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Review Article

A Review on Biological Activities of Hydrazone Derivatives

Neha Singh, Ritu Ranjana, Manju Kumari, Birendra kumar

Department of Chemistry, Gaya College, Gaya, 823001(Bihar), India

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ABSTRACT

The present paper, put forth a brief account on biological activities of hydrazone derivatives. Hydrazones are present in many of the bioactive heterocyclic compounds that are of very important use because of their various biological and clinical applications. The synthesis and the importance of hydrazides were studied by many researchers shows various biological, medical and industrial activities. Hydrazones have been demonstrated to possess, among other, antimicrobial, antimycobacterial, antidepressant, anticonvulsant, anticancer, antimalarial, vasodilator activity, etc. The ease of preparation, increased hydrolytic stability relative to imines, and tendency toward crystallinity are all desirable characteristics of hydrazones. Due to these positive traits, hydrazones have been under study for a long time.

Keywords: Hydrazones, biological activity, Acyl hydrazones.

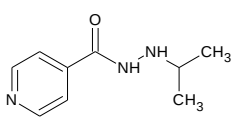
INTRODUCTION

Hydrazone moiety plays an important key role in heterocyclic chemistry[1-7]. Hydrazone is a class of organic compounds with structure $R_1R_2C=NNH_2$. They are related to ketones and aldehydes by the replacement of the oxygen with the NNH_2 functional group. They are formed usually by the action of hydrazine on ketones or aldehydes[8-9]. The alpha – hydrogen atom of hydrazones is more nucleophilic as compared to ketones because alpha – hydrogen atom of hydrazone is 10 times more acidic than ketones[10-11]. The most significant reactivity of hydrazones is the nucleophilicity of hydrogen carbon atom. Hydrazone is a versatile moiety that exhibits a wide variety of biological activities. Acyl hydrazones are a very old class of molecules: the first example of N-acylhydrazines was mentioned in 1850,[12] and a number of N-unsubstituted, mono-and disubstituted acylhydrazines were discovered and explored by the scientists worldwide. Compounds of general formula ArCONHN=C(R) Ar' are known as N-acyl hydrazones. Acyl hydrazones have been extensively investigated in recent years as they were found to be associated with various biological activities have promising analytical properties and can be used as catalysts. The cyclic products of acylhydrazones are an important class of heterocyclic compounds with a wide range of biological activities[13-17]. They are synthesized by simply refluxing acid hydrazide with various carbonyl compounds in methanol or ethanol. Due to the simplest reaction conditions, diversified chemical libraries may be constructed for discovering potential bioactive molecules. The resulting double bond between C and N of the hydrazones contributes to the formation of geometrical isomers (syn and anti). Geometrical isomerism may have some important role in the bioactivity of the acyl hydrazones hence their studies are very crucial to develop synthetic methods for selective synthesis of a particular isomer. In recent years, broad study of hydrazides and their derivative demonstrated diverse biological activities. During literature survey, several articles have been found with good therapeutic activities of acyl hydrazones. Hydrazones possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. Recently, hydrazide-hydrazones have gained great importance due to their diverse biological properties including antibacterial, antifungal, anticonvulsant, antiinflammatory, antimalarial and antituberculosis activities. In the literature studies we found that a large number of series of substituted hydrazide-hydrazone derivatives were synthesized for *in-vitro* antimicrobial activities against wide variety of microorganisms.

Hydrazone Derivatives – Its biological importance

Hydrazonone nucleus exhibited immense pharmacological activities. Hydrazones are present in many of the bioactive heterocyclic compounds that are of very important use because of their various biological and clinical applications. Hydrazone-based coupling methods are used in medical biotechnology to couple drugs to targeted antibodies, e.g. antibodies against a certain type of cancer cell. The hydrazone-based bond is stable at neutral pH (in the blood), but is rapidly destroyed in the acidic environment of lysosomes of the cell. The drug is thereby released in the cell, where it exerts its function[18]. Hydrazides also have been used for analytical chemistry as chelating agents[19]. Various effective compounds for example iproniazide just like isoniazide is used as antitubercular drug[20]. Nifuroxazide is an oral nitrofuran antibiotic, used in anti-dehydration and colitis treatment, "neutralises microbacterials" in diarrhoea, and has "a spectrum which covers most enteropathogenic microbacterials, *Shigella, Escherichia coli, Salmonella, Staphylococci, Klebsiella, Yersinia*".

