Structure Activity Relationship and Mechanism of Action of Hydrazide Derivatives as Antimicrobial Molecule

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ABSTRACT

Hydrazide and their heterocyclic derivatives exhibiting wide range of biological activities. Among different biological activities antimicrobial, antitubercular, antiamoebic and antimalarial are noteworthy. Further, presence of different substituents and derivatization to heterocyclic ring of hydrazide derivatives affect biological outcomes to a great extent. Therefore, researchers have synthesized compounds containing hydrazides and their heterocyclic derivatives with variable substituents as target molecules and evaluated their biological activities. Present review describes the antimicrobial importance of hydrazide derivatives along with their structure activity relationship. Moreover, we have put a light on targets of antimicrobial hydrazide derivatives through which they induce biological effects. Present review will be helpful in designing and structure activity relationship study of bioactive hydrazide derivatives.

Keywords: Antimicrobial, Antitubercular, Antiamoebic, Antimalarial, Hydrazides, Heterocyclics.

INTRODUCTION

Hydrazide-Hydrazone derivatives containing –NHN=CH- moiety represent an overwhelming and rapid developing field in modern medicinal chemistry. [1] Reported data indicated that hydrazide derivatives have significant biological activities such as anti-inflammatory [2], antimalarial [3], antimicrobial [4], antileishmanial [5], anticonvulsant [6], antitubercular [7] and antitumor [8]. Examples of clinically used drugs having hydrazide moiety presented in Table 1.

Further reported data and studies performed by us revealed that antimicrobial activity is most significant among different activities for hydrazide derivatives [10-13]. Therefore, in present study we attempted to compile reported data of most active hydrazides having antimicrobial activity and their mechanism of action. Present review will help the researchers in understanding the structure activity relationship (SAR) and mechanism of action of hydrazide derivatives.

Mechanism of action of existing antimicrobial hydrazides and related drugs

Isoniazide (hydrazide of nicotinic acid) activation leads to inhibition of the synthesis of mycolic acid, an important component of the mycobacterial cell wall. Two enzymes involved in the cycle of the fatty acid biosynthesis, namely an enoyl-acyl carrier protein reductase (InhA) and β-ketoacyl- acyl carrier protein synthase, are believed to be targets of the activated isoniazid. [14]

Thiazolidinones, hydrazide derivative inhibit the biosynthesis of the peptidoglycan polymer essential for cell wall via inhibition of MurB enzyme of bacteria. MurB enzyme causes reduction of enolpyruvyl uridine diphosphate N-acetylglucosamine (EP-UNAG) to uridine diphosphate N-acetylmuramic acid (UNAM), is a unique target for antibacterial activity of thiazolidinones. [15]
Hydrazone derivatives viz. 2-azetidinones (β-lactam antibiotics) are one of the most prescribed chemotherapeutic agents used in medicine to treat bacterial infections. 2-Azetidinone molecules act by forming a covalent adduct with membrane-bound bacterial transpeptidase, which are also known as penicillin-binding proteins, involved in the biosynthesis of cell walls. On the basis of this mechanism, inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover, due to their β-lactamase inhibitory action, 2-azetidinones based heterocycles represent an attractive target against microorganisms. [16]

### Table 1 Examples of drugs containing hydrazone moiety [9]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of Drug</th>
<th>Biological activity</th>
<th>Chemical Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Isoniazide</td>
<td>Antituberculosis</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>2.</td>
<td>Nifuroxazide</td>
<td>Antibiotic</td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>3.</td>
<td>Nifurtimox</td>
<td>Antiamoebic</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>4.</td>
<td>Isocarboxazide</td>
<td>Antidepressant</td>
<td><img src="image4" alt="Chemical Structure" /></td>
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<tr>
<td>5.</td>
<td>Iproniazide</td>
<td>Antituberculosis</td>
<td><img src="image5" alt="Chemical Structure" /></td>
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</tbody>
</table>

**Hydrazone derivative as antibacterial and antifungal agents**

Biphenyl-4-carboxylic acid hydrazone-hydrazone derivatives have been synthesized by Deep et al. All the compounds were tested for their in vitro antimicrobial activity against two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa) and two Gram-positive strains (Bacillus subtilis and Staphylococcus aureus) and fungal strain Candida albicans and Aspergillus niger using tube dilution method, all synthesized compounds exhibited promising activity (MIC = 25 μM/mL). Result of antimicrobial activity indicated that presence of p-NO₂ and p-Cl increased antifungal and antimicrobial activities. [17]

