BIOLOGICAL ACTIVITIES OF HYDRAZONE DERIVATIVES IN THE NEW MILLENNIUM

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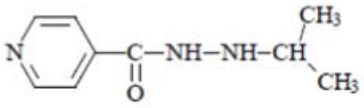
ABSTRACT:
Hydrazones are present in many of the bioactive heterocyclic compounds that are of wide interest because of their diverse biological and clinical applications. This created interest in researchers who have synthesized variety of hydrazone derivatives and screened them for their various biological activities viz. anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, anticancer, vasodialator, antiviral, antischistosomiasis, anti-HIV, anthelmintic, antidiabetic and trypanocidal activities. Hydrazones possessing an azometine –NHN=CH- proton constitute an important class of compounds as target structures and evaluated their biological activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities.

Keyword: Hydrazone, hydrazides-hydrazones, biological activity, isoniazid.

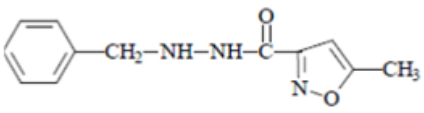
1. Introduction :

Hydrazones are of wide interest because of their diverse biological and clinical applications. This created interest in researchers who have synthesized variety of hydrazone derivatives and screened them for their various biological activities. In the present study, we have made an attempt to collect biological properties of hydrazone derivatives reported in the new millennium.

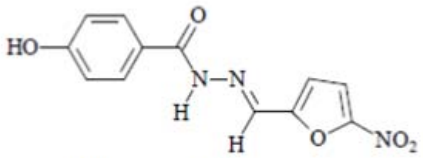
Hydrazide-hydrazone compounds are not only intermediates but they are also very effective organic compounds in their own right. When they are used as intermediates, coupling products can be synthesized by using the active hydrozen component of –CONHN=CH- azometine group[1]. Many effective compounds, such as iproniazide (i) and isocarboxazide (ii), are synthesized by reduction of hydrazide-hydrazones. Iproniazid, like INH is used in the treatment of tuberculosis. It has also displays an antidepressant effect and patient appear to have a better mood during the treatment. Another clinically effective hydrazide-hydrazones is nifuroxazide (iii), which is used as an intestinal antiseptic.



Iproniazide (i)



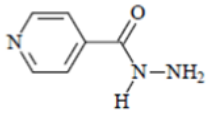
Isocarboxazide (ii)



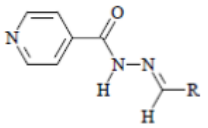
Nifuroxazide (iii)

Hydrazone have been demonstrated to possess, among other, anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, anticancer, vasodialator, antiviral, antischistosomiasis, anti-HIV, anthelmintic, antidiabetic, and trypanocidal activities. For example, 2-Chloroquinolinyl hydrazone derivative are anticonvulsants[2] ribavirin hydrazone derivatives are anticancer [3], hydrazones of indane-1,3-dione are anticoagulant and antimicrobial[4], 4-arylhydrazono-2-pyrazoline-5-one derivatives are antitubercular activity[5]. In addition, some of the new hydrazide hydrazones which are recently synthesized were active against *M. tuberculosis* H37Rv between the concentrations of 0.78-6.25 µg\ml.[6] Synthesis of a series of hydrazide- hydrzones via the

reaction of cyanoacetyl hydrazine with bromo (4-methoxyacetophenone) reported for antidepressant, sedative and analgesic activities[7].



Isoniazid (iv)



hydrazide-hydrazones (v)

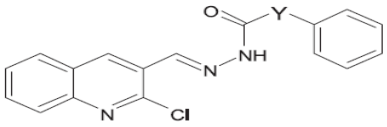
Isonicotinic acid hydrazide (isoniazid,INH) (iv) has very high in vivo inhibitory activity towards M. tuberculosis H37rv. Sah and Peoples synthesized INH(iv)hydrazide-hydrazones(v) by reacting INH with various aldehyde and ketones [8].These compounds were reported to have inhibitory activity in mice infected with various strains of M.tuberculosis. They also showed less toxicity in these mice than INH. Buu-Hoi *et al*. synthesized some hydrazide-hydrazones that were reported to have lower toxicity than hydrazides because of the blockage of –NH2 group. These findings further support the growing importance of the synthesis of hydrazide-hydrazones compound[9,10]. Iron is necessary for the biochemical reactions of living organisms. Desferrioxamine is an agent which is used for the treatment of a complication called "Iron Overload Disease". Researchers have synthesized hydrazones of INH by using various aldehydes and their iron complexes and evaluated these complexes for their antitumoralactivity[10].

It has been known that the hydrazide (like INH)form α-ketoglutaric acid and form hydrazones with vitamin B6 and pyruvic acid **.**It is clinically important that when tuberculosis patient are treated with INH, reaction of INH with vitamin B6 leads to formation of a hydrazone and development of vitamin B6 deficiency, therefore, patients who are treated with INH should be administered vitamin B6.This review critically evaluates the pharmacological activity of hydrazones that were reported in the past ten years.

2. Biological activity:

2.1. Anticonvulsant Activity: Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been archived during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity.

Suresh kumar *et al* (2010) worked on 2-Chloroquinolinyl Hydrazone (vi) derivatives having anticonvulsant activity. These compounds were believed to interact at two locations on a putative binding site designated as hydrogen binding domain and hydrophobic binding area as proposed by Dimmock *et al*.[3]



2-Chloroquinolinyl Hydrazone (vi)

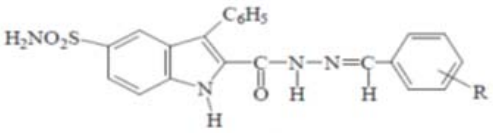
Nadeem Siddiqui *et al*(2008) synthesized a series of 2-(1H-indol-3-yl)acetyl-N-(substituted phenyl) hydrazine carbothioamides and their related heterocyclic derivatives. The anticonvulsant evaluation of compounds in mice at 30, 100 and 300 mg kg–1 by i.p. MES (maximal electroshock seizure)**,** drugs used as standards