**Author for Correspondence*



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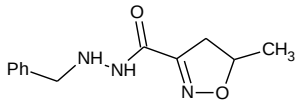

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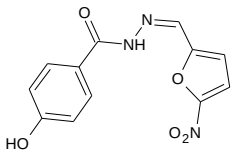

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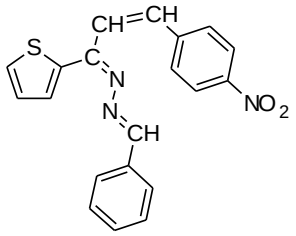

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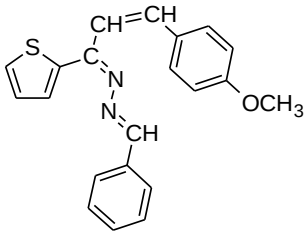

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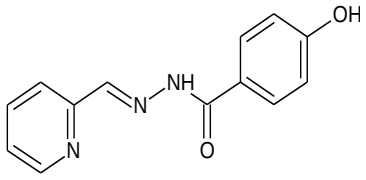

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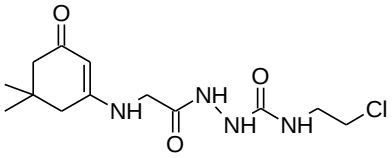

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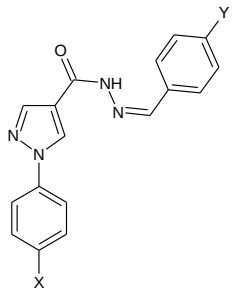

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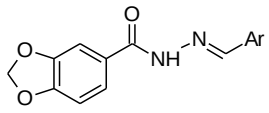
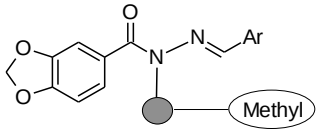


LASSBio-294 Ar = thienyl



LASSBio-785 Ar = thienyl
LASSBio-1003 Ar = furanyl
LASSBio-1004 Ar = phenyl
LASSBio-1456 Ar = pyrrolyl

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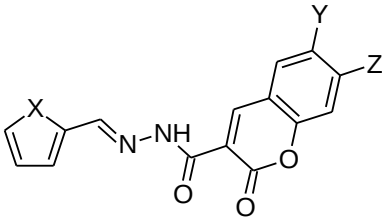

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Antioxidant activity

Anjoo Kamboj *et. al*.[21] synthesized new hydrazone derivatives from thiophene chalcone (1,2) and evaluated for their antioxidant activity. It has been found that the presence of nitro and methoxy group enhanced the antioxidant activity of the synthesized compounds.

Activity against Toxoplasma gondii

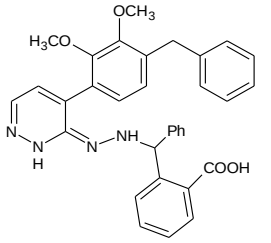
P. C. Lima *et al*. synthesized new hydrazone molecule (3) and that compound showed protection against hydrogen peroxide mediated cytotoxicity in Freidreich's ataxia fibroblasts using novel iron chelators of the 2-pyridyl carboxaldehyde isonicotinoyl hydrazone class[22].

Antiviral Activity

Most of the antiviral drugs now available are designed to help deal with HIV, herpes viruses, the hepatitis B and C viruses and influenza A and B viruses. Designing safe and effective antiviral drugs is difficult, because viruses use the host's cells to replicate. This makes it difficult to find targets for the drug that would interfere with the virus without also harming the host organism's cells. Moreover, the major difficulty in developing vaccines and anti-viral drugs is due to viral variation. El-Sabbagh and Rady[23] evaluated acyclic hydrazone (4) derivatives which showed a higher *in vitro* cytotoxic activity against hepatoma cell line (HepG2).

Leshmanicidal activity

1-Substitutedphenyl -*N*′- [(substitutedphenyl) methylene]-1*H* pyrazole-4-carbohydrazides were synthesized and their leishmanicidal and cytotoxic effects were compared to the prototype drugs (ketoconazole, benznidazole, allopurinol



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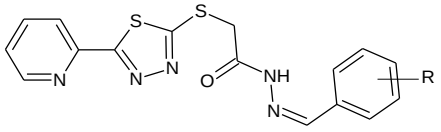
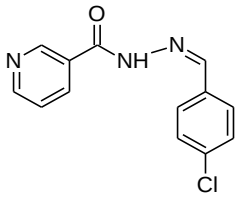


