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Therapeutic Review Exploring Antimicrobial Potential of Hydrazones as Promising Lead

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ABSTRACT

This review includes detailed study of structures of various hydrazones synthesized and evaluated for their antimicrobial activity. Hydrazone is a class of organic compounds with structure $R_1R_2C=NNH_2$. Hydrazones containing an azomethine -NHN=CH- proton which leads to an important class of compounds for new drug development. Hydrazones are present in many of the bioactive heterocyclic compounds that are of very important use because of their various biological and clinical applications. Therefore, many researchers have synthesized these compounds as target structures and evaluated their antimicrobial activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities.

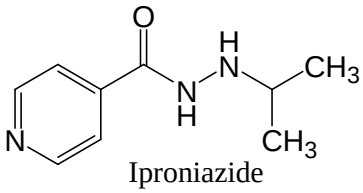
Key Words: Hydrazones, Hydrazide, Antifungal Activity, Antimicrobial Activity.

INTRODUCTION

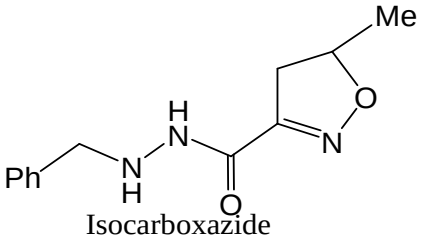
The need to design new compounds to deal with the resistant strains has become one of the most important areas of research today. Hydrazone is a versatile moiety that exhibits a wide variety of biological activities. A hydrazone is a class of organic compounds with the structure $R_1R_2C=NNH_2$. Hydrazones are basically related to ketones and aldehydes. Hydrazones are formed by the replacement of the oxygen of carbonyl compounds with the $-NNH_2$ functional group. Hydrazones act as reactants in many important reactions e.g. hydrazone iodination, Shapiro reaction and Bamford-Stevens reaction to form vinyl compounds. Also a hydrazone act as an intermediate in Wolff–Kishner reduction. Hydrazone can also be synthesized by the Japp–Klingemann reaction (from β-keto-acids or β-keto-esters and aryl diazonium salts). N,N'-dialkyl type of hydrazones can be hydrolysed, reduced and oxidised, this leads to formation of amines by reduction of N-N bond. The carbon atom of the C=N bond can react with organometallic nucleophiles. The alpha-hydrogen atom of hydrazones is more nucleophilic as compared to ketones because alpha-hydrogen atom of hydrazones is 10 times more acidic than ketones[1,2].

Hydrazones are mainly synthesized by refluxing the appropriate quantity of substituted hydrazines/hydrazides with ketones and aldehydes in appropriate solvents like tetrahydrofuran, butanol, methanol, glacial acetic acid, ethanol, ethanol-glacial acetic acid etc. Hydrazones can also be synthesized by using coupling of aryldiazonium salts with active hydrogen compounds[3].

Hydrazones compounds are not only intermediates but they are also very effective organic compounds. They can be used as intermediates to synthesize coupling products by using the active hydrogen of –CONHN=CH- azomethine group. Various effective compounds for example: iproniazide and isocarboxazide. They are synthesized by reduction of hydrazide-hydrazones. Iproniazide just like isoniazide is used as antitubercular drug[4].



Iproniazide



Isocarboxazide

The most significant reactivity of hydrazones is the nucleophilicity of hydrazone carbon atom. This was noted since more than hundred years. Thus reactions like Mannich reaction, coupling reaction and halogenations have took place readily at such carbon. Recently Michael type addition was also described. Hydrazone nitrogen atom however remains the main site for attack by acylating and alkylating agents. It seemed that hard nucleophiles attack preferentially nitrogen atom, while soft ones attack preferentially at carbon atom. The functional substituents retain their established reactivity pattern although generally become more electrophilic. Also multidentate reagents in several cases afford rings involving hydrazone moiety. In addition a variety of intramolecular cyclizations leading to cinnolines have been reported. This review showed diverse hydrazones with antimicrobial activity[5,6].

Antimicrobial Activity of Hydrazone

The fast resistance of bacteria against antibiotics has become a widespread medical problem. Treatment options for these infections are often limited, especially in debilitated and immune compromised patients. The dramatically rising incidence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists.

Paola Vicini et al synthesized a few hydrazones of 1,2-benzisothiazole hydrazides and evaluated their antimicrobial activity against Gram positive bacteria *Bacillus subtilis, Staphylococcus aureus* in comparision to ampicillin as reference standard. Compounds **(1a)** and **(1d)** proved to be the most effective against *B. subtilis*; these compounds in combination with **(1b)** were the only ones also active against Gram negative bacteria (*Escherichia coli*). They reported that benzisothiazolones show antifungal properties against *Saccharomyces cerevisiae* and *Candida tropicalis*. Compounds **(1a), (1b), (1d)** and **(1e)** were also active against *Aspergillus niger* **(Fig. 1)**[7].

