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Pharmacological aspects of hydrazides and hydrazide derivatives

Farmakologiczne aspekty hydrazydów i pochodnych związków hydrazydowych

Streszczenie

Intensywne poszukiwania nowych leków przeciwbakteryjnych, łącznie ze środkami przeciwguźliczymi, dyktowane są występowaniem zjawiska wielolekowej oporności bakteryjnej. Hydrazydy uważane są za kluczowe intermediaty i wartościowy początkowy materiał dla nowych biologicznie aktywnych związków chemicznych. Ocenę biologicznych właściwości przeciwbakteryjnych lub/i przeciwgrzybiczych wykonuje się dla ponad 70% ostatnio zaprezentowanych syntetycznych pochodnych hydrazydowych. Najpowszechniej stosowanym hydrazydem jest przeciwgruźliczy lek izoniazyd/hydrazyd kwasu izonikotynowego (NIH). Hydrazydowe związki chemiczne posiadają charakterystyczną wspólną grupę funkcjonalną, w której występuje wiązanie kowalencyjne azot-azot, z czterema podstawnikami, z których przynajmniej jeden stanowi acyl, z kolei pochodne związki hydrazynowe nie posiadają grupy acylowej. Hydrazydy mogą być dalej sklasyfikowane na podstawie rodzaju pierwiastków przyłączonych do tlenu: karbohydrazydy, sulfonohydrazydy, fosfodihydrazydy, hydrazydy hydrazonowe oraz hydrazydy ftalowe. Poza właściwościami przeciwbakteryjnymi i przeciwgrzybicznymi, pochodne związki hydrazydowe stały się ostatnio

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interesujące z uwagi na ich właściwości przeciwzapalne. Ftalowa pochodna hydrazydowa tamerit/galavit została pomyślnie wprowadzona do terapii u ludzi.
Słowa kluczowe: Hydrazydy, hydrazonowe-hydrazydy, izoniazyd, phthalhydrazides, tamerit, galavit

Summary

Intense search for new antimicrobials, including anti-tuberculosis drugs, is dictated by the phenomenon of bacterial multidrug resistance. Hydrazides are considered the key intermediate and valuable starting material for some novel biologically active compounds. Over 70% of recently reported synthetic hydrazide derivatives are evaluated for antimicrobial and/or antifungal activity. The most frequently applied hydrazide is an anti-tuberculosis drug isoniazid/isonicotinic acid hydrazide (NIH). Hydrazide chemicals are sharing a common functional group characterized by a nitrogen-to-nitrogen covalent bond with four substituents with at least one of them being an acyl group, whereas the related hydrazines do not carry an acyl group. Hydrazides can be further classified by atom attached to the oxygen: carbohydrazides, sulfonohydrazides, phosphonic dihydrazides, hydrazone-hydrazides and phthalhydrazides. In addition to their antibacterial and antifungal activities, hydrazide derivatives have recently attracted continuing interest because of their anti-inflammatory properties. A phthalhydrazide derivative tamerit/galavit has been successfully introduced for human therapies.
Keywords: Hydrazides, hydrazone-hydrazides, isoniazid, phthalhydrazides, tamerit, galavit

Abbreviations: DILI: drug-induced liver injury, ESBLs: extended-spectrum β-lactamase bacteria, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, INH: isonicotinic acid hydrazide (isoniazid), IL 1: interleukin 1, MAH: mono-acetyl hydrazine, MRSA: methycillin-resistant *Staphylococcus aureus*, NSAIDs: non-steroidal anti-inflammatory drugs, ROS: reactive oxygen species, TNF-α: tumor necrosis factor-α, VRE: vancomycin-resistant enterococci, WHO: World Health Organization.

General characterization of hydrazones and hydrazides

Over the past few decades, intense search for new antibiotics is dictated by the phenomenon of bacterial multidrug resistance. Common multidrug-resistant bacteria are vancomycin-resistant enterococci (VRE), methycillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (Gram-negative) bacteria (ESBLs), *Enterobacter*

species, *E coli, Klebsiella pneumonie, Pseudomonas aeruginosa*, and many others, including multidrug-resistant *Mycobacterium tuberculosis*. Several mechanisms are employed by micorganisms to attain the multidrug resistance, generally following appropriate mutations and horizontal gene transfer. Clearly, antibiotic-resistant bacteria are able to transfer copies of the resistance-coding DNA to other bacteria, even distantly related to them. Several bacterial and fungal defense mechanisms have been described, such as producing drug-degrading enzymes, modifying targets of the drug thus rendering the drugs ineffective, or over-expressing the efflux enzymes, exporting the drug out of the cells. Novel antimicrobial drugs are urgently necessary to combat the common multidrug resistance of microorganisms. Among new candidate drugs, some hydrazone/hydrazide derivatives with remarkable antimicrobial activity have been described [1, 2].

