Hydrazones and their metal complexes: A short review on their biological potential

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Article History:
Received on: 28 Jul 2020
Revised on: 30 Aug 2020
Accepted on: 07 Sep 2020

Keywords:
Hydrazones, Coordination chemistry, Anti-tuberculcar, Azomethines

ABSTRACT

Hydrazones belong to complexes are beneficial in different fields for their essential role in the development of a range of stable complexes in the coordination chemistry. Different researchers have reported the various medicinal properties of hydrazones. Hydrazone and its metal complexes are useful for the detection of some organic components from pharmaceutical formulations. These metallic compounds act as a catalyst for conducting various chemical reactions and help in making different chemical complexes that are effective against bacteria, fungi, and many other microbes. Aromatic hydrazone derivatives can measure the concentration of low molecular weight aldehyde and ketone complexes. Hydrazones possess numerous medicinal properties, including antimicrobial, anti-cancer, antidepressant, anti-tuberculcar, anti-viral, etc. For the new drug discovery, hydrazones/azomethines are considered to be an important class of compound. From molecular biology to pharmaceutical formulation, organic chemistry, new drug development process, the importance of hydrazone and its metal complexes is immense. The present review aims to highlight the reported biological activities related to hydrazones for the last decade.

INTRODUCTION

A group of organic compounds, Hydrazones are formed by the synthesis of ketones or aldehydes with hydrazine, which has the functional group =N−NH2 in the replacement of oxygen (Figure 1).

Hydrazone complexes act as an intermediate in many chemical reactions; one of them is Fischer indole synthesis that makes indole group which can be found in many drugs. It’s proven to be useful intermediate in the conversion of ketones into highly sterically hindered thioketones. A new series of quinoline ligands of hydrazones are tested against H37 RV strain of Mycobacterium tuberculosis by MIC (Minimum Inhibitory Concentration) method (Mandewale et al., 2015). The build-out of the field of bioinorganic chemistry with hydrazone complexes has increased interest as biological important chemical compounds from aryl hydrazones are acting as...
Shambaditya Goswami et al., Int. J. Res. Pharm. Sci., 2020, 11 (SPL4), 1440-1447

Enzyme inhibitors and also useful for pharmacological applications (Dharamraj et al., 2001). Hydrazones bonded drugs are moored in blood’s neutral pH, i.e. 7.4 that rapidly destroy the lysosome’s acidic environment. Hydrazones are used in medical biotechnology for making drugs through the coupling methods that target antibodies against certain types of cancer cells (Wu and Senter, 2005). Since the metal complexes of hydrazones possess significant potencies, i.e. antimicrobial, antidepressant, anti-inflammatory, anti-malarial, anti-cancer, anti-fungal, anti-tubercular, anti-viral, cardioprotective etc. and they have a high impact on diagnosis and therapy in medical practice, this write up aims to highlight the diverse biological activities of hydrazone and its metal complexes from 2000 to 2020 (Figure 2).

METHODOLOGY

The various works of literature, scientific papers, original articles are surveyed and reviewed from different search engines viz. Research Gate, Google Scholar, PubChem, ChemSpider, Scopus etc. for this write up. The authors have gone through and reviewed many full-text articles with abbreviations as hydrazone and its metal complexes; imidazole based heterocyclic compounds, biological potencies of hydrazones and its derivatives, QSAR study of these metal complexes etc. for the successful review. The authors drew all the structures in ACD/ChemSketch 2017.2.1(Freeware).

BIOLGICAL POTENTIAL OF HYDRAZONE DERIVATIVES

Antimicrobial activities

Chemicals are used to resist transmittable diseases against different bacteria. As an antibacterial agent, hydrazones containing imidazoles fight against different bacterial strains. In one research paper, Researchers have evaluated the antibacterial activity of cobalt(II), nickel(II), zinc(II), copper(II) and cadmium(II) complexes of acetophenone-4-amino benzoyl hydrazone and 4-hydroxy acetophenone-4-amino benzoyl hydrazone against *Escherichia coli* and *Aspergillus niger*. They also reported that copper(II) is more active than zinc(II) of these hydrazone complexes at every concentration. The authors of the previous research have reported the antibacterial activity of 2, 3, 4-pent aneotroine-3[4-[(5-nitro-2-furyl)methylene hydrazide]carbonyl]phenyl] hydrazone against *Staphylococcus aureus* and *Mycobacterium tuberculosis* (Savini et al., 2004).

Fungal infections are generally observed as topical or systemic infections in humans, animals as well as plants. The antifungal potency of the metal complexes is less than the activation of their parent ligands. The previous research also reported regarding the evaluation of hydrazone derivatives (iodophenyl thiazole derivative) to show its inhibitory effect against *Candida* Species. The indole derivatives of hydrazone were also reported as an effective agent against *Candida albicans*. The new eighteen derivatives were evaluated by the researchers in which indol-3-yl derivatives were proved to be more potent. The researchers modified the hydrazine-thiazole ring in two ways—firstly, the modification of indane part and secondly, replacement of phenol moiety (Maillard et al., 2013).

