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HYDRAZIDE DERIVATIVES AND ITS BIOLOGICAL POTENTIAL-A REVIEW

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ABSTRACT

In the present review we are discussing the importance of different hydrazide derivatives for tuberculosis and other disease conditions. Hydrazides are the compounds which can be mainly synthesised by the reaction between acids and hyrazines. Also they can be synthesised from chalcones. Due to the functional group similarity with the well established antitubercular drug isoniazid, most of the hydrazide and its derivatives show activity against *Mycobacterium tuberculosis.* Hyrazides and its derivatives also possess various biological activities such as antibacterial, fungicidal, anticonvulsant, antimalarial, antitumor etc. The article aims the review of recent developments in the synthesis and biological potentials of hydrazide derivatives.

Keywords: Hydrazides, Antimycobacterial, Antibacterial, Antifungal.

INTRODUCTION

Hydrazides constitute an important class of biologically active organic compounds and their therapeutic use due to R-CO-$NHNH_2$ is well documented in the literature. Hydrazides and their condensation products are reported to possess wide range of biological activities including antibacterial, tuberculostatic properties, HIV inhibitors and antifungal [1]. Hydrazines and their derivatives constitute an important class of compounds that has found wide utility in organic synthesis. In recent years the N-N linkage has been used as a key structural motif in various bioactive agents. In particular an increasing number of N-N bond containing heterocycles and peptidomimetics have made their way in to commercial applications as pharmaceutical and agricultural agents. Hydrazides have also been used as important intermediates in synthesis of various heterocyclic compounds such as 1,2,4-triazoles ,1,3,4-thia diazole,1,3,4-oxa diazoles,1,2,4,5-tetrazoles which are known to possess diverse pharmacological properties.

Tuberculosis is a chronic granulomatous disease caused by Mycobacterium tuberculosis and is a major health problem in developing countries. One third of the world's current population has been infected with M.*tuberculosis* and new infection occurs at a rate of one per second. It is endemic in most developing countries and resurgent in developed and developing countries with high rates of HIV infection. Now a days multi drug resistant TB(MDR TB) and extensively drug resistant TB(XDR TB)are common. Multi-drug resistant strains of M.*tuberculosis* seriously threaten TB control prevention efforts. Drug resistance in M.*tuberculosis* is primarily due to accumulation of mutation in the drug target genes. These mutation led either to an altered target (eg: RNA polymerase inrifampin) or to a change in titration of the drug (eg:Inh A in isoniazid resistance) [2]. Now a day, a number of first line drugs are available for the treatment of TB, but most of them exhibit a variety of side effects. Hydrazides are an important anti TB agent used first line agent for tuberculosis therapy. Hydrazide plays an important role in shortening the therapy.

SYNTHESIS OF HYDRAZIDE DERIVATIVES:

Hydrazides from carboxylic acids

The carboxylic acids (3.0 mmol) was ground with

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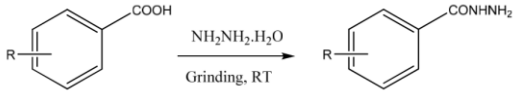
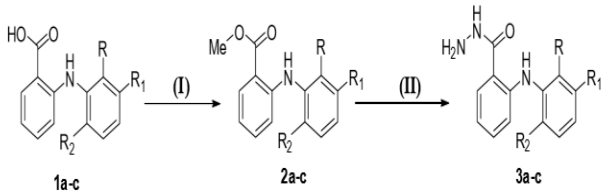
hydrazine hydrate (80 %, 3.75 mmol) by a pestle in a mortar for 3-5 minutes and left for digestion (10 minutes) when the reaction mixture set into a solid mass. The solid mass was crystallized from ethanol to give hydrazides [3].



Conventional synthesis of fenamic acid hydrazides

Reagents and conditions: 1.MeOH/H_2SO_4, reflux 12-18 hour,80-85%, 2 $NH_2NH_2.H_2O$, reflux 1.5-12 hour,80-96% [4].