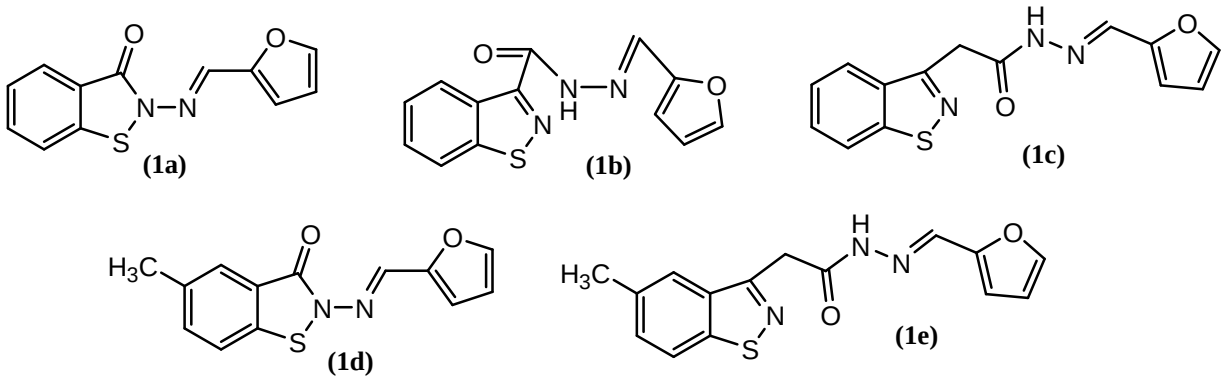


Fig. 1. Hydrazones of 1,2-benzisothiazole hydrazides

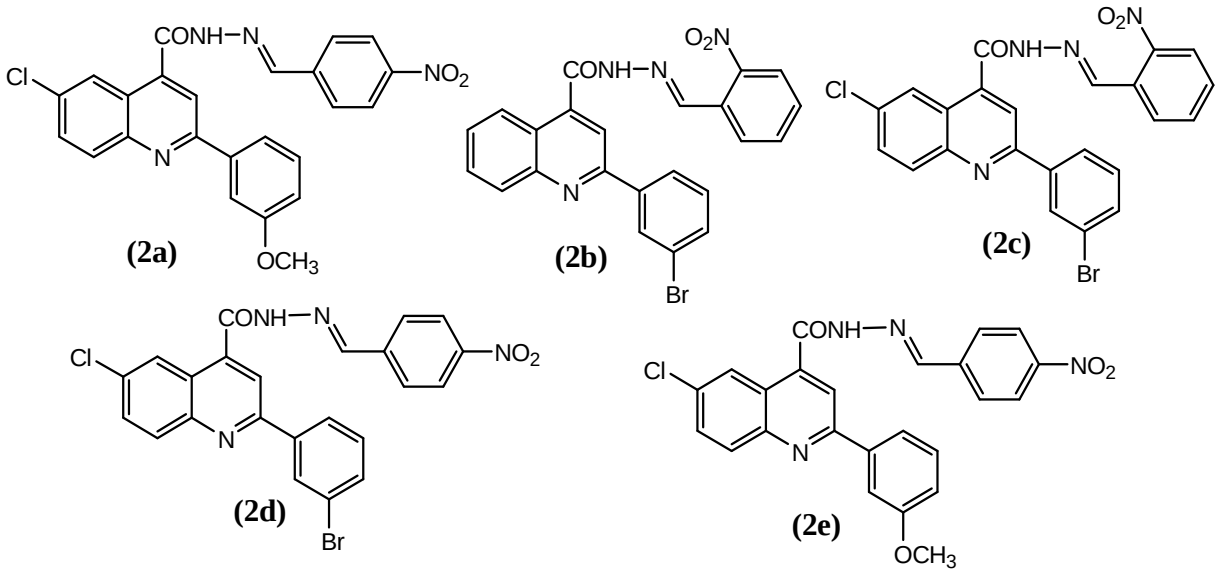
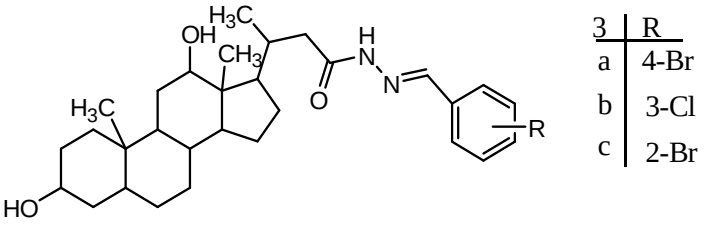


Fig. 2. Hydrazones of 2-aryl-quinoline-4-carboxylic acid

Kamel A. Metwally et al synthesized hydrazones of 2-aryl-quinoline-4-carboxylic acid hydrazides and evaluated for antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Compound **(2a)** displayed an antifungal activity comparable to that of nystatin. The most potent compounds were **(2b), (2c), (2d)** and **(2e) (Fig. 2)**[8].

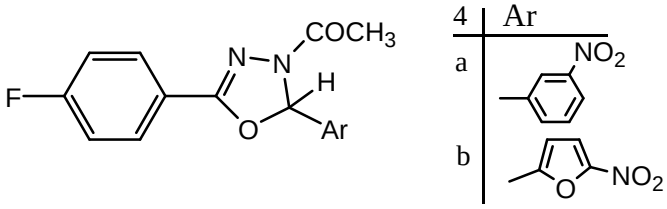
Raed A. Al-Qawasmeh et al synthesized cholic acid hydrazone analogues and evaluated for their antimicrobial activity against *Staphylococcus aureus, E. faecalis* and *Bacillus megaterium, E. coli, Pseudomonas aeruginosa* and *Enterobacter aerogenes*. Most compounds showed stronger antimicrobial activity than cefaclor and cefixime. Compounds **(3a), (3b)** and **(3c)** indicated 15 fold stronger antimicrobial activities against *Enterobacter faecalis* **(Fig. 3)**[9].

Sevim Rollas et al synthesized some new hydrazones of 4-fluorobenzoic acid hydrazide and evaluated their antimicrobial activity against *S. aureus*, *E. coli*, *P. aeruginosa* and *C. albicans.* Compound **(4a)** having m-nitrophenyl was more active than the corresponding p-nitrophenyl derivative. The most active compound was **(4b)** having 5-nitro-2-furanyl moiety **(Fig. 4)**[10].



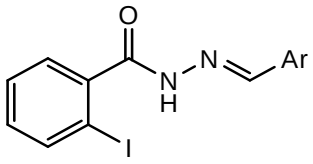
3	R
a	4-Br
b	3-Cl
c	2-Br

Fig. 3. Hydrazones of cholic acid



4	Ar
a	NO_2
b	NO_2

Fig. 4. Hydrazones of 4-fluorobenzoic acid hydrazide



5	Ar
a	Cinnamaldehyde
b	Furan
c	o-Hydroxyphenyl
d	p-Hydroxyphenyl

Fig. 5. Hydrazones of 2-iodobenzoic acid

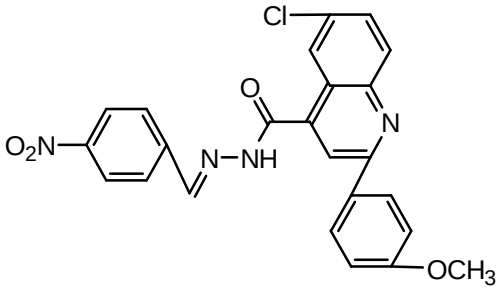


Fig. 6. Hydrazones of 2-arylquinoline-4-carboxylic acid

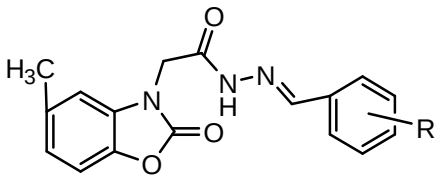
Harer Sunil L. et al synthesized some 2-iodo-N'-[(1E)-substitutedphenylmethylidene] benzohydrazide analogues and evaluated their antibacterial activity against different strains of bacteria were used as *Bacillus subtili*, *Staphylococcus aureus*, *Kleibsella pneumoniae*, and *Pseudomonas aeruginosa* using by norfloxacin as reference drug. The antifungal activity was evaluated against *Aspergillus niger*, *Candida albicans* by using griseofulvin as reference drug. Compounds **(5a-5d) (Fig. 5)** were highly significant against tested pathogenic microorganism[11].

Metwally et al synthesized a new series of 2-arylquinoline-4-carboxylic acid hydrazide-hydrazones and evaluated their *in-vitro* antimicrobial activity against *Staphylococcus aureus*,

Escherichia coli and *Candida albicans*. Out of the synthesized compounds 6-chloro-2- (4-methoxyphenyl)quinoline-4-carboxylic acid (4-nitrobenzylidene)hydrazide **(Fig. 6)** was found to be most potent[12].

Nesrin Gokhan-Kelekci et al synthesized arylidene hydrazides as cis–trans conformers by treatment of acetic acid hydrazide containing 5-methyl-2-benzoxazolinone with aldehyde and ketones. The compounds were evaluated for their antimicrobial activities. It is worth mentioning that compounds **(7a-7c) (Fig. 7)** showed moderate inhibitory activities against *Candida krusei, Candida albicans* and *Candida parapsilosis*[13].

