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Review of the importance of Hydrazide and its Derivatives in Organic synthesis†

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Abstract: Organic acid hydrazides includes a vast group of organic derivatives of hydrazines containing the active functional group (-C(=O)NHNH2). 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, has different biological activities. The organic chemist shows more interest in the 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 for many other purposes. These acid hydrazides and their derivatives were found to be useful synthons 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 hydrazones as well as antibacterial, antifungal, and antiviral potentials have been elaborated in brief.

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

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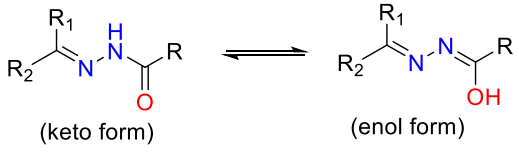
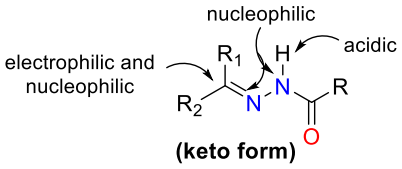
1. Introduction

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 shows keto-enol (amido-iminol) tautomerism. They usually exist in keto form in the solid-state; while it retains an equilibrium between keto and enol, when in a solution state.



Acid hydrazones react with 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 atom and acidic N-H proton.

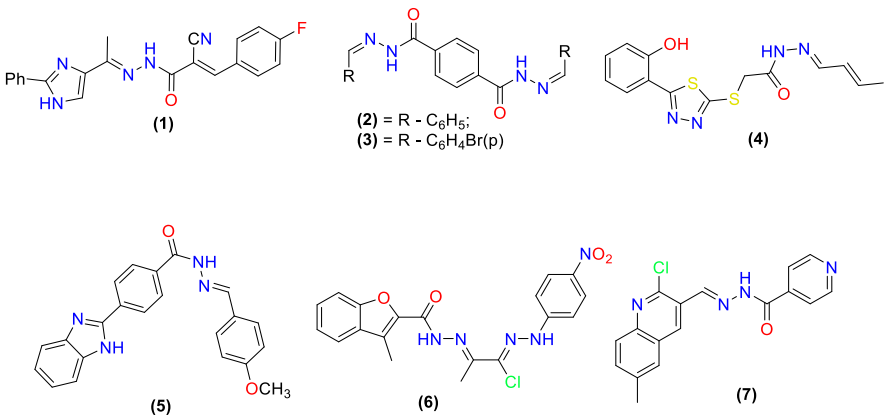


Such hydrazones were previously synthesized in the laboratory by heating substituted hydrazides or hydrazine with aldehydes or ketones in different organic solvents such as ethanol, methanol, butanol, tetrahydrofuran, and in some cases with ethanol-glacial acetic acid or acetic acid alone. Hydrazone acts as a very important intermediate for the synthesis of heterocyclic compounds and has different biological activities. The organic chemistry depicted more interest towards the acid hydrazides and their derivatives because of their unique properties. These derivatives are having wide applications such as chemical preservers for plants, drugs, for manufacturing polymers, glues, in industry, and many other purposes [**1**]. These acid hydrazides and their derivatives were found to be useful synthons for various heterocyclic five, six or seven membered rings with one or more heteroatoms that were exhibited great biological, pharmacological and industrial applications such as antibacterial agents, pharmaceuticals, herbicides, antimalarial, antimycobacterial, anticonvulsant, anti-inflammatory, antidepressant, anticancer, antimicrobial activities and dyes [**2-12**]. The hydrazides and their derivatives can be converted into various heterocyclic compounds either by cyclisation or cyclo-addition with numerous reagents.

