A Review of the Biological Activity of Amidrazone Derivatives

Renata Paprocka 1,*, Małgorzata Wiese-Szadkowska 2, Tomasz Kosmalski 1, Daria Frisch 1, Magdalena Ratajczak 1, Bożena Modzelewska-Banachiewicz 1 and Renata Studzińska 1

1 Department of Organic Chemistry, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Jurasza Str. 2, 85-089 Bydgoszcz, Poland
2 Department of Immunology, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, M. Curie-Skłodowska Str. 9, 85-094 Bydgoszcz, Poland
* Correspondence: renata.bursa@cm.umk.pl

Abstract: Amidrazones are widely used in chemical synthesis, industry and agriculture. We compiled some of the most important findings on the biological activities of amidrazones described in the years 2010–2022. The data were obtained using the ScienceDirect, Reaxys and Google Scholar search engines with keywords (amidrazone, carboxyhydrizamidem, carboximidohydrazide, aminoguandine) and structure strategies. Compounds with significant biological activities were included in the review. The described structures derived from amidrazones include: amidrazone derivatives; amidoguanidine derivatives; complexes obtained using amidrazones as ligands; and some cyclic compounds obtained from amidrazones and/or containing an amidrazone moiety in their structures. This review includes chapters based on compound activities, including: tuberculostatic, antibacterial, antifungal, antiparasitic, antiviral, anti-inflammatory, cytoprotective, and antitumor compounds, as well as furin and acetylcholinesterase inhibitors. Detailed information on the compounds tested in vivo, along the mechanisms of action and toxicity of the selected amidrazone derivatives, are described. We describe examples of compounds that have a chance of becoming drugs due to promising preclinical or clinical research, as well as old drugs with new therapeutic targets (repositioning) which have the potential to be used in the treatment of other diseases. The described examples prove that amidrazone derivatives are a potential source of new therapeutic substances and deserve further research.

Keywords: amidrazone; amidoguanidine; antibacterial; antifungal; antiparasitic; antitumor; anti-inflammatory

1. Introduction

Amidrazones (hydrazones of acid amides) are organic compounds represented by the general structure presented in Figure 1a. These compounds are characterized by three nitrogen atoms ($N^1$, $N^2$ and $N^3$), of which only two, $N^1$ and $N^3$, may be substituted with alkyl or aryl groups. Amidrazones can exhibit tautomeration due to the transfer between the nitrogen atoms $N^3$ and $N^2$ [1,2]. Amidrazones are monoacid bases which form salts with inorganic acids, among which the most widely known are the hydrochlorides [2].

![Figure 1](https://example.com/figure1.png)

Figure 1. (a) The general structure of amidrazones, showing the numbering of the nitrogen atoms and the possible phenomenon of tautomeration. (b) The structure of aminoguanidine.

Amidrazones constitute a group of interesting compounds used mainly as precursors for the synthesis of five-, six- and seven-membered heterocyclic systems. Simple meth-
ods of obtaining 1,2,4-triazole, thiatriazole and 1,2,4-triazine derivatives [3], tetrazole [4] derivatives and other derivatives [1] from amidrazones have been described previously. Due to the presence of nitrogen atoms, amidrazones can form complexes with transition metals [2].

The nomenclature of amidrazones has evolved in recent years. In older papers, amidrazones are named after the acid theoretically obtained from them by hydrolysis (e.g., CH₃C(=NNH₂)NH₂ is acetamidrazone) [1,2]. Currently, the International Union of Pure and Applied Chemistry (IUPAC) recommends a different numbering and nomenclature of amidrazones (R-C(=N-NH₂)-NH₂ as carbohydrazonamides and R-C(=NH)-NH-NH₂ as carboximidohydrazides [5]). However, the previous nomenclature is still widespread in many published papers. For example, on sciencedirect.com, in 2010–2021, the word “amidrazone” gave 243 results, while “carbohydrazonamide” gave only 15. Therefore, in this work, the original nomenclature and numbering of the nitrogen atoms in amidrazones were adopted (Figure 1a).

Aminoguanidine (NH₂)₂-C=N-NH₂ (Figure 1b) is a simple, non-toxic compound that is closely related to amidrazones. Some authors of older publications do not classify it among the amidrazones [2], while others do consider it an amidrazone [1]. Taking into account the similarity of aminoguanidine to amidrazones in terms of its structure, application in the synthesis of heterocyclic compounds and the biological activities of the obtained products, in this work, aminoguanidine and its derivatives are presented among the amidrazone derivatives.

Many amidrazones and their derivatives exhibit a broad spectrum of biological activities, e.g., antibacterial [6], antifungal [6,7], antimalarial [8], antiviral [9], anti-inflammatory [10], analgesic [10], anticonvulsant [11] and insulin-mimetic [12], and as thrombin inhibitors [13]. Despite the presence of some review articles on amidrazone chemistry [1,2], a comprehensive study of the biological activity of amidrazones is still lacking. The last review concerning the biological activities of aminoguanidine derivatives was published back in 2009 [14], which justifies the presentation of the up-to-date information in this field. In addition, the diversity of the nomenclature used in medicinal chemistry literature for amidrazone derivatives (i.e., amidrazones, carbohydrazonamides, aminoguanidines, guanidines, amidinohydrazones, hydrazones, hydrazidines and others) makes it difficult for researchers to discover information about the biological activities of these compounds by using keywords, in the case of a person who is unfamiliar with the subject. Therefore, a double search strategy was used in the search for articles, using both keywords (amidrazone, carbohydrazonamide, carboximidohydrazide, aminoguanidine) and structure strategies. The best selected compounds with significant biological activities were included in the review. The data were obtained using the ScienceDirect, Reaxys and Google Scholar searching engines.

This work encapsulates some of the most important findings on the biological activities exhibited by amidrazone derivatives described from 2010–2022. The described structures derived from amidrazones include: (a) amidrazone derivatives; (b) aminoguanidine derivatives; (c) complexes obtained using amidrazones as ligands; and (d) some examples of cyclic compounds obtained from amidrazones and/or containing an amidrazone moiety in their structures (e.g., 1, 32, 51). We also discuss their toxicity, mechanism of action and potential use in preclinical trials.

2. Results
2.1. Antimicrobial Activity
2.1.1. Tuberculostatic Activity

Delpazolid (1, Figure 2), also called LCB01 0371, was the first compound containing a cyclic amidrazone moiety that was developed to treat multi-drug-resistant tuberculosis. Delpazolid successfully passed the phase I clinical trials, confirming its safety (maximum tolerated dose in humans = 2400 mg) [15]. A phase II study is currently recruiting, which explores the combination of delpazolid with bedaquiline, moxifloxacin and delamanid in...
patients with newly diagnosed, uncomplicated, drug-sensitive pulmonary tuberculosis [16].

Compounds 2–5, which possess a 2-pyridylamidrazono moiety, demonstrated tuberculostatic activity against Mycobacterium gordonae (MIC = 2–8.8 µM). Derivatives 2–3 inhibited the growth of M. tuberculosis (MIC = 4.4 µM). Interestingly, compounds 4–5, substituted with chloride or bromide atoms instead of nitro group, were even 7-fold more active against Mycobacterium kansasii than isoniazid (MIC = 4.2 µM) [17].