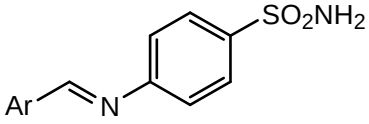
S. Guniz Kucukguzel et al synthesized diflunisal hydrazide- hydrazones and evaluated their biological activity. Compound **(8a) (Fig. 8)** found to have activity against *Staphylococcus epidermis* and *Staphylococcus aureus*. Compound **(8b) (Fig. 8)** found to be more active against *Acinetobacter calcoaceticus* as compared to cefepime used as standard[14].



7	R
a	H
b	-CH_3
c	-OCH_3

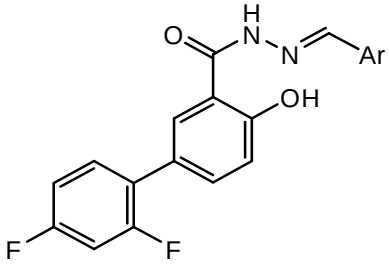
Fig. 7. Hydrazones of 5-methyl-2-benzoxazolinone

Santosh Kumar synthesized Schiff bases of sulfonamides and evaluated their antimicrobial activity against bacteria and fungi namely *B. subtilis, S. aureus, E. coli, S. typhi* and *C. albicans, A. niger*. Among these Schiff bases of sulphanilamide, compound bearing trimethoxy group **(9a)**, methoxy group **(9b)** and furan ring **(9c)** has shown good activity against all the tested bacteria and fungi **(Fig. 9)**[15].



9	Ar
a	3,4,5-Trimethoxyphenyl
b	4-Methoxyphenyl
c	3-Nitrophenyl

Fig. 9. Schiff bases of sulfonamide



8	Ar
a	5-nitro-2-furyl
b	2,4,6-trimethylphenyl

Fig. 8. Diflunisal hydrazide/hydrazones

N.G. Kandile et al synthesized hydrazones from 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene]hydrazines and diacetyl. They screened synthesized products for their antimicrobial activity against *Staphylococcus aureus* and *Streptococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The hydrazone derivative (1-[4-(2-methoxybenzyl)-6-methylphenyl pyridazin-3(2*H*)-ylidene]hydrazine **(Fig. 10)** showed the highest biological activity[16].

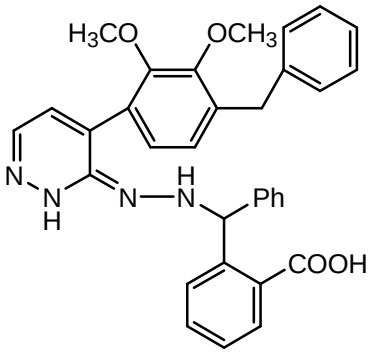


Fig. 10. Hydrazones of 1-[4-(2-methoxybenzyl) -6-arylpyridazin-3(2H)-ylidene] hydrazines

Balasubramanian Narasimhan et al synthesized benzylidene/2-chlorobenzylidene hydrazides and evaluated them for *in-vitro* antibacterial, antifungal and antiviral activities. Their study showed that compounds having chloro and nitro substituents were the most active ones. The results revealed that the most active compound was 4-fluoro-benzoic acid [2-(1-nitro-vinylsulfanyl)-allylidene]hydrazide **(Fig. 11)** having bactericidal activity against *B. subtilis* and *E. coli* respectively[17].

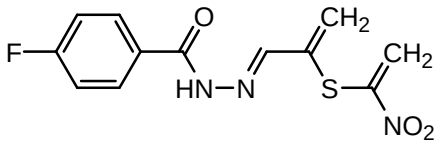


Fig. 11. 4-Fluoro-benzoic acid [2-(1-nitro-vinylsulfanyl)-allylidene]-hydrazide

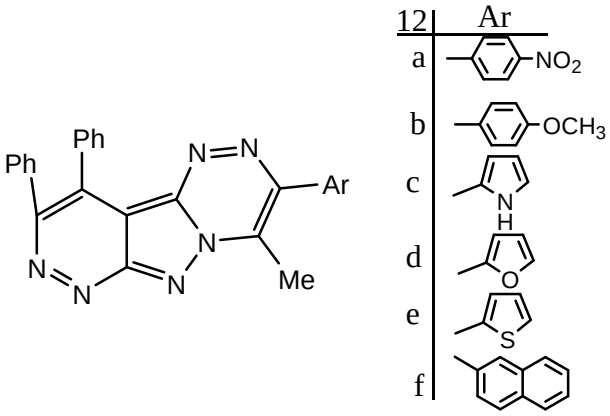
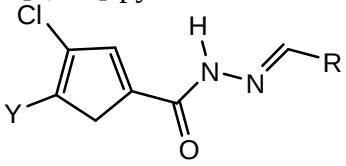


Fig. 12. Hydrazones of 3-diazo-4,5-diphenyl pyrazolo[3,4-d]-pyridazine



Y= Cl/H
R= mono/di/tri- substituted aryl/alkyl

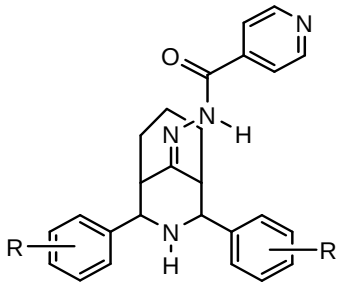
Fig. 13. Hydrazones of 1H-pyrrole-2-carbo hydrazide

Ali Deeb et al synthesized hydrazones from treatment of carbohydrazide with aromatic aldehyde. They synthesized carbohydrazide from treatment of 3-diazo-4,5-diphenylpyrazolo[3,4-d]-pyridazine with ethyl aceto-acetate and hydrazine hydrate . They evaluated their *in-vitro* antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and also antifungal activity against *Candida albicans*. Compounds **(12a-12f) (Fig. 12)** found to have maximum antimicrobial activity[18].

Vikas N. Telvekar et al synthesized chloropyrrole molecules designed by molecular hybridization of common pharmacophores as potential antimicrobial agents. Based on biological activity evaluation data, it was observed that activity increases as the number of chlorines on pyrrole core increases. The 1H-pyrrole-2-carbohydrazide showed good activity equivalent to standard drug ciprofloxacin **(Fig. 13)**. Thus, these compounds can act as potential lead for further antibacterial studies[19].

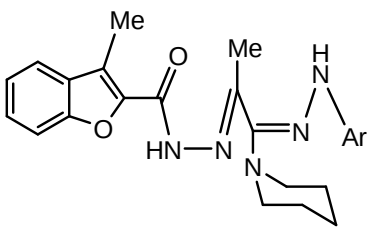
K. Pandiarajan et al synthesized some 2r,4c-diaryl-3-azabicyclo[3.3.1]nonan-9-one-N-isonicotinoylhydrazone derivatives and evaluated their antimicrobial activity. They found that some compounds have significant antibacterial and antifungal activity. Though all the compounds showed good antimicrobial activity but **(14a-14d) (Fig. 14)** exhibited activity against all the tested (bacterial and fungal) microorganisms[20].

Hatem A. Abdel-Aziz et al synthesized benzofuran-based (1E)-1-(piperidin-1-yl)-N^2-arylamidrazones and evaluated their antimicrobial activity against clinically isolated strains of human fungal pathogens and exhibited a significant potency against Gram-positive bacteria by using griseofulvin and amoxicillin as references for antifungal and antibacterial screening. It was reported that the compounds **(15a-15c) (Fig. 15)** showed good antimicrobial activity against clinically isolated strains of human fungal pathogens and exhibited a significant potency against Gram-positive bacteria. The effect of most potent antifungal compound **(15c)** was against *Aspergillus fumigatus* and *Candida albicans*[21].

