REVIEW ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

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

Kushal Nath Mishra[1], Shambaditya Goswami[*2], Kumudhavalli M.V.[3], Kamal Saini[2], Nikita Pal[2], Nilesh Sharma[2], Pragya Pandey[2]

[1]Department of Chemistry, Institute of Technology and Management, GIDA, Gorakhpur-273209, Uttar Pradesh, India
[2]Department of Pharmacy, NIMS Institute of Pharmacy, NIMS University, Jaipur-303121, Rajasthan, India
[3]Department of Pharmaceutical Chemistry, Vinayaka Mission College of Pharmacy, Vinayaka Mission Research Foundation (Deemed University), Salem-636008, Tamil Nadu, India

Article History:

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

Keywords:

Hydrazones,
Coordination chemistry,
Anti-tubercular,
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-tubercular, 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.

*Corresponding Author

Name: Shambaditya Goswami
Phone:
Email: shambampharma@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11iSPL4.4319

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

A group of organic compounds, Hydrazones are formed by the synthesis of ketones or aldehydes with hydrazine, which has the functional group =N−NH_2in 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 enzyme inhibitors and also useful for pharmacological applications (Dharamaraj *et al.*, 2001). Hydrazone bonded drugs are moored in blood's neutral pH, i.e. 7.4 that rapidly destroy the lysosome's acidic environment. Hydrazonesare 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, antifungal, anti-tubercular, anti-viral, cardioprotective etc. and they have a high impact on diagnosis and therapy in medical practice, this writes 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).

BIOLOGICAL 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 aneotrione-3[4-[(5-nitro-2-furyl)methylene hydrazide]carbonyl]phenyl] hydrazone against *Staphylococcus aureus* and *Mycobacterium tuberculosis* (Savini *et al.*, 2004).

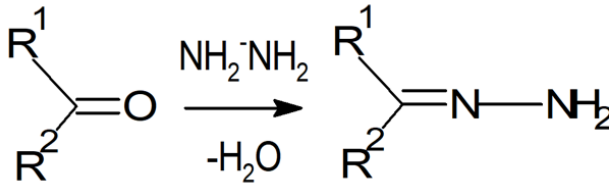

Figure 1: Formation of Hydrazones from ketones/aldehydes

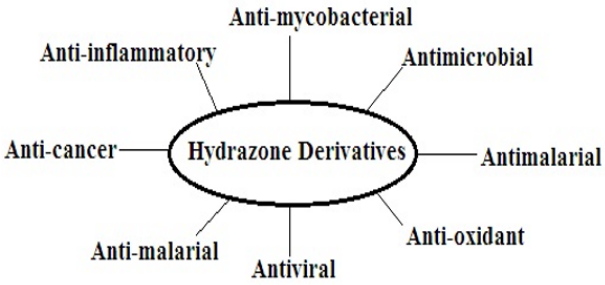

Figure 2: Versatile Biological Potential of Hydrazone Derivatives

Some novel transition metal complexes of benzylidene-hydrazo derivatives containing quinoline ring were evaluated against some Gram (+)ve, Gram (-) ve and fungi. Thiosemicarbazone, along with hydrazone derivatives, has promising effectiveness against *Mycobacterium tuberculosis,* and ethyl-2-arylhydrazone-3-oxobytyrates has antibacterial activity against *Staphylococcus aureus* (Pavan *et al.*, 2010).