Another 2-pyridylamidrazono derivatives, 6 and 7, showed a strong tuberculostatic activity against the standard H37Rv strain and clinically isolated drug-resistant M. tuberculosis strains (MIC = 0.4 µg/mL) [18].

Derivative 8, containing an aminoguanidine moiety, showed strong tuberculostatic activity against (MIC = 0.78 µM), and low cytotoxicity to, human embryonic kidney cells. The mechanism of 8 was the inhibition of the enoyl acyl carrier protein reductase enzyme (InhA), which was confirmed in vitro and in computational studies [19].

2.1.2. Antibacterial Activity

Several compounds with antibacterial activities are presented in Figure 3.

The previously mentioned compounds 6–7 exhibited a significant antibacterial activity against several Gram-positive bacterial strains (Staphylococcus epidermidis, Micrococcus luteus, Bacillus subtilis, Bacillus cereus and Streptococcus mutans), with MIC values of 0.12–1.95 µg/mL. Additionally, derivative 6 showed an activity against Staphylococcus aureus comparable to ciprofloxacin and vancomycin. Interestingly, the replacement of the pyrrolidine ring found in compound 6 with a morpholine moiety present in compound 7 resulted in an approximately twofold decrease in its anti-tuberculosis and antibacterial activities against Gram-positive strains in comparison with the starting compounds of 6–7 [18]. Compound 9, containing an isatin moiety, demonstrated stronger antibacterial activity against S. aureus (MIC = 4 µg/mL) than ciprofloxacin [20].

The chloride or bromide salts of (N1-phenyl)phenylamidrazono (10) and its derivatives, 11–14, showed antimicrobial activity. The strongest bactericidal activity against S. aureus was demonstrated by compounds 12 (minimal bactericidal concentration MBC = 4 µg/mL) and 14 (MBC = 8 µg/mL), while derivatives 10, 11 and 13 showed similar activity to nifuroxazide (MBC = 16 µg/mL) [21].

Figure 2. The structures of tuberculostatic compounds 1–8.
Among the N<sup>1</sup>-(carbazol-3-yl) substituted amidrazones 15–17, compound 15, with incorporated morpholine, was bacteriostatic (MIC = 1.56 µg/mL) against B. cereus [22]. Compound 16 showed bactericidal activity against standard S. aureus and clinically isolated MRSA strains (MBC = 3.125 µg/mL). Compound 17 exhibited antibacterial activity against the Gram-negative strain of Klebsiella pneumoniae (MBC = 6.25 µg/mL and MIC = 3.125 µg/mL) [22].

Another method of amidrazone modification is the creation of their hybrids with antimicrobial drugs, i.e., ciprofloxacin (18–19) or metronidazole (20–21). Compounds 18–19 showed antibacterial activity against Escherichia coli (MIC<sub>50</sub> = 0.2 µg/mL), Pseudomonas aeruginosa (MIC<sub>50</sub> = 6.25 µg/mL), Helicobacter pylori (MIC<sub>50</sub> = 4 µg/mL) and S. aureus (only 18, MIC<sub>50</sub> = 6.25 µg/mL). However, both compounds were less active than ciprofloxacin alone [23]. Amidrazones 20 and 21 showed selective activity against metronidazole-resistant H. pylori (MIC = 8 and 16 µg/mL, respectively) [23].

Among the aminoguanidine derivatives 22–31, the 1,3,4-oxadiazole derivative 22 showed strong antibacterial activity against Gram-negative E. coli and Salmonella typhimurium and the Gram-positive S. aureus, Enterococcus faecium and Streptococcus agalactiae bacterial strains [24].
The chalcone-incorporated derivatives 23–24 showed a wide range of antimicrobial activities against S. aureus, S. mutans, MRSA, E. coli, S. typhimurium and P. aeruginosa (MIC = 1–8 µg/mL) [25].

The 1,2-diazole derivatives 25–26 showed strong antimicrobial activity (MIC = 1–4 µg/mL) against Gram-positive (S. aureus, MRSA, quinolone-resistant S. aureus, S. mutans) and Gram-negative (E. coli, S. typhimurium) bacterial strains [26].

Aminoguanidine derivative 27 demonstrated a wide range of antimicrobial activities, with an MIC value of 1 µM/mL against eight strains (including S. aureus, S. mutans, E.coli, C. albicans, MRSA and Quinolone-resistant S. aureus). The inhibition of the dihydrofolate reductase (DHFR) protein is a possible mechanism of action of 27 [27].

Aminoguanidine derivative 28 showed stronger antibacterial activity towards multidrug-resistant strains (S. aureus, E. coli, MIC = 0.56–2.24 µmol/L) than the five antibiotics used (gatifloxacin, moxiflocaxin, norfloxacin, oxacillin, and penicillin), as well as low cytotoxicity to normal HEK 293T cells. The activity of 28 could be connected to its binding to the E. coli FabH-CoA receptor [28].

Aminoguanidine derivative 29 showed antibacterial activity against B. subtilis (MIC = 4 µg/mL) and eight other bacterial strains (MIC = 4 µg/mL). The mechanism of action of 29 was its interaction with β-ketoacyl-acyl carrier protein synthase III (FabH) [29].

Thiazole derivatives 30–31 demonstrated strong bactericidal activity against the S. aureus, MRSA and VRSA bacterial strains (in most cases, MIC = MBC = 2 µg/mL) and were active against MRSA in several animal models. Compound 30 demonstrated resistance to the microsomal cytochrome P450 and stability during metabolism. However, it interacted with enzymes connected to bacterial wall synthesis (such as undecaprenyl diphosphate synthase and undecaprenyl diphosphate phosphatase). Due to its similar activity (but in lower doses) to that of vancomycin in mice, compound 30 may be a new leading structure in the treatment of drug-resistant bacterial strains [30].

Gold(III) complex 32 obtained by the reaction of amidrazone with HAuCl₄, showed antibacterial activity against S. aureus (MIC = 4 µg/mL) and lower toxicity to mice fibroblasts (IC₅₀ = 41.8 µg/mL), which suggests the good selectivity of this compound [31].

2.1.3. Antifungal Activity

Among the previously mentioned amidrazone derivatives 10–14, the strongest fungistatic activity against C. albicans was exhibited by compounds 11 (MIC = 4 µg/mL) and 10 (MIC = 8 µg/mL). Additionally, derivative 11 was fungicidal at a concentration of 16 µg/mL against Aspergillus niger and Aspergillus brasiliensis [32]. The presence of a nitro group in the position R₁ of compound 11 seems to increase its antifungal activity. Contrarily, the addition of a four-nitro substituent in the N₁-phenyl rings of compounds 12 and 14 decreased their antifungal properties but elevated their antibacterial activity.

The also previously mentioned aminoguanidine derivatives 23–27 showed strong antifungal activity against C. albicans (MIC = 1–8 µg/mL) [25,26]. The strongest effect on this fungal strain was observed for derivative 22, containing two aminoguanidine groups (MIC = 0.015–0.5 µg/mL, MBC = 0.031–1 µg/mL) [24].

Compound 33 (Figure 4) exhibited antifungal activity against Candida albicans (MIC = 16 µg/mL) [26]. Pyrazinylamidrazone 34 exhibited antifungal activity against the clinical strain C. albicans (MIC = 16 µg/mL). The replacement of the phenyl ring of compound 34 with a hydrogen or a methyl group resulted in the total disappearance of the antifungal activity of the obtained derivatives, which underlines the importance of the phenyl substituent in this position [33].
Figure 4. The structures of antifungal compounds 33–43.