2. Medicinal Chemistry

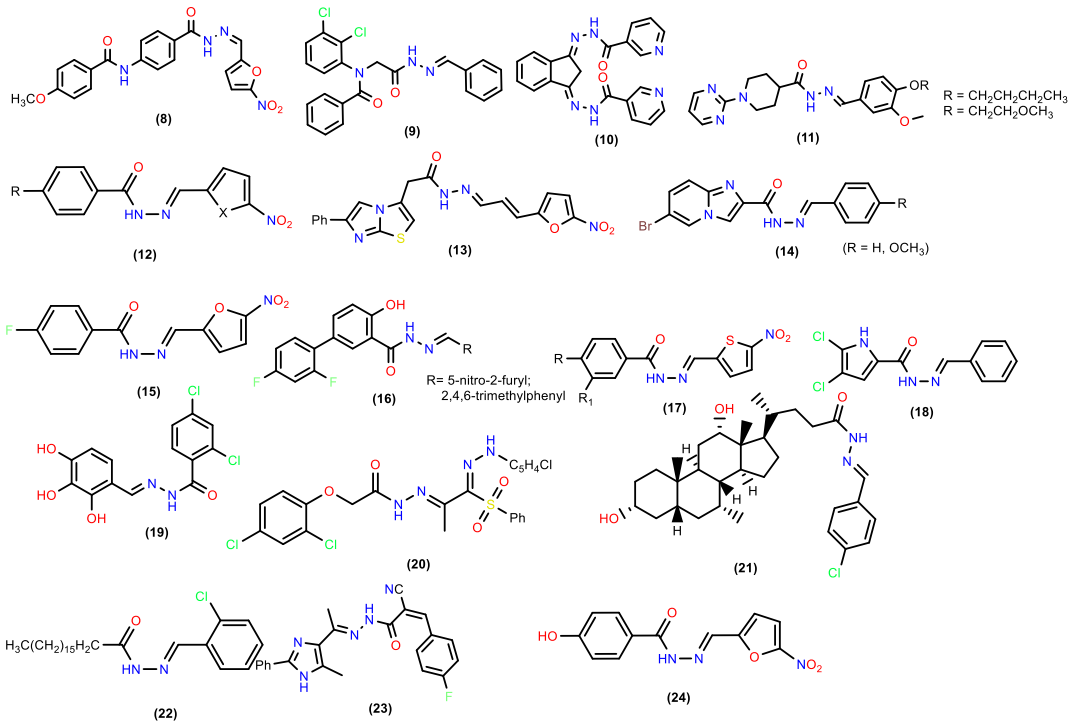
2.1 Antibacterial activity

In the past few decades, bacterial and fungi strains have developed resistance against conventional drugs and therefore, multi drug-resistant bacterial and fungi infections are becoming serious healthcare problems all over the world. Therefore, for the medicinal chemist, searching for new antimicrobial agents is a never-ending and important task. Chemists looking for the different pharmacophores, among them acid hydrazones/hydrazides is one of the challenging important targets. Nowadays, the number of acid hydrazones and their derivatives have been synthesized, characterized and evaluated for their antimicrobial activity. There is the number of reported hydrazones 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); quinoline-pyridine nucleus containing hydrazone (7) were synthesized and screened for their antibacterial activity against different bacterial strains [**13-18**].



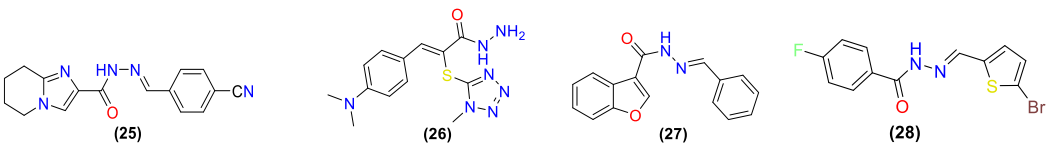
Some amide containing hydrazones (8) and (9); some piperidine/pyridine based hydrazones (10) and (11); heterocyclic ring containing hydrazones (12); such as Nifuroxazide;

thiophene based hydrazones (17); imidazo[2,1-b]thiazole based hydrazones (13); imidazo[1,2-a]pyridine based hydrazones (14); nitrofurans based hydrazones (15); some other biphenylhydrazones (16); chloropyrrole based aroylhydrazone (18) and (19); Aryloxyacetic acid hydrazide (20); cholic acid-based hydrazones (21); benzyledine-hydrazides (22); and imidazole bearing hydrazones (23, 24) showed good anti-bacterial activities [**19-34**].