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),

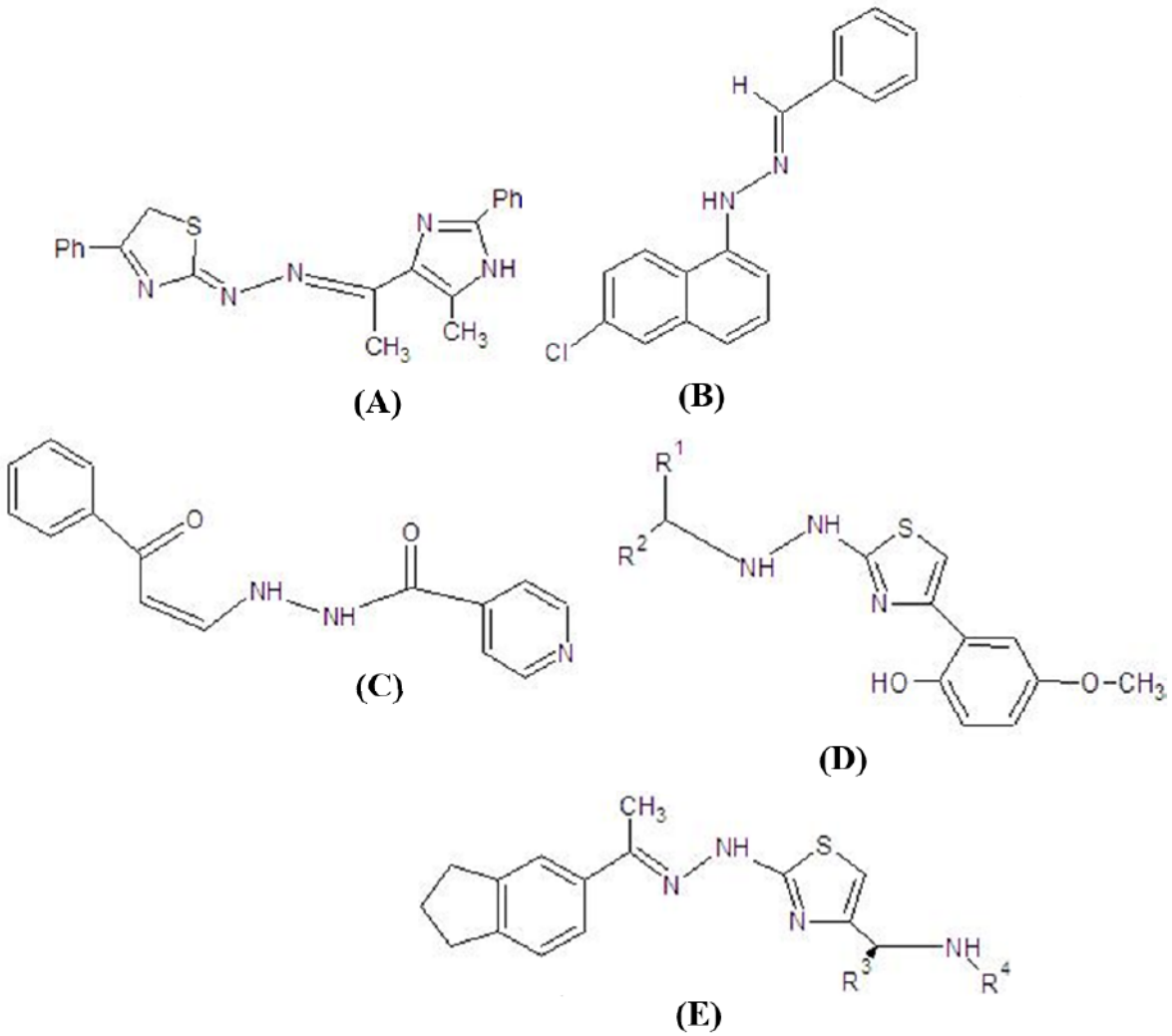

Figure 3: Some of the important hydrazone derivatives with antimicrobial potential (A) Hydrazones containing Imidazoles; (B) Benzylidene-hydrazo derivatives containing Quinoline ring; (C) Mono-benzoyl acetoneisonicotinoyl hydrazone; (D) 2-hydrazino-1,3-thiazoles: Modification in indane moiety; (E) 2-hydrazino-1,3-thiazoles: Substitution inphenol moiety