The imidazolylamidrazones derivatives 35–37 demonstrated fungistatic activity against *Candida krusei* (MIC = 3.1–6.3 µg/mL) and *Candida neoformans* (MIC = 2–4 µg/mL) [34]. Derivatives 35–37 also displayed a strong inhibitory effect on biofilm development in the case of *Candida* spp. biofilms on nanohydroxyapatite substrate, and the strongest effect was observed for compound 36 [35]. The mechanism of action of compounds 35–37 seems to be connected with the production of reactive oxygen species [36]. Amidrazone-quinolone hybrids 38–39 showed an antifungal activity in vitro against *C. albicans* comparable to that of fluconazole [37].

Among compounds 40–42 (which can also be classified as vic-dioximes), derivative 40 showed a stronger activity than nystatin against the *C. glabrata*, *C. utilis* and *S. cerevisiae* fungal strains (in all cases, MIC = 4 µg/mL) [38]. Compound 41, which contains a methylfuryl moiety instead of a methylphenyl moiety, demonstrated less antifungal activity against *S. cerevisiae* (MIC = 16 µg/mL) than 40, along with antibacterial activity against *B. cereus* (MIC = 8 µg/mL) and *Streptococcus pneumoniae* (MIC = 16 µg/mL). Derivative 42, which possesses a pyridine ring, was selective to the *Candida tropicalis* fungal strain (MIC = 8 µg/mL) [39]. Compound 43 showed antifungal activity against *C. albicans*, *C. krusei*, *Micosporum canis* and *Trichophyton mentagrophytes* (MIC = 0.5–3.9 µg/mL) and a lower toxicity to *danio zebrafish* than voriconazole [40].

2.2. Antiparasitic Activity

In an attempt to obtain antiparasitic agents, amidrazones were enriched with benznidazole (44–45), metronidazole (20–21) or ciprofloxacin (18) moieties. Derivatives 44 and 45 (Figure 5) demonstrated similar activities to benznidazole against the trypomastigota forms of *Trypanosoma cruzi* (IC$_{50}$ = 9.5 and 12.85 µM, respectively; benznidazol IC$_{50}$ = 10.26 µM). Both compounds were selective to parasite cells, especially derivative 45, with a selectivity index value of about 33 [41]. Compounds 18 and 21 were revealed to possess an antitrichomonal activity about two times stronger than that of metronidazole against *Trichomonas vaginalis* [34]. Compound 20 showed antigiardial activity comparable to metronidazole against *Giardia lamblia* (IC$_{50}$ = 5.6–7.2 µg/mL) [23].

Likewise, aminoguanidine derivatives 46–50 were studied as antiparasitic agents. Robenidine (46) is an antibiotic used in veterinary medicine which, in current research, has shown an antigiardial activity against *G. lamblia* comparable to that of metronidazole. In contrast to the reference drug, compound 46 completely inhibited the adherence of trophozoides and is a candidate for a new generation of antigiardial drugs [42].
Guanabenz (47) is a known antihypertensive drug currently drawing attention for the purpose of other medicinal uses. It has exhibited antiparasitic activity against the replicative stages of Toxoplasma and Plasmodium falciparum [43]. Guanabenz inhibited the Toxoplasma dephosphorylation enzyme eIF2α. This translational control is critical during infections with both the replicative and latent forms of Toxoplasma [43,44]. In mice models, guanabenz extended the survival of mice acutely infected with Toxoplasma within 2–3 days [44] and reduced the number of brain cysts in chronically infected mice [43].

Aminoguanidine derivatives 48–50 showed antileishmanial activity against amastigotes of Leishmania chagasi (IC50 = 0.6–7.27 μM) comparable to pentamidine (IC50 = 4.4 μM). Compounds 48–50 showed a 50–80 times higher toxicity to amastigotes than to murine macrophages. The mechanism of action of the most promising compound, 50, is probably related to its interaction with the active site of the trypanothione reductase enzyme, interfering in the redox system of L. chagasi amastigotes [45].

The 1,2,4-triazole derivative 51, obtained from amidrazone, showed strong anthelmintic activity (2.475 μg/μL) against Rhabditis nematodes. Due to its stronger activity than albendazole and low toxicity to PBMC, compound 51 could be a candidate for the development of new anthelmintic drugs [46].

2.3. Antiviral Activity

Amidrazon derivative 52 (Figure 6) reduced the number of plaques of herpes simplex type-1 (HSV-1) on Vero cells by 67% [47]. Amidrazon 53, with a pyrazoloisoxazole moiety, showed antiviral activity against two HIV strains studied in two leukemia cell lines (EC50 = 0.17–0.46 nM). Compound 53 was two times more effective than the anti-HIV drug efavirenz and about two times less toxic to uninfected cell lines. Compound 53 exhibited strong inhibitory activity towards HIV reverse transcriptase (HIV-RT). Molecular docking confirmed that compound 53 strongly interacts with the HIV-RT active pocket, which enables its classification as a potential non-nucleoside reverse transcriptase inhibitor [48].

Figure 5. The structures of antiparasitic compounds 44–51.

Figure 6. The structures of antiviral compounds 52–53.
2.4. Anti-Inflammatory Activity

Derivatives of N1,N3-substituted 2-pyridamidrazones 54–57 (Figure 7) were studied in order to assess their anti-inflammatory activity in mitogen-stimulated peripheral blood mononuclear cells (PBMC). Compound 54 decreased the production of TNF-α by 43% and showed no toxicity to PBMC at a concentration of 100 µg/mL [49].

![Figure 7. The structures of anti-inflammatory compounds 54–65.](image)

Compound 55, at a concentration of 10 µg/mL, inhibited the production of the pro-inflammatory cytokine IL-6 by 35% [50]. The median lethal dose of 55 (i.p.) in mice was identified as 417 mg/kg. Compound 55, at a concentration of 21 mg/kg, reduced rat hind paw edema to a greater extent than diclofenac at a dose of 50 mg/kg. Moreover, derivative 55 demonstrated antinociceptive activity in mice comparable to that of morphine but with a longer duration of action. In summary, compound 55 could be a potential non-steroidal anti-inflammatory drug [50].

Compound 56, at a concentration of 10 µg/mL, inhibited the production of TNF-α in PBMC stimulated by lipopolysaccharide (LPS) by 53% [51]. Compound 57, at a concentration of 50 µg/mL, showed no toxicity but strongly inhibited the proliferation of PBMC activated by anti-CD3 antibodies or phytohaemagglutinin by 90–99%, and the observed effects were comparable to or stronger than those of ibuprofen. The mechanism of action of derivative 57 is cell cycle arrest at the G1 phase [52].

Additionally, some 1,2,4-triazole derivatives obtained by the cyclisation of amidrazones, similar to 56–57, showed a strong significant anti-inflammatory activity comparable to ibuprofen’s inhibition of PHA-stimulated PBMC proliferation and TNF-α production [46,53].

