Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2015; 7(2): 154-161

ISSN- 0975 1556

Review Article

Antimicrobial Potential of Hydrazide-Hydrazone Derivatives: A Review

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Available Online: 1st March, 2015

ABSTRACT
Over the past few decades, search for newer antimicrobials remains an area of intensive investigation in the field of medicinal chemistry due to resistance developed by micro-organism to conventional antibiotics. Hydrazide-hydrazone derivatives play an important role in development of various pharmacological activities such as anticonvulsant, antimalarial, analgesic, anti-inflammatory, antiplatelet, antimicrobial, antihypertensive, antiviral, anti-tubercular, antiproliferative and antitumor activities. This review highlights antimicrobial activity shown by various hydrazide-hydrazone derivatives.

Keywords: Hydrazide-hydrazone, Antimicrobial, Analgesic, Anti-inflammatory, Anticonvulsant

INTRODUCTION

Hydrazones possess an azometine -NHN=CH- proton that has found wide utility in organic synthesis.[1-2] While hydrazones have traditionally been employed as moiety for the derivatization and characterization of carbonyl compounds, in recent years the N-N linkage has been used as a key structural motif in various bioactive agents.[2-4] A number of hydrazone derivatives have been reported to various biological activities like anticonvulsant, antimalarial, analgesic, anti-inflammatory, antiplatelet, antimicrobial, antihypertensive, antiviral, anti-tubercular, antiproliferative and antitumor activities.[5-22] This review highlights antimicrobial activity shown by various hydrazide-hydrazone derivatives.

Antimicrobial Activity

Antimicrobials are one of most significant weapons in fighting bacterial infections. Throughout history, there has been a continual battle between humans and the multitude of microorganisms that cause infection and disease.[23-24] CDC (Centers for Disease Control) estimated that 19 million new infections occur each year.[25-26] Bacteria and fungi generally develop drug resistance in three ways: producing metabolizing enzymes for the degradation of the drugs, modifying their targets to render the drugs ineffective, and expressing a high level of efflux proteins that 'pump' the drug out in order to lower its concentration.[27-30] The increasing cases of microbial resistance pose a major concern to the scientific community and have become a threat for human life worldwide.[31-32] Moreover, invasive microbial infections caused by multi-drug-resistant Gram-positive bacteria and microbes are difficult to diagnose and treat. They are the major cause of morbidity and mortality especially in immunosuppressed and hospital-acquired patients.[33-35] To overcome these problems, the development of new and safe antimicrobial agents with better effectiveness is required day by day. In this review some synthesized hydrazones with remarkable antimicrobial activity has been discussed.

Hydrazones of [(2-Benzothiazolylthio)acetyl]hydrazine were synthesized and screened for antimicrobial activity against *Escherichia coli, Pseudomom aeruginosa, Streptococcus faecalis, Staphylococcus aureus, Candida albicans, Candih pseudotropicalk, Candida pmpsilosis* and *Candida stellatoidea*. All the compounds are highly potent against the yeast like fungi and bacteria tested, **1a** and **1b** being more potent than the others against *Candidu sfellatoidea*.[36]

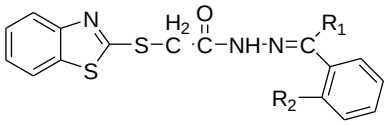
Three series of new Schiff bases and hydrazones of substituted pyrazole were synthesized and antimicrobial activity of these derivatives was carried out. Among the synthesized compounds, compound **2a** showed more potent antimicrobial activity than standard.[37]

A series of hydrazones of 1,2-benzisothiazole hydrazides as well as their cyclic and acyclic 1,2-benzisothiazole parent hydrazides, were synthesised and evaluated as antibacterial and antifungal agents. Compounds **3** and **4** proved to be the most effective against B. subtilis.[38]

