capacity of benzofuroxan derivatives and their in vivo tumor-suppressing properties have rendered them indispensable in the development of anticancer pharmaceuticals. It is noteworthy that these heterogeneous compounds can generate various forms of nitric oxide (NO), including its two redox forms: nitroxyl (HNO) and oxidized form (NO^+) [26,52].

Following the initial publications on the anti-oncological potential of benzofuraxans, a plethora of derivatives have been



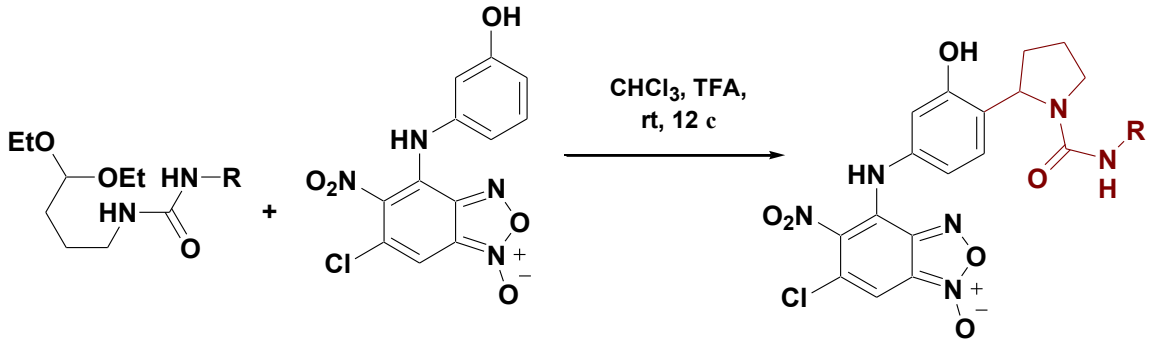
Scheme 12 – Incorporation of the benzofuroxan fragment into the diclofenac molecule [46]

synthesized and subjected to mutagenicity testing against an array of cancer cell lines. A subset of benzofuroxano structural variants has been observed to impede the proliferation of M-HeLa cells at the cellular level, while others have exhibited divergent responses. Conversely, certain derivatives have exhibited pronounced efficacy in the context of P388 lymphoma and Ehrlich ascites in murine models [26,47,53]. Of particular interest is the observation that the potent anti-cancer effect associated with these molecules is linked to certain properties. It has been demonstrated that the ability to impede DNA polymerase and the occurrence of individual- and dual-stranded DNA damage [47] are associated with these compounds. It has been established that individual-strand DNA damage is efficiently restored via a variety of intersegmental DNA recovery mechanisms [47]. Conversely, the restoration of numerous damaged sites is considerably more challenging and has the potential to culminate in cell death. One study [54] demonstrated the presence of electron-accumulating nitrocompounds. The presence of electron-accumulating groups in the benzofuroxan group of nucleosides has been demonstrated to contribute to the process of mutagenesis.

