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Review Article

BIOLOGICAL ACTIVITIES OF HYDRAZONES: A REVIEW

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ABSTRACT

Hydrazone derivatives of carbonyl compounds constitute an important class of biologically active compounds. Literature studies on hydrazones have shown that these derivatives possess a wide variety of biological activities such as antitumor, anti-bacterial, antiviral, antihypertensive, anticonvulsant, anti-Inflammatory and analgesic activities, vasorelaxant activity, and anticoagulant activity and anti protozoal activities etc. During literature survey it was found that no single review is available solely on the biological activities of hydrazones. The present review provides a compendium of different biological activities possessed by hydrazones.

Keywords: Biological activities, Hydrazones

INTRODUCTION

Hydrazones constitute an important class of biologically active drug molecules[1] which has attracted attention of medicinal chemists due to their wide range of pharmacological properties. These compounds are being synthesized as drugs by many researchers in order to combat diseases with minimal toxicity and maximal effects. These predictions has provided therapeutic pathway to develop new effective biologically active hydrazones.

A number of hydrazone derivatives have been reported to exert notably antimicrobial, antihypertensive, anticonvulsant, analgesic, anti-inflammatory, antituberculosis, antitumoral, antiproliferative and antimalarial activities[2]. Biological activities of various hydrazones are well reported in literature. This review highlights diverse pharmacological activities shown by hydrazones.

Antimicrobial activity

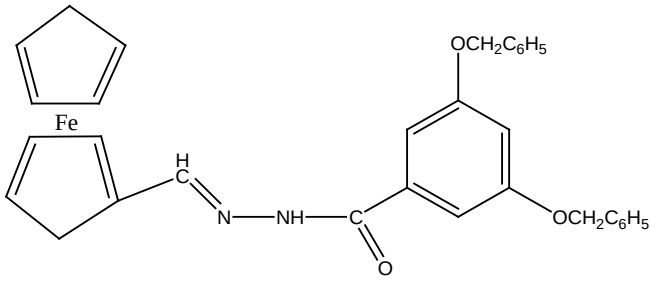
In an urge to develop new antimicrobial compound, a number of hydrazones were tested for their antimicrobial activities because of the evolution of drug-resistant microbial pathogens.

Some derivatives of flavanol hydrazones were synthesized and screened for their *in vitro* anti-bacterial activity against 25 strains of Gram –ve and Gram +ve pathogenic bacteria. The synthesized compounds demonstrated inhibitory effect (MIC< 392 µg/ml) against few pathogenic bacterial strains. These hydrazones possessed activity against methicillin-resistant *Staphylococcus aureus* strain may be due to the presence of carbonyl region and hydroxyl group[3].

A series of quinoxaline derivatives was synthesized and evaluated for their antimicrobial activity. The compounds which were bearing highly electronegative chloro and fluoro substituents at the para position of phenyl ring exhibited good activity as compared to those compounds having these atoms at either ortho or meta position or the other compounds containing the less electronegative/ electropositive substituent at these positions[4].

Thirty new hydrazones of 1-phenyl, 1-benzyl and 1-benzhydryl - 4 - amino piperazines were tested for antibacterial activities against *E.coli, Staphylococcus aureas, B. subtilis* and antifungal activities against *Candida albicans* and *Saccharomyces cerevisiae*. Among thirty hydrazones, 1- benzhydryl- 4 - isonicotinylidene amino piperazine showed a broad spectrum of activity[5].

A new chelating ligand, (1-formylferrocene)-3,5-dibenzyloxybenzoyl hydrazone (HL) **1a** and three transition metal complexes,ML2 [M *5* Cu(II), Ni(II), Zn(II)] were synthesized by Lin *et. al.*[6]. They evaluated antibacterial activities of the compounds. Preliminary studies indicated that the ligand and its three complexes were active against *S. aureus*, but were unefffective against *E. coli*.