Hydrazones ($R_1R_2C=NNH_2$) and their derivatives are a class of compounds with carbon and nitrogen as active centers of their biological properties. The biological activities and applications of hydrazone derivatives were reviewed by several authors [3-8]. Hydrazides, the acylated derivatives of hydrazine, belong to the superfamily of heterocyclic compounds containing carbon and nitrogen as active centers of their biological properties. More precisely, hydrazide chemicals are sharing a common functional group characterized by a nitrogen to nitrogen covalent bond with four substituents, with at least one of them being an acyl group, whereas the related hydrazines do not carry an acyl group. Hydrazides can be further classified by atom attached to the oxygen: carbohydrazides, sulfonohydrazides, phosphonic dihydrazides, hydrazone-hydrazides and phthalhydrazides. N-alkyl hydrazides can be synthetized by reduction of hydrazones [9]. Among the existing antimicrobial hydrazides and related drugs, 2-azetidiones (β-lactamase inhibitors) are one of the most prescribed chemotherapeutic agents. Thiazolidinediones, hydrazide derivatives, inhibit the biosyntesis of the bacterial cell wall peptidoglycan. Several other drugs containing hydrazide moiety are in use, such as nifuroxazide (antibiotic), nifurtimox (antiameboic), isocarbazide (antidepressant), iproniazide (anti-tuberculosis) [2], tamerit/galavit (anti-inflammatory) [10, 11]. Overall, hydrazides themselves or mixed in more complex drugs have been primarily used in medicine as antibacterial agents.

Hydrazides are important starting materials for a wide range of derivatives, uti-

lizable as potential pharmaceutical products for human use. Over 70% of recently reported synthetics of hydrazide derivatives were evaluated for antimicrobial and/or antifungal activity in preclinical studies (Table 1).

Table 1.
Recent applications of hydrazides as starting material for synthesis of pharmaceuticals for preclinical and clinical studies

Synthesis of hydrazide derivatives Reference	**Intended use as a pharmaceutical product**
^{99}Tc-radiolabelled isoniazid 12	radiological, diagnostics
Fatty acid hydrazides 13	antibacterial, antifungal
Hydrazide-hydrazone derivatives 14	antidepressant, sedative, analgesic
Oxadiazolones and oxazolidinones 14	antibacterial
Aliphatic hydrazide derivatives 16	antifungal
Hydrazinylnicotinohydrazides 17	antimicrobial
Izoniazid-enaminone 18	anti-tuberculosis
Isoniazid complexes 19	anti-tuberculosis
Hydrazide-hydrazone derivatives 20	antitumor
Ruthenium(II)-hydrazide complexes 21	antiproliferative
Hydrazide-based formamides 22	enzyme inhibition, antioxidant, antimicrobial
Thiazolyl hydrazides 23	antibacterial, antifungal
Phthalazine derivatives 24	antibacterial, antifungal

Methoxybenzene hydrazides 25	antimicrobial
Hydrazide Schiff's bases 26, 27	antioxidant, antibacterial
Salicylaldehyde hydrazides 28	antifungal
Coumarin hydrazide derivatives 29	antimicrobial
Indole carboaldehyde derivatives 30	antimicrobial
Undecenoic acid hydrazides 31	antimicrobial
Phtalazinedione derivatives 32	antimicrobial, antioxidant

Hydrazones and hydrazone-hydrazides

Hydrazones possess an azometine -NHN=CH- proton that has found broad utility in organic synthesis. The biological activities and applications of hydrazone derivatives were reviewed by several authors [33-36]. The synthesis of novel hydrazone derivatives is promising because of their potential use as antimicrobial or therapeutic drugs. For example, new aryl hydrazone derivatives, containing thiazole moiety, displayed a fair degree of antimicrobial activity [23]. Analgetic activity of new hybrid molecules, containing both hydrazone and 2-phenoxyphenyl structures, was confirmed *in vivo* [37]. Some changes were made in the aryl group attached to acyl and imine subunits at N-acetyl hydrazide (NAH) moiety. These NAH derivatives were examined *in vivo* in acute inflammation model showing anti-tumor necrosis factor-alpha (TNF-α) and anti-inflammatory properties. All these new compounds reduced leukocyte migration, TNF-α level, NO production, inhibition of NF-κB enzyme expression and inhibition of ROS production, however with poor aqueous solubility [38].