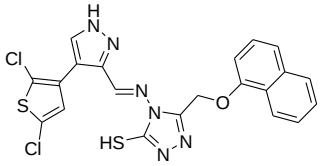
A series of new ω-nitro-1,2,4-oxadiazole-5-carbaldehyde hydrazones synthesized and were tested with respect to a series of standard microbial strains and characterized by minimum inhibiting concentrations. The most pronounced antimicrobial activity in the series of compounds studied with respect to the four standard microbial strains was observed for compounds **5** and **6**.[39]

4-substituted derivatives of 3-[(5-methyl-2-benzoxazolinone-3-yl)methyl]-1*H*-1,2,4-triazole-5-(4*H*)-thione were synthesized and screened for antimicrobial

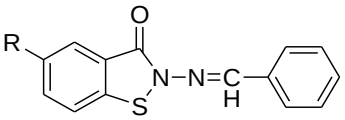
**Author for Correspondence*



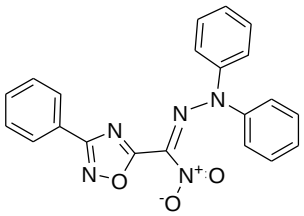
Compound	R_1	R_2
1a	CH_3	2-OH
1b	CH_3	4-OCH_3



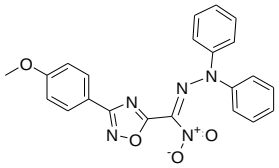
*Compound **2a***



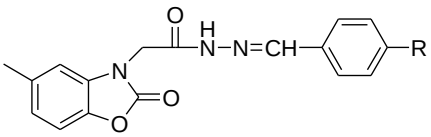
Compound	*R*
3	H
4	CH_3



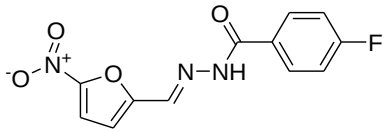
*Compound **5***



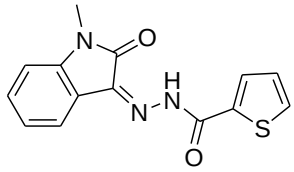
*Compound **6***



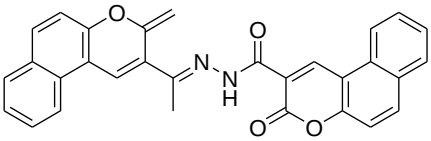
Compound	*R*
7a	H
7b	CH_3
7c	-OCH_3



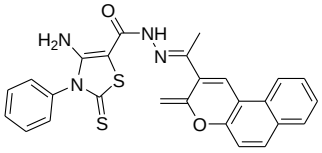
*Compound **8***



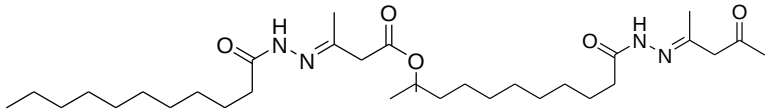
*Compound **9***



*Compound **10***



*Compound **11***



*Compound **12***

*Compound **13***

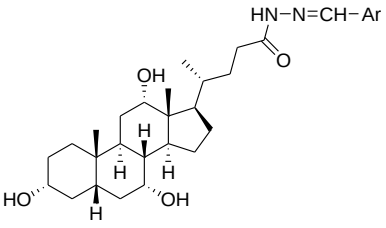
activity. Most of the compounds were inactive against bacteria, but they showed promising antifungal activity. It is worth mentioning that compounds **7a, 7b, 7c** showed moderate inhibitory activities against *Candida krusei*, *Candida albicans* and *Candida parapsilosis*.[40]

A series of hydrazide hydrazones and 1,3,4-oxadiazolines of 4-fluorobenzoic acid hydrazide synthesized and was tested for their antibacterial and antifungal activities against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Candida albicans. From these compounds, 4-fluorobenzoic acid[(5-nitro-2-furanyl)methylene]hydrazide (**8**) showed equal activity with ceftriaxone against *S. aureus*.[41]