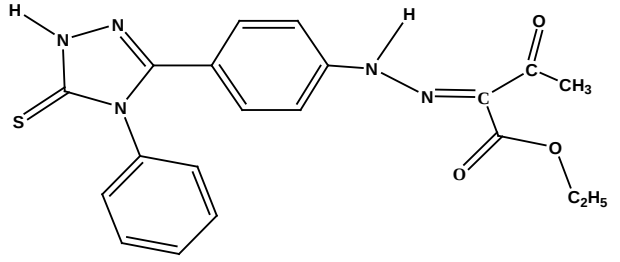


1a

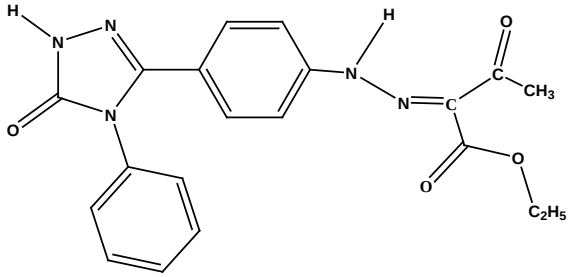
Some N-(1-benzyl-2-phenylethylidene)-N′-[4-(aryl) thiazol-2-yl] hydrazone and N-(1-phenylbutylidene)-N′-[4-(aryl) thiazol-2-yl] hydrazone derivatives were synthesized and evaluated for antifungal activity. Their antifungal activities against standard and clinical strands of *Candida albicans*, *Candida glabrata*, *Candida utilis*, *Candida tropicalis*, *Candida krusei*, *Candida zeylanoides*, and *Candida parapsilosis* were observed and were found to be significant[7].

2-pyrimidinylhydrazones have been developed that are poisonous to fungi that may prove to be potent fungicides. These compounds showed considerable activity *in vitro* and *in vivo* against plant pathogenic fungi as well as some phytotoxicity to the host plant. 2-pyrimidinylhydrazones having steric congestion in the vicinity of the hydrazone bond as well as alkyl substituent(s) on the pyrimidine ring have high fungicidal activity. Results revealed that both 2-pyrimidinyl hydrazine moiety and hydrazone bond are essential for fungicidal activity[8].

Ethyl 2-arylhydrazono-3-oxobutyrates were synthesized in order to determine their antimicrobial properties. Compound **2a** showed good activity against *S. aureus* whereas the others had no remarkable activity on this strain. Compound **2b** was found to be more active than the other compounds against *Mycobacterium fortuitum* at a MIC value of 32µg/mL[9].

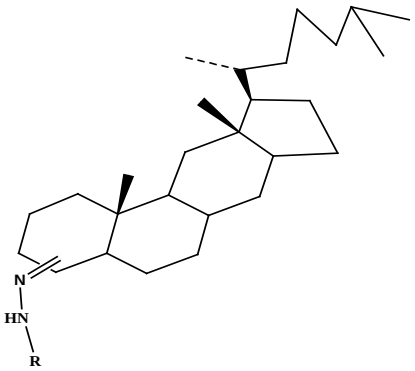


2a



2b

A series of hydrazones **3** synthesized from various cholesterol derivatives were screened for their *in vitro* antimicrobial properties against human pathogens. The tosylhydrazone cholesterol derivatives exhibited significant activities against *C. albicans* (CIP 1663-80) at a concentration of 1.5 µg/mL. The antimicrobial activity was highly dependent on the structure of the different compounds involved[10].

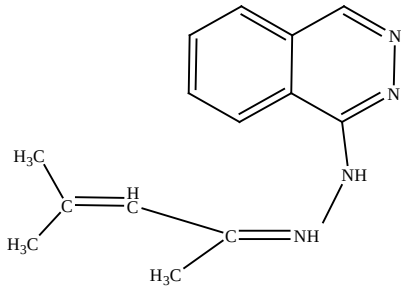


3

A series of 2-chloro-6-methylquinoline hydrazones were synthesized by the reaction of substituted acylhydrazines, semicarbazide, thiosemicarbazide, and Isoniazid Hydrazide (INH) with 2-chloro-3-formyl-6-methylquinoline in ethanol. These hydrazones were tested for antimicrobial activity. It was elucidated that maximum antibacterial activity was exhibited by compounds bearing the 4-fluoro-, 4-chloro-, 4-nitro-, and 2, 4-dicloro- group in the benzoyl ring[11].