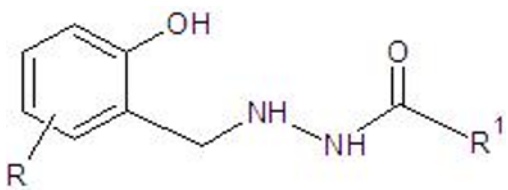

Figure 4: Acylhydrazones

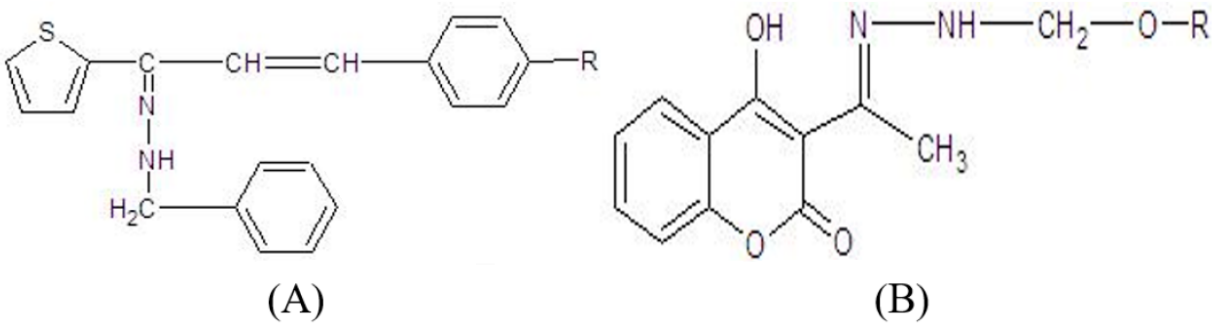

Figure 5: Some of the important hydrazone derivatives with antioxidant potential (A) Hydrazones derivative of thiophene (B)Hydroxycoumarin N-acylhydrazones