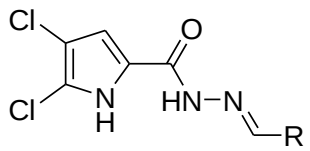
Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of 2-thiophenecarbonyl and isonicotinoyl hydrazones of 3-(N-methyl)isatin (**9a** and **9b**, respectively) were synthesized. The *in vitro* antimicrobial activity of all these compounds was tested against several bacteria and fungi. **9a** and its complexes exhibited a strong inhibition of the growth of *Haemophilus influenzae* and good antibacterial properties towards *Bacillus subtilis*.[42]

Synthesis and antimicrobial activity of some novel hydrazide, benzochromenone, dihydropyridine, pyrrole, thiazole and thiophene derivatives have been reported. It was observed that compounds **10** and **11** exhibited the highest activity against *S. aureus* and *E. coli*.[43]

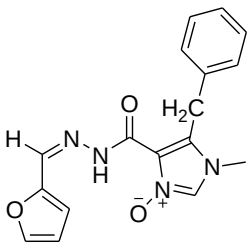
Carbonyl group of methyl acetoacetate and acetylacetone was employed to synthesize the hydrazones and screened for their antimicrobial activity. Results obtained from the antibacterial activity showed that some of the syn thesized



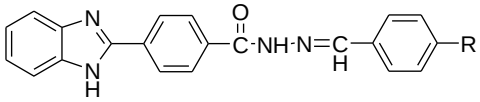
Compound	*Ar*
14a	*p*-BrC_6H_4-
14b	*m*-ClC_6H_4-
14c	*o*-BrC_6H_4-



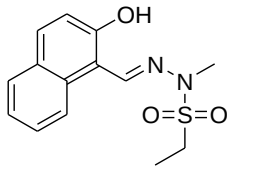
Compound	*R*
15a	*2,5-$(CH_3)_2C_6H_3$-*
15b	*4-$CH_3C_6H_4$-*
15c	*4-ClC_6H_4-*



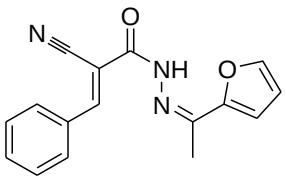
*Compound **16***



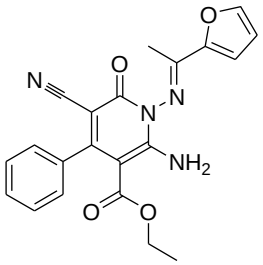
Compound	*R*
17a	*-H*
17b	*-OH*
17c	-$N(CH_3)_2$
17d	*-Cl*
17e	*-Br*
17f	*-F*
17g	*-CH_3*
17h	*-OCH_3*



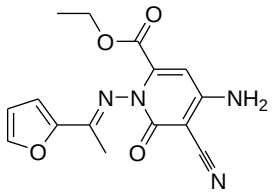
*Compound **18***



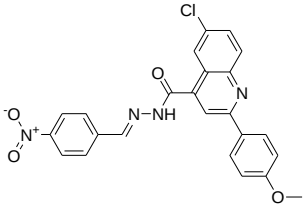
*Compound **19***



*Compound **20***



*Compound **21***



*Compound **22***

hydrazones i.e. hydrazones **12** and **13**, may be considered promising antibacterial agents.[44]

Synthesis and antimicrobial activity of cholic acid hydrazone analogues has been reported. Compounds **14a**, **14b** and **14c** indicated 15-fold stronger antimicrobial activities against *Enterobacter faecalis* compared to Cefaclor and Cefixime.[45]

Some novel chloropyrrole derivatives of aroyl hydrazones and chalcones incorporating common pharmacophore of pyoluteorin derivatives were synthesized and tested for antimicrobial activity. Few 1*H*-pyrrole-2-carbohydrazide derivatives shows activity equivalent to the standard drug ciprofloxacin. Aroyl hydrazones **15a**, **15b**, and **15c** were found to be more active than other compounds.[46]