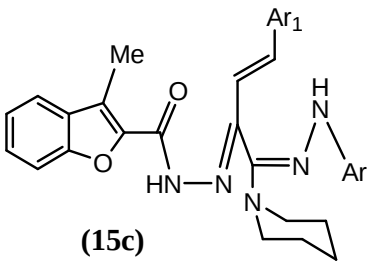


14	R
a	4-Cl
b	4-F
c	3-OCH_3
d	3-Cl

Fig. 14. N-isonicotinoyl based hydrazone



(15a, 15b)

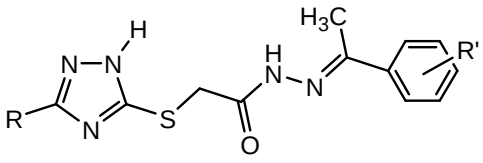


(15c)

15	Ar	Ar_1
a	$-C_6H_5$	-
b	4-NO_2-C_6H_4	-
c	4-Br-C_6H_4	4-Cl-C_6H_4

Fig. 15. Benzofuran-based (1E)-1-(piperidin-1-yl)-N-arylamidrazones

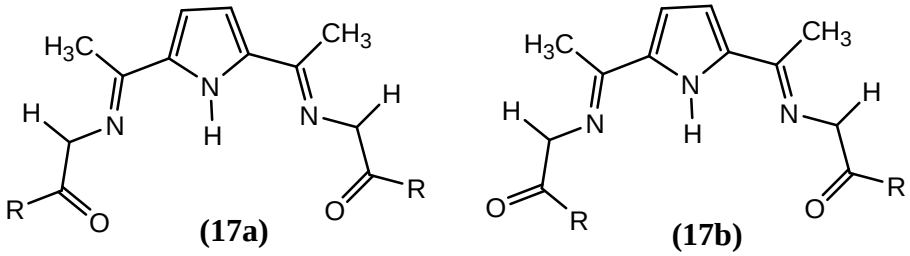
Seyhan Ersan et al synthesized N-[(α-methyl) benzylidene]-(3-substituted-1,2,4-triazol-5-yl-thio)acetohydrazides and evaluated for antimicrobial activity against Gram (+) and Gram (-) bacteria. They showed moderate activity against *Candida* species. The highest activities were reported by compounds **(16a-16d) (Fig. 16)**, all carrying a Cl or NO_2 group on the benzylidene moiety[22].



16	R	R'
a	H	4-NO_2
b	-CH_3	4-NO_2
c	-C_2H_5	4-Cl
d	-C_2H_5	4-NO_2

Fig. 16. Hydrazones of N-[(1-methyl) benzylidene]-(3-substituted-1,2,4-triazol-5-yl-thio) acetohydrazides

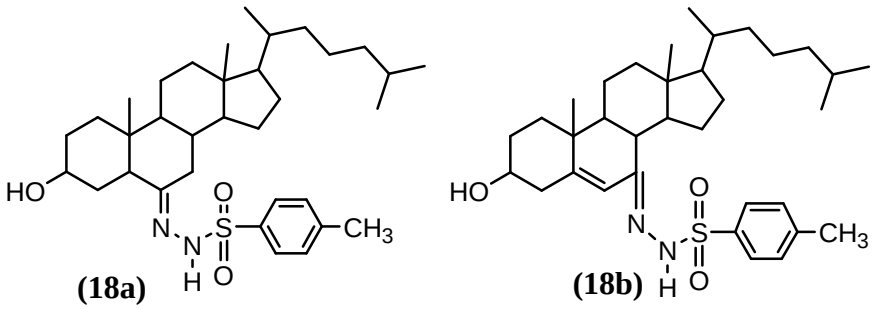
F. Zaniet al synthesized organotin complexes with pyrrole-2,5-dicarboxaldehyde bis(acylhydrazones) and evaluated their antimicrobial activity and genotoxicity against Gram positive and Gram negative bacteria. It was reported that for the preparation of all the complexes to an ethanol solution of SnR_2Cl_2 (R.C_2H_5, n-C_4H_9, $C_6H_5CH_2$, C_6H_5) an equimolar amount of the hydrazone was added and refluxed. Complexes of type **(17a)** and **(17b)** were synthesized **(Fig. 17)** and found to have high activity[23].



(17a) **(17b)**

Fig. 17. Organotin complexes with pyrrole-2,5-dicarboxaldehyde bis(acylhydrazones)

Jean Michel Brunel et al synthesized cholesterol-hydrazone derivatives and evaluated them for antifungal activity against *Candida albicans.* The activity was highly dependent on the structure of the different compounds involved. The best results were reported with tosylhydrazone cholesterol derivatives **(18a)** and **(18b) (Fig. 18)** exhibiting activities against *Candida albicans*[24].



(18a) **(18b)**

Fig. 18. Hydrazones of cholesterol

P. Kumar et al synthesized substituted benzoic acid benzylidene/furan-2-yl-methylene hydrazides and evaluated their antimicrobial activities against *B. subtilis, S. aureus* and *Candida albicans.* The results of antimicrobial study indicated that the presence of electron withdrawing

groups on the benzoic acid moiety improved antimicrobial activity. They reported that the presence of heterocyclic ring furan contribute nothing to the antimicrobial activity of substituted hydrazides. This was evidenced by the high antimicrobial activity of compounds **(19a-19c) (Fig. 19)** which has two electron donating groups in comparison to other compounds i.e. their presence increases the branching of the molecule as well as increases the electron density and makes them to be the most effective ones against the organisms under test[25].

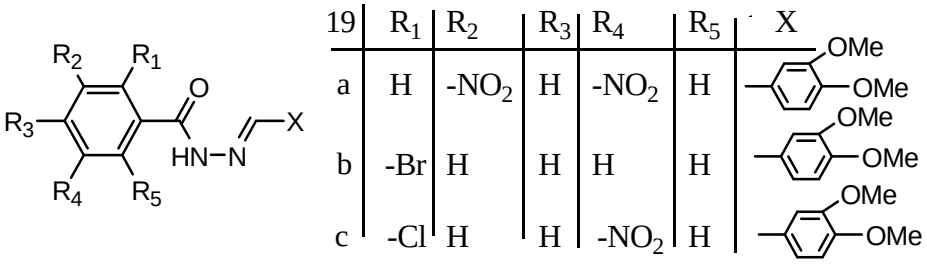


Fig. 19. Hydrazones of substituted benzoic acid

Luisa Savini et al synthesized new α-(N)-heterocyclic hydrazones and evaluated their anticancer, anti-HIV and antimicrobial activity. They evaluated their antimicrobial activity against *Staphylococcus epidermidis*, *Bacillus cereus* (bacterial strains), *Saccharomyces cerevisiae*, *Candida albicans* (yeasts) and *Aspergillus fumigates* (fungus). The most active compound was found to be containing 4-methyl-2-quinolyl heterocyclic moiety **(Fig. 20)**[26].