Anti-inflammatory activity was also reported for amidrazone-derived pyrrole-2,5-dione derivatives 58–59. Compound 58, possessing two phenyl substituents, significantly reduced the production of IL-6 (by 64%) in LPS-stimulated PBMC cultures. Both compounds 58 and 59 inhibited the proliferation of PBMC even at a low dose of 10 µg/mL, and the strongest effect was observed for the latter, possessing two 2-pyridine rings [54].

The previously mentioned N1,N3-substituted amidrazones 38–39 showed an anti-inflammatory activity in protein denaturation assays comparable to that of the sodium salt of diclofenac. Both derivatives showed a stronger antioxidant activity than ascorbic acid [37].

Indoleamidrazone derivatives 60–63 produced a stronger reduction in carrageenan-induced rat paw edema in rats than indomethacin. In general, compounds possessing nitro or methoxy substituents at the para position showed stronger anti-inflammatory effects than derivatives possessing the same groups in the meta position [55].
Naphthylamidrazone derivative 64 revealed properties preventing the adverse effects of a chronic inflammatory reaction in the articular chondrocytes through a mechanism involving the ASIC1a channels, which are sensitive to the acidification of the environment. Compound 64, in a concentration range of 6.25–50 µM, caused a significant inhibition of the ASIC1a protein expression in the joint chondrocytes comparable to amiloride (a weak non-selective ASIC1 inhibitor). Additionally, compound 64, at a dose of 25 µM, decreased the number of Ca^{2+} ions in the acidic environment of isolated rat articular chondrocytes by 69%, which is almost three times higher than the effect of amiloride at a dose of 100 µM. In summary, it can be stated that compound 64 is a potential drug for rheumatoid arthritis [56].

Aminoguanidine (AG) has been shown to possess strong anti-inflammatory and antioxidant activities in multiple ways. It inhibits the formation of highly reactive advanced glycosylation end products in the course of advanced diabetes. AG passed phase III clinical trials in diabetic patients. Although high doses of AG induced side effects, including liver dysfunction, low doses of AG therapy could be promising for the treatment of renal diseases [57].

Aminoguanidine derivatives 23–26 were studied in tests on xylene-induced ear edema in mice. Compound 23 showed an anti-inflammatory activity similar to indomethacin. However, compound 24, with a bromine atom at position 3, was about two times less effective [25]. Derivatives 25 and 26 were about two times stronger as anti-inflammatory agents than indomethacin [26].

Aminoguanidine derivative 65 was studied in an LPS-stimulated neonatal sepsis mice model. The mechanism of compound 65 was connected to a decreased pro-inflammatory cytokine release and COX-2 expression, as well as the suppression of microglia activation. Additionally, septic mice treated with derivative 65 did not exhibit the cognitive impairment and the anxiety behavior caused by LPS [58].

2.5. Cytoprotective Activity

Some aminoguanidine derivatives, such as guanabenz (47), sephin1 (66) and raphin1 (50), possess cytoprotective activities (Figure 8). The effects of those compounds are connected with the reduced deposition of proteins of abnormal conformation, which are present in many neurodegenerative diseases, such as Alzheimer’s, Parkinson’s, amyotrophic lateral sclerosis (ALS) and others. Guanabenz and sephin1 are inhibitors of the stress-induced transcription factor R15A. They prolong eIF2α (translation initiation factor) phosphorylation and, in consequence, cause the transient attenuation of protein synthesis induced by endoplasmic reticulum (ER) stress [59]. Guanabenz is currently in clinical trials as a method for the management of multiple sclerosis [60] and amyotrophic lateral sclerosis [61,62]. Guanabenz has also been shown to reduce neuroinflammation in mice with latent toxoplasmosis and reversed the behavioral changes in the studied rodents [63]. Sephin1 has passed phase I clinical trials and is being developed for treating Charcot-Marie-Tooth disease [64]. Moreover, sephin1 showed protective activity in a mouse model of multiple sclerosis [65].

![Figure 8. The structures of cytoprotective compounds 46–48 and 66.](image-url)

Raphin1 is an inhibitor of the constitutively expressed transcription factor R15B, which may be useful when combating a wide range diseases, as it could enable the increase in the control capacity of the protein quality by transiently increasing eIF2α phosphorylation and translation attenuation. It was effective in a mouse model of Huntington’s disease [66]. Moreover, the previously mentioned robenidine showed cytoprotective properties [67].
2.6. Antitumor Activity

Many piperazine-incorporating amidrazones, including 18–19, 67–72 and 74–79 (Figure 9), were studied as antineoplastic agents. Compounds 67 and 68, in a panel of 55 different cancer cell lines, produced medium IC\textsubscript{50} values of 4.81 µM and 4.92 µM, respectively, which were similar to the values of the total growth inhibition (TGI = 4.47 and 4.52 µM, respectively). This underlines their strong anti-cancer properties [68]. Moreover, amidrazones 69–70 showed antiproliferative activity against several cancer cell lines, including leukemia K562, breast MCF-7 (Table 1), prostate PC-3 and colon HCT (in all cases, IC\textsubscript{50} = 1.9–3.9 µM) [69].

![Figure 9. The structures of antitumor compounds 67–91.](image-url)
Amidrazones possessing a thiophenyl (71–72), flavone (73–74) or coumarin (75) moiety, as well as bisamidrazone derivative 79, showed antiproliferative activity against the MCF-7 and K562 cancerous cell lines (Table 1). Compounds 72, 76 and 79 had low toxicity to human fibroblasts in vitro. Molecular docking revealed a similarity of compounds 72–76 with imatinib (a drug belonging to the group of tyrosine kinase inhibitors) during interactions with bcr-abl tyrosine kinase, which may indicate a similar mechanism of action of those compounds [70–76]. Alternatively, according to in silico studies, derivative 79 could act as an effective inhibitor of phosphatidylinositol 3-kinase, the hyperactivity of which was observed in cells of the MCF-7 line [77].

### Table 1. IC₅₀ values of select compounds against MCF-7 and K562 cancerous cell lines.

| Comp. | IC₅₀ MCF-7 | IC₅₀ K562 | Ref. |
|-------|------------|-----------|------|
| 69    | 2.50 µM    | 3.10 µM   | [69] |
| 70    | 2.70 µM    | 3.50 µM   | [69] |
| 71    | 7.26 µM    | 9.91 µM   | [70] |
| 72    | >50 µM     | 1.02 µM   | [71] |
| 73    | 5.18 µM    | 2.89 µM   | [72] |
| 74    | 5.91 µM    | 5.02 µM   | [73] |
| 75    | 20.20 µM   | 9.30 µM   | [74] |
| 76    | 4.50 µM    | 1.10 µM   | [75] |
| 79    | 4.30 µM    | 3.00 µM   | [77] |
| 81    | 0.09 µM    | -         | [78] |

Ciprofloxacin derivatives 18–19 showed antiproliferative activity against the HeLa and MCF-7 cancerous cells [23]. Amidrazones 78–79, which possess a chloroquine moiety, showed antiproliferative activity against the cervix HeLa and MCF-7 cancer cells [23].

Indoleamidrazone 80 inhibited the proliferation of MCF-7 cells by 68% at a concentration of 100 µg/mL [55]. As previously mentioned, the similar compounds 60–63, which possess nitro- or methoxy-phenyl substituents instead of the benzyl observed in 80, were inactive, except for derivative 63, which showed a 61.5% growth inhibition of MCF-7 cells [55].