![Chemical Structure](image6)

1. R = Cl or NO₂

Wang et al. synthesized vanillic acyl hydrazone derivatives and evaluated their in vitro antibacterial activities against E. coli, P. aeruginosa, S. aureus, and B. subtilis by broth dilution method. The result of antimicrobial evaluation indicated that compound (E)-N-(3,5-dichloro-2-hydroxybenzylidene)-4-hydroxy-3-methoxy benzohydrazide (2) was most active against E. coli among synthesized derivatives (MIC = 0.39 μg/ml). The highest activity of compound 2 may be due to the formation of hydrogen bond with target site by hydroxyl group present in synthesized derivatives. [18]

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Altintop et al. synthesized hydrazone derivatives by condensation of 2-[(1-methyl-1H-tetrazol-5-yl)thio] acetohydrazide with aromatic aldehydes/ketones and evaluated their *in vitro* anticandidal activity against *C. albicans*, *C. krusei*, *C. parapsilosis* by micro dilution method. The result of antimicrobial evaluation showed that compound N’-(4-(dimethyl amino)benzylidene)-2-[(1-methyl-1H-tetrazol-5-yl)thio]acetohydrazide (3) was most active among synthesized derivatives (MIC = 0.05 mg/ml) and comparable with standard drug Ketoconazole (MIC= 0.031 mg/ml) against *C. albicans*. [19]

Pieczonka et al. reported synthesis of 3-oxido-1H-imidazole-4-carbohydrazides and evaluated their *in vitro* antibacterial activities against *E. coli*, *S. aureus* and *S. epidermidis* by micro dilution method. Compound 1-benzyl-5-methyl-N’-[(Z)-(5-nitro-2-furyl) methylidene]-1H-imidazole-4-carbohydrazide-3-oxide (4) was found to be most effective against *S. epidermidis* having MIC value of 4 µg/ml. Antimicrobial results analysis showed that presence of furyl ring with electron withdrawing nitro group is responsible for high potency of compound 4. [20]

Kumar et al. synthesized hydrazone derivatives and evaluated their *in vitro* antibacterial activity against *S. aureus*. The most active compound was found to be (E)-5-bromo-2-hydroxy-N’-[1-(1-methyl)-1H-indole-2-yl]ethylidene]benzohydrazide (5) (MIC = 1 µg/ml) among the synthesized derivatives due to presence of electron donating hydroxyl and electron withdrawing bromo groups. [21]

Plech et al. synthesized a novel series of 1,2,4-triazole-ciprofloxacin hybrids and evaluated their antibacterial activities against *M. luteus*, *E. coli*, *P. mirabilis*, *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *B. subtilis* and *B. cereus* by agar diffusion method. Compound 1-cyclopropyl-7-(4-((4-(2,4-dichlorophenyl)-3-(3-hydroxyphenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6) was found to be most potent (MIC = 0.35 µM/ml) against *S. aureus* among the synthesized derivatives due to the presence of m-hydroxyl phenyl moiety attached with triazole ring. [22]
Emary et al. reported a novel series of indeno[2,1-e]pyrazolo[3,4-b]pyrazin-5-one derivatives and studied their antifungal activities against *Trichophyton rubrum, Aspergillus flavus* by broth dilution method. Compound (Z)-2-(3-methyl-1-phenylindeno[2,1-e]pyrazolo[3,4-b]pyrazin-5(1H)-ylidene) hydrazine carbothioamide (7) was found to be most active (MIC = 0.3 mg/ml) among synthesized derivatives whereas, MIC value of standard drug Clotrimazole was 0.08 mg/ml against *T. rubrum.* [23]

Manjunatha et al. synthesized a series of 1,3,4-oxadiazole derivatives and evaluated their antibacterial activities against *S. aureus, E. coli, P. aeruginosa* and *K. pneumonia* by serial plate dilution method. Compound 5-(4-isobutylphenyl)ethyl-3-(morpholin-4-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione (8) was found to be most potent having MIC value 6.25 µg/ml against tested strains. Structure activity relationship (SAR) of synthesized derivatives revealed the importance of hydrophobic 4-isobutyphenyl ethyl moiety in improving the antibacterial activity. [24]