Al-Shaalan (2011) investigated different metal complexes with the modified Schiff base of hydrazone nucleus with quinolone moiety. The metal complexes like copper (II), cobalt (II), manganese (II), nickel (II), iron (II) and uranium dioxide (VI) were used in the study. Moreover, the researchers proved that all the complexes were highly effective against...
Figure 3: Some of the important hydrazone derivatives with antimicrobial potential (A) Hydrazones containing Imidazoles; (B) Benzylidene-hydrazo derivatives containing Quinoline ring; (C) Mono-benzoyl acetoneisonicotinoyl hydrazone; (D) 2-hydrazino-1,3-thiazoles: Modification in indane moiety; (E) 2-hydrazino-1,3-thiazoles: Substitution in phenol moiety

Figure 4: Acylhydrazones
Figure 5: Some of the important hydrazone derivatives with antioxidant potential (A) Hydrazones derivative of thiophene (B) Hydroxycoumarin N-acylhydrazones

Figure 6: Some of the important hydrazone derivatives with anticancer potential (A) Hydrazino-pyrazoles derivatives (B) Hydrazino-pyrimidine derivatives (C) Acyl hydrazones derivatives with furan

Figure 7: Some of the important hydrazone derivatives with anti-inflammatory potential (A) Aryl hydrazones derivatives of mefenamic acid (B) Salicaldehydechloro benzoyl hydrazone derivatives
Gram (+)ve and gram (-)bacteria and fungi. Novel pyrazole-amide derivatives attached with hydrazone moiety were subsequently analyzed for potent antifungal activities against *Gibberellaceae*.

Kandle and co-workers synthesized hydrazone metal complexes from 1-[4-(2-methoxybenzyl)-6-aryl pyridazine-3(2H)-ylidene]hydrazines and diacetyl. These synthesized products have the antimicrobial activity against *S.aureus, S.faecalis, E. coli* and *P.aeruginosa*. The hydrazone derivative (1-[4-(2-methoxybenzyl)-6-methyl phenyl pyridazine-3(2H)-ylidene] hydrazine shows the highest biological activity than the former product (Kandle *et al.*, 2009). Hydrazone derivatives containing transition metal complexes are synthesized and evaluated for antimicrobial activity of N2-substituted alkylidene/arylidene-6-phenylimidazothiazole-3-acetic acid hydrazides, which show antibacterial activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Deep *et al.* (2010) designed biphenyl-4-carboxylic acid hydrazide which has the potency against a harmful strain of *Escherichia coli, Pseudomonas aeruginosa* and positive strain of *Bacillus subtilis, Staphylo-*

Cancer is a lethal disease involving uncontrolled cell division with a high level of penetrating potency affecting almost every organ of the body. Some of the dihydropyridines, thiophenes and thiazole derivatives were synthesized by the derivatives of acetohydrazides and evaluated for anti-cancer activ-
ity against the breast cancer cell line (MCF7) of humans (Al-Said et al., 2011). Hydrazone derivatives containing pyrazole ring (Figure 6A) were synthesized and were checked for anti-cancer activity against adenocarcinoma of the human breast.

Pyrazole-pyrimidine derivatives with benzene-sulfonohydrazide as PI3K (Phosphoinositide-3-kinases) p110α inhibitors were evaluated against the human tumour xenograft model (Kendall et al., 2012). Some imidazo-[1,3,4]-thiadiazole-5-carbohydrazides (Figure 6B) were reported to be useful for their inhibitory effects on the growth of a wide range of cancer cell lines (Cocco et al., 2006).

Some novel substituted phenyl methylene-imidazole-thiadiazole-carbohydrazidehydrazones were synthesized and evaluated for the anti-cancer activity in human cell lines.

The cytotoxic action of acyl hydrazones was evaluated against leukaemia (HL-60) and melanoma. Benzimidazole-hydrazine derivatives were reported as active anti-cancer compounds as they showed potent effect against different cell lines like epithelial cells of alveoli (A549), lung tissue-adenocarcinomas (PC-9), colorectal cell line (HCT116), liver (HepG2) and melanoma cell line (A-375) (Liu et al., 2012).

Acyl hydrazones derivatives with furan (Figure 6C) were also reported as an active cytotoxic agent against lung carcinomic cell lines, whereas, palladium-based hydrazones were effective against human head and neck squamous carcinomic cell lines. Derivatives of acetyl-pyridine and benzoyl-pyridine of hydrazones were evaluated against human brain tumour cell lines (Abu-Surrah et al., 2010).

**Anti-viral activity:**

Viruses are microscopic parasites that replicate only inside the living cell of an organism. It infects all types of organisms-humans, animals as well as plants. Some novel acridines and hydrazone derivatives obtained from β-diketone (dimedone) were reported as potent anti-viral drugs, and the evaluation was carried out against Hepatitis A Virus (El-Sabbagh and Rady, 2009). Acyl-hydrazones were synthesized with natural amino acids and triethylamine. These acyl-hydrazones derivatives were targeted against HIV (human immune deficiency virus) type-1, and promising results were obtained in which EC50 were reported as 0.21 and 0.17 μM (Tian et al., 2009).