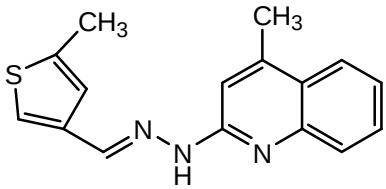


Fig. 20. N-(4-Methyl-quinolin-2-yl)-N'-(5-methyl -thiophen-3-ylmethylene)-hydrazine

Katarina K. Andelkovic et al synthesized Ni(II) and Zn(II) complexes with N',N'2-bis[(1E)-1-(2-pyridyl)ethylidene]propanedihydrazide and evaluated their antimicrobial activity against *Staphylococcus aureus*, *Micrococcus lysodeikticus*, *Bacillus subtilis* and Gram negative bacteia *Escherichia coli*. The most active compound was found to have general structure shown in **(Fig. 21)**[27].

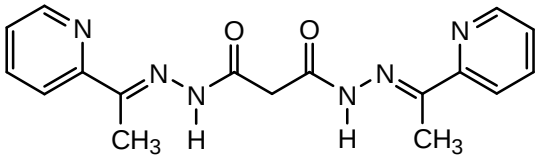
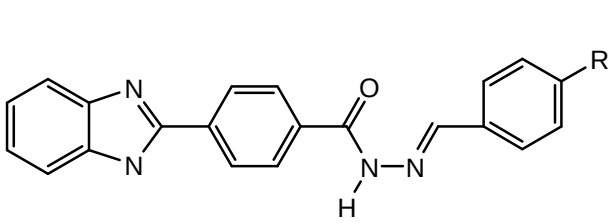


Fig. 21. N',N'2-bis[(1E)-1-(2-pyridyl) ethylidene]propanedihydrazide

Yusuf Ozkay et al synthesized benzimidazole derivatives bearing hydrazone moiety and evaluated their antimicrobial activity. Most of the reported compounds found to be significantly effective against *Proteus vulgaris*, *Staphylococcus typhimurium*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The compounds **(22a-22e)** and the compound **(22g)** were more potent

than chloramphenicol (reference) against *P. vulgaris* and *P. aeruginosa* respectively **(Fig. 22)**. The compounds **(22a)**, **(22d)** and **(22g)** were found to be as active as ketaconazole against *C. albicans* and *C. tropicalis* respectively[28].



22	R
a	H
b	-OH
c	$-N(CH_3)_2$
d	-Cl
e	-Br
f	$-CH_3$
g	$-OCH_3$

Fig. 22. Hydrazones of benzimidazole

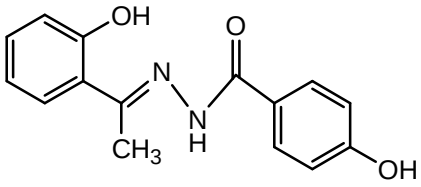
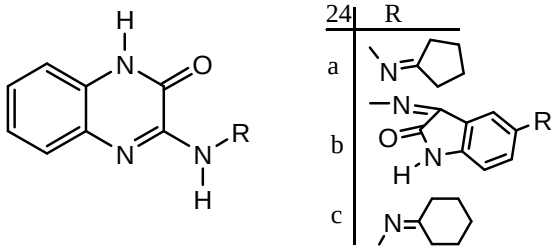


Fig. 23. Hydrazone of 2- hydroxyl acetophenone 4-hydroxybenzoic acid

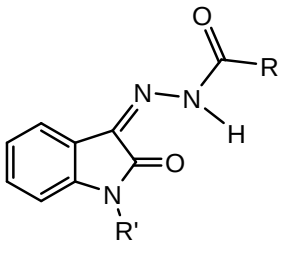
M.R. Prathapachandra Kurup et al synthesized copper(II) ternary complexes of 2-hydroxyl acetophenone-4-hydroxybenzoic acid hydrazone and evaluated for their antimicrobial activity against Gram positive microorganism *Staphylococcus aureus*, *Bacillus subtilis* and Gram negative bacteria *E. coli*, *Salmonella paratyphi*, *Vibrio cholerae* etc. General structure of these hydrazone was given in **(Fig. 23)**[29].

Olayinka O. Ajani et al synthesized 2-quinoxalinone-3-hydrazone derivatives and evaluated their antimicrobial activity against multi-drug resistance microorganisms such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus faecium* and *Scedosporium apiospernum.* The compounds **(24a-24d) (Fig. 24)** were found to be more potent as compared to reference drug[30].



24	R
a	
b	
c	

Fig. 24. 2-Quinoxalinone-3-hydrazone



25	R	R'
a	H	
b	H	
c	$-CH_3$	

Fig. 25. Acylhydrazones of 3-isatin and 3-(N-methyl) isatin

Maria C. Rodriguez-Arguelles et al synthesized metal(II) complexes of acylhydrazones of 3-isatin and 3-(N-methyl)isatin and determined their antibacterial and antifungal activity. Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of 2-thiophenecarbonyl hydrazone of 3-isatin **(25a)**, 2-furoic hydrazones of 3-isatin **(25b)** and 3-(N-methyl)isatin **(25c)** were synthesized **(Fig. 25)**. Antimicrobial activity of the free ligands and their complexes were reported against a panel of Gram positive and Gram negative bacteria, yeasts and moulds. Among the tested microorganisms *Haemophilus influenzae* was the most sensitive strain, especially to **(25a)** and its complexes[31].

P. Mazza et al synthesized organotin compounds with 2,6-diacetylpyridine nicotinoyl and isonicotinoyl hydrazones and evaluated their antimicrobial activity **(Fig. 26)**. The main feature reported was the presence of a tin atom in both the complex ionic units. The coordination polyhedron was reported to be a pentagonal bipyramid in the cation and a trigonal bipyramid in the anion. It was reported that among the organotin compounds diethyl derivative shows antibacterial activity but no antifungal activity. In contrast the phenyl derivatives possess antimicrobial activity against both bacteria and fungi. As reported in the literature triphenyl derivatives are more active than the diphenyl compounds against Gram positive bacteria and fungi. Triphenyl derivatives were inactive against *E. coli*[32].

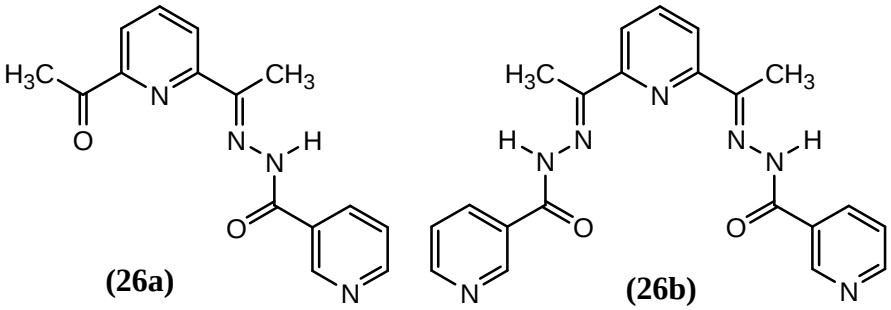


Fig. 26. Hydrzone of 2,6-diacetylpyridine nicotinoyl and isonicotinoyl

P. R. Athappan et al synthesized mixed ligand complexes of cobalt(III) phenanthroline/bipyridyl and benzoylhydrazones and evaluated their antimicrobial activity. Cobalt(III) complexes of the type $[Co(N\text{-}N)_2L](ClO_4)_2$. H_2O [where L = anionic form of para-substituted benzaldehyde–benzoylhydrazone ($BHBX^-$); X = H, Me, OMe, OH, Cl or NO_2; N-N-2,20-bipyridine (bpy) or 1,10-phenanthroline (phen)] were reported **(Fig. 27)**. These complexes are also found to have good antimicrobial activity[33].