	R
a	4-Cl
b	2-Br
c	4-Br
d	2-F
e	3-F
f	2,6-Dichloro
g	2,4-Dimethyl
h	3-methoxy

(9)



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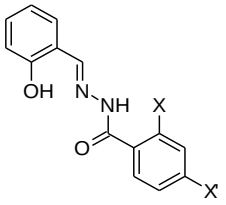
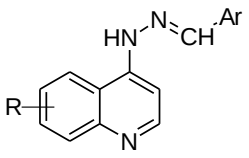
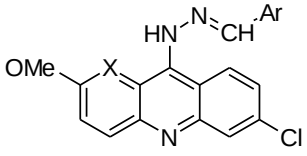


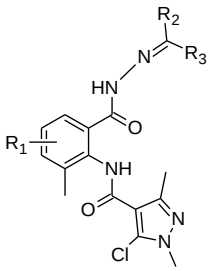
H_2LASSBio-466 : X=Cl, X'=H

H_2LASSBio-1064 : X=H, X'=Cl

(11)







(12) (13)

and pentamidine) *in vitro*. The 1*H*-pyrazole-4-carbohydrazide derivatives (5) with X = Br, Y = NO_2 and X = NO_2, Y = Cl demonstrated the highest activity and they were more effective on promastigotes forms of *L. amazonensis* than on *L. chagasi* and *L. braziliensis* species.

Vasodilator Activity

Vasodilators are used to treat conditions such as hypertension, wherein the patient has an abnormally high blood pressure, as well as angina, congestive heart failure, and erectile dysfunction, and where maintaining a lower blood pressure reduces the patient's risk of developing other cardiac problems. Arthur E. Kümmerle *et. al.*[24] disclose the synthesis, vasodilatory activity, and identification of bioactive conformation of new *N*-acylhydrazone and *N*-methyl-*N*-acylhydrazone derivatives (6), structurally designed by bioisosteric replacements of previously described cardioactive compounds LASSBio-294 and its *N*-methyl derivative LASSBio-785. Some of these novel derivatives presented improved vasorelaxant properties, being new cardiovascular drug candidates.

Antitumoral Activity

Drug resistance is a major impediment for cancer treatment, to overcome it Tamer Nasr *et.al.*[25] designed and synthesized sixteen coumarins bearing hydrazide–hydrazone moiety (7) and evaluated them against human drug-resistant pancreatic carcinoma (Panc-1) cells and drug-sensitive (hepatic carcinoma; Hep-G2 and leukemia; CCRF) cell lines *in vitro*. Bromocoumarins were found to be the most active antitumor agent against drug-resistant pancreatic carcinoma cells. They concluded that could be a potent anticancer drug to overcome drug resistance in cancer and it could be highly beneficial for patients in the clinic.

Antimicrobial Activity

N. G. Kandile and co-workers[26] synthesized hydrazones from 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene]hydrazines and diacetyl. The synthesized products were screened for antimicrobial activity against *Staphylococcus aureus* and *Streptococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa.* The hydrazone derivative (1-[4-(2-methoxybenzyl)-6-methylphenylpyridazin-3(2H)-ylidene]hydrazine (8) showed the highest biological activity.

Antimycobacterial Activity

Antimycobacterial drugs are used in the treatment of diseases caused by members of the *Mycobacterium*genus, including tuberculosis (TB) and leprosy, which have affected man since antiquity, and the nontuberculous mycobacterioses (NTM) that are increasingly recognised. Mycobacteria are unusual; they are slow growing with a thick waxy cell wall made of lipid rich material which makes penetration by drugs problematic. A large number of new agents with novel mechanisms of action are being trialled to assess their efficacy in treating mycobacterial disease. Maria Grazia Mamolo *et.al*[27] synthesized [5-(pyridin-2yl)-1,3,4-thiadiazole-2-ylthio]acetic acid

arylidene-hydrazide derivatives (9) and evaluated their activity against *Mycobacterium tuberculosis* and *Mycobacterium avium*. Compounds exhibited moderate *in-vitro* antimycobacterial activity against the tested strain of *Mycobacterium tuberculosis* and *Mycobacterium avium*.

Anticonvulsant Activity

Epilepsy is a common neurological disorder consisting of recurrent, unprovoked, sudden alterations in behaviour caused by abnormal electrical discharges in the brain (seizures). A series of aryl acid hydrazones of substituted aromatic acid hydrazides were synthesised and evaluated for anticonvulsant activity. Compound N^1-(4-chlorobenzylidene) nicotinohydrazide (10) was found to be the most potent analog with ED_{50} value of 16.1 mg/kg and protective index ($PI = TD_{50}/ED_{50}$) value of >20, which was much greater than that of the prototype drug phenytoin ($PI = 6.9$)[28].