Antihypertensive activity

M. Minami *et.al.*[12] elucidated the effects of a new vasodilating antihypertensive drug, budralazine **4,** mesityl oxide -1- phthalazinyl hydrazone on drinking behavior of water and humoral factors including plasma norepinephrine (NE), angiotensin II (A II), arginine vasopressin (AVP), serotonin (5-HT) concentrations, urinary aldosterone and catecholamine excretion rates in rats. The results suggested that budralazine is active on renin angiotensin aldosterone system in comparison to sympathetic nervous system.



Budralazine

Mesityl oxide -1- phthalazinyl hydrazone

4

Anticonvulsant activity

Epilepsy is most common neurological disorder, second to stroke. The number of drugs useful for the treatment of epilepsy is remarkably small. New epileptic drugs have been developed that may constitute novel and effective therapies for epilepsies.

It was found that both 2- oxobenzoxazoline and 2-oxobenzothiazoline hydrazone derivatives exhibited remarkable anticonvulsant activity[13]. 5 - chloro - 2(3H) - benzoxazolinone - 3 - acetyl - 2 - (o-methoxybenzaldehyde) - hydrazone, 5 - chloro - 2(3H) - benzoxazolinone - 3 - acetyl - 2 - (o-methybenzaldehyde) - hydrazone, 5 - chloro - 2(3H) - benzoxazolinone - 3 - acetyl - 2 - (p - methylbenzaldehyde) - hydrazone, 5 - chloro - 2(3H) - benzoxazolinone - 3 - acetyl - 2 - (p - nitrobenzaldehyde) - hydrazone, and 5 - chloro - 2(3H) - benzoxazolinone - 3 - acetyl - 2 - (p - dimethylaminobenzaldehyde) - hydrazone were significantly active than phenytoin (a commercial antiepileptic drug) in the tests.

The hydrazones along with hydrazines, semicarbazones and thiosemicarbazones which are derived from pyridyl ketones have been found to be nonneurotoxic antiepileptic drugs and are potent orally active. Their use has been proposed in the treatment of convulsive disorders such as epilepsy, in the treatment of stroke and other neurological disorders such as Parkinson's disease[14]. They act as excitatory amino acid antagonists and inhibitors of L-glutamate neurotransmission. These compounds afford protection in the maximal electroshock seizure (MES) model in both mice and rats, by either route, intraperitoneal and oral. The study represents them as glutamate antagonists.

Hydrazones in addition to Schiff and Mannich bases of isatin were evaluated for anticonvulsant activity by maximal electroshock method (MES) and metrazol-induced convulsions (MET) at different dose levels[15]. Neurotoxicity of the compounds was also noticed at the same dose levels. Eight compounds of the series denoted significant anticonvulsant activity at 30 mg/kg dose level. 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one showed to be the most potent compound of the series with 87% protection at 100 mg/kg and an ED(50) of 53.61 mg/kg (MET).

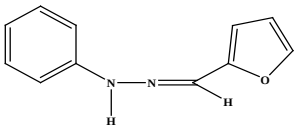
Anti-Inflammatory and Analgesic activity

Non-steroidal anti-inflammatory drugs (NSAIDS) are largely used in the treatment of pain and inflammation. Hydrazones that are dual inhibitors of both cyclooxygenase (COX) and 5-lipooxygenase (5-LO) are being studied as potential analgesic and anti-inflammatory agents in comparison to NSAIDS[16].

Fifteen different isatin [N-(2-alkylbenzoxazole-5-carbonyl)] hydrazones were synthesized and screened for analgesic, antidepressant and H1-antihistaminic activities[17]. These compounds were also studied for their effect on pentobarbitone - induced narcosis. Results revealed that three compounds bearing a methyl substituent at 7 - position of the benzoxazole system exhibits good analgesic activity, in relation to standard.

Schiff bases and phenyl hydrazone of isatins, synthesized by reacting isatin and the appropriate aromatic primary amine / hydrazines were screened for analgesic, antiinflammatory and antipyretic activity[18]. 1 - Diphenylaminomethyl - 3 - (1 - naphthylimino) -1,3 - dihydroindol - 3 - one, 3 - (1 - naphthylimino) - 5 - bromo - 1,3 - dihydroindol - 2 - one and 1 - diphenylaminomethyl - 3 - (4 - methylphenylimino) - 1,3 - dihydroindol - 3 - one exhibited the highest analgesic, anti-inflammatory and antipyretic activity respectively.