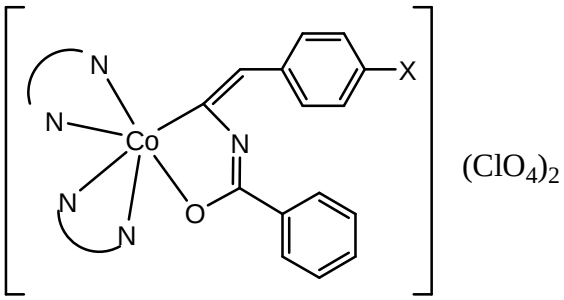


Fig. 27. Complex of cobalt(III) phenanthroline/bipyridyl and benzoylhydrazones

M. Carcelli et al synthesized 2,6-diacetylpyridine-bis(acylhydrazone) **(28a-28e) (Fig. 28)** and their complexes with some first transition metal ions. Antimicrobial activity of hydrazones and metal complexes was reported against various Gram positive and Gram negative bacteria's. The X-ray crystal structure of $[Cu(dapt)_2]$ complexes was also investigated and it was reported that it consists of two dimeric units in which both copper atoms have six-fold co-ordination **(Fig. 28)**.

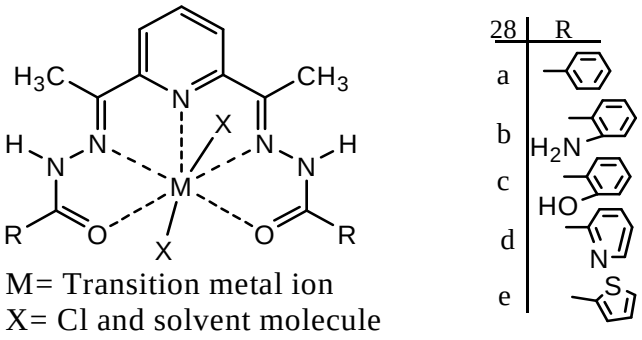


Fig. 28. Complex of 2,6-diacetylpyridine-bis(acylhydrazone)

Literature showed that complexes have similar or reduced activity as compared to hydrazone ligand itself. Only iron complexes were found to be more active than chelating agent itself[34]. G. Bergamascbi et al synthesized organotin complexes with pyrrole-2-carboxaldehyde monoacylhydrazones and evaluated their antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus, Escherichia coli* and *Aspergillus niger*.

A series of organotin complexes with pyrrole-2-carboxaldehyde-2-hydroxybenzoylbydrazone and pyrrole-2-carboxaldehyde-2-picolinoylhydrazone were investigated **(Fig. 29)**. It was found that complexes exhibit antibacterial properties higher than those of the corresponding ligands but they turn out to be less potent than the parent organotin compounds[35].

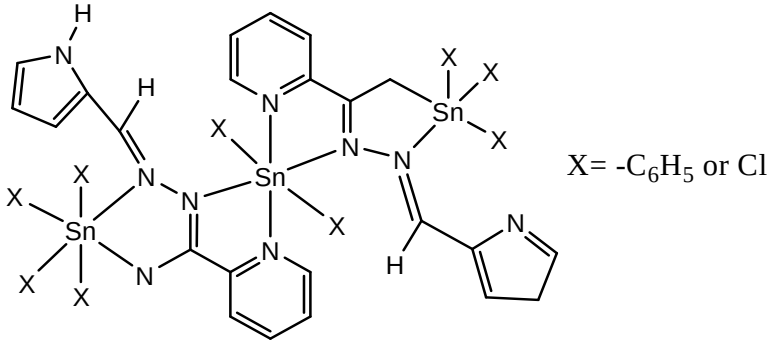
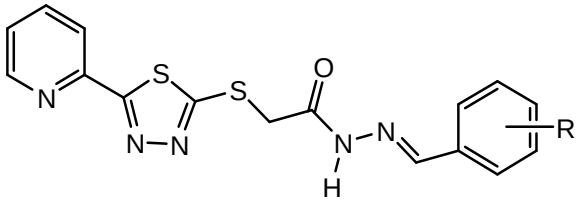


Fig. 29. Organotin complexes of pyrrole-2-carboxaldehydemonoacylhydrazones

Maria Grazia Mamolo et al synthesized [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid arylidene-hydrazide derivatives and evaluated their antimicrobial activity against *Mycobacterium tuberculosis, Mycobacterium avium, Staphylococcus aureus, Escherichia coli* and two strains of *Candida albicans.* Only compounds **(30a)**, **(30b)**, **(30c)**, **(30e)** and **(30f)** exhibited a moderate *in-vitro* antimycobacterial activity against the tested strain of *Mycobacterium tuberculosis* **(Fig. 30)**. Compounds **(30c)**, **(30d)**, **(30g)** and **(30h) (Fig. 30)** found to be moderately active against *Mycobacterium avium*[36].

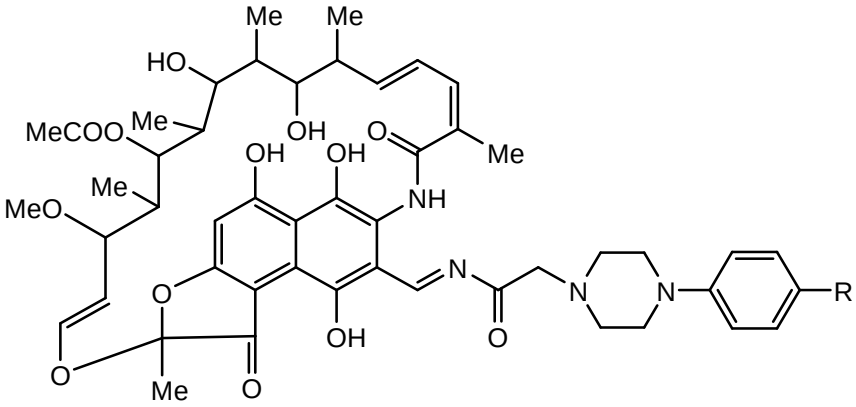


30	R	30	R
a	4-Cl	e	3-F
b	2-Br	f	2,6-Dichloro
c	4-Br	g	2,4-Dimethyl
d	2-F	h	3-Methoxy

Fig. 30. Hydrazones of [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid

David K. Yung et al synthesized 3-formylrifamycin-N- (4-substituted phenyl) piperazinoacetyl hydrazones **(31a-31n) (Fig. 31)** and evaluated their antimicrobial activity against *Bacillus subtilis, Staphylococcus aureus* and *Mycobacterium tuberculosis* but not as active as rifampin.

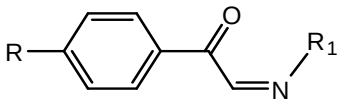
E. It was reported that some compounds were more active than rifampin. Also it was reported that the activity was dependent upon the electronic and steric effects of the phenyl substituents[37].