Patel et al. reported synthesis of thiazolidinone derivatives and evaluated their antimicrobial activities against different bacteria i.e. *S. aureus, B. cereus, E. coli, P. aeruginosa, K. pneumoniae, S. typhi, P. vulgaris, S. flexneri* by micro dilution method. The results of antimicrobial activity showed that compound 4-(4-[4-[2-(2,4-dichlorophenyl)-5-(4-ethylpiperazin-1-ylmethyl)-4-oxothiazolidin-3-yl]-phenyl amino]-6-dimethylamino-[1,3,5] triazin-2-ylxoy]-1-methyl-1H-quinolin-2-one (9) was most potent against *S. aureus* among all synthesized derivatives (MIC = 6.25 µg/ml). SAR analysis of synthesized derivatives indicated that high potency of compound 9 was due to presence of dichlorophenyl moiety. [25]
Seelam et al. synthesized a novel series of fused 1,2,4-triazole derivatives and evaluated their antibacterial activities against B. subtilis, B. thuringiensis, E. coli, P. aeruginosa by agar diffusion method. Compound 3-(4-chlorophenyl)-6-(p-tolyl)-3,3a-dihydro-2H-pyrazolo[3',4',5:3,4]thiazolo[3,2-b][1,2,4]-triazole (10) was found to have better activity against all the tested microorganisms than other synthesized derivatives (MIC = 3.125 µg/ml). Analysis of activity data showed that high potency of compound 10 due to the presence of electron-negative chlorine atom. [26]

Gaikwad et al. reported thiazole substituted benzotriazole derivatives and evaluated their antibacterial activity against S. aureus, E. coli, B. subtilis and P. aeruginosa by micro broth dilution method. The results of antimicrobial activities showed that compound 1-(1-(3,5-bis(trifluoromethyl)phenyl)-2-(1H-1,2,4-triazol-1-yl)ethylidene)-2-(4-(4-fluorophenyl)thiazol-2-yl)hydrazine (11) was most active one against P. aeruginosa, among all the synthesized derivatives (MIC = 16 µg/ml). The high potency of synthesized compound (11) due to presence of electron withdrawing trifluoromethyl group at meta position of phenyl ring. [27]

Gaikwad et al. also reported antifungal activity of synthesized derivatives against fungal strains A. niger, C. albicans. The results of antifungal activities showed that compound 1-(1-(3,5-bis (trifluoro methyl) phenyl)-2-(1H-1,2,4-triazol-1-yl)ethylidene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (12) was most potent against A. niger among all synthesized derivatives (MIC = 16 µg/ml). The present results once again indicated the presence of electron-negative trifluoromethyl group in improving antifungal activity of synthesized hydrazide derivatives. Moreover, above study revealed the significance of p-fluorophenyl and p-chlorophenyl ring, attached at 4th position of thiazole ring in antibacterial and antifungal activities, respectively. [27]

Ozkay et al. reported benzimidazole derivatives bearing hydrazone moiety and evaluated their antibacterial activity against P. vulgaris, S. typhimurium, K. pneumoniae and P. aeruginosa by broth micro dilution method. The results of antibacterial activity showed that compound (E)-4-(1H-benz[d]imidazol-2-yl)-N'-(4-chloro benzylidene) benzo hydrazide (13) was found to be most potent against S. typhimurium among all synthesized derivatives (MIC = 6.25 µg/ml). High potency of aforementioned compound was due to presence of electron withdrawing chlorine group. [28]
Refat et al. synthesized (benzochromen-2-yl)ethylidene acetoxyhydrazide derivatives and evaluated their in vitro antibacterial activities against S. aureus and E. coli by broth micro dilution method. Compound 3-oxo-N-(1-(3-oxo-3H-benzo[f]chromen-2-yl)ethylidene)-3H-benzo[f]chromene-2-carboxyhydrazide (14) was found to be most active one against S. aureus with MIC value = 62.5 µg/ml among the synthesized derivatives. The antimicrobial results signify the presence of pyran ring in improving the antibacterial activity of synthesized derivatives. [29]