Few 6 - substituted - 3(2H) - pyridazinone - 2 - acetyl - 2 - (*p* - substituted benzal) hydrazone derivatives were synthesized as analgesic and anti-inflammatory agents. None of the compounds was found to show gastric ulcerogenic effect in comparison with reference nonsteroidal anti-inflammatory drugs (NSAIDs)[19].



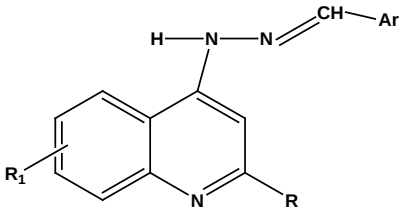
5

2-(2-formylfuryl) pyridylhydrazone, **6** possessed anti-inflammatory activity and showed a 79 % inhibition of pleurisy at a dose of 80.1µmol/kg. The results indicated that this compound was able to complex Ca^{2+} in *in vitro* experiments at 100 µM concentrations, indicating that these series of compounds can act as Ca^{2+} scavenger and result in platelet aggregation[20].

Antituberculosis activity

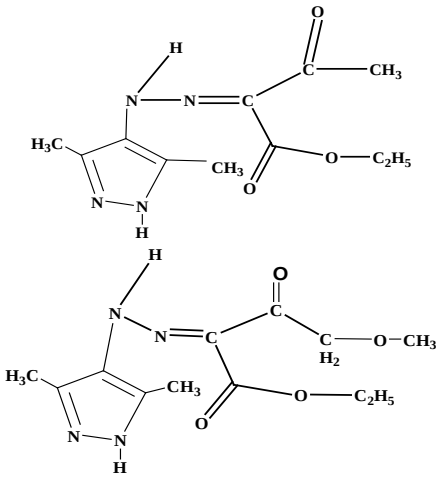
Tuberculosis (TB) is the leading single-agent infectious disease killer in the world. The major challenges for tuberculosis control are the development of multidrug-resistant tuberculosis (MDRTB) strains. As a result, there is a pressing need for new antitubercular agents acting with greater potency and efficacy than the current existing drugs[21].

Savini *et.al.*[22] synthesized a series of 4-quinolylhydrazones **6** which were tested against *M. tuberculosis* H37Rv. Most of the derivatives exhibited antitubercular properties. Two compounds were identified with the highest activity.



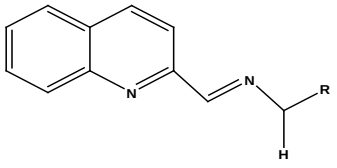
6

The Synthesized hydrazones of ethyl 2 - [(3, 5 - dimethylpyrazole - 4 - yl) hydrazono] - 3 – oxobutyrate, **7a and** methyl 2 - [(3,5 - dimethylpyrazole - 4 - yl) hydrazono] - 4 - methoxy - 3 –oxobutyrate, **7b** showed 29 and 28% inhibition against *M. tuberculosis* H37Rv, respectively[23].

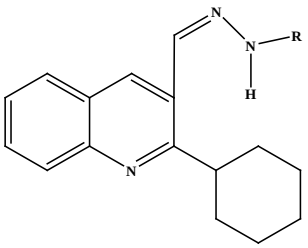


7a **7b**

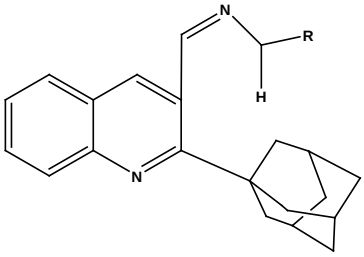
Nayyar *et. al.*[24] observed that *N* - (2 -fluorophenyl) - *N*′ - quinoline - 2 - yl -methylenehydrazine **8a**, *N* - (2 - adamantan - 1 - yl) - *N*′ - quinoline - 4 - yl - methylene) - N′ - 4 - fluorophenyl) hydrazine **8b** and *N* - (2 -cyclohexyl) - *N*′ - quinoline - 4 - yl - methylene) - (2 - fluorophenyl) hydrazine **8c** were the most active compounds against drug-sensitive *M. tuberculosis* H37 strain. These compounds exhibited 99% inhibition at the lowest tested concentration of 3.125µg/mL.