31	R	31	R
a	H	h	$-NO_2$
b	Me	i	$-CF_3$
c	Et	j	-F
d	i-Pr	k	-Cl
e	t-Bu	l	-Br
f	OMe	m	-CN
g	OPh	n	-NHCOMe

Fig. 31. 3-Formylrifamycin-N- (4-substitutedphenyl)piperazinoacetyl hydrazones

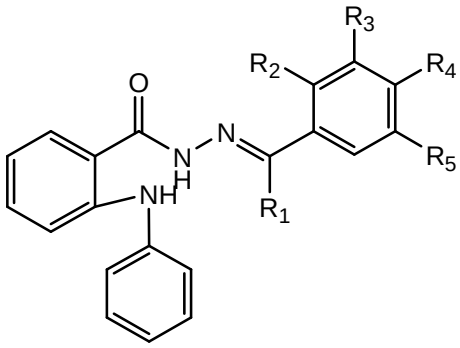
Massarani et al synthesized arylglyoxal N,N-disubstituted hydrazone and evaluated their antifungal activity against *Candida albicans* and *Trichophyton mentagrophytes.* No compound found to have measurable activity against *Candida albicans* but some compounds **(32a-32f)** were found to be effective against *Trichophyton mentagrophytes* **(Fig. 32)**[38].



32	R	R"
a	-Cl	$-N(CH_3)_2$
b	C_6H_5O	$-N(CH_3)_2$
c	-Cl	$-N(CH_3)_2$
d	$-NO_2$	$-N(CH_3)_2$
e	$-C_6H_5$	$-N(CH_3)_2$
f	C_6H_5O	N-piperidine

Fig. 32. Arylglyoxal-N,N-disubstituted hydrazone

Bharat Parashar et al synthesized some novel N-arylhydrazone derivatives of N-phenyl anthranilic acid and evaluated their antimicrobial activity. A series of N-arylhydrazone derivatives **(33a-33j) (Fig. 33)** were reported from N-phenyl anthranilic acid[39].

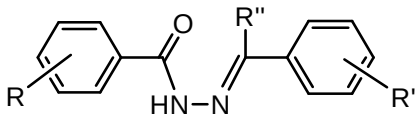


33	R_1	R_2	R	R_4	R_5
a	H	H	H	H	H
b	H	OH	H	H	H
c	H	H	H	OH	H
d	H	H	OMe	OH	H
e	H	Br	OH	OMe	H
f	H	H	OH	OMe	H
g	H	H	H	Cl	H
h	H	H	H	$N(Me)_2$	H
i	H	OH	$C(Me)_3$	H	$C(Me)_3$
j	Me	H	H	H	H

Fig. 33. N-Arylhydrazone derivatives of N-phenyl anthranilic acid

Rajput A. P. et al synthesized benzaldehyde substituted phenyl carbonyl hydrazones and their formylation using Vilsmeier-Haack reaction. The compounds were evaluated for antimicrobial activity against bacterial strains *Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium.* It was reported that the compounds **(34a)** and **(34b) (Fig. 34)** were active against *P. vulgaris* and other compounds were found inactive against *P. vulgaris, S. aureus* and *S. typhimurium*. Compounds **(34c), (34d)** and **(34e) (Fig. 34)** were reported to have significant activity against *S. aureus* whereas **(34d)** was found to be active against *E. coli* **(Fig. 34)**[40].

Singh U. K. et al synthesized Schiff's and N-Mannich bases of isatin and its derivatives with 4-amino-N-carbamimidoylbenzene sulfonamide. They screened these compounds for antibacterial activity against Gram positive and Gram negative bacterial strains by comparing with 4-amino-N-carbamimidoylbenzene sulfonamide as reference compound. It was reported that all compounds have very significant and better antibacterial activity in comparison to the standard drug. The most active compound against all Gram positive and Gram negative bacterial strains was compound **(35) (Fig. 35)**. It was found that substitution by Cl atom at 5-position produced most active antibacterial compound of the series[41].



33	R	R'	R''
a	4-OH	H	H
b	H	H	H
c	4-Cl	$4-OCH_3$	H
d	4-Cl	4-OH	-CHO
e	4-Cl	H	-CHO
f	4-Cl	$4-OCH_3$	-CHO

Fig. 34. Benzaldehyde substituted phenyl carbonyl hydrazones

Umesh K. Singh et al synthesized some sulfonamide Schiff's bases. The derivatives were subjected to antimicrobial activity using different bacterial strains with respect to ciprofloxacin as standard antibiotics. It has been reported that all compounds have good to moderate antibacterial activity, but compounds **(36a), (36b)** and **(36c)** have very significant results against *S. epidermidis* **(Fig. 36)**[42].

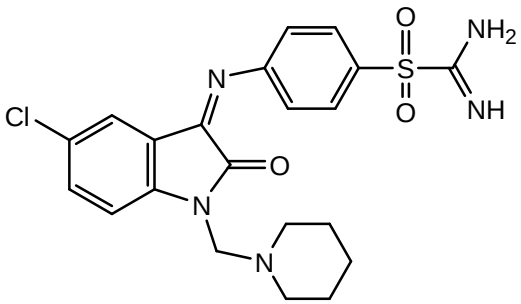
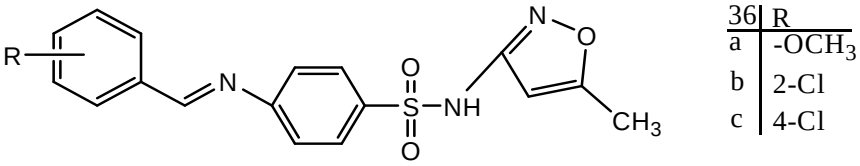
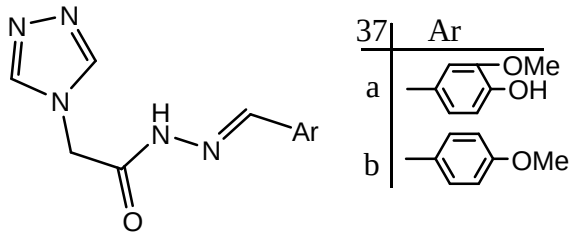


Fig. 35. Hydrazone of Schiff's and N-Mannich bases of isatin



36	R
a	-OCH_3
b	2-Cl
c	4-Cl

Fig. 36. Sulfonamide Schiff's bases



37	Ar
a	OMe, OH
b	OMe

Fig. 37. Triazole based Schiff's bases

R. R. Somani et al synthesized some newer triazole based Schiff's bases. The targeted compounds were subjected to antibacterial activity test against pathogenic bacteria. Two compounds **(37a)** and **(37b)** found to have promising antibacterial activity as compared to other analogues **(Fig. 37)**[43].

Perumal Panneerselvam et al synthesized some novel Schiff's bases of 5-subsituted isatin and evaluated their antibacterial activity. Most of the synthesized compounds exhibited significant antibacterial and antifungal activities. 5-Fluoro-(4-(4-nitrobenzylideneamino)-phenylimino) indolin-2-one **(38)** was found to exhibit the most potent *in-vitro* antimicrobial activity **(Fig. 38)**[44].