Aminoguanidine derivative 81 demonstrated strong antiproliferative activity against MCF-7 and an inhibitory effect on tubulin polymerization (IC₅₀ = 8.4 µM). Molecular docking revealed that the probable mechanism of derivative 81 may be connected with colchicine biding [78]. Compound 82 showed a potent inhibition of ribosomal kinase RSK2 and MCF-7 tumor cell growth inhibition [79].

Computational methods were used to identify compounds with anticancer properties. Aminoguanidine derivative 83 was one of the predicted compounds, with a confirmed antiproliferative activity against HL-60 leukemia cells (IC₅₀ = 11 µM) and low to towards Vero cells (IC₅₀ > 100 µM) [80].

Compound 84 showed antiproliferative activity against the HL-60, K562 and HT-29 cell lines (IC₅₀ = 8.9–12.5 µmol/L), and it was more effective than etoposide against the latter two lines [81]. Compound 85 showed high antitumor activity against the MDA-MB-231, MCF-7, HEP-G2 and SMMC-7721 cancer lines (IC₅₀ = 2.31–3.75 µM). Compound 85 induced apoptosis by downregulating Bcl-2 and upregulating Bax protein levels in MDA-MB-231 cancer cells [82].

Pd(II) complex 86 showed high cytotoxicity to various cancerous cell lines, including DU-145, MCF-7, HCT-116 and breast MDA231 (IC₅₀ = 0.143–0.492 µM). However it was not toxic to skin fibroblasts [83]. The similar Pd(II) complex 87 showed also antiproliferative activity towards MCF-7 and T47D breast cancer lines and very low cytotoxicity to normal Vero cells [84]. Complexes 88–89 showed cytotoxic activity against HT-29, HCT-116 ++/+ and HCT-116 −/−, as well as selectivity to cancerous cells [85].

Cu(II) complex 90 showed antiproliferative activity against the Colo-205 adenocarcinoma cell line and low toxicity to MRC-5 human lung fibroblasts [86]. Another Cu(II) complex, 91, at concentration 100 µg/mL, showed a similar (almost total) antiproliferative
activity to cisplatin against colon CX-1 and colon SW-948 cancer and epidermal A431 cell lines but was about 12-fold less toxic than the reference drug [49].

In 2022, two publications describing the antitumor activity of \( N^1 \)-benzylidene(pyrazine-2-carboxyhydrazonamide) complexes were published. The strongest activity was reported for the cobalt complex against glioma U87 MG cancerous cells (IC\(_{50} = 7.69 \mu\text{g/mL}\)) [87,88]. However, the structures of those complexes have not been precisely specified.

2.7. Furin Inhibition

Furin is a trans-membrane protein which plays an important role in many bacterial and viral diseases, tumorigenesis, neurodegenerative disorders and diabetes [89]. It has recently been shown that furin inhibitors can be used to successfully block the entry of the SARS-COV-2 virus [90]. Aminoguanidine derivatives 92 and 93 (Figure 10) showed furin inhibitory activity (\( K_i = 0.46 \mu\text{M} \) and 0.58 \( \mu\text{M} \), respectively). Additionally, derivative 92 also showed inhibitory activity against trypsin, while compound 93 was also a thrombin inhibitor [89].

![Figure 10. The structures of furin inhibitors 92–93.](image)

2.8. Acetylcholinesterase Inhibition

Several compounds were identified as potential acetylcholinesterase (AChE) or butyrylcholinesterase (BChE) inhibitors in the search for potential drug candidates for treating Alzheimer’s disease (Figure 11, Table 2). Compound 75 showed high activity against, and selectivity to, BChE and was about 3900 times stronger in its activity against this enzyme than tacrine [91].

![Figure 11. The structure of compound 94–96.](image)

| Comp.  | IC\(_{50}\) AChE [\( \mu\text{M} \)] | IC\(_{50}\) BChE [\( \mu\text{M} \)] | Ref. |
|--------|----------------------------------|-------------------------------|------|
| 75     | 24.25 \( \pm \) 2.97            | 0.002 \( \pm \) 0.0014        | [91] |
| 94     | 17.95 \( \pm \) 0.90            | 17.51 \( \pm \) 0.21          | [92] |
| 95     | 28.16 \( \pm \) 0.98            | 1.69 \( \pm \) 0.17           | [92] |
| 96     | 24.75 \( \pm \) 0.17            | \( >500 \)                     | [92] |
| tacrine| 0.124 \( \pm \) 0.02            | 7.8 \( \pm \) 0.06             | [91] |
| rivastigmine | 56.10 \( \pm \) 1.41 | 38.40 \( \pm \) 1.97       | [92] |
Aminoguanidine derivative 94 showed a threefold stronger AChE inhibitory activity than rivastigmine and no selectivity towards BChE. Compound 95 was a selective inhibitor of BChE, with an approximately 16-fold lower AChE inhibitory activity, while derivative 96 was a selective AChE inhibitor. This proves the great potential of aminoguanidine derivatives, which may, in the future, act as inhibitors of various types of cholinesterases [92].

3. Summary

We compiled the biological activities of amidrazones derivatives described in the years 2010–2022. Antimicrobial, antitumor, anti-inflammatory and antiparasitic activities constitute the main kinds of exhibited biological activities. The most important compounds studied in vitro are presented in Table 3, together with their activity details. Due to their advanced stages in preclinical studies, they form an important group, from which new therapeutic substances may emerge. Compounds with known mechanisms of action are summarized in Table 4.

**Table 3. Biological activity of selected amidrazones studied in vivo.**

| Comp. | Activity | Animal Model | Dose     | Effect                           | Reference Drug                      | Ref. |
|-------|----------|--------------|----------|----------------------------------|-------------------------------------|------|
| 23    | anti-inflammatory | xylene-induced ear edema test in mice | 100 mg/kg | 92.45% edema reduction | indomethacin 89.38% reduction, ibuprofen 87.36% reduction | [25] |
| 25    | anti-inflammatory | xylene-induced ear edema test in mice | 50 mg/kg  | 93.56% edema reduction          | indomethacin 45.23% reduction, ibuprofen 29.56% reduction | [26] |
| 26    | anti-inflammatory | xylene-induced ear edema test in mice | 50 mg/kg  | 81.65% edema reduction          | indomethacin 45.23% reduction, ibuprofen 29.56% reduction | [26] |
| 30    | antibacterial | MRSA-infected C. elegans | 20 mg/mL | reduction in the MRSA burden by ~90% | vancomycin ~90% reduction | [30] |
| 31    | antibacterial | MRSA murine skin infection | 2% suspension | 73% reduction in MRSA burden 77% reduction in MRSA burden by ~90% | vancomycin 66% reduction, fucidic acid 78% reduction | [30] |
| 31    | antibacterial | MRSA-infected mice | 20 mg/kg  | 71% reduction in MRSA burden | vancomycin ~90% reduction, fucidic acid 78% reduction | [30] |
| 55    | anti-inflammatory | carrageenan-induced rat hind paw edema | 21 mg/kg | 65–73% edema reduction (0.5–2 h) analgesic effect (0.5–2 h) | diclofenac 50–58% edema reduction (0.5–8 h) | [50] |
| 60    | anti-inflammatory | carrageenan-induced rat hind paw edema | 65 mg/kg | 89.3% edema reduction | indomethacin 46% edema reduction | [55] |
| 61    | anti-inflammatory | carrageenan-induced rat hind paw edema | 65 mg/kg | 87.7% edema reduction | indomethacin 46% edema reduction | [55] |
| 62    | anti-inflammatory | carrageenan-induced rat hind paw edema | 61 mg/kg | 80.7% edema reduction | indomethacin 46% edema reduction | [55] |
| 63    | anti-inflammatory | carrageenan-induced rat hind paw edema | 61 mg/kg | 79.5% edema reduction | indomethacin 46% edema reduction | [55] |
Table 3. Cont.