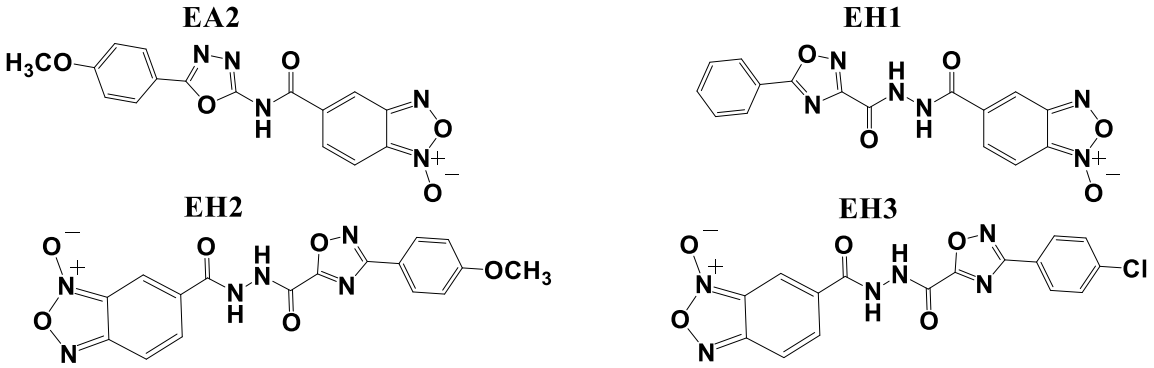
A modular approach based on Mannich n-(4,4-diethoxybutyl)urea reactions was used to develop a method for obtaining new 2-(hetero)aryl-pyrrolidine-1-carboxamides containing benzofuroxan fragments (scheme 13) [26,53]. The anticancer functionality associated with these communities was studied both *in vitro* and *in vivo*. Some compounds exhibited *in vitro* activity against M-HELA cancer cell lines that was twice as potent as the reference drug tamoxifen, while their cytotoxicity against normal Chang Liver cells was not higher than that of tamoxifen. *In vivo* studies showed an increase in survival duration (ils) of up to 44,7% and up to 83% of the animals surviving the 60-day observation period. Thus, these compounds have been identified as promising candidates for further development as anticancer agents [54]. The research by Smolobochkin and colleagues has notable limitations, such as a lack of detailed understanding of how the synthesized compounds exert their anticancer and anti-biofilm effects, limited *in vivo* studies to confirm the promising *in vitro* results, and insufficient investigation into their toxicity and pharmacokinetic behavior. These gaps hinder the potential for developing the 2-(het)arylpyrrolidine derivatives into practical therapeutic options [55].

Furthermore, it is imperative to acknowledge the significance of NO as a constituent element of the mechanism of non-specific immunity [56]. It is a component that protects against numerous pathogens, including bacteria, viruses, and fungi [56]. Numerous publications have documented the pronounced fungicidal properties of so-called 'hybrid' benzoyl derivatives, which are derived from benzoyl itself [56]. The furfuryl fragment is comprised of known pharmaceuticohor fragments (aminosides, nitrates of amino alcohols, phenols and polyene antibiotics) [57]. The investigation focused on the efficacy of 4,6-dinitro-5,7-dichlorobenzofuroxan analogue in combating trichomonads. The level of orthonin mentagrophytes was found to be four times higher than that of the antifungal drug nystatin [58]. The present study investigates the high activity of benzofuroxan compounds against phytotrophogenic fungi (*Rhizomucoraceae*, *Sclerotin*) [59]. The following were identified: *Clorotium, Fusarium, Gramineum*, and *Phytophtora sarcasii* [59], in addition to the antibiotic-resistant *Staphylococcus bacillus* [59,60].

Benzofuroxan derivatives are promising compounds for the *in vitro* antiparasitic activity in trophozoites of *T.vaginalis* (treatment of trichomoniasis). It has been hypothesized that the NO moiety of these substances may be capable of releasing toxic radicals, such as NO, which have been shown to generate reactive oxygen and nitrogen species. These radicals have been identified as the cause of the destabilization of the Trypanosoma cell membrane. A similar mechanism can be applied to *T. vaginalis*, as the activity of these compounds is associated with their ability to inhibit the cellular respiration of the parasites [61]. However, the study does not explore the potential for Trichomonas vaginalis to develop resistance to benzofuroxan derivatives over time. This is a major limitation, as the emergence of resistance could ultimately render these compounds ineffective, undermining their long-term therapeutic utility.



Scheme 13 – Synthesis of new 2-(hetero)aryl-pyrrolidine-1-carboxamides containing benzofuroxan fragments [18,54]



Scheme 14 – Benzofuroxan compounds used against *T. Vaginalis:* EA2, EH1, EH2, EH3[61]

In recent decades, significant advancements have been made in the field of anticancer drug development. However, despite these efforts, there is still a lack of effective medications available to treat cancer. Despite the significant progress made in the field, the development of effective anti-cancer drugs has not been achieved. The majority of anticancer drugs in clinical use exhibit inadequate aqueous solubility, a property that can compromise their effectiveness. Furthermore, there is a risk of adverse effects associated with oral ingestion, as well as with intramuscular and intravenous injection [62].