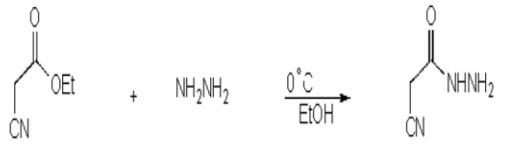
a, R = H, R_1 = CF_3, R_2 = H
b, R = Me, R_1 = Me, R_2 = H
c, R = Cl, R_1 = Me, R_2 = Cl

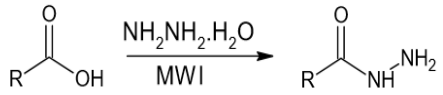


Solvent free one pot method for the preparation of hydrazides from corresponding acids under microwave irradiation [5].

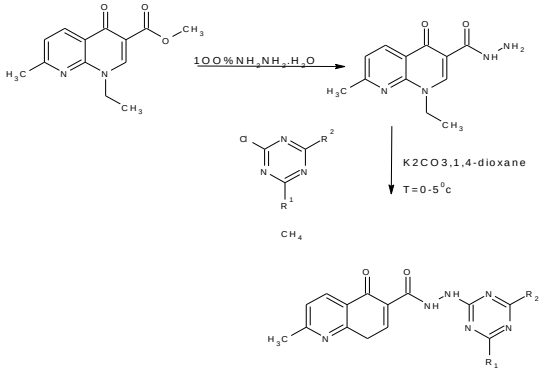
Synthesis of cyanoacetic acid hydrazides

Cyanoacetic acid hydrazide was obtained by careful addition of hydrazine hydrate to ethyl cyanoacetate in ethanol with stirring at 0°C [6].

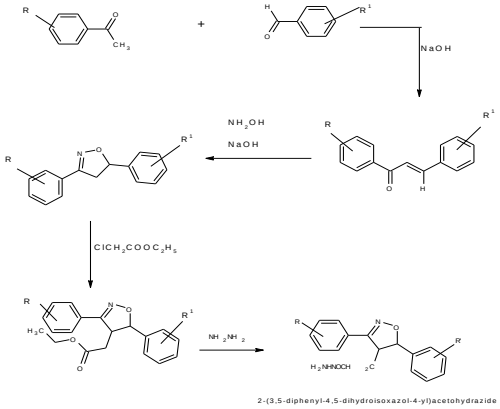




Synthesis of Nalidixic acid hydrazides [7]

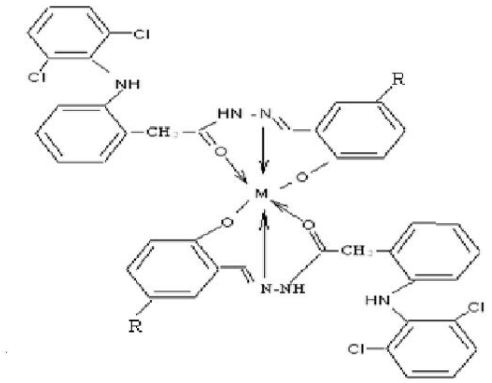


Synthesis of hydrazide derivative from chalcone [8]



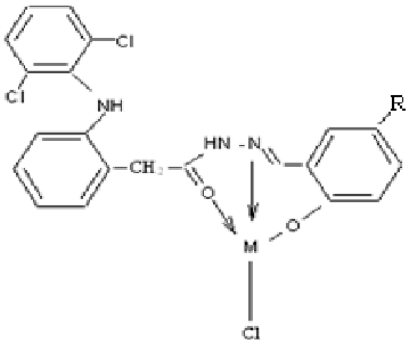
BIOLOGICAL POTENTIAL OF HYDRAZIDE DERIVATIVES

Kashinath and co-workers synthesized and characterized Schiff bases derived from 2-[2-(2,6-dichloro phenyl amino)phenyl acetyl hydrazides and salicyl aldehydes and their Cu(II), Zn(II), Cd(II), and Hg(II) complexes. They screened the compounds and found that all the complexes show the anti-microbial activity [9].