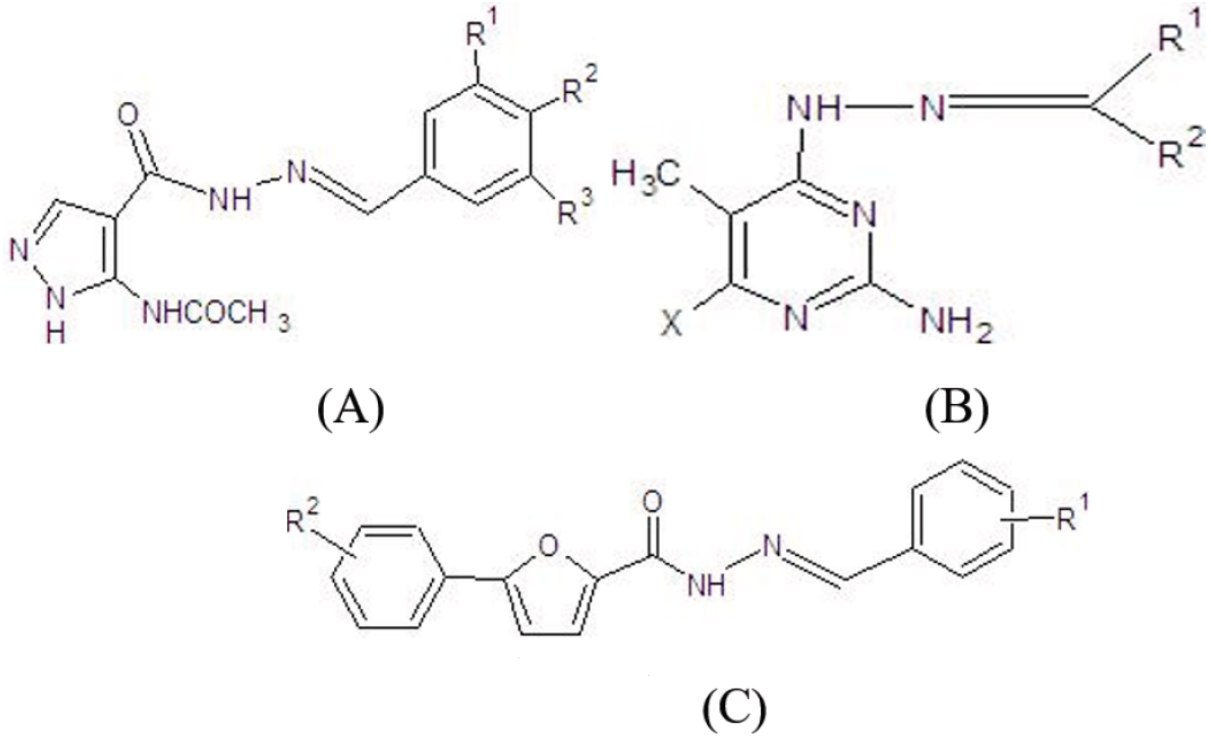

Figure 6: Some of the important hydrazone derivatives withanticancer potential(A) Hydrazino-pyrazoles derivatives (B) Hydrazino-pyrimidine derivatives (C)Acyl hydrazones derivatives with furan

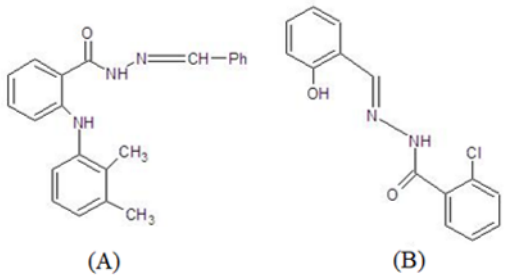

Figure 7: Some of the important hydrazone derivatives with antinflammatory potential (A) Aryl hydrazones derivatives of mefenamic acid (B) Salicaldehydechloro benzoyl hydrazone derivatives

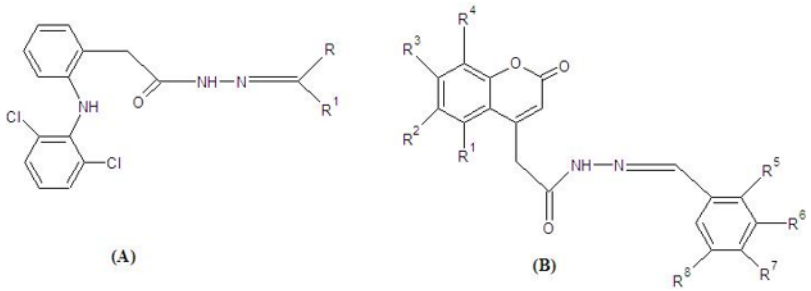

Figure 8: Some of the importanthydrazone derivatives with Anti-mycobacterialpotential (A) Diclofenac acid hydrazones(B) Benzylidenehydrazide derivatives

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 Gram (+)ve and gram (-)bacteria and fungi. Novel pyrazole-amide derivatives attached with hydrazone moiety were subsequently analyzed for potent antifungal activities against *Gibberellazeae*.

Kandile 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 (Kandile *et al.*, 2009). Hydrazone derivatives containing transition metal complexes are synthesized and evaluated for antimicrobial activity of N2-substituted alkylidene/arylidene-6-phenylimidazothiazole-3-aceticacidhydrazides, 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, Staphylococcus aureus*. New sulfonylhydrazone derivatives and their nickel complexes show their antibacterial activity against gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis, Bacillusmagaterium*) and gram-negative bacteria (*Salmonella enteritidis*, *Escherichia coli*) by using Minimum Inhibitory Concentration (MICs) method. Some of the important structures bearing antimicrobial activity have been mentioned in Figure 3 **.**

Anti-malarial activity

Malaria is a global burden as it causes morbidity in developing countries. Melnyk *et al.* (2006) synthesized and established a library of acyl-hydrazones (Figure 4) to evaluate the potency of these compounds against *Plasmodium falciparum*. Among them, eleven were more potent candidature. 4-Chloro-phenyl, 4-Methoxy-phenyl, and 4-*tert*-Butyl-phenyl derivatives showed maximum potency without any toxicity.