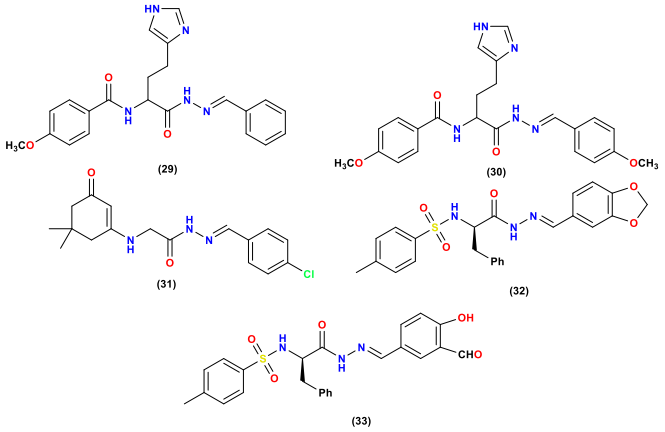
2.2. Anti-fungal activities

Fungal species cause many superficial or systemic infections in plants, animals, human beings as well as in livestock. Many synthetic chemists are studying antifungal activities. There are many synthesized hydrazone derivatives available in the literature and studied for their anti-fungal 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) [**35-38**].



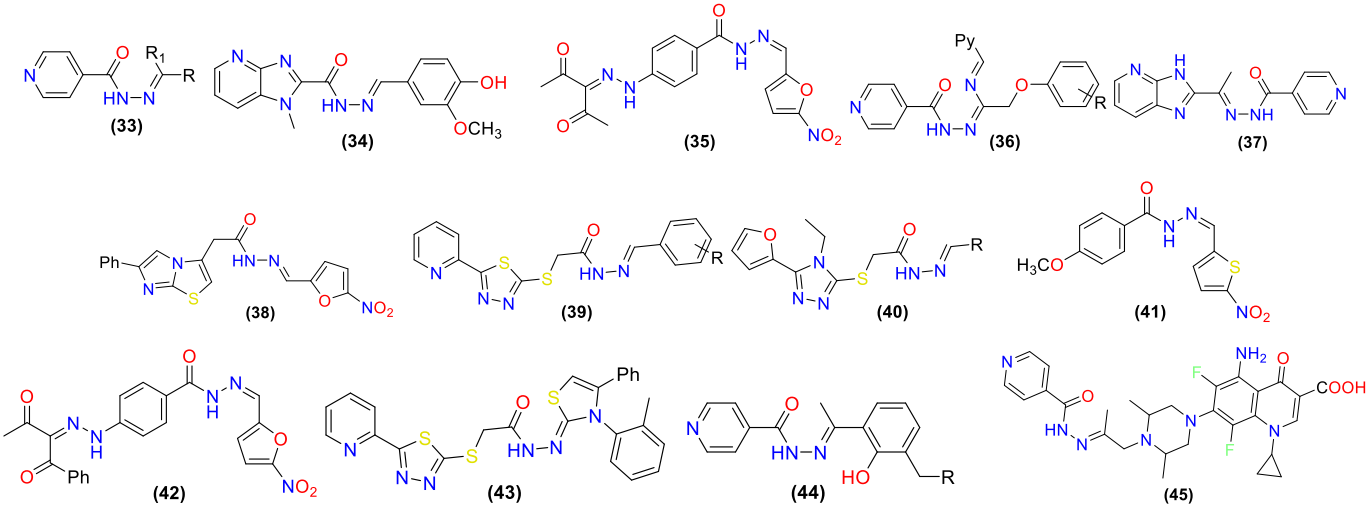
2.3. Antiviral activity

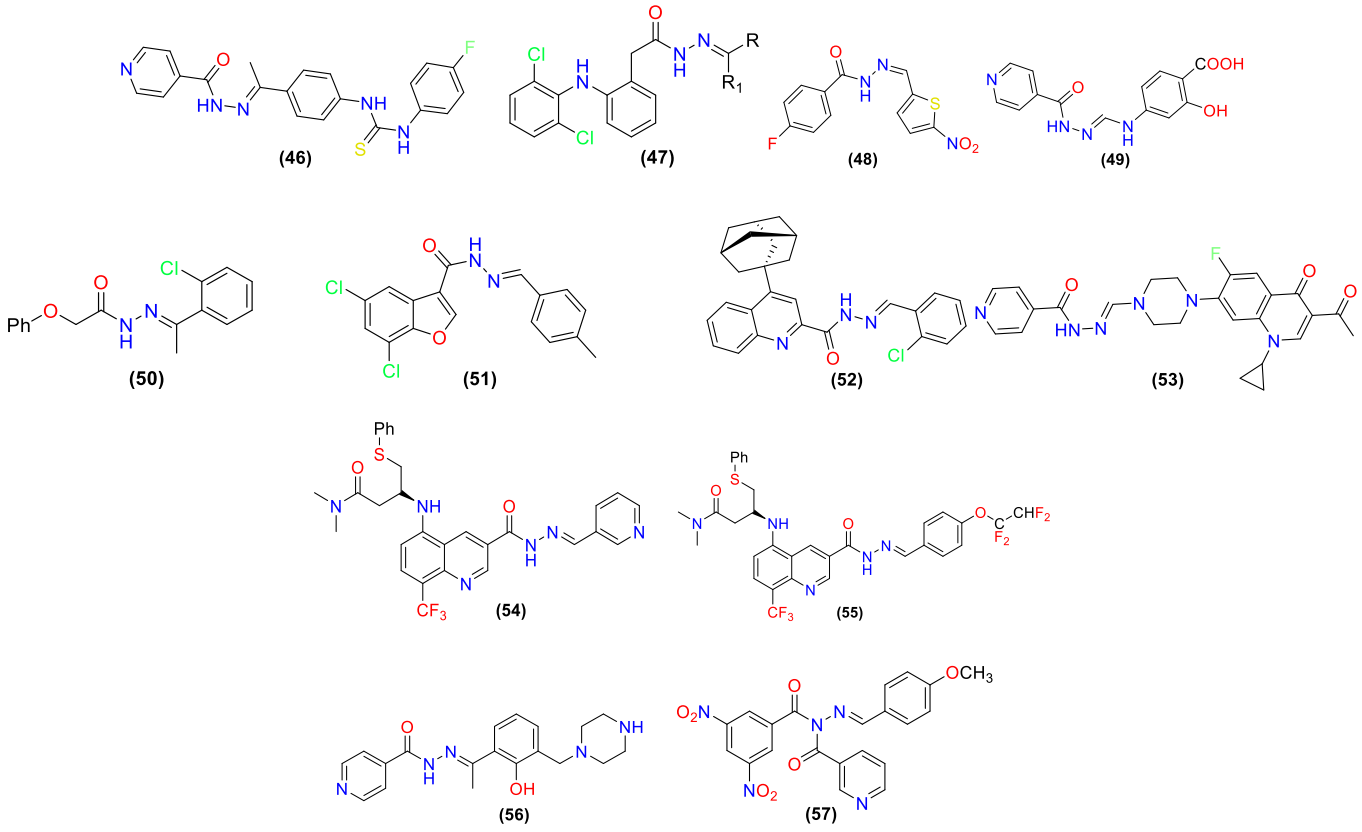
The virus is a small infectious agent, which can replicate only inside the living cell of an organism. They can cause immense harmful effects to the host body. It infects all types of organisms like humans, animals as well as plants. Several hydrazones are showing potent antiviral activities against different viral strains or had lower MIC values, such as imidazole-amide containing acid hydrazones (29-31) and sulfonamide containing acid hydrazones (32, 33) [**39-41**].



2.4. Antitubercular activity

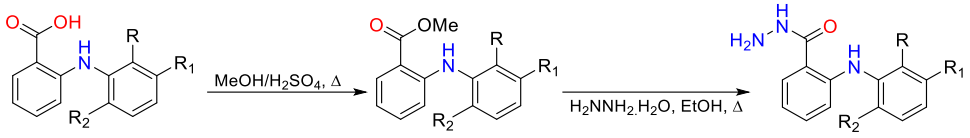
Tuberculosis is a highly spreading infectious, chronic and most prevalent disease. It causes more than three million deaths every year [**42**]. Different strains of *Mycobacterium tuberculosis* can cause infections in the different parts of the body especially in the lungs, liver and bones. Tuberculosis becomes a serious health problem because of the developed resistance to front-line TB drugs such as isoniazid and rifampin. It 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*, and mostly tested against virulent H37Rv strain. These include 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 [**43-59**]. Some other hydrazones such as aryloxyhydrazone derivatives, benzofuran 3 carbohydrazide derivatives, and 2 substituted quinoline based hydrazones (52) were also synthesized, characterized and studied for their anti-TB activities. Several acid hydrazones showed potent antimycobacterial activity. Compound (53) was the most active (MIC = 1.56 µg/ml, IC_{50} = 5.06 µg/ml and SI = 401) among different synthesized hydrazone 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 [**43-66**].