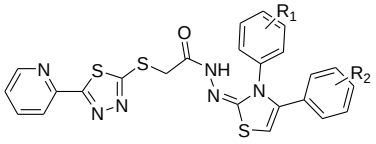
Synthesis and evaluation of antimicrobial activity of hydrazones derived from 3-oxido-1*H*-imidazole-4-carbohydrazides have been reported. Among the synthesized compounds, especially **16** containing non-substituted furan ring proved that the presence of the nitro group was essential for acquiring antibacterial activity.[47]

Some new benzimidazole derivatives bearing hydrazone moiety were synthesized and screened them for potential antibacterial and antifungal activities. The compounds **17b, 17d, 17e, 17g** and the compounds **17a-17e, 17h** were more potent than reference against *P. vulgaris* and *P. aeruginosa*, respectively.[48]

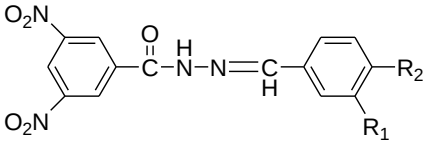
2-Hydroxy-1-naphthaldehyde-N-methyl ethane sulfonyl hydrazone (**18**) was synthesized and screened against E. coli, P. aeruginosa, S. enteritis, S. aureus and B. cereus. The compound possesses a broad spectrum of activity against the tested microorganisms. It shows relatively better activity against Gram-negative than Gram-positive bacterias.[49]

Synthesis and antimicrobial activity of a series of hydrazide-hydrzones via the reaction of cyano acetyl hydrazine with 2-acetylfuran has been reported. Compounds 2a, 6b and 7b are highly active compounds against *B. Cereus*.[50]

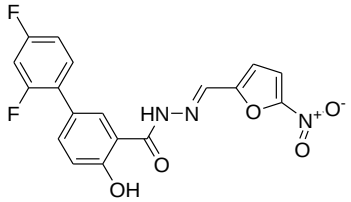
A novel series of 2-arylquinoline-4-carboxylic acid hydrazide–hydrazones was synthesized and evaluated for their *in vitro* antimicrobial activity against *S. aureus*



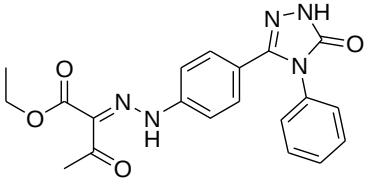
Compound	*R_1*	*R_2*
23a	4-Cl	H
23b	4-CH_3	H

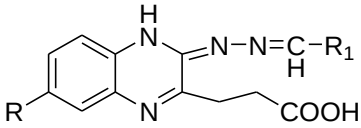


Compound	*R_1*	*R_2*
24a	-OEt	-OH
24b	H	-NO_2

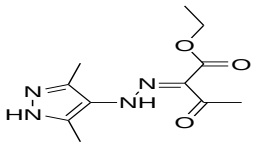


*Compound **24a***





Compound	*R_1*	*R_2*
26a	H	4F-C_6H_4
26d	H	4OH-C_6H_4
26k	-CH_3	4F-C_6H_4
26n	-CH_3	4Cl-C_6H_4



*Compound **27d***

(example for Gram-positive bacteria), *Escherichia coli* (example for Gram-negative bacteria) and *Candida albicans*. Compound **22** was found to be the most potent among the test hydrazones.[51]

A series of [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid (3,4-diaryl-3H-thiazol-2-ylidene)-hydrazide derivatives was synthesized and screened for Antimycobacterial activity. Compounds 1o and 1u (*para*-substituted) were moderately active toward all the clinical isolates of *M. tuberculosis*.[52]

A series of 3-ethoxy-4-hydroxybenzylidene/4-nitrobenzylidene hydrazides was synthesized and tested for *in vitro* antimicrobial activity. It can be seen from the results of antimicrobial activity that the activity increases with increase in chain length of acid portion of synthesized compounds. The presence of electron withdrawing group (NO_2) in compounds **24a** and **24b** makes them highly active antimicrobial agents.[53]