Anti-oxidant activity

Oxidative stress is the leading cause of many degenerative and severe diseases *viz.*diabetes Mellitus, IHD (ischemic heart disease), atherosclerosis, cancer etc. In recent years anti-oxidant has an essential role as it can neutralize the ROS (reactive-oxygen-species) and free radicals.

New hydrazone derivatives are synthesized from thiophenechalcone (Figure 5A) and evaluated for their anti-oxidant activity. It has been found that the presence of $-NO_2$ and $-OCH_3$ group enhanced the anti-oxidant activity of the synthesized compounds (Kamboj *et al.*, 2014). Significant anti-oxidant activity of hydrazones attached with imidazoline ring was reported in the previous research.

Coumarin, a benzo-pyrone derivative, is a significant plant source derivative that is synthesized by the metabolism of phenylalanine. Hydroxy-coumarin heterocyclic derivatives were analyzed for different activities along with anti-oxidant properties. Acetyl hydroxyl coumarin acyl hydrazones derivatives were prepared with hydroxyl-coumarin derivatives and selective hydrazides (Figure 5B). Anti-oxidant activity was performed by the inhibition of DPPH (2,2-diphenyl-1-pirylhydrazil) and lipid peroxidation. Some oxadiazole, pyrazoleandisoxazole derivatives were synthesized by using di-aryl hydrazones with the help of chloramine-T followed by reaction with hydrazine hydrate. These compounds were analyzed for DPPH scavenging potential (at 10μg/ml concentration) and after that were proved as potent anti-oxidant candidates (Kotali *et al.*, 2016).

Anti-cancer activity

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 activity 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 benzenesulfonohydrazide 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-hydrazone 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 EC_{50} 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-arylhydrazone 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 sev-

eral novel hydrazone derivatives that were assessed for the antimycobacterial activity. Among them, diclofenac acid hydrazones (Figure 8A) were synthesized from diclofenac, methanol, sulphuric acid with dichloro substituted phenyl amino phenyl Acetohydrazides for the *in-vivo* antimycobacterial activities against *Mycobacterium tuberculosis.*

The findings showed that 1-cyclopropyl-6-fluoro-8-methoxy-7-[N4-(2-(2-(2,6-dichloro phenylamino)phenyl) 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 (Sriram *et al.*, 2006).

Researchers used coumarin-4-acetic acid hydrazides to synthesize benzylidene derivatives that were evaluated against *M. tuberculosis.* The benzylidene hydrazide derivatives (Figure 8B) of 4-adamantan-1-yl-quinoline-2-carboxylic acid showed the maximum inhibition (99% at 1μg/ml) while comparing with isoniazid, the standard treatment. 4-(adamantan-1-yl)-2-substituted quinolines were also tested for the same. Some heterocyclic arylidene-hydrazide derivatives were also synthesized and evaluated their derivatives for the *in-vitro* antimycobacterial activity against the tested strain of *Mycobacterium tuberculosis* and *Mycobacterium avium* (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 coordination chemistry. The metal complexes and their parent ligands have a significant impact on clinical 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 minimizing the toxic side-effects. As hydrazones and its metal complexes possess antibacterial, anti-oxidant, analgesic, anti-inflammatory, anti-cancer properties, so this review article focuses the development of newer compounds from hydrazones with proper designing, synthesis and structure-activity relationship (SAR).

ACKNOWLEDGEMENT

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

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

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

REFERENCES

Abu-Surrah, A. S., Safieh, K. A. A., Ahmad, I. M., Abdalla, M. Y., Ayoub, M. T., Qaroush, A. K., Abu-Mahtheieh, A. M. 2010. New palladium(II) complexes bearing pyrazole-based Schiff base ligands: Synthesis, characterization and cytotoxicity. *European Journal of Medicinal Chemistry*, 45(2):471–475.

Al-Said, M. S., Bashandy, M. S., Al-qasoumi, S. I., Ghorab, M. M. 2011. Anti-breast cancer activity of some novel 1,2-dihydropyridine, thiophene and thiazole derivatives. *European Journal of Medicinal Chemistry*, 46(1):137–141.