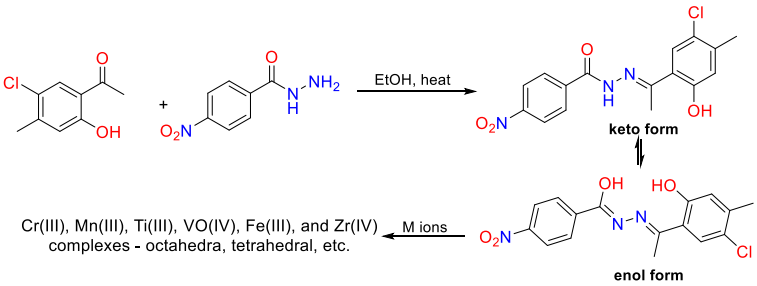


3. Different synthetic routes of hydrazine, hydrazones and their derivatives

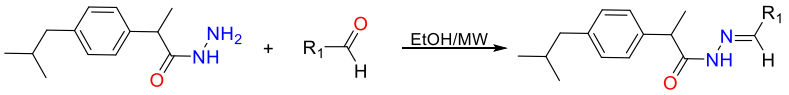
Fenamic hydrazides were synthesized from the corresponding fenamic acids through esters intermediates. Fenamic acids were esterified in methanol by using sulfuric acid, and under reflux conditions for 12-18 hrs. These esters were then treated with hydrazine hydrate (under reflux for 1.5-12 hrs) [**67, 68**].



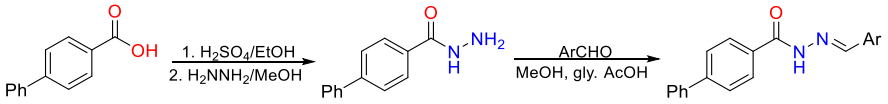
Acyl hydrazones act as mono-nucleating hydrazone ligands, which are easily obtained by the condensation of acyl hydrazides and substituted aldehydes in ethanol under reflux conditions. These ligands act as a powerful bidentate ligand and forms complexes with different transition metals. One of the acyl hydrazones, 2-hydroxy-5-chloro-4-methylacetophenone-4-nitrobenzoylhydrazone was synthesized from 4-nitrobenzoyl hydrazide and 2-hydroxy-5-chloro-4-methyl acetophenone in ethanol and got easily coordinated as a tridentate ligand to Cr(III), Mn(III), Ti(III), VO(IV), Fe(III), and Zr(IV) under reflux conditions [**69**].



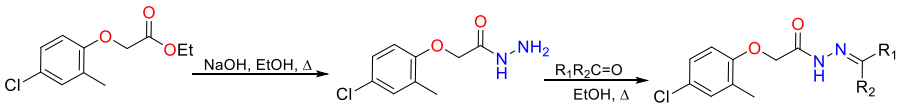
A series of substituted ibuprofen-based acyl hydrazones were synthesized under microwave irradiations and by conventional methods in a small quantity of methanol from ibuprofen hydrazide and aryl aldehydes [**70**].



Several biphenyl-4-carboxylic acid hydrazide-hydrazones were synthesized from biphenyl-4-carboxylic acid hydrazide and substituted benzaldehyde in methanol and presence of glacial acetic acid. All synthesized compounds showed 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)benzohydrazide with various aromatic ketones and aldehydes [**71-73**].



Acylhydrazide Schiff base derivatives were prepared by acetic acid-catalyzed condensation of acylhyrazide with different aromatic aldehydes and acetophenones in ethanol under reflux conditions [**74**].



4. Conclusion

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

Supplementary Materials: Not applicable

Author Contributions: Conceptualization, SM and BT; methodology, BT; software, SM; writing—review and editing, BT; visualization, SM and AP; supervision, AP.

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

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