8a

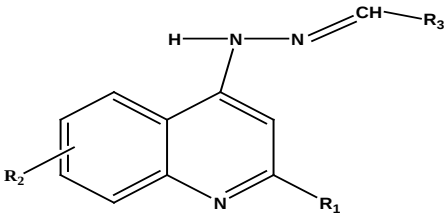


8b



8c

A series of 4-quinolyl hydrazones **9** were synthesized and screened *in-vitro* for antitubercular activity against *Mycobacterium tuberculosis*. Most of the compounds showed 100% inhibitory activity against *M. tuberculosis* at a concentration of 6.25µg/mL in cellular assays. These compounds were identified as potent antitubercular agents[25].

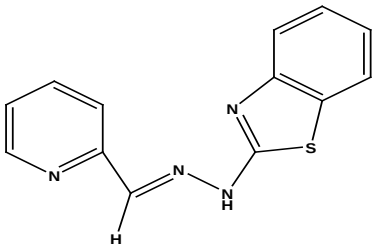


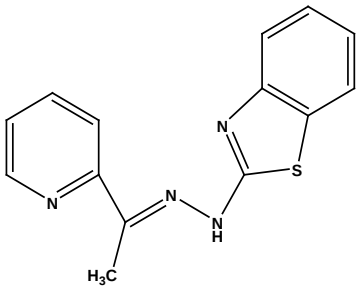
9

A series of hydrazone and 3-nitrovinyl analogs of indole-3-carboxaldehydes and related compounds were synthesized. These compounds were screened for antitubercular activity against *Mycobacterium tuberculosis H37R (V)* in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA). Several compounds showed inhibitory activity against *M. tuberculosis* in primary screening assays at a concentration 6.25 µg/mL[26].

Antitumor activity

The search for antitumor drugs has led to the discovery of several hydrazones having antitumor activities. Novel 2-benzimidazolyl-, 2-benzoxazolyl- and 2-benzothiazolyl hydrazones **10** are synthesized from 2-formylpyridine, 2-acylpyridines, acetyldiazines and acetyl(iso)quinolines These compounds exhibited potent cytotoxic and antitumor activities and are also useful against multidrug-resistant cancer cells. The antiproliferative activity of the compounds has been tested in various tumor cell lines[27].

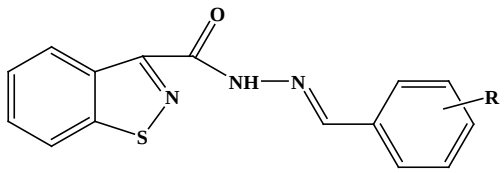




2-benzothiazolyl hydrazones

10

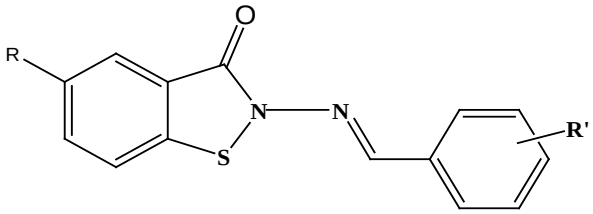
Several benzo[d] isothiazole hydrazones were screened for their potential antiretroviral activity. The compounds showed to be cytotoxic for MT-4 cells. New derivatives which were rationally designed and synthesized were tested for antiproliferative activity against several leukaemia and solid tumour cell lines. Compound **11** showed to be the most active compound and the segment -CO-NH-N=CH-2-C_6H_4 (OH)-proved to be very important for biological activity. The result suggested that there was intramolecular hydrogen bond formation or favorable mutual disposition between two important centers in the pharmacophore[28].



R= 2- OH

11

P. Viccini et. al.[29] synthesized new analogues of benzisothiazole hydrazones **12** . Target compounds were tested in MT-4 cells cultures for their anti-HIV activities against wild type HIV-1. HIV strains carrying clinically relevant mutations (EFVR, Y181C and K103/Y181C) showed good activity against wild type HIV-1 and against the EFV^R mutant. The benzo[d] isothiazol-3(2H)-one moiety is an essential structural requirement for the antiretroviral activity. Compounds 1a and1c showed good activity against HIV-1 wild type, while compounds 1a, 1b, 1d,1e, 1f, 4a, 4b, 4c and 4d showed good activity against the EFV^R mutant.