The dissolution of oncological pharmaceuticals in aqueous solutions is a pivotal factor in determining their efficacy. In certain instances, the utilization of excipients with deleterious side effects may be imperative. To illustrate, the intraoral administration of the investigational kinase suppressant NEXAVAR® (SORAFENIB) finds application in the management of gastric and hepatic cell proliferations [63]. In accordance with the system for the categorization of pharmaceuticals according to their bioavailability, sorafenib is designated as follows: This is a consequence of its categorization as a compound with limited soluble potential and elevated permeation characteristics. Sorafenib demonstrates minimal soluble properties and exhibits a sluggish dissolution rate within the digestive system, which is the pivotal phase for its absorptive process and ensuing interaction with initial metabolic processes. This results in a diminished bioavailability when administered orally [64]. Poor aqueous solubility of sorafenib results in lack of therapeutic effect or acute toxicity [65,66].

Our research group previously synthesized a series of novel amino-containing derivatives of benzofuroxan by substituting the chlorine atom in 4,6-dichloro-5-nitrobenzofuroxan with various aliphatic and aromatic amine fragments. These compounds exhibited promising anticancer properties, demonstrating high activity against several cancer cell lines and low cytotoxicity toward normal cells [47]. In particular, the derivatives displayed selective cytotoxicity against cervical carcinoma (M-HeLa) and human breast adenocarcinoma (MCF-7) cell lines, with efficacy comparable to the reference drug doxorubicin and significantly surpassing tamoxifen in terms of anticancer effects. Additionally, the compounds showed potent activity against glioblastoma cells (T98G).

Although benzofuroxans are known for their wide spectrum of biological activities, their medical application has been substantially limited by poor water solubility, which hinders the development of effective pharmaceutical formulations. Building upon our previous findings, we have now directed our efforts toward overcoming this limitation by synthesizing novel water-soluble salts of benzofuroxan derivatives. These compounds are of particular interest as environmentally friendly agents with strong biological activity against phytopathogens affecting major cereal and leguminous crops, including rice, barley, wheat, alfalfa, sweet clover, and sweet sorghum. The study focuses on converting previously insoluble benzofuroxan derivatives characterized by the presence of a terminal tertiary nitrogen atom into water-soluble forms. This strategy enhances their potential use in both agricultural and medical applications while preserving their high bioactivity [47].

Importantly, while this research builds on the advanced methodologies of the Russian scientific school, it also contributes to the expansion of this knowledge within Kazakhstan. By involving Kazakhstani researchers [35, 47,53, 67], the research lays a foundation for the development of innovative drug design and agrochemical approaches in Kazakhstan, fostering scientific growth and strengthening international collaboration in this emerging field.

3. Conclusion

Benzofuroxan compounds are characterized by their NO-donor properties and consist of structures that combine benzofuroxan molecules with various biologically active substances, making them promising for use in medicinal chemistry. Unlike other NO-donor agents, benzofuroxans provide a slow release of NO, which helps to prolong their

biological effectsit is important to acknowledge the potential of benzofuroxan-based reactions, encompassing the maintenance of the furoxan cycle (involving the substitution of one or two readily exhaling chlorine atoms) and the disruption of the furoxan ring [53,67]. This renders research in the domain of N-oxide-containing heterocycles highly promising from a synthetic perspective, particularly concerning the development of new heterocyclic compounds with valuable practical applications.

This review touches on recent studies of benzofuroxan derivatives as potential antituberculosis, antibacterial, cardiovascular, gastrointestinal and neurodegenerative disorder agents. Some furoxan derivatives, for example, CAS 1609 and CHF 2363 [4], have been observed to have powerful vasodilatory effects, which could help to relax vascular smooth muscle and therefore assist in managing conditions related to blood flow. It has been suggested that 2-(hetero)aryl-pyrrolidine-1-carboxamides containing benzofuroxan fragments could be ideal starting points for further investigations. It is possible that they could be promising candidates for further development as anti-cancer agents [4]. Therefore, it could be worthwhile to consider both of them as ideal starting points for further investigations.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the data presented in this article.

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CRediT authorship contribution statement

M.N. Zhanakov: writing - original draft, conceptualization, methodology, data collection, formal analysis, visualization. Zh.K. Zhatkanbayeva: reviewing and editing, project management, resources. E.A. Chugunova: reviewing and editing, resources. N.I. Akylbekov: literature search, data analysis, visualization. Ye.Ye. Zhatkanbayev: conceptualization, validation, reviewing, and editing.

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