M = Zn(II), Cd((II), Hg(II)

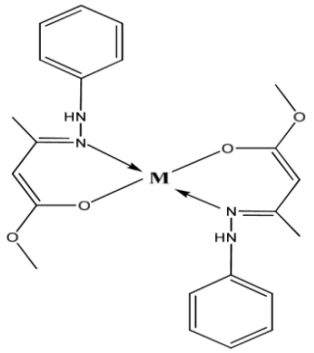
(1)



Where R=H, Br M = Cu(II) ,Ni(II) and Co(II)

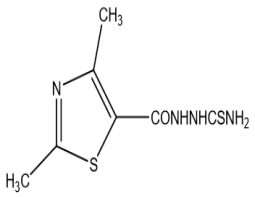
(2)

Ushma Joshi and co-workers treated phenyl hydrazide with methyl acetoacetate in presence of con. HCl,Methyl-3-(2-phenyl hydrazono)butanoate (MPB) was formed. It was characterized. The chelates of transition metal ions Cu^{2+}, Ni^{2}, Co^{2+}, Mn^{2+} of MPB were prepared. The antifungal activity of MPB and its metal chelates were screened against various fungi. The results show that all these samples are good antifungal agents [10].



Metal complex of methyl-3-(2-phenylhydrazono)butanoate. M=Cu^{2+}, Co^{2+}, Ni^{2+},Mn^{2+} and Zn^{2+}(3)

Shailey Singhal *et al* prepared thiosemicarbazides and thiosemicarbazones and they found that different biological activities of thiocarbazides such as antibacterial, antifungal, anti tubercular,anti convulsant and anti tumour activity.They prepared thiosemicarbazide by the addition of hydrazides into various isothiocyanate derivatives of thiosemicarbazides and thiosemicarbazones have been found to have excellent antibacterial agents 1-(2,4-dimethylthiazole-5-carboxyl)-N-4 ethylthiosemicarbazide 4 , 1-(4-fluorobenzoyl)-N-4-ethylthiosemicarbazide 5 [11].



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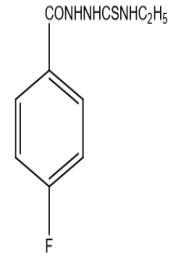
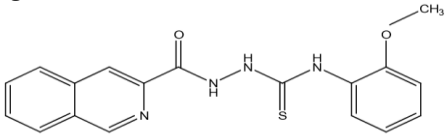


(5)

They studied about the in-vitro antifungal potency of isoquinoline derivatives of 4-aryl thiosemicarbazides. Six series of the derivatives were synthesized and evaluated against *Candida albicans*. Two isoquinoline derivatives with an o-methoxy and o-methyl group at phenyl ring (6 and 7) were found to be the most potent antifungals.



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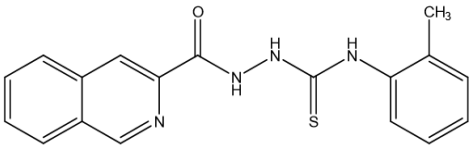
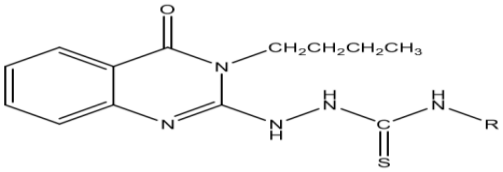


(7)

A new series of novel 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides were synthesized by the reaction of 3-butyl-2-hydrazino quinazolin 4-(3H)one with various methyl esters of di thiocarbamic acid. In vitro antitubercular activity of all the tested compounds using H37RV strain on Middle brook 7H11 agar slants with OADC growth supplement, illustrated the inhibited growth of Mycrobacterium tuberculosis at microgram concentration. Among the test compounds, 1-(4-oxo-3-butyl-3,4dihydroquinazolin-2-yl)-4-(2-nitrophenyl) thiosemi carbazide 8, 1-(4-oxo-3-butyl 3,4-dihydroquinazolin-2-yl)-4-(4-chlorophenyl) thiosemicarbazide 9 and 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(2-pyridyl) thiosemi carbazide 10 were found to be appreciably active against *M. tuberculosis* with MIC of 6 µg/ml.