1a-1f, R=H

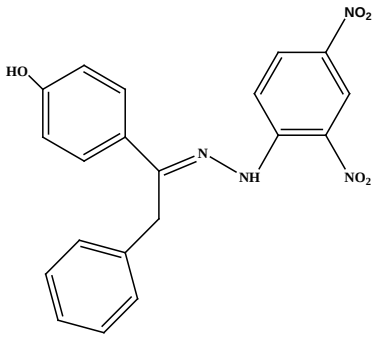
1	R'
a	H
b	3-F
c	4-F
d	4-Cl
e	2-OH
f	4-OH

4a-4d, R=CH_3

4	R'
a	4-F
b	4-Cl
c	3-NO_2
d	3-OH

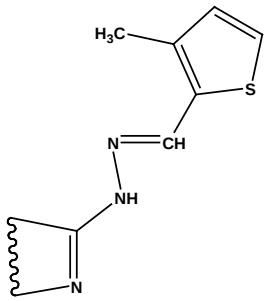
12

Some diphenolic hydrazones exhibited 70% uterotrophic inhibition, whereas compound **13** exhibited cytotoxicity in the range of 50-70% against MCF-7 and ZR-75-1 human malignant breast cell lines[30].

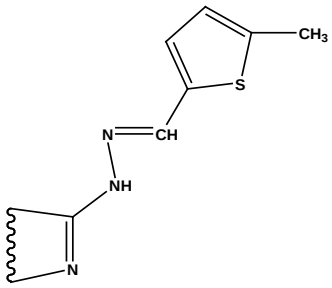


13

Some recently synthesized 3 - and 5 - methylthiophene-2-carboxaldehyde α - (*N*) - heterocyclic hydrazone **(14 a, 14 b)** derivatives were the most active compound of the series. These compounds were found to possess antiproliferative properties and exhibited tumor growth inhibition activity against all cell lines at GI50 values between 1.63 and 26.5 mM[31].



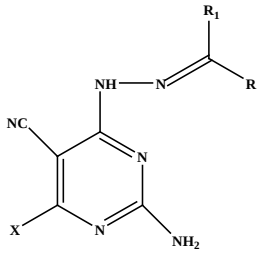
14a



14b

A series of novel ribavirin hydrazone derivatives were synthesized by reacting ribavirin hydrazine with benzaldehyde or acetophenone derivatives in *A549* cells. These compounds were screened for antitumor activity. One compound was found to be active at 20 μM[32].

Hydrazinopyrimidine derivatives **15** were synthesized and evaluated for their *in vitro* antitumor activity. These compounds were tested in nine different types of human cancers. Some of the newly synthesized compounds demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5} M to 10^{-7} M concentrations[33].



15

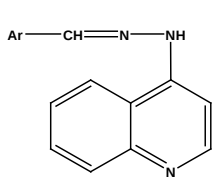
Antimalarial activity

Malaria is a major health problem in poverty-striken regions where new antiparasitic drugs are required at an affordable price. Malaria is caused by parasitic protozoa of the genus *plasmodium*. There is a need of intensive search for compounds having antimalarial activity against multi-drug resistant *plasmodium falciparum*.

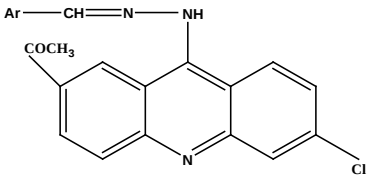
A. Walcourt *et.al*.[34] investigated antimalarial activity of novel aroyl hydrazone and thiosemicarbazone Fe chelators. These compounds inhibited the growth of tumor cell lines in cell culture [Blood 100(2002)666] suggesting them to be highly active. The most effective chelators examined were 2 - hydroxy - 1 - napthaldehyde - 4 - phenyl -3 - thiosemicarbazone.