| Comp. | Activity | Animal Model | Dose | Effect | Reference Drug | Ref. |
|-------|----------|--------------|------|--------|----------------|------|
| 65    | anti-inflammatory neonatal sepsis treatment | LPS-induced sepsis in neonatal mice | 50 mg/kg | reduction in anxiety-like behavior and cognitive disorders in adult life | - | [58] |

Table 4. Mechanism of action and molecular targets of select amidrazone derivatives.

| Comp. | Activity | Mechanism | Ref. |
|-------|----------|-----------|------|
| AG    | anti-inflammatory | suppression of oxidative stress, inhibition of IL-1β, IL-6, and Foxp3 mRNA upregulation | [57] |
| 1     | antituberculous | inhibiting protein synthesis via direct binding to the bacterial ribosomal subunit | [15] |
| 8     | antibacterial | inhA inhibition | [19] |
| 27    | antibacterial | inhibition of DHFR protein | [27] |
| 28    | antibacterial | interaction with E. coli FabH-CoA receptor. | [28] |
| 29    | antibacterial | interaction with β-ketoacyl-ACP synthase III (FabH) | [29] |
| 30    | antibacterial | inhibitor of undecaprenyl diphosphate phosphatase and undecaprenyl diphosphate | [30] |
| 38–39 | antifungal | interaction with DNA (intercalation) | [37] |
| 43    | antifungal | inhibition of 14-α-demethylase (CYP51) | [40] |
| 46    | antigiardial | inhibition of adherence of trophozoites | [42] |
| 47    | cytoprotective | inhibition of R15A, inhibition of dephosphorylation of enzyme eIF2α | [59] |
| 48    | cytoprotective | inhibition of R15B, inhibition of dephosphorylation of enzyme eIF2α | [66] |
| 48–50 | antiparasitic | binding trypanothione reductase enzyme | [45] |
| 53    | antiviral | inhibition of HIV-RT | [48] |
| 54    | anti-inflammatory | decreasing production of TNF-α | [49] |
| 55    | anti-inflammatory | decreasing production of IL-6 | [50] |
| 56    | anti-inflammatory | decreasing production of TNF-α | [51] |
| 57    | anti-inflammatory | G1 phase arrest | [52] |
| 58    | anti-inflammatory | decreasing production of IL-6 | [54] |
| 60–63 | anti-inflammatory | inhibition of COX-1 and COX-2 | [55] |
| 64    | antianarthritic | inhibition of NFκB activation | [58] |
| 65    | anti-inflammatory | inhibition of expression of ASIC1a protein | [56] |
| 66    | cytoprotective | inhibition of R15A, inhibition of dephosphorylation of enzyme eIF2α | [59] |
| 72    | antitumor | tyrosine kinase brc-abl inhibitor | [71] |
| 73    | antitumor | tyrosine kinase brc-abl inhibitor | [72] |
| 74    | antitumor | tyrosine kinase brc-abl inhibitor | [73] |
| 75    | antitumor | tyrosine kinase brc-abl inhibitor | [74] |
| 76    | antitumor | tyrosine kinase brc-abl inhibitor | [75] |
| 79    | antitumor | phosphatidylinositol 3-kinase inhibitor | [77] |
| 81    | antitumor | inhibition of tubulin polymerization, colchicine binding | [78] |
| 82    | antitumor | inhibition of ribosomal kinase RSK2 | [79] |
| 92    | enzyme inhibition | furin inhibitor, trypsin inhibitor | [89] |
| 93    | enzyme inhibition | furin inhibitor, thrombin inhibitor | [89] |
| 95    | enzyme inhibition | BChE inhibitor | [91] |
| 94    | enzyme inhibition | AChE and BChE inhibitor | [92] |
| 95–96 | enzyme inhibition | BChE inhibitor | [92] |

Among the antimicrobial agents, delpazolid showed a low toxicity and high efficacy and is undergoing further clinical trials for the treatment of tuberculosis. The 2-pyridylamidrazone moiety determines the anti-mycobacterial properties of compounds 2–7. It is worth noting that the amidrazones with the unsubstituted nitrogen N<sup>3</sup> (2–7, 9–14 and 33–37) showed stronger antimicrobial properties than amidrazones 54–55, which are N<sup>3</sup>-substituted with aryl rings [49,50]. In general, aminoguanidine derivatives 22–31 revealed a wider range of antimicrobial activities, as well as stronger antibacterial and antifungal properties than amidrazones 9–21. Moreover, derivative 22, which possesses two aminoguanidine groups, showed the strongest antimicrobial effects. Aminoguanidine
derivatives 30–31 showed significant antibacterial effects in various animal models and deserve further research.

Eight derivatives (23, 25–26, 55, 60–63) showed significant anti-inflammatory activity in rodents. Moreover, the anti-inflammatory effect of compound 65, used in the research on the treatment of neonatal anti-sepsis in mice, deserves greater attention.

Amidrazones demonstrated a diverse number of antitumor mechanisms, acting as brc-abl kinase inhibitors (72–76), an inhibitor of phosphatidylinositol 3-kinase (79), an inhibitor of tubulin polymerization (81) and an inhibitor of ribosomal kinase RSK2 (82), which indicates their potential in the search for new anti-cancer drugs. Compound 72 showed the highest selectivity and may be a future drug candidate for leukemia.

Aminoguanidine derivatives exhibited cytoprotective activity and inhibited cholinesterases. Their possession of both these mechanism simultaneously could be useful in the search for a cure for Alzheimer’s disease. The phosphorylation of eIF2α translation initiation factor by guanabenz, sephin1 or raphin1 is promising in regard to the prevention and treatment of many neurodegenerative diseases. For example, guanabenz, an old-generation antihypertensive drug, is currently being studied for new potential medical applications, including the treatment of amyotrophic lateral sclerosis, multiple sclerosis and parasitic toxoplasmosis.

Amidrazones showed moderate toxicity in various models (Table 5). However, among the derivatives with the lowest toxicity, as many as five (44–45, 56–57 and 59) contain an acyl group at atom N1, which may be valuable for the synthesis of new derivatives with more advantageous properties.