**Anti-inflammatory activity:**

Inflammation is a localized physical, chemical or biological response of the immune system, understanding by injury any process able to cause tissue or cellular damages. Non-steroidal anti-inflammatory drugs (NSAIDs) of different classes were used as analgesics and hence used in the treatment of pain and inflammation. In the past years, aryl hydrazones were synthesized as the derivatives of mefenamic acid (Figure 7A) and were evaluated for the anti-inflammatory effects (Almasirad et al., 2005).

The synthesis of zinc(II) complexes with salicylaldehyde-2-chlorobenzoyl hydrazone (Figure 7B) and its region isomersalicylaldehyde-4-chlorobenzoyl hydrazone are combined and make a pharmacological evaluation of all acyl hydrazones and zinc(II) complexes in animal models of peripheral and central nociception and acute inflammation. The authors proved that all the compounds could inhibit peritonitis while compared to indomethacin (Júnior et al., 2011). Some furoxanyl-acyl hydrazones derivatives were also reported as analgesics and anti-inflammatory drugs (Hernández et al., 2012).

Some novel aryl-hydrazones were successfully evaluated for anti-inflammatory activity. Pyridyl-aryl hydrazone derivatives were also proved to be potent for the analgesic and anti-inflammatory along with antiplatelet activities. The most trusted mechanism as suggested for the activity was the interference with the arachidonic acid metabolism, and formyl furanepyridyl hydrazone derivative was proved as most potent (79% inhibition of pleurisy) (Rajitha et al., 2011). Salicaldehydechlorobenzyl (2 and 4 substituted) hydrazones and their complexes with zinc were evaluated for the anti-inflammatory and anti-nociceptive activity in animal models, and all the compounds were reported for their significant inhibition of acetic acid writhing responses. Inhibition of zymosan-induced peritonitis was recorded while comparing with indomethacin as standard (Júnior et al., 2011).

**Antimycobacterial activity**

Tuberculosis is a contagious bacterial disease, which is responsible for the mortality of nearly three million people every year worldwide. The drugs which are used to treat infections caused by Mycobacterium that include leprosy and tuberculosis (TB) are called as antimycobacterial or anti-tubercular agents. Some of the agents are rifampicin, isoniazid, ethambutol etc. Some novel approach has been attempted by the researchers (Dasgupta, 2012). The researcher put their efforts to synthesize several novel hydrazone derivatives that were assessed for the antimycobacterial activity. Among them, diclofenac acid hydrazones (Figure 8A) were synthe-
sized from diclofenac, methanol, sulphuric acid with dichloro substituted phenyl amino phenyl Aceto-
hydrazides for the \textit{in-vivo} antimycobacterial activities against 	extit{Mycobacterium tuberculosis}.

The findings showed that 1-cyclopropyl-6-fluoro-
8-methoxy-7-[N4-(2-(2-(2,6-dichloro phenylamino)
acetyl)-3-methyl]-N1-piperazinyl]-
4-oxo-1,4-dihydro-3 quinoline carboxylic acid
was proved to be the most active candidate while
compared with standard drug Isoniazid (\textit{Sriram
et al.}, 2006).

Researchers used coumarin-4-acetic acid
hydrazides to synthesize benzylidene derivative
that were evaluated against \textit{M. tuberculosis}.
The benzylidene hydrazide derivatives (Figure 8B)
of 4-adamantan-1-yl-quinoline-2-carboxylic acid
showed the maximum inhibition (99\% at 1\mu g/ml)
while comparing with isoniazid, the standard treat-
ment. 4-(adamantan-1-yl)-2-substituted quinolines
were also tested for the same. Some heterocyclic
arylidene-hydrazide derivatives were also synthe-
sized and evaluated their derivatives for the \textit{in-vitro}
antimycobacterial activity against the tested strain
of \textit{Mycobacterium tuberculosis} and \textit{Mycobacterium
avium} (\textit{Mamolo et al.}, 2003).

**CONCLUSION**

The synthesis and application of medicines from
bioinorganic complexes is a rapidly developing field
due to the formation of stable compounds in coor-
dination chemistry. The metal complexes and their
parent ligands have a significant impact on clini-

cal practice as diagnostic and therapeutic agents.
Advances and innovations in bioinorganic chemistry
are essential for improving the design of compounds
to maximize its therapeutic effects along with mini-
mizing the toxic side-effects. As hydrazones and its
metal complexes possess antibacterial, anti-oxidant,
algesic, anti-inflammatory, anti-cancer proper-
ties, so this review article focuses the development
of newer compounds from hydrazones with proper
designing, synthesis and structure-activity relation-
ship (SAR).

**ACKNOWLEDGEMENT**

The authors would like to express their gratitude to
the management and director of Institute of Tech-
nology and Management, GIDA, Gorakhpur, Uttar
Pradesh and NIMS Institute of Pharmacy, NIMS Uni-
versity, Jaipur, Rajasthan for the immense support
to carry this review work.

**Funding Support**

The authors declare that they have no funding sup-
port for this study.

**Conflict of Interest**

The authors declare that they have no conflict of
interest for this study.

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