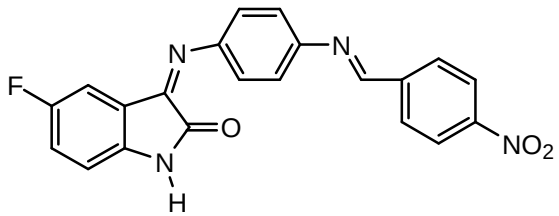
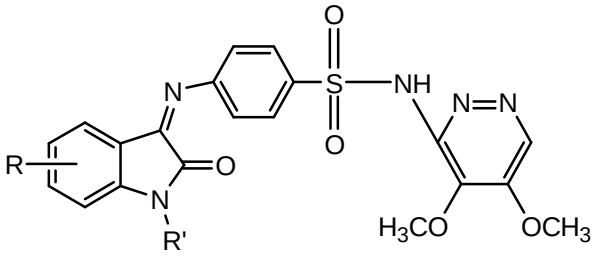


Fig. 38. 5-Fluoro-3-{4-[(4-nitro-benzylidene)-amino]-phenylimino}-1,3-dihydro-indol-2-one

Umesh K. Singh et al synthesized Schiff's and Mannich bases of 1H-indole-2,3-dione derivatives and evaluated their antimicrobial activity in comparision to reference drug sulfadoxine.

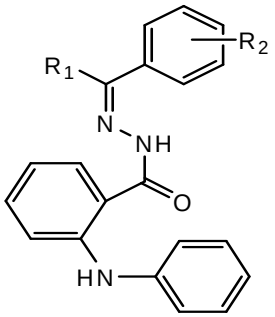
It was found that both Schiff's **(39a, 39b)** and Mannich bases **(39c, 39d)** were active but Schiff bases showed better antibacterial activity than Mannich bases. Substitution by CH_3 and Cl at 5 position produced maximum activity against Gram negative strain *E. coli* **(Fig. 39)**[45].



39	R	R'
a	$-CH_3$	H
b	Cl	H

Fig. 39. Schiff's and Mannich bases of 1H-Indole-2,3-dione derivatives

Bharat Parashar et al synthesized some N-aryl hydrazones by microwave synthesis. It was found that the presence of fluoro, chloro or nitro groups in the moiety enhances its antibacterial activity. However, the degree of inhibition varied both with the test compound as well as with the bacterial species. Compounds **(40a), (40b), (40c), (40d), (40e)** and **(40f)** found to have significant activity against *S. aboni*, *S. aureus* and *P. aeruginosa* **(Fig. 40)**[46].



40	R_1	R_2
a	H	H
b	H	3-OH
c	H	$3-NO_2$
d	H	$4-NO_2$
e	H	-Cl
f	$-CH_3$	$4-CH_3$

Fig.40. N-aryl hydrazones

Ananad S. Aswar et al synthesized some chelate polymers of poly-Schiff base ligand **(41)**. They study biological activity of the ligand and its chelate polymers by screening them against various microorganisms. It was reported that ligand and its all polychelates showed considerable antimicrobial activity against all test organisms used in the study **(Fig. 41)**[47].

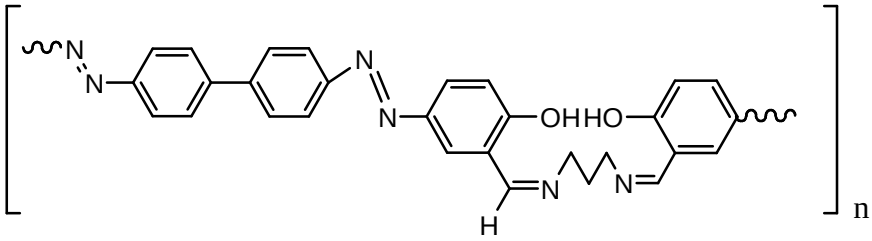


Fig. 41. Chelate polymers of poly-Schiff base ligand

P. Sudhir Kumar et al synthesized Schiff and Mannich bases of isatin derivatives with 4-amino-4,5-dihydro-1H-1,2,4-triazole-5-ones **(42)**. The synthesized compounds were evaluated for their possible biological activities. All compound having considerable biological activity **(Fig. 42)**[48].

Chhajed S.S. et al synthesized some novel Schiff and Mannich bases of isatin and its derivatives with quinoline. They evaluated their antibacterial activity against various Gram positive and Gram negative bacteria and anti fungal activity against various fungal stains compared with standard drug (sulphamethoxazole and ketoconazole). It was reported that all compounds showed moderate to good activity out of which compound **(43a)** and **(43b)** showed maximum activity **(Fig. 43)**[49].

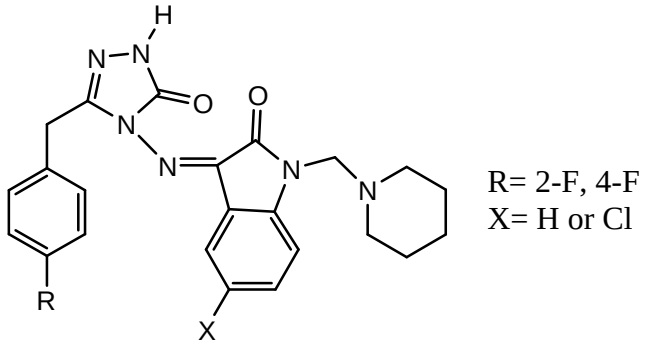


Fig. 42. Schiff and Mannich bases of isatin derivatives

Marıa C. Rodrıguez-Arguelles et al synthesized complexes of 2-thiophenecarbonyl and isonicotinoyl hydrazones of 3-(N-methyl) isatin and evaluated their antimicrobial activity against several bacteria and fungi. It was found that the drug and its complexes exhibited good antibacterial properties towards *Bacillus subtilis*. The antibacterial activity was confirmed against various Gram positive bacteria, including methicillin-resistant *Staphylococcus aureus*. Yeasts and moulds found to have low susceptibility. Therefore by their study it was found that the antimicrobial activity of the thiophene derivatives was greater than that of the isonicotinic analogues[50].

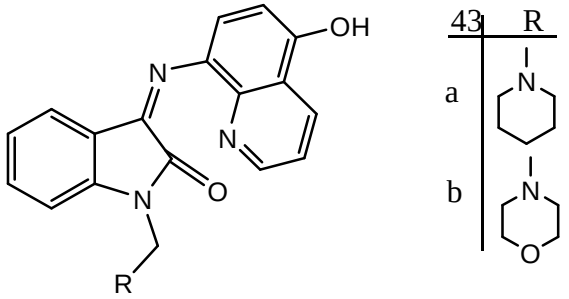


Fig. 43. Schiff and Mannich bases of isatin and its derivatives with quinoline

CONCLUSION

In the literature studies we found that a large number of series of substituted hydrazide-hydrazone derivatives were synthesized for their *in-vitro* antimicrobial activities against wide variety of microorganisms. The results of these studies indicated that the presence of electron withdrawing groups on the aromatic ring improves antimicrobial activity and the presence of both electron withdrawing and donating groups leads to specified changes in the antimicrobial activity. Further, in case of metal complex studies it was found that complexes has DNA binding and cleavage properties and were more active towards a recombination deficient bacterial strain, indicating the cell inhibitory effect. All these findings support the need for further investigations to clarify the features underlying the various biological activities of these new hydrazone derivatives.

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