A series of hydrazones of 1,2-benzisothiazole hydrazides as well as their cyclic and acyclic 1,2-benzisothiazole parent hydrazides, were synthesized and successfully evaluated as antibacterial and antifungal agents [1]. Generally hydrazone-hydrazides are known as antimicrobial compounds with activity against both Gram-positive and Gram-negative microorganisms. Derivatives of hydrazide-hydrazone play an important role in development of various pharmacolog-

ical activities such as anticonvulsant, antimalarial, analgesic, anti-inflammatory, antiplatelet, antimicrobial, antihypertensive, antiviral, anti-tubercular, antiproliferative and antitumor activities.

Phthalhydrazides

Phthalhydrazides, bicyclic nitrogen-containing phtalimide derivatives, are well-known heterocyclic chemicals possessing biological, industrial, and other properties including chemiluminescence phenomenon of cyclic diacylhydrazide/ luminol (5-amino-2,3-dihydrophtalazine-1,4-dione). A number of methods have been reported for the synthesis of phthalazine derivatives including reaction of phtahlhydrazide and acetylendedicarboxylates in the presence of N-heterocycles [39]. Pyrazolones are heterocyclic compounds containing one ketonic group and two nitrogen atoms adjacent to each other [40]. A new series of pyrazolo[1,2-*b*] phthalazine derivatives bearing 5-aryloxypyrazole nucleus was evaluated for their antimicrobial, anti-tuberculosis and antioxidant activities [41].

Phthalhydrazide galavit/tamerit (monosodium 5-amino-2,3-dihydro-1,4-phthalazine dione), available for over two decades in Russian Federation [10, 11], was applied in addition to standard therapies in patients of different age (10–75 years) with several pathologies, sometimes with concomitant diseases. Clinical effects of this phthalhydrazide derivative were described in viral hepatitis B, viral hepatitis C, otitis media, chronic bronchitis, children typhoid fever, benign prostatic hyperplasia (BPH), female endometriosis, and in wounds healing [10]. Generally the positive clinical effects of the tamerit/galavit therapy were related to a better control of ongoing inflammatory processes in the course of disease. Importantly, in all cases/diseases mentioned, no worsening of the patients' condition was observed after the tamerit/galavit treatment and not a single patient has developed any drug-related adverse effect. It is worth to point out that no adverse effects were noted in the viral hepatitis patients under prolonged tamerit/galavit therapy. Concentrations of serum cytokines interleukin 1 (IL-1) and TNF-α and enzymatic markers of liver damage significantly decreased in tamerit/galavit-receiving patients, as compared to standard therapy, indicating low risk of the incidence of drug-induced liver injury (DILI). Overall clinical signs of the disease were less pronounced at the end of the tamerit/galavit therapy, including diminished fatigue, appetites improvement, disappearing of skin itching, and normal bilirubin level [10, 11].

Isoniazid

The most frequently applied and studied anti-tuberculosis agent is isoniazid, isonicotinic acid hydrazide (INH). Some 60 years after its discovery, isoniazid is still a centerpiece of anti-tuberculosis therapy. According to some authors, the drug itself is not toxic for *Mycobacterium tuberculosis*, however, after passive diffusion into the mycobacterial cells, acts as a prodrug and is enzymatically activated by the bacterial multifunctional catalase-peroxidase KatG [42]. Isoniazid inhibits the synthesis of mycolic acid, a component of the mycobacterial cell wall. Also some enzymes involved in fatty acids biosynthesis are believed to be targets of activated isoniazid [2].

Co-infection with tuberculosis of people living with human immunodeficiency virus (HIV) is the most frequent life-threatening mix of diseases. A preventive therapy 300 mg isoniazid daily for at least 6 months is recommended by World Health Organization (WHO) for adult and adolescent people living with HIV. In children living with HIV the isoniazid preventive therapy reduced early mortality by 50% and incidence of tuberculosis by 70% [43]. The anti-tuberculosis effects of isonizid include inhibition of the bacterial cell wall lipid synthesis, depletion of nucleic acid pools and metabolic depression, however, a strong selection for INH-resistant mutants is possible at a site of the *katG* gene. Mycobacterial resistance to INH trigerred development of new potential antimycobacterial agents, including isoniazide derivatives (Table 1), diarylquinoline derivatives and nitroimidazo-compounds.