Antidepressant Activity

Depression is one of the most prevalent psychopathologies in the the world. It is characterized by anhedonia or the loss of interest or pleasure in normal daily activities and feelings of sadness. Its therapy relies on classical antidepressant drugs such as monoamine oxidase inhibitors and drugs that inhibit the reuptake of catecholamines. Hydrazone derivatives play an important role as non-specific MAO inhibitors. These include drugs like phenelezine, isocarboxazid and iproniazid. S. N. Pandeya *et.al.*[29] synthesized fifteen hydrazone and semicarbazone derivatives which showed significant antidepressant activity at 10mg/kg.

Analgesic and Antiinflammatory Activity

Inflammation is a response of the immune system to physical and/or chemical and/or biological injury, understanding by injury any process able to cause tissue or cellular damages. Non-steroidal anti-inflammatory drugs (NSAIDs) are largely used in the treatment of pain and inflammation. Hydrazones that are dual inhibitors of both cyclooxygenase (COX) and 5-lipoxygenase (5-LO) are being studied as potential analgesic and anti-inflammatory agents in comparison to NSAIDs[30]. Walfrido Bispo Júnior *et.al.*[31] described the synthesis of zinc(II) complexes with salicylaldehyde 2-chlorobenzoyl hydrazone (H_2LASSBio-466) (11) and its regioisomer salicylaldehyde 4-chlorobenzoyl hydrazone (H_2LASSBio-1064), together with a pharmacological evaluation of all acylhydrazones and zinc(II) complexes in animal models of peripheral and central nociception and acute inflammation. All compounds showed levels of inhibition of zymosan-induced peritonitis comparable or superior to indomethacin, indicating an expressive anti-inflammatory profile.

Antimalarial Activity

Parasitic diseases caused by unicellular protozoa account for a huge burden of morbidity, mortality and economic deprivation across the globe. There is a need of intensive search for compounds having antimalarial activity against multi-drug resistant plasmodium falciparum. A series of *N*1-arylidene-*N*2-quinolyl- and *N*2-acrydinylhydrazones (12) were synthesized and tested for their antimalarial properties, reported by Sandra Gemma *et. al.*[32] These compounds showed remarkable anti-plasmodial activity in vitro especially against chloroquine-resistant strains. Their potent biological activity makes them promising lead structures for the development of new antimalarial drugs.

Radioprotective Properties

Acyl hydrazones of salicylaldehyde subsequently attracted attention. It displays radioprotective properties[33].

Hydrazones as enzyme inhibitors

A class of N - arylsulfonyl hydrazones has been developed as novel inhibitors of IMP-1, a *metallo-β-lactamase*. Structure-activity relationship studies suggested that there is a requirement for bulky aromatic substituents on each side of the sulfonyl hydrazone backbone so that these compounds may serve as efficient inhibitors of IMP-1. Molecular modeling has provided structural basis for the anti-metallo-β-lactamase activity shown by this class of compounds[34].

Antifungal Activity

A novel series of pyrazole amide derivatives (13) bearing hydrazone moieties[35] were synthesized. All of the compounds were subjected to fungicidal activities in vitro against *G. zeae*, *F. oxysporium* and *C. mandshurica*. The results indicated that the synthesized compounds possessed good antifungal activities against the tested fungi.

Other activities

The hydrazones are used as whole transporting agents in organic layer photo conductors, as quantitative analytical reagents, especially in colorimetric and fluorimetric determination of metal ions[36,37]. Furthermore, some hydrazones have also been used as herbicides, insecticides, nematocides, rodenticides, and plant growth regulators[38] as well as plasticizers and stabilizers for polymers[39,40]. The metal complexes of hydrazones have potential applications as catalysts[41], luminescent probes[42] and molecular sensors[43].

CONCLUSION

The present review highlights the biological activities of hydrazone derivatives, such as analgesic, anti-inflammatory, antihypertensive, vasodilatory, anticonvulsant activites, antioxidant, Leshmanicidal activity, antiviral, antitumoral, antimycobacterial, antimicrobial, antimalarial antidepressant activities. Therefore, these observations have been guiding for the development of hydrazones, which can be a lead nucleus for future developments to get safer and effective compounds.

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