A series of quinolylhydrazones were synthesized and their antimalarial activity was evaluated against the chloroquine-sensitive strain of *Plasmodium falciparum*. One of the compounds displayed an activity 6 fold higher than chloroquine (CQ) and none of the active compound was found to inhibit β - hematin formation *in vitro* in the same range as chloroquine[35].

A series of *N*1-arylidene - *N*2 - quinolyl and *N*2 - acrydinylhydrazones (**16a, 16b**) were synthesized and tested for their antimalarial properties. The synthesized compounds showed an antiplasmodial activity against the chloroquine-sensitive D10 strain in the same range of chloroquine (CQ)[36].



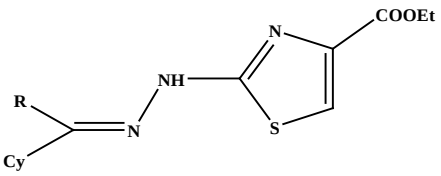
16 a



16 b

Antitoxoplasma activity

A new series of 4-acyl-2-thiazolylhydrazone derivatives **17** was synthesized and screened for its *in vitro* activity against *Toxoplasma gondii*. Parasite growth inhibition and cytotoxicity, inhibition of replication, and inhibition of parasite invasion of host cells was also observed. The biological results indicated that some substances showed antitoxoplasmic effect against intracellular *T. gondii* tachyzoites cultivated *in* vitro[37].



17

Vasorelaxant activity

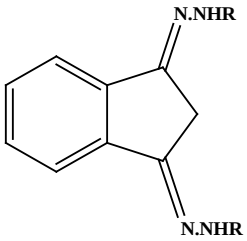
Zhao *et. al*. [38] synthesized series of twenty benzopyran - 4 - one hydrazone derivatives, N - aminoacetyl - (6 - cyano - 3,4 - dihydrospiro [2H - 1 - benzopyran - 2,1'-cyclohexane] - 4) - one hydrazone , 2 - (6 - cyano - 3, 4 - dihydro - 2H - 1 - benzopyran - 4 - ylene) hydrazinethiocarboxamide derivatives and N - (2 - arylethyl) aminoacetyl - (6 - cyano -3,4 - dihydro - 2H - 1 - benzopyran) - 4 - one hydrazone were tested for their vasorelaxant activity in low (30 mmol.L-1) and high (80 mmol.L-1) KCl-induced contraction of rat aorta in order to search potential potassium channel openers *in vitro*. The results indicated that some compounds showed vasorelaxant activities at micromolar concentrations.

Antiviral activity

Novel hydrazones of lupane and 19 - β - 28 - epoxy - 18 - α - oleanane type were synthesized via interaction of 2, 3 - secotriterpenic aldehydonitriles with substituted hydrazines. Acetylhydrazone of 1 - cyano - 2, 3 - seco - 19 - β - 28 - epoxy – 18 - α - olean - 3 - al exhibited a high prophylactic activity 0.00016 μg/ml to vesicular stomatitis virus and inhibited a virus reproduction in primarily infected cells in 0.21 μg/mL concentration[39].

Anticoagulant activity

Various hydrazones and carbazones **18** were synthesized by condensation of hydrazines and carbazides with Indane -1, 3- dione. All the synthesized compounds have been evaluated for their anticoagulant activity. Both the compounds showed significant activities[40].



R = H, C_6H_5, $CONH_2$, $CSNH_2$

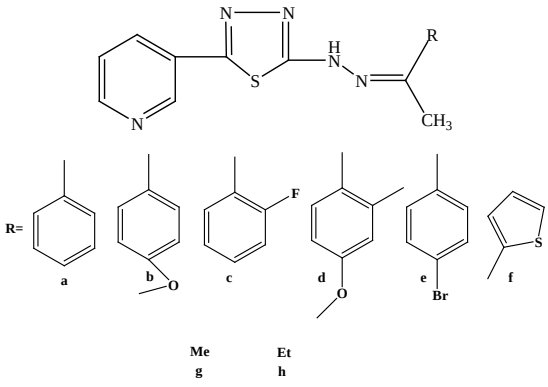
18

Antileishmanicidal activity

New hydrazones of thiophene carboxaldehydes were tested against three *Leishmania* strains. Leishmanicidal activity was assessed against promastigotes of *Leishmania* strains grown *in vitro* in nutrient broth medium. The minimum inhibitory concentrations were evaluated against pentamidine, as a reference drug. Several compounds exhibited significant leishmanicidal activity; only one compound was ten times more active than pentamidine[41].