Several diflunisal hydrazide-hydrazone derivatives namely 2',4'-difluoro-4-hydroxybiphenyl-3-carboxylic acid [(5-nitro-2-furyl/substitutedphenyl)methylene] hydrazide have been synthesized and screened for their antimycobacterial activity against *Mycobacterium tuberculosis*, antimicrobial activities against various bacteria, fungi and yeast species. 2',4'-Difluoro-4-hydroxybiphenyl-3-carboxylic acid[(5-nitro-2-furyl)methylene]hydrazide **25a** have shown activity against *Staphylococcus epidermis* and *Staphylococcus aureus.*[54]

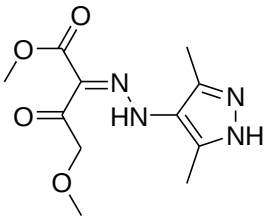
Ethyl 2-arylhydrazono-3-oxobutyrates, 5-(4-aminophenyl)-2,4-dihydro-4-phenyl-3*H*-1,2,4-triazole-3-one and 1-[4-(benzoylamino)benzoyl]-4-phenylsemicarbazide were synthesized in order to determine their antimicrobial properties. Compound Ethyl 2-[4-(2,4-dihydro-4-phenyl-3*H*-1,2,4-triazole-3-one-5-yl)phenylhydrazono]-3-oxobutyrate **25a** was the most active derivative against *M. fortuitum.*[55]

Hydrazones derivatives of quinoxalinone were synthesized and evaluated for their antimicrobial activity. Compounds **26a, 26d, 26k** and **26n** showed comparatively good activity against both types of microorganisms.[56]

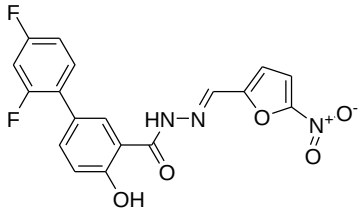
Several new hydrazone derivatives were prepared by the reaction of some active hydrogen compounds with the diazonium salts of 4-amino-3,5-di/1,3,5-trimethylpyrazoles. *In vitro* antituberculosis activity of these compounds was tested on Mycobacterium tuberculosis H37Rv at 6.25 µg/ml. Both hydrazone products, ethyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-3-oxobutyrate (**27d**) and methyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-4-methoxy-3-oxobutyrate (**27e**) showed 29 and 28% inhibition against *M. tuberculosis*, respectively.[57]

The 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2*H*)-ylidene] hydrazines or their tautomeric structures were condensed with different aldehydes, dialdehydes, ketones, a-dicarbonyl compounds and simple carbohydrates to afford the hydrazones and dihydrazones. Some of these compounds were screened for their antimicrobial activity against *Staphylococcus aureus* and *Streptococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The hydrazone derivative **28d** (1-[4-(2-methoxybenzyl)-6-methylphenyl pyridazin-3(2*H*)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine) showed the highest biological activity.[58]

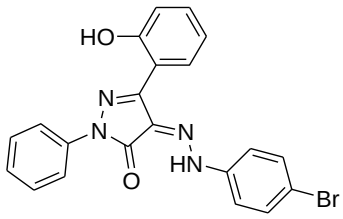
Novel azopyrazolin-5-one dyes ere synthesized by the regioselective reaction of phenylhydrazine with 2,3,4-chromantrione-3-arylhydrazones and screened for antimicrobial activity. Among the pyrazoline-5-one derivatives, compound **29** (MIC 3.125 mg/ml) having a p-bromo group on the phenyl ring was found to be most