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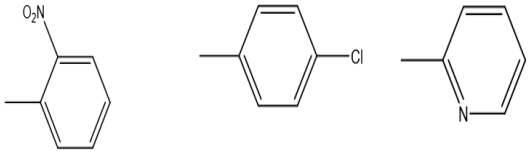
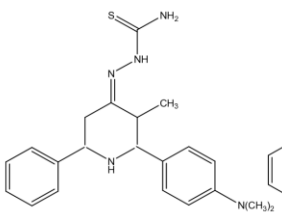


8 9 10

Thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones were synthesized by reaction with thiosemicarbazide using microwave irradiation . All the derivatives were evaluated for their in-vivo anticonvulsant activity by maximal electroshock (MES) method in rats, among which three, i.e. 2[4(dimethylamino)phenyl]-3-methyl-6-phenyl-piperidin-4thiosemicarbazone 11, 2-(4-hydroxyphenyl)-3-methyl-6-phenylpiperidin-4-thiosemi carbazone 12, and 3-isopropyl-2-(4-methoxyphenyl)-6-phenylpiperidin-4-thiosemicarbazone 13, showed maximum activity.



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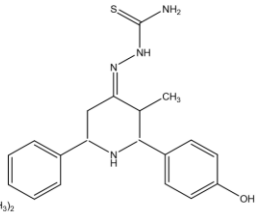

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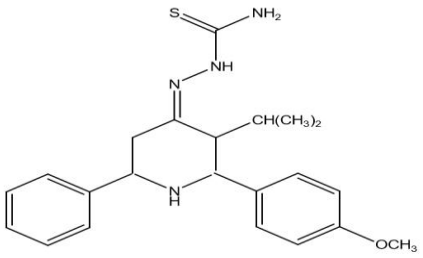
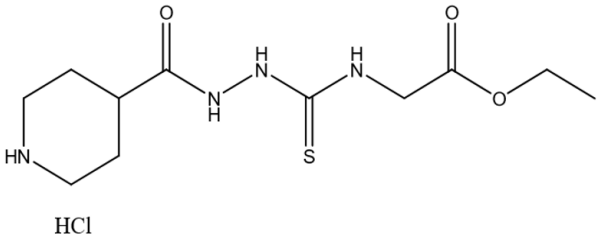


(13)

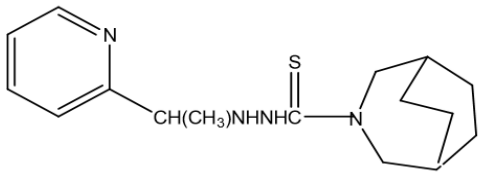
Cytotoxic effect of 4-ethoxycarbonylmethyl-1-(piperidine-4-ylcarbonyl)-thiosemicarbazidehydrochloride (14) was measured using an MTT assay and it was observed that the compound decreased the number of viable cells in both estrogen receptor-positive MCF-7 and estrogen receptor-negative MDA-MB-23 breast cancer cells, with IC50 values of 146±2 and 132±2µM, respectively .



HCl

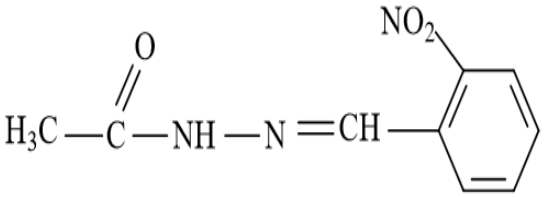
(14)

Klayman DL *et al.* Synthesized and investigated substituted 1-[l-(2-pyridyl)ethyl]-3-thiosemicarbazides as potential antimalarial agents. These compounds were somewhat more active as antimalarial agents in *Plasmodium berghei* infected mice than the corresponding thiosemicarbazones; however, the enhancement of activity was accompanied by an increase in toxicity. 3-azabicyclo [3.2.2] nonane-3-carbothioic acid 2-[1-(2-pyridyl) ethyl]hydrazide 15 has been reported to be the most potent antimalarial agent which could cure two test animals at a dose of 10mg/kg [12].