A series of hydrazide derivatives were evaluated for their in vitro antibacterial activities against E. coli, and S. aureus. Compound N-((2R,3R)-3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)-3-(4-chlorophenyl)-1H-pyrazole-5-carboxamide (15) was found to be most active against E. coli having MIC value of 0.010 µg/ml. High potency of compound (15) may be due to the presence of hydrogen bond forming hydroxy and electron negative chloro groups. Result analysis of present study showed the significance of azetidinone and pyrazole rings in antibacterial and antifungal activities, respectively. [30]

Pathak et al. synthesized 3-(4-chlorophenyl)-4-substituted pyrazoles derivatives and evaluated their in vitro antifungal activities against C. krusei, C. neoformans, A. niger, A. flavus by national committee for clinical laboratory standards. Compound 3-(4-chlorophenyl)-N-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)-1H-pyrazole-5-carboxamide (16) was found to be most potent having MIC value of 6.3 µg/mL. Antimicrobial result analysis showed that hydrogen bond forming hydroxyl group and electron withdrawing chlorine group are responsible for high potency of synthesized derivatives. [30]

Lee et al. synthesized hydrazide derivatives as selective inhibitors of S. aureus β-ketoacyl acyl carrier protein synthase III and evaluated their in vitro activity by serial broth dilution method. (E)-2, 4-dichloro-N-(2, 3, 4-trihydroxybenzylidene)benzoylhydrazide (17) was found to be most potent (MIC = 2 µg/ml) among the synthesized derivatives. The highest activity of compound (17) may be due to formation of hydrogen bond by hydroxyl groups with target site. [31]

Kumar et al. synthesized benzylidene hydrazides analogues and evaluated their in vitro antifungal activities against A. niger and C. albican by tube dilution method. The result of antifungal evaluation indicated that N'-benzylidene-3, 5-dimethoxybenzoylhydrazide (18) was most effective against A. niger among all synthesized derivatives (MIC = 1.60
The potency of synthesized derivatives (18) may be due to presence of electron donating methoxy substituent on the phenyl ring. [32]

Kumar et al. synthesized of benzylidene hydrazide derivatives and evaluated their in vitro antibacterial activities against S. aureus, B. subtilis, and E. coli by tube dilution method. Compound N'-benzylidenedodecanedihydrazone (19) was found to be most active against S. aureus among synthesized derivatives (MIC = 1.49 µM/ml). The present results depicted the importance of long chain fatty acid in improving antibacterial activity of synthesized hydrazide derivatives. [32]

Malhotra et al. reported a novel series of (Z)-2-(5-(biphenyl-4-yl)-3-(1-(imino)ethy1)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol derivatives and evaluated their in vitro antibacterial activities against S. aureus, E. coli, B. subtilis and P. aeruginosa antifungal activity against C. albican and A. niger by disc-diffusion method. The results of antibacterial activity showed that compound (Z)-2-(5-(biphenyl-4-yl)-3-(1-(4-nitrophenyl)iminio)ethy1)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (20) was found to be most potent against B. subtilis, C. albican and A. niger among the synthesized derivatives (MIC = 6 µg/ml). The high potency of compound (20) may be due to the presence of electron withdrawing nitro group at para position of phenyl ring. [33]

Tajudeen et al. reported isonicotinohydrazide and evaluated their antibacterial activities against B. subtilis, S. aureus, S. pyogenes, E. faecalis, E. coli, K. pneumonia by agar diffusion and macro dilution tube method. Compound (E)-N'-(3,5-dimethoxybenzylidene)isonicotinohydrazide (21) was found to be potent (MIC = 250 µg/ml) against all microorganisms as compared to other synthesized derivatives, due to the presence of electron donating OCH₃ group at meta position of phenyl ring. [34]