Hydrazide safety issues

Generally, substituted amides and hydrazides of 1,4-dicarboxylic acid, as well as their linear derivatives (esters, amides and hydrazides) were characterized by low toxicity [44]. Isoniazid is cleared mostly by the liver, primarily by acetylation to acetyl-izoniazid and further to mono-acetyl hydrazine (MAH) and to nontoxic diacetyl hydrazine [42]. The incidence and severity of DILI in tuberculosis patients taking isoniazid is variable in different geographic groups and those co-infected with HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV). Patients with polymorphism of fast acetylation excrete more than 90% of the drug as acetyl-isoniazid, whereas at slow acetylation polymorphism, 67% of the drug is excreted as acetyl-izoniazid, and to a substantial degree as unchanged drug. The cause-effect relationship between acetylation rate and isoniazid-related DILI is controversial [45]. Satisfactory safety data and promising pharmacotherapy effects were reported for different

treatment protocols for phthalhydrazide tamerit/galavit [10, 11], although teratogenicity, mutagenicity and carcinogenic potential of phthalhydrazides require further elaboration. Phthalhydrazide luminol did not exhibit mutagenic activity in *Salmonella typhimurium* test with or without S9 metabolic activation [46].

Hydrazide anti-inflammatory activity

Common target in many therapeutic efforts to improve patients-relevant outcomes related to chronic inflammation is combating the oxidative stress. Inflammation, oxidative stress and production of reactive oxygen species (ROS) are frequent symptoms of degenerative diseases, autoimmunity, cancer and infections. High nonphysiological ROS generation can lead to DNA damage, lipid peroxidation, protein modification, and other pathological effects. Pharmacotherapeutic strategies based on scavenging of pro-oxidant molecules, however, can be unsuccessful [47]. Also treatment of inflammation by the most prescribed pharmaceuticals, non-steroidal anti-inflammatory drugs (NSAIDs), can be frequently complicated by several adverse effects, particularly gastrointestinal bleeding, ulceration and perforation. Alternative strategies involve silencing of activated macrophages and granulocytes, inhibition of enzymatic elements of oxidative burst reaction, activation of endogenous antioxidant defense systems and possible functional repair of ROS-induced damage. For some targets, the respective pharmacology is advanced to clinical development, for others several drugs are already in clinical use [9,10,48]. For example, comparable to the standard drug diclofenac, several nicotinic acid hydrazides having NO_2 substitution at *ortho* and *meta* position, exhibited comparable anti-inflammatory activity [48]. When compared to diclofenac-related decrease of inflammation (35-74% reduction), the anti-inflammatory potential of acetohydrazide derivatives was similar (32–58% reduction) [49]. Anti-inflammatory and anti-TNF-α activities were recently reported for N-acylhydrazone derivatives [38, 50, 51].

Involvement of macrophages in human inflammatory diseases can be both detrimental but also protective. According to this bipolar model, the classically activated pro-inflammatory M1 phenotype can be possibly reprogrammed to anti-inflammatory M2 macrophages. For example, recruited by injury, the inflammatory monocytes mature to M1 macrophages, release ROS and proinflammatory cytokines, and attract neighboring monocytes to clear the wound debris and necrotic tissue. Once this process ter-

minates, neutrophils undergo apoptotic elimination and second monocyte population arrive, mostly from tissue-resident macrophages. These monocytes evolve into M2 macrophages and govern the wound remodellng [52]. Over the years, this M1/M2 classification has been proven to be too general as several other subpopulations have been described, demonstrating a continuum of different polarization states of macrophages. Pharmacological targeting of macrophages can be possible, reducing the expression and production of pro-inflammatory cytokines, including TNF-α [53]. We hope to evidence the macrophage-targeting effects of phthalhydrazide galavit/tamerit (monosodium 5-amino-2,3-dihydro-1,4-phthalazine dione), as the macrophage silencing was observed both in preclinical and clinical studies [10, 11]. In summary, macrophage deletion might not be the ideal clinical approach since macrophages can fulfill both detrimental and protective functions. However, macrophage-specific therapeutic strategies are expected in combating inflammation [54].

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