Table 5. The toxicity of selected amidrazones in various animal or normal cell models.

| Comp. | Animal Model     | Time | Toxicity       | Ref.  |
|-------|------------------|------|----------------|-------|
| 18    | brine shrimp     | 24 h | IC50 > 50 µg/mL | [23]  |
| 19    | brine shrimp     | 24 h | IC50 > 50 µg/mL | [23]  |
| 20    | brine shrimp     | 24 h | IC50 > 12.5 µg/mL | [23]  |
| 21    | brine shrimp     | 24 h | IC50 > 12.5 µg/mL | [23]  |
| 43    | zebrafish embryos| 96 h | LC50 = 8.2 µg/mL | [40]  |
| 55    | Swiss mice       | -    | LD50 = 417 mg/kg | [50]  |
| 78    | brine shrimp     | 24 h | IC50 > 50 µg/mL | [23]  |

| Comp. | Studied cells    | Origin | Toxicity       | Ref.  |
|-------|------------------|--------|----------------|-------|
| 2     | Vero monkey      | monkey | IC50 = 28.7 µM | [17]  |
| 3     | Vero monkey      | monkey | IC50 = 23.1 µM | [17]  |
| 4     | Vero monkey      | monkey | IC50 = 27.8 µM | [17]  |
| 5     | Vero monkey      | monkey | IC50 = 298 µM  | [17]  |
| 6     | fibroblasts      | human  | IC50 = 10.39 µg/mL | [18]  |
| 7     | fibroblasts      | human  | IC50 = 3.29 µg/mL | [18]  |
| 28    | HEK 293T         | human  | IC50 = 56.39 µmol/L | [28]  |
| 32    | fibroblasts      | mice   | IC50 = 41.8 µg/mL | [31]  |
| 43    | MRC-5            | human  | IC50 = 2.5 µg/mL | [40]  |
| 23    | LO2              | human  | IC50 = 18.1 µg/mL | [25]  |
| 30–31 | HRT-18           | human  | IC50 > 32 µg/mL | [30]  |
| 44    | macrophages      | mice   | IC50 = 79.59 µM | [41]  |
| 45    | macrophages      | mice   | IC50 = 423.33 µM | [41]  |
| 46    | RAW264.7         | mice   | IC50 = 17.1 µM  | [42]  |
| 48–50 | J774.A1          | mice   | IC50 > 10 µM    | [45]  |
| 51    | PBMC             | human  | IC50 > 100 µg/mL | [46]  |
| 54    | PBMC             | human  | IC50 > 100 µg/mL | [49]  |
| 56    | PBMC             | human  | IC50 > 10 µg/mL  | [51]  |
| 57    | PBMC             | human  | IC50 > 50 µg/mL  | [52]  |
| 58–59 | PBMC             | human  | IC50 > 100 µg/mL | [54]  |
| 64    | chondrocytes     | rat    | IC50 > 25 µM    | [56]  |
| 72    | fibroblasts      | human  | IC50 > 50 µM    | [71]  |
| 76    | fibroblasts      | human  | IC50 = 15 µM    | [75]  |
| 83    | Vero monkey      | monkey | IC50 > 100 µM   | [80]  |
A useful property of amidrazones is their use as ligands for the synthesis of complexes with metals, which provides researchers with the opportunity to obtain new compounds with anti-tumor (e.g., [86]) or antibacterial (32) properties.

4. Conclusions

Amidrazones remain an interesting area for researchers, as evidenced by the latest works from 2022. Many derivatives described in this review show strong biological activities and deserve more detailed research in this field. We hope that this article, which systematizes the knowledge about the biological activities of amidrazones, will increase the scientific interest in these compounds and, in effect, will encourage the development of novel derivatives and their introduction to research in preclinical and clinical studies.

**Author Contributions:** Conceptualization, R.P.; methodology, R.P.; investigation, R.P. and D.F.; writing—original draft preparation, R.P. and M.W.-S.; writing—review and editing, T.K., M.R., B.M.-B. and R.S.; visualization, R.P.; supervision, R.S.; project administration R.P.; funding acquisition, R.P. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Nicolaus Copernicus University (PDB). The APC was funded by the Nicolaus Copernicus University (IDUB).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Abbreviations**

AChE acetylcholinesterase  
BChE butyrylcholinesterase  
CNS central nervous system  
COX cyclooxygenase  
EC$_{50}$ half maximal effective concentration  
HIV-RT HIV reverse transcriptase  
IC$_{50}$ half-maximal inhibitory concentration  
IL-6 interleukin-6  
LD$_{50}$ dose which causes the death of 50% of a group of test animals  
LPS lipopolysaccharide  
MBC minimal bactericidal concentration  
MIC minimal inhibitory concentration  
MRSA methicillin-resistant *Staphylococcus aureus*  
MSSA methicillin-susceptible *Staphylococcus aureus*  
PBMC peripheral blood mononuclear cell  
TNF-α tumor necrosis factor
26. Li, Y.-R.; Li, C.; Liu, J.-C.; Guo, M.; Zhang, T.-Y.; Sun, L.-P.; Zheng, C.-J.; Piao, H.-R. Synthesis and biological evaluation of 1,3-dialky pyrazole derivatives as potential antibacterial and anti-inflammatory agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5082–5087. [CrossRef]

27. Bai, X.; Zhao, L.; Liu, Z.; Li, Y.; Zhang, T.; Liu, X. Synthesis and antibacterial activity evaluation of aminoguanidine or dihydrotriazine derivatives. *Indian J. Biochem. Biophys.* **2019**, *56*, 301–308. Available online: http://ojn.nscir.res.in/index.php/JBB/article/view/27399/0 (accessed on 15 September 2022).

28. Song, M.; Wang, S.; Wang, Z.; Fu, Z.; Zhou, S.; Cheng, H.; Liang, Z.; Deng, X. Synthesis, antimicrobial and cytotoxic activities, and molecular docking studies of N-arylsulfonylindoles containing an aminoguanidine, a semicarbazide, and a thiosemicarbazide moiety. *Eur. J. Med. Chem.* **2019**, *166*, 108–118. [CrossRef]

29. Yao, X.; Hu, H.; Wang, S.; Song, M.; Zhou, Q. Synthesis, Antimicrobial Activity, and Molecular Docking Studies of Aminoguanidine Derivatives Containing an Acylhydrazone Moiety. *Iran. J. Pharm. Res.* **2021**, *20*, 536–545. [CrossRef]

30. Elsebæi, M.; Mohammad, H.; Abouf, M.; Abutaleb, N.; Hegazy, Y.A.; Ghiaty, A.; Chen, L.; Zhang, J.; Malwal, S.R.; Oldfield, E.; et al. Alkynyl-containing phenylthiazoles: Systemically active antibacterial agents effective against methicillin-resistant Staphylococcus aureus (MRSA). *Eur. J. Med. Chem.* **2018**, *148*, 195–209. [CrossRef]

31. Paprocka, R.; Modzelewska-Banachiewicz, B.; Pazyrska, L.; Mazur, L.; Kutkowska, J.; Niedzielska, D.; Pyszewski, M.; Wietrzyk, J.; Sączewski, J. Synthesis, crystal structure, $^{1}H$, $^{13}C$ and $^{15}N$ NMR studies, and biological evaluation of a new amidrazone-derived Au(III) complex. *J. Mol. Struct.* **2019**, *1176*, 357–365. [CrossRef]

32. Senina, A.S.; Gurina, S.V.; Moskvin, A.V. Antimicrobial activity of amidrazone hydrohalogenides. *Farmaciuca* **2017**, *66*, 41–44.