Antioxidant activity

K.J. Prathap *et. al*. [42] synthesized a new series of Ketone 1-(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-hydrazone derivatives (**19a-19h**) by the condensation of 1-(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl) hydrazine with substituted and unsubstituted ketones. They evaluated their antioxidant property by using 1, 1-diphenyl-2-picrylhydrazil (DPPH) method. All the compounds demontrated good antioxidant activity due to the presence of (–NH–N=) moiety attached to aryl and heteroaryl nuclei thereby, stabilizing the free radical.



19

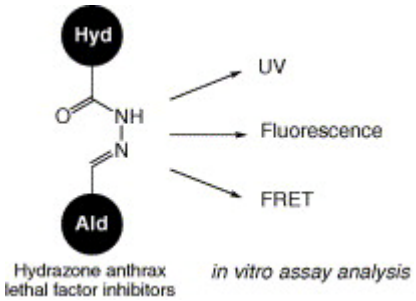
Other activities

The hydrazones are used as hole transporting agents in organic layer photo conductors, as quantitative analytical reagents, especially in colorimetric and fluorimetric determination of metal ions[43-45]. Furthermore, some hydrazones have also been used as herbicides, insecticides, nematocides, rodenticides, and plant growth regulators[44] as well as plasticizers and stabilizers for polymers[46-47]. The metal complexes of hydrazones have potential applications as catalysts[48], luminescent probes[49] and molecular sensors[50].

Hydrazones as enzyme inhibitors

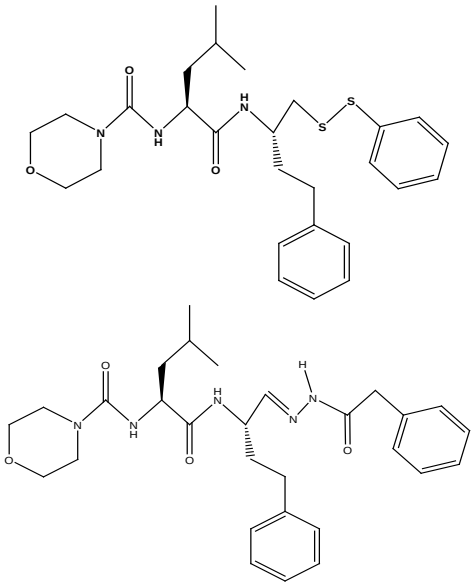
A class of N - arylsulfonyl hydrazones has been developed as novel inhibitors of IMP-1, a *metallo-β-lactamase*. Structure-activity relationship studies suggested that there is a requirement for bulky aromatic substituents on each side of the sulfonyl hydrazone backbone so that these compounds may serve as efficient inhibitors of IMP-1. Molecular modeling has provided structural basis for the anti-metallo-β-lactamase activity shown by this class of compounds[51].

A series of hydrazones **20** were evaluated as potential inhibitors of anthrax lethal factor. The hydrazones were screened for their activity using one UV-based and two fluorescence-based *in vitro* assays. The study indicated that several inhibitors with IC_{50} values occur in the micromolar range. There were significant differences in the types of inhibition observed with the different assays[52].



20

Kinetic analysis of the dipeptidyl disulfides and dipeptidyl benzoylhydrazones (2**1a, 21b**) indicated that these inhibitors act as irreversible inhibitors of Cathepsin S. The benzoylhydrazones were shown to be potent inhibitors of Cathepsin S processing of Class II associated invariant peptide both *in vitro* and *in vivo*[53].



21a **21b**

Hydrazones and phenyl hydrazones of different aryl aldehydes were synthesized and their effect on endogenous proteolysis in liver was studied. It was observed that *p* - nitro benzaldehyde hydrazone exhibited maximum inhibitory effect[54-55].

N. Raghav *et.al.*[56-57] evaluated the effect of hydrazones and phenyl hydrazones of simple aryl aldehydes along with their semicarbazones and thiosemicarbazones on the activity of liver alkaline and acid phosphatase.

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