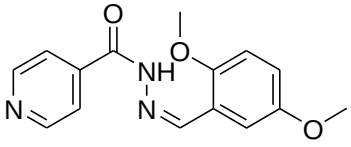
*Compound **27e***



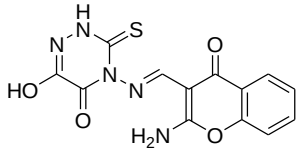
*Compound **28d***



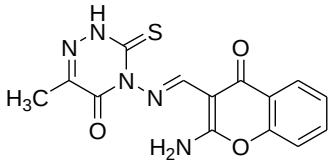
*Compound **29***



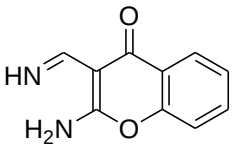
*Compound **30***



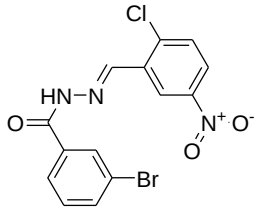
*Compound **31***



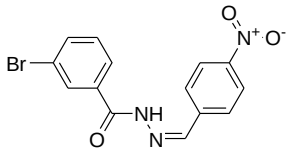
*Compound **32***



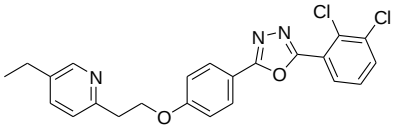
*Compound **33***



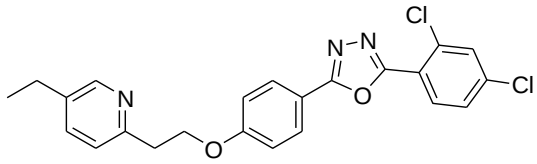
*Compound **34***



*Compound **35***



*Compound **36c***



*Compound **36d***

potent antibacterial agent against Gram-positive S. aureus compared to the standard drug Cephalothin.[59]

A series of isonicotinyl hydrazones and their 4-thiazolidinones was synthesized and were evaluated for their *in vitro* antimicrobial activity against a spectrum of non-resistant and resistant microbial organisms. Among the synthesized hydrazones, compound **30** with a 2,5 dimethoxy substitution on the aryl ring was found to be the most active compound in the series against *S. aureus*, *E. coli*, *P. chrysogenum* and *A. terrus*.[60]

Some heterocyclic schiff bases were synthesized from 2-Amino-3-formylchromone and evaluated for antimicrobial activity. Compounds **31**, **32** and **33** showed high activity toward the tested fungi.[60]

Two new hydrazone compounds, 3-bromo-N′-(2-chloro-5-nitrobenzylidene)-benzohydrazide **34** and 3-bromo-N′-(4-nitrobenzylidene)benzohydrazide **35**, have been synthesized and screened for antimicrobial activities. The results show that the two compounds have potential antimicrobial activities against *Klebsiella pneumonia* and it was notable that the activities of **34** are stronger than those of **35**, indicating that the chloro-substitute group is a good choice in search for antibmicrobial materials.[61]

Some new [4,5-bis-(4-methoxyphenyl)-1*H*-imidazole-2-yl]mercaptoacetic acid derivatives have been synthesized and evaluated for antimicrobial activity. None of the compounds showed significant antimicrobial activity.[62]

A series of novel 2-{4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl}-5-substituted-1,3,4-oxadiazoles were synthesized by the oxidative cyclisation of hydrazones derived from 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde and aroylhydrazines. The synthesized compounds were evaluated for their antimicrobial activity and were compared with standard drugs. Out of the compounds studied, compounds **36c** and **36d** showed significant inhibition.[63]

CONCLUSION

Hydrazide-hydrazone derivatives have attracted considerable attention due to their interesting chemical and structural properties. Hydrazones constitute an important class of compounds demonstrated remarkable activity against both Gram-positive and Gram-negative microorganisms. Further, structure-activity relationship studies may serve as a basis for chemical modifications directed towards the development of potential bioactive compounds of clinical interest. Various hydrazide-hydrazones have shown good efficiency and this may be a solid basis for further research on such compounds.

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