(15)

Salawu and co workers synthesized a series of new acid hydrazides by the reaction of novel ligands Acetic acid (3- chloro – 4 – hydroxyl benzylidene)-hydrazide (16), Acetic acid (2 – nitro – benzaylidene)hydrazide (17) with cadimium (II) bromide , These new complexes were characterized by elemental analysis, IR spectroscopy and UV spectral techniques. This newly synthesized compounds have been tested against grampositive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative bacteria (*E.coli and Salmonella typhi*) for their antibacterial activity [13].



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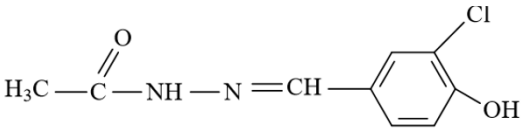
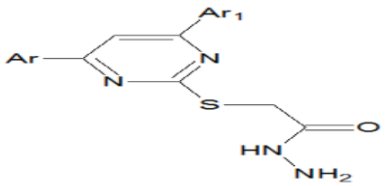
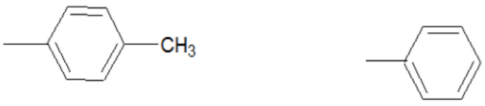


(17)

Sonia D *et al* Synthesized some novel pyrimidine derivatives by using chalcone and thiourea.10 different compounds thus formed were further reacted with ethylchloroacetate and then with hydrazine hydrochloride. The synthesized pyrimidine thioesterhydrazide were subjected to docking studies against protein Human Cyclin Dependent Kinase 2 complexed with the CDK4 inhibitor (IGII) using Argus Lab software.From these compounds compound 4 was found to be the best anti cancer agent [14].

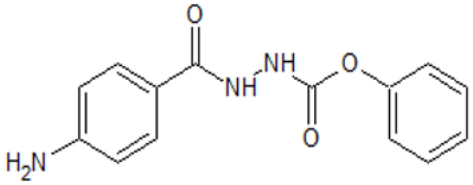


$ArAr_1$



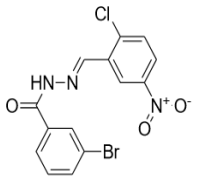
(18)

Muddassar Siddique and co workers synthesized hydrazide based formamides from substituted hydrazides and their structure were confirmed by FTIR and elemental analysis.The synthesized formamides show fluctuation in results against anti oxidant studies. Majority of the produced formamides are inactive against E.*coli* bacteria but on the other hand most of the formamide derivatives are dynamic against *Candida albicans* [15].



(19)

Zhu Hai-Yun found that two new hydrazone compounds, 3-bromo-N´- (2-chloro5-nitrobenzylidene)-benzohydrazide (19) and 3-bromo-N´-(4-nitrobenzylidene) benzohydrazide (20), have been synthesized and screened for antimicrobial activities. The results show that the two compounds have potential antimicrobial activities against *Klebsiella pneumonia* and it was notable that the activities of 19 are stronger than those of 20, indicating that the chloro-substitute group is a good choice in search for antibmicrobial materials [16].



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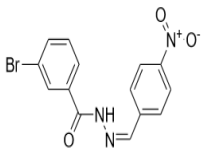

(20)

CONCLUSION

Hydrazide and related heterocyclic compounds were reported to have anti-mycobacterial, anti-bacterial, anti-fungal, anti-tumour, anti malarialand anti-convulsant properties. It has been found that hydrazide derivatives can be synthesized in different ways. Summarizing that the hydrazide and related heterocyclic compounds possess good activities that can be utilized for the development of new chemical entities to treat tuberculosis and various other conditions.

ACKNOWLEDGEMENT

None

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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