Al-Shaalan, N. H. 2011. Synthesis, Characterization and Biological Activities of Cu(II), Co(II), Mn(II), Fe(II), and UO2(VI) Complexes with a New Schiff Base Hydrazone: O-Hydroxyacetophenone-7-chloro-4-quinoline Hydrazone. *Molecules*, 16(10):8629–8645.

Almasirad, A., Tajik, M., Bakhtiari, D., Shafiee, A., Abdollahi, M., Zamani, M. J., Khorasani, R., Esmaily, H. 2005. Synthesis and analgesic activity of N-arylhydrazone derivatives of mefenamic acid. *J Pharm PharmSci*, 8(3):419–425.

Cocco, M. T., Congiu, C., Lilliu, V., Onnis, V. 2006. Synthesis and in vitro antitumoral activity of new hydrazinopyrimidine-5-carbonitrile derivatives. *Bioorganic & Medicinal Chemistry*, 14(2):366–372.

Dasgupta, A. 2012. Advances in antibiotic measurement. *Advances in Clinical Chemistry*, 56:75–104.

Deep, A., Jain, S., Sharma, P. C., Verma, P., Kumar, Dora, C. P. 2010. Design and biological evaluation of biphenyl-4- carboxylic acid hydrazide-hydrazone for antimicrobial activity. *ActaPoloniaePharmaceutica-Drug Res*, 67(3):255–259.

Dharamaraj, N., Viswanathamurthi, Natarajan, K. 2001. Ruthenium (II) complexes containing bidentate Schiff bases and their antifungal activity. *Transition Metal Chemistry*, 26(1-2):105–109.

El-Sabbagh, O. I., Rady, H. M. 2009. Synthesis of new acridines and hydrazones derived from cyclic β-diketone for cytotoxic and antiviral eval-

uation. *European Journal of Medicinal Chemistry*, 44(9):3680–3686.

Hernández, P., Cabrera, M., Lavaggi, M. L., Celano, L., Tiscornia, I., da Costa, T. R., Thomson, L., Bollati-Fogolín, M., Miranda, A. L. P., Lima, L. M., Barreiro, E. J., González, M., Cerecetto, H. 2012. Discovery of new orally effective analgesic and anti-inflammatory hybrid furoxanyl N-acylhydrazone derivatives. *Bioorganic & Medicinal Chemistry*, 20(6):2158–2171.

Júnior, W. B., Alexandre-Moreira, M. S., Alves, M. A., Perez-Rebolledo, A., Parrilha, G. L., Castellano, E. E., Piro, O. E., Barreiro, E. J., Lima, L. M., Beraldo, H. 2011. Analgesic and Anti-Inflammatory Activities of Salicylaldehyde 2-Chlorobenzoyl Hydrazone (H2LASSBio-466), Salicylaldehyde 4-Chlorobenzoyl Hydrazone (H2LASSBio-1064) and Their Zinc(II) Complexes. *Molecules*, 16(8):6902–6915.

Kamboj, A., Randhawa, H., Saluja, A. K. 2014. Synthesis, pharmacological evaluation and computational studies of some novel hydrazone derivatives of thiophenechalcone as antimicrobial and antioxidant agents. *World Journal of Pharmaceutical Research*, 3(2):3146–3159.

Kandile, N. G., Mohamed, M. I., Zaky, H., Mohamed, H. M. 2009. Novel pyridazine derivatives: Synthesis and antimicrobial activity evaluation. *European Journal of Medicinal Chemistry*, 44(5):1989–1996.

Kendall, J. D., Giddens, A. C., Tsang, K. Y., Frédérick, R., Marshall, E. S., Singh, R., Lill, C. L., Lee, W.-J., Kolekar, S., Chao, M., Malik, A., Yu, S., Chaussade, C., Buchanan, C., Rewcastle, G. W., Baguley, B. C., Flanagan, J. U., Jamieson, S. M., Denny, W. A., Shepherd, P. R. 2012. Novel pyrazolo[1,5-a]pyridines as p110α-selective PI3 kinase inhibitors: Exploring the benzenesulfonohydrazide SAR. *Bioorganic & Medicinal Chemistry*, 20(1):58–68.