Thomas and their research group reported 4-hydroxy-8-trifluoromethyl-quinoline derivatives and evaluated their antibacterial activities against E. coli, S. aureus, P. aeruginosa, K. pneumoniae and S. pyogenes using serial plate dilution method. Compound 2-[[4-hydroxy-8-(trifluoromethyl) quinolin-3-yl] carbonyl]-N-(4-methoxyphenyl)hydrizine carboxamide (22) showed better antibacterial activity against K. pneumoniae among all synthesized derivatives (MIC = 0.1 µg/ml). The highest potency of compound (22) was due to the presence of p-methoxy substituted phenyl and trifluoromethyl group at quinoline ring. [35]
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Zhang et al. synthesized benzimidazole derivatives and evaluated their antimicrobial activities against different bacteria i.e. Methicillin-resistant S. aureus, B. subtilis, M. luteus, E. coli, S. dysenteriae, P. aeruginosa, E. typhosa by micro broth dilution method. N\(^2\), N\(^5\)-bis[(1-decyl-1H-benzoimidazol-2-yl)methyl]-3,4-dimethylthiophene-2,5-dicarbohydrazide (23) was found to be most potent against S. aureus among all synthesized derivatives (MIC = 2 µg/ml). The SAR of above antimicrobial results indicated the importance of long chain alkyl group in improving antibacterial activity. Increased potency of compound 23 is due to the high lipophilicity and hence they can easily penetrate inside lipophilic cell wall. [36]

Kocyigit-Kaymakcioglu et al. synthesized 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4 oxadiazoles derivatives and evaluated their in vitro antifungal activity against C. albicans using the micro-dilution broth assay. (E)-1-(2-(4- (dimethylamino)styryl)-5-(4-fluorophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (24) was found to be most effective having MIC value 125 µg/ml and equal to standard drug Ketoconazole (125µg/ml) against C. albicans. [37]

Narang et al. reported (naphthalen-1-ylxy)-acetic acid benzylidene/(1-phenyl ethylidene)hydrazide derivatives and evaluated their in vitro antibacterial activities against S. aureus, B. subtilis, and E. coli by serial tube dilution method. Compound (E)-N\(^1\)-(4-hydroxy-3-methoxybenzylidene)-2-(naphthalen-1-ylxy)aceto hydrazide (25) was found to be most active one against B. subtilis among all synthesized derivatives (MIC = 1.45 µg/ml). SAR studies of synthesized hydrazide derivatives indicated the importance of hydrogen bond forming hydroxyl group and electron donating methoxy group in improving antibacterial activity of synthesized derivatives. [38]

In same study synthesized hydrazide derivatives were also evaluated their in vitro antifungal activities against C. albicans and A. niger. The results of antifungal activity showed that compound N\(^1\)-(1-(2-bromo-4-cyanophenyl)ethylidene)-2-(naphthalen-1-ylxy)acetohydrazide (26) was most effective against C. albicans
among all synthesized derivatives (MIC = 2.13 µg/ml) due to presence of electronegative o-Br and p-CN substituent on phenyl ring. [38]

Tasneem et al. reported synthesis of Schiff bases and azetidinones derivatives with 1,2,4-triazoles and screened their antibacterial activity against B. subtilis, S. aureus, E. coli, P. aeruginosa, E. faecalis, K. pneumoniae. The results of antibacterial activity showed that compound 2-[4-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-4-[3-chloro-2-(4-anil-syl)-4-oxo-azetidin-1-yl]-5-methyl-3-oxo-2,4-dihydro-[1,2,4]-triazole (27) was most effective against all microorganisms among all synthesized derivatives (MIC = 12 µg/ml). The present antimicrobial result revealed the importance of 2-azetidinone and p-methoxy phenyl ring in contributing antibacterial activity of synthesized derivatives. [39]

ZA Kaplanlcki synthesized oxadiazole derivatives and evaluated their in vitro antifungal activities against C. albicans, C. glabrata, C. tropicalis, C. krusei, C. parapsilosis, and C. albicans by micro broth dilution method. Compound 2-[5-[(pyrimidin-2-yl)thio)methyl]-1,3,4-oxadiazol-2-ylthio]acetophenone (28) was most active (MIC = 0.007 mg/ml) among synthesized derivatives, whereas MIC value of standard drug Ketoconazole was 0.001 mg/ml against C. glabrata. [40].

Khidre et al. synthesized 1- substituted amino-4,6-dimethyl-2-oxo-pyridine-3-carbonitrile analogues and evaluated their antibacterial and antifungal activities against S. aureus, B. subtilis, P. aeruginosa, E. coli, A. fumigatus, G. candidum, C. albicans and S. racemosum by agar well diffusion method. Compound 29(a-b) showed better antibacterial and antifungal activities as compared to other synthesized derivatives against S. aureus (MIC = 24.4 and 26.4 µg/ml) and A. fumigates (MIC = 19.2 and 22.5 µg/ml). SAR study showed the significance of bromine substituted phthalimide ring in improving antimicrobial activity [41].

