Mini-Review of the Importance of Hydrazides and Their Derivatives—Synthesis and Biological Activity †

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Abstract: Organic acid hydrazides include a vast group of organic derivatives of hydrazines containing the active functional group (-C(=O)NH-NH2). Acid hydrazones were important bidentate ligands and show keto-enol (amido-iminol) tautomerism. They usually exist in keto form in the solid-state while in equilibrium between keto and enol forms in solution state. Such hydrazones were synthesized in the laboratory by heating substituted hydrazides or hydrazines with corresponding aldehydes or ketones in different organic solvents such as ethanol, methanol, butanol, tetrahydrofuran, etc., and some cases with the ethanol-glacial acetic acid or acetic acid alone. Hydrozones are very important intermediates for the synthesis of heterocyclic compounds and also have different biological activities. The organic chemist would have more interest in the synthesis of acid hydrazides and their derivatives because of their properties. These derivatives having wide applications as chemical preservers for plants, drugs, for manufacturing polymers, glues, etc., in industry and many other purposes. These acid hydrazides and their derivatives were found to be useful synths for various heterocyclic five, six or seven-membered rings with one or more heteroatoms that were exhibited great biological, pharmacological and industrial applications. This paper will present a review of the chemistry and pharmacological potentials of hydrazide-hydrazones. The various synthetic routes for hydrazone, as well as antibacterial, antifungal and antiviral potentials, have been elaborated in brief.

Keywords: hydrazones; medicinal chemistry; synthesis; pharmacology; organic chemistry

1. Introduction

Organic acid hydrazides include the vast group of organic derivatives of hydrazine containing the active functional group (-C(=O)-NH-NH2). Acid hydrazones are important bidentate ligands, which show keto-enol (amido-iminol) tautomerism. They usually exist in the keto form in the solid-state while it retains an equilibrium between keto and enol, when in a solution state (Figure 1).

\[
\begin{align*}
\text{(keto form)} & \quad \begin{array}{c}
\text{R}_1 \ N \ N \ \text{R} \\
\end{array} & \quad \begin{array}{c}
\text{R}_2 \ N \ N \ \text{R} \\
\end{array} \\
\text{(enol form)} & \quad \begin{array}{c}
\text{R}_1 \ N \ \text{OH} \\
\end{array} & \quad \begin{array}{c}
\text{R}_2 \\
\end{array}
\end{align*}
\]

Figure 1. Schematic representation of keto and enol form of acid hydrazones.

Acid hydrazones can react with both electrophiles and nucleophiles simultaneously. They are widely used for the synthesis of heterocyclic compounds. Those compounds...
contain nucleophilic nitrogen (imine and amino type), both electrophilic and nucleophilic imine carbon atoms and acidic N-H proton (Figure 2).

![Schematic representation of possible attacking positions in keto form of acid hydrazones.](image)

**Figure 2.** Schematic representation of possible attacking positions in keto form of acid hydrazones.

Such hydrazones were previously synthesized in the laboratory by heating substituted hydrazides or hydrazine with aldehydes or ketones in different organic solvents such as ethanol, methanol, butanol, tetrahydrofuran and, in some cases, with ethanol-glacial acetic acid or acetic acid alone. Hydrazones are very important intermediates for the synthesis of various heterocyclic compounds and usually have wider biological activities. These derivatives have broad applications such as chemical preservers for plants, drugs, for manufacturing polymers, glues, in industry and for many other purposes [1]. These acid hydrazides and their derivatives were found to be useful synthons for the synthesis of various heterocyclic five, six or seven-membered rings with one or more heteroatoms. These compounds were previously exhibited excellent biological, pharmacological and industrial applications such as antibacterial agents, pharmaceuticals, herbicides, antimalarial, antimycobacterial, anticonvulsant, anti-inflammatory, antidepressant, anticancer, antimicrobial activities and dyes [2–12]. Hydrazides and their derivatives could be transformed into various heterocyclic compounds either by cyclisation or cyclo-addition with numerous reagents.

2. Medicinal Chemistry

2.1. Antibacterial Activity

In the past few decades, bacterial and fungal strains have developed resistance towards conventional drugs and, therefore, multidrug-resistant bacterial and fungi infections are becoming serious threats to healthcare settings all over the world. Therefore, for medicinal chemists, the search for new antimicrobial agents is a never-ending and important task. Chemists are constantly looking for different pharmacophores, among them, acid hydrazones/hydrazides are one of the challenging synthons. Numbers of acid hydrazones and their derivatives were synthesized, characterized and evaluated for their antimicrobial activity. There were various reports having hydrazone motif bearing imidazoles (1), different thiazolidinone derivatives (2, 3), 1,3,4-thiadiazole based hydrazone derivative (4), benzimidazole bearing hydrazone derivative (5); benzofuran based hydrazones (6); and quinoline-pyridine nucleus containing hydrazones (7). These derivatives were also screened for their antibacterial activity against different bacterial strains [13–18] (Figure 3).

![Anti-bacterial compounds (1–7) based on hydrazide scaffold.](image)

**Figure 3.** Anti-bacterial compounds (1–7) based on hydrazide scaffold.

Some amide containing hydrazones (8) and (9); some piperidine/pyridine based hydrazones (10) and (11); heterocyclic ring containing hydrazones (12); such as Nifurox-
azole; thiophene based hydrazones (17); imidazo[2,1-b]thiazole based hydrazones (13); imidazo[1,2-a]pyridine based hydrazones (14); nitrofurans based hydrazones (15); biphenylhydrazones (16); chloropyrrole based aroylhydrazone (18) and (19); aryloxycetic acid hydrazide (20); cholic acid-based hydrazones (21); benzyleidine-hydrazides (22); and imidazole bearing hydrazones (23, 24) were demonstrated good antibacterial activities [11,19–33] (Figure 4).