Kotali, A., Nasiopoulou, D., Tsoleridis, C., Harris, P., Kontogiorgis, C., Hadjipavlou-Litina, D. 2016. Antioxidant Activity of 3-[N-(Acylhydrazono)ethyl]-4-hydroxy-coumarins. *Molecules*, 21(2):1–11.

Liu, T., Sun, C., Xing, X., Jing, L., Tan, R., Luo, Y., Huang, W., Song, H., Li, Z., Zhao, Y. 2012. Synthesis and evaluation of 2-[2-(phenylthiomethyl)-1H-benzo[d] imidazol-1-yl)acetohydrazide derivatives as antitumor agents. *Bioorganic & Medicinal Chemistry Letters*, 22(9):3122–3125.

Maillard, L. T., Bertout, S., Quinonéro, O., Akalin, G., Turan-Zitouni, G., Fulcrand, P., Demirci, F., Martinez, J., Masurier, N. 2013. Synthesis and anti-Candida activity of novel 2-hydrazino-1,3-thiazole derivatives. *Bioorganic & Medicinal Chemistry Letters*, 23(6):1803–1807.

Mamolo, M. G., Falagiani, V., Zampieri, D., Vio, L., Banfi, E., Scialino, G. 2003. Synthesis and antimycobacterial activity of (3,4-diaryl-3H-thiazol-2-ylidene)-hydrazide derivatives. *Il Farmaco*, 58(9):631–637.

Mandewale, M. C., Thorat, B., Shelke, D., Yamgar, R. 2015. Synthesis and Biological Evaluation of New Hydrazone Derivatives of Quinoline and Their Cu(II) and Zn(II) Complexes againstMycobacterium tuberculosis. *Bioinorganic Chemistry and Applications*, 2015:1–14.

Melnyk, P., Leroux, V., Sergheraert, C., Grellier, P. 2006. Design, synthesis and in vitro antimalarial activity of an acylhydrazone library. *Bioorganic & Medicinal Chemistry Letters*, 16(1):31–35.

Pavan, F. R., Maia, P. I. S., Leite, S. R., Deflon, V. M., Batista, A. A., Sato, D. N., Franzblau, S. G., Leite, C. Q. 2010. Thiosemicarbazones, semicarbazones, dithiocarbazates and hydrazide/hydrazones: Anti – Mycobacterium tuberculosis activity and cytotoxicity. *European Journal of Medicinal Chemistry*, 45(5):1898–1905.

Rajitha, G., Saideepa, N., Praneetha, P. 2011. Synthesis and evaluation of N-(α- benzamidocinnamoyl) aryl hydrazone moiety as a promising heterocyclic scaffold. *Eur. J. Med. Chem*, 49:411–416.

Savini, L., Chiasserini, L., Travagli, V., Pellerano, C., Novellino, E., Cosentino, S., Pisano, M. B. 2004. New α-(N)-heterocyclichydrazones: evaluation of anticancer, anti-HIV and antimicrobial activity. *European Journal of Medicinal Chemistry*, 39(2):113–122.

Sriram, D., Yogeeswari, P., Vandana Devakaram, R. 2006. Synthesis, in vitro and in vivo antimycobacterial activities of diclofenac acid hydrazones and amides. *Bioorganic & Medicinal Chemistry*, 14(9):3113–3118.

Tian, B., He, M., Tang, S., Hewlett, I., Tan, Z., Li, J., Jin, Y., Yang, M. 2009. Synthesis and antiviral activities of novel acylhydrazone derivatives targeting HIV-1 capsid protein. *Bioorganic & Medicinal Chemistry Letters*, 19(8):2162–2167.

Wu, A. M., Senter, P. D. 2005. Arming antibodies: prospects and challenges for immunoconjugates. *Nature Biotechnology*, 23(9):1137–1146.