Secci et al. reported (4-(4-iodophenyl)-thiazol-2-yl) hydrazine derivatives and evaluated their antifungal activities against C. albicans and C. krusei by Microtiter plate method. (E)-2-(2-(1-(furan-2-yl)ethylidene)hydrazinyl)-4-(4-
iodophenyl)thiazole (30) was found to be most potent among all synthesized derivatives (MIC value = 0.25-2.00 µg/ml) and even more active as compared to standard drug clotrimazole (MIC= 2 µg/ml) against C. albicans. SAR study of synthesized derivatives showed incorporation of furan ring improved antifungal activity [42].

Gupta et al. reported salicylaldehyde schiff bases of 2-aminopyridine derivatives and evaluated their antibacterial activity against S. aureus and E. coli by serial dilution method. (E)-4-bromo-2-((pyridin-2-ylimino)methyl)phenol (31) was found to be most potent against S. aureus among all synthesized derivatives (MIC value = 0.625 µg/ml). Antimicrobial results once again proved the importance of electron negative bromine group and hydrogen bond forming hydroxyl group (with target sites) in enhancing antibacterial activity [43].

Malladi et al. synthesized schiff bases analogues and screened their antibacterial activities against S. aureus, B. subtilis, E. coli and P. aeruginosa by serial dilution method. Compound 5-ethyl-4-(((3-(4-fluorophenyl)-1H-pyrazol-4-yl)methylene)amino)-4H-1,2,4-triazole-3-thiol (32) showed better antibacterial activity against S. aureus (MIC =3.125 µg/ml). High potency of compound (32) due to the presence of electron withdrawing fluoro group on phenyl ring [44].

Hydrazide as antimalarial agents
Thuy et al. synthesized quinolinyl hydrazone derivatives and screened their in vitro antimalarial activities to chloroquine-sensitive (T96) and chloroquine-resistant (K1) strains of P. falciparum. Among the synthesized compounds, 4-((E)-((3-(E)-1-(2-(7-chloroquinolin-4-yl)hydrazone)ethyl)phenylimino)methyl)phenol (33) exhibited strong antimalarial activity at IC_{50} of 103.4 ng/mL and 18.76 ng/mL against both strains of P. falciparum. The high potency of compound (33) may be due to presence of hydroxyl group, as it is normally involved in H-bond formation with target [45].

Acharya et al. synthesized 1,3,5-trisubstituted pyrazolines derivatives and evaluated their in vitro antimalarial efficacy against chloroquine sensitive (MRC-02) as well as chloroquine resistant (RKL9) strains of P. falciparum by serial tube dilution method. Compound 3-(4-hydroxy-phenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-pyrazol-1-yl)-pyridin-3-yl methanone (34) was most active one among all synthesized derivatives (IC_{50} = 0.0425 µM). The presence of hydroxyl and methoxy moieties proved the importance in enhancing antimalarial activity [46].
Hydrazide as antitubercular agents

Telvekar et al. reported N-benzylidene benzofuran-3-carbohydrazide derivatives and evaluated their in vitro antituberculosis (anti-TB) activity against *M. tuberculosis* by micro titer plate method. The results of antimicrobial activity showed compound (E) -N-benzylidenebenzofuran-3-carbohydrazide (35) was most potent among all synthesized derivatives (MIC = 2 µg/ml). The SAR study indicated that the presence of benzofuran ring was significant in improving the antimycobacterial activity of synthesized hydrazide derivatives. [47]

Pathak et al. synthesized 3-(4-chlorophenyl)-4-substituted pyrazole hydrazides and evaluated their in vitro antitubercular activity against *M. tuberculosis* using the BACTEC 460 radiometric system. Compound N-(2R, 3R)-3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-3-(4-chlorophenyl)-1H-pyrazole-5-carboxamide (36) was found to be most effective having MIC value of 0.35 µg/ml. The highest antitubercular activity of compound (36) may be due to presence of hydrogen bond forming hydroxyl group and electron withdrawing chloro group [30].