33. Kumar, N.S.; Pradeep, T.; Jani, G.; Silpa, D.; Kumar, B.V. Design, synthesis, and antimicrobial screening of novel pyridyl-2-...
72. Habashneh, A.Y.; Zihlif, M.A.; Imraish, A.; Taha, M.O.; El-Abadelah, M.M. Synthesis and Antitumor Activities of Some New
Pharmaceuticals 2022, 15, 1219
73. Abu-Aisheh, M.N.; Mustafa, M.S.; El-Abadelah, M.M.; Naffa, R.G.; Ismail, S.I.; Zühlif, M.A.; Taha, M.O.; Mubarak, M.S. Synthesis and biological activity assays of some new N1-(flavon-7-yl)amidrazone derivatives and related congeners. Eur. J. Med. Chem. 2012, 54, 65–74. [CrossRef]

74. Mustafa, M.S.; El-Abadelah, M.M.; Zühlif, M.A.; Naffa, R.; Mubarak, M.S. Synthesis, and Antitumor Activity of Some N1-(Coumarin-7-yl) Amidrazones and Related Congeners. Molecules 2011, 16, 4305–4317. [CrossRef]

75. Sweidan, K.; Zalloum, H.; Sabbah, D.A.; Idris, G.; Abudosh, K.; Mubarak, M.S. Synthesis, characterization, and anticancer evaluation of some new N1-(anthraquinon-2-yl) amidrazone derivatives. Can. J. Chem. 2018, 96, 1123–1128. [CrossRef]

76. Sabbah, D.A.; Hajjo, R.; Sweidan, K.; Zhong, H.A. An Integrative Informatics Approach to Explain the Mechanism of Action of N1-(Anthraquinon-2-yl) Amidrazones as BCR/ABL Inhibitors. Curr. Comput. Aided-Drug Des. 2020, 17, 817–830. [CrossRef]

77. Al-Qtaitat, M.A.; El-Abadelah, M.M.; Sabbah, D.A.; Bardaweel, S.; Sweidan, K.; Sabri, S.S.; Mubarak, M.S. Synthesis, characterization, and bioactivity of new bisamidrazone derivatives as possible anticancer agents. Med. Chem. Res. 2018, 27, 1419–1431. [CrossRef]

78. Qian, Y.; Zhang, H.-J.; Lv, P.-C.; Zhu, H.-L. Synthesis, molecular modeling and biological evaluation of guanidine derivatives as novel antitubulin agents. Bioorg. Med. Chem. 2010, 18, 8218–8225. [CrossRef]

79. Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Lannigan, D.; Smith, J.; Scudiero, D.; et al. Imidazo[2,1-d]thiazole guanlyhydrazones as RSK2 inhibitors. Eur. J. Med. Chem. 2011, 46, 4311–4323. [CrossRef]

80. Basu, A.; Sinha, B.N.; Saiko, P.; Graser, G.; Szekeres, T. N-Hydroxy-N′-aminoguanidines as anti-cancer lead molecule: QSAR, synthesis and biological evaluation. Bioorg. Med. Chem. Lett. 2011, 21, 3324–3328. [CrossRef]

81. Silva, F.P.L.; Dantas, B.B.; Martins, G.V.F.; De Araújo, D.A.M.; Vasconcellos, M.L.A.D.A. Synthesis and Anticancer Activities of Novel Guanyldihydrazone and Aminoguanidine Tetrahydropyran Derivatives. Molecules 2016, 21, 671. [CrossRef]

82. Liu, D.C.; Gao, M.J.; Huo, Q.; Ma, T.; Wang, Y.; Wu, C.Z. Design, synthesis, and apoptosis-promoting effect evaluation of novel pyrazole with benzo[d]thiazole derivatives containing aminoguanidine units. J. Enzym. Inhib. Med. Chem. 2019, 34, 829–837. [CrossRef]

83. Al-Noaimi, M.; Awwadi, F.F.; Mansi, I.A.; Sawwwan, M.; Abu-Imaileh, B.; Dege, N. Polymorphism, spectroscopic, DFT and anticancer activity of a palladium(II) complex with a thiophen azoimine-quinoiline NNN′ ligand. Polyhedron 2022, 211, 115541. [CrossRef]

84. Al-Noaimi, M.; Awwadi, F.F.; Talib, W.; Atia, S.; Hammud, H.H. Cis and trans- palladium (II) complexes derived from SNN amidrazine pincer ligand: Synthesis, crystal structures and biological evaluation. J. Mol. Struct. 2019, 1197, 282–291. [CrossRef]

85. Lapasam, A.; Pinder, E.; Phillips, R.M.; Kaminsky, W.; Kollipara, M.R. Synthesis and Anticancer Activities of Novel Guanyldihydrazone and Aminoguanidine Tetrahydropyran Derivatives. Molecules 2016, 21, 671. [CrossRef]

86. Dömötör, O.; May, N.V.; Gál, G.T.; Spengler, G.; Dobrova, A.; Arion, V.B.; Enyedy, É.A. Solution Equilibrium Studies on Salicylidene Amino-guanidine Schiff Base Metal Complexes: Impact of the Hybridization with L-Proline on Stability, Redox Activity and Cytotoxicity. Molecules 2022, 27, 2044. [CrossRef]

87. Climova, A.; Pivovarova, E.; Rogalewicz, B.; Raducka, A.; Szczesio, M.; Korona-Głowniak, I.; Korga-Plewko, A.; Iwan, M.; Gobis, K.; Czylkowska, A. New Coordination Compounds Based on a Pyrazine Derivative: Design, Characterization, and Biological Study. Molecules 2022, 27, 3467. [CrossRef]

88. Czylkowska, A.; Rogalewicz, B.; Szczesio, M.; Raducka, A.; Gobis, K.; Szymański, P.; Czarnecka, K.; Camargo, B.C.; Szczytko, J.; Babich, A.; et al. Antitumor Activity against A549 Cancer Cells of Three Novel Complexes Supported by Coating with Silver Nanoparticles. Int. J. Mol. Sci. 2022, 23, 2980. [CrossRef]

89. Sielaff, F.; Than, M.E.; Bevec, D.; Lindberg, I.; Steinmetzer, T. New furin inhibitors based on weakly basic amidinohydrazones. Bioorg. Med. Chem. Lett. 2011, 21, 836–840. [CrossRef]

90. Cheng, Y.-W.; Chao, T.-L.; Li, C.-L.; Chiu, M.-F.; Kao, H.-C.; Pang, W.-H.; Lin, C.-H.; Tsai, Y.-M.; Lee, W.-H.; et al. Furin Inhibitors Block SARS-CoV-2 Spike Protein Cleavage to Suppress Virus Production and Cytopathic Effects. Cell Rep. 2020, 33, 108254. [CrossRef]

91. Abu-Aisheh, M.N.; Al-Aboudi, A.; Mustafa, M.S.; El-Abadelah, M.M.; Ali, S.Y.; Ul-Haq, Z.; Mubarak, M.S. Coumarin derivatives as acetyl- and butyrylcholinesterase inhibitors: An in vitro, molecular docking, and molecular dynamics simulations study. Helthyon 2019, 5, e01552. [CrossRef]

92. Krátky, M.; Štěpánková, Š.; Konečná, K.; Svrčková, K.; Maixnerová, J.; Švarcová, M.; Jandourek, O.; Trejtnar, F.; Vinslová, J. Novel Aminoguanidine Hydrazone Analogues: From Potential Antimicrobial Agents to Potent Cholinesterase Inhibitors. Pharmaceuticals 2021, 14, 1229. [CrossRef]