![Figure 4. Antimycobacterial compounds (8–24) based on hydrazide scaffold.](image)

2.2. Anti-Fungal Activities

Many fungal species may cause many superficial or systemic infections in plants, animals, human beings and also in livestock. Today, synthetic chemists are involved in identifying newer antifungal agents with unique mechanisms. There are many synthesized hydrazone derivatives available in the literature which were also studied for their antifungal activity. Some of them were found to be potent antifungal agents or showed promising antifungal activities against different fungi strains, which included scaffolds such as imidazo[1,2-a]pyridine derivative (25), tetrazole based acid hydrazide (26), benzofuran based hydrazone (27) and 5-bromothiophene-2-yl based hydrazones (28) [34–37] (Figure 5).

![Figure 5. Antifungal compounds (25–28) based on hydrazide scaffold.](image)

2.3. Antiviral Activity

The virus is a small infectious agent, which can replicate only inside the living cell of an organism. They can cause immense harmful effects to the host body. They mostly infect all types of organisms, including humans, animals and plants. Several reported hydrazones were showed potent antiviral activities against different viral strains or had lower MIC values, such as imidazole-amide containing acid hydrazones (29–31) and sulfonamide containing acid hydrazones (32, 33) [38–40] (Figure 6).
Tuberculosis is a highly spreading infectious, chronic and most prevalent disease. It causes more than three million deaths every year [41]. Different strains of *Mycobacterium tuberculosis* can cause infections in the different parts of the body especially in the lungs, liver and bones. Tuberculosis becomes a serious health problem because of the developed resistance to front-line TB drugs such as isoniazid and rifampin. This indicates the need for more effective drugs for the efficient management of tuberculosis. Some hydrazones (33–57) were synthesized and studied for their anti-TB activity against various strains of *mycobacterium tuberculosis*. These included derivatives such as isoniazid derived hydrazones; pyridylmethyleneamino derivatives of isonicotinoylhydrazones; imidazo[4,5-b]pyridine based hydrazones; 5-nitro-2-furyl based hydrazones; 2-substituted 5-(Pyridine-2-yl)-1,3,4-thiadiazole based hydrazones; 1,2,4-triazole-3-mercaptoacetic acid hydrazones; 5-nitro-thiophene containing arylhydrazone; and diclofenac acid hydrazones [42–57]. Some other hydrazones such as aryloxyhydrazone derivatives, benzofuran-3-carboxyhydrazide derivatives and 2-substituted quinoline based hydrazones (52) were also synthesized, characterized and studied for their anti-TB activities. Several acid hydrazones were also demonstrated potent antmycobacterial activity. Compound (53) was the most active (MIC = 1.56 μg/mL, IC50 = 5.06 μg/mL and SI = 401) among differently synthesized hydrazine derivatives. Compound (53) was found to be better than those of “first-line" or “second line" drugs commonly used to treat TB. Compounds (54, 55), (56) and (57) were displayed significant and promising antitubercular activity (Figure 7) [42–64].
3. Different Synthetic Routes of Hydrazine, Hydrazones and Their Derivatives

Fenamic hydrazides (60) were synthesized from corresponding fenamic acids (58) through esters intermediates (59). Fenamic acids were previously esterified in methanol by using sulfuric acid and under reflux conditions for 12–18 h. These esters were then treated with hydrazine hydrate (under reflux for 1.5–12 h) [65,66] (Scheme 1).

Scheme 1. Synthesis of fenamic acid hydrazides from the corresponding fenamic acids (58).

Acyl hydrazones act as mono-nucleating hydrazone ligands, which are easily obtained by condensing acyl hydrazides 62 and substituted aldehydes 61 in ethanol under reflux conditions. These ligands act as a powerful bidentate ligand 63, 64 and forms complexes with different transition metals. One of the acyl hydrazones, 2-hydroxy-5-chloro-4-methylacetophenone-4-nitrobenzoylhydrazone 63 was synthesized from 4-nitrobenzoylhydrazide 62 and 2-hydroxy-5-chloro-4-methyl acetophenone 61 in ethanol and got easily coordinated as a tridentate ligand 64 to Cr(III), Mn(III), Ti(III), VO(IV), Fe(III) and Zr(IV) under reflux conditions [67] (Scheme 2).
Scheme 2. Synthesis of coordinated tridentate ligands 64.

A series of substituted ibuprofen-based acyl hydrazones 67 was synthesized under microwave irradiations and by conventional methods using a small quantity of methanol from ibuprofen hydrazide 65 and aryl aldehydes 66 [68] (Scheme 3).


Several biphenyl-4-carboxylic acid hydrazide-hydrazones 70 were prepared from biphenyl-4-carboxylic acid hydrazide 69 and substituted benzaldehyde using methanol and glacial acetic acid combinations. All synthesized compounds were noted promising antimicrobial activity. Varieties of phenylacetohydrazones were synthesized by using HCl as a catalyst. N-Arylhydrazone derivatives of N-phenyl anthranilic acid were synthesized by condensing 2-(phenylamino) benzo hydrazide with various aromatic ketones and aldehydes [10,69,70] (Scheme 4).


Acylhydrazide Schiff base derivatives were prepared by acetic acid-catalyzed condensation of acylhydrazide with different aromatic aldehydes and acetophenones in ethanol under reflux conditions [71] (Scheme 5).


4. Conclusions

To summarize, hydrazone coupled motifs are having an immense pharmacological potential and can be used for synthesizing newer novel motifs with higher potencies. We have also summarized various synthetic routes to synthesis these derivatives.

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