Jordao et al. synthesized N-benzylidene benzofuran-3-carbohydrazide derivatives and evaluated their antimycobacterial activities against *M. tuberculosis* using broth macro dilution method. Compound (E)-5-methyl-N-(5-nitrofuran-2-yl)methylene)-1-(phenylamino)-1H-1,2,3-triazole-4-carbohydrazide (37) was most active one among all synthesized derivatives (MIC = 2.5 µg/ml). The presence of the furyl ring with electro-negative NO₂ group was responsible for improving antitubercular activity of synthesized hydrazide derivatives [48].
Thomas et al. also reported their in vitro antmycobacterial activity against M. tuberculosis, M. smegmatis and M. fortuitum by Resazurin assay method. The results of activity showed compound 4-hydroxy-8-trifluoromethylquinoline-3-carboxylicacid(5-methyl-3H-imidazol-4-ylmethylene)hydrazide (38) was most active one against M. tuberculosis, among all synthesized derivatives (MIC = 0.625 µg/ml) and this may be due to the incorporation of lipophilic indole and 8- trifluoromethyl-quinoline hydrazone moieties in synthesized derivatives [35].

Pavan et al. synthesized thiosemicarbazones, semicarbazones, dithiocarbazates and their hydrazide/hydrazones derivatives and evaluated their antitubercular activities against M. tuberculosis by Resazurin Microtitre Assay. 2-(Di(pyridin-2-yl)methylene)-N-phenyl hydrazine carbothioamide (39) was found to be most potent among all synthesized derivatives (MIC = 0.78 µg/ml). The present antimicrobial results revealed the importance of pyridine ring in contributing antitubercular activity of synthesized derivatives [7].

Shahar et al. reported 1,3,4-oxadiazole derivatives and evaluated their in vitro antmycobacterial activity against M. tuberculosis using BACTEC 460 radiometric system. 2-(2-naphthoxyxymethyl)-5-phenoxyethyl-1,3,4-oxadiazole (40) was found to be most effective having MIC value 6.25 µg/ml. The presence of hydrophobic β-naphthoxy methyl group at position 2 and a phenoxy methyl group at position 5 of 1,3,4-oxadiazole lead to increment in antitubercular activity as compared to other synthesized derivatives [49].

**Hydrazide as antiamoebic agents**

Siddiqui et al. synthesized hydrazones of hydrazones and benzimidazole derivatives and evaluated in vitro antiamoebic activity against E. histolytica by micro dilution method. Compound N′-(4-methylbenzylidene)isonicotinohydrazide (41) was most active among synthesized derivatives (IC₅₀ = 0.131 µM). Further, analysis of antiamoebic results showed the importance of p-methyl substituted phenyl ring in improving activity of synthesized hydrazide derivative (41) against E. histolytic [50].

Wani et al. reported synthesis of pyrazoline derivatives by cyclization of chalcones with 2-[5-(4-methoxyphenyl)-1H-tetrazol-1-yl]acetohydrazide and evaluated in vitro for antiamoebic activity against E. histolytica by micro dilution method. The results of antiamoebic activity showed that compound 1-(3,5-di-p-tolyl-4,5-dihydro-1H-pyrazol-1-yl)-2-(5-(4-methoxy phenyl) -1H-tetrazol-1-yl)ethanone (42) was most potent among all synthesized derivatives (IC₅₀ = 0.86 µM). SAR results revealed that presence of electron releasing groups (OCH₃, CH₃) on phenyl ring was important for antiamoebic acity [51].
CONCLUSION

Reported data showed that hydrazide derivatives have a good antibacterial, antifungal, antitubercular, anti-inflammatory, and antimalarial potential. Different studies indicated that hydrazide-hydrazone derivatives with electron withdrawing groups (viz. NO₂, Cl) and electron donating groups (viz. OCH₃, N(CH₃)₂) have significant role in antimicrobial and antimalarial activities. Further, derivatization of hydrazides to nitrogen containing heterocyclic rings (viz. pyrazole, oxadiazole, azetidin-2-ones etc.) also improved the antimicrobial activities. In case of antitubercular activity presence of azetidin-2-ones, pyrazole, pyridine, nitro substituted furan moieties and trifluoromethyl group enhanced the activity. Presence of electron donating methyl and methoxy groups also improved the antiamoebic activity of hydrazide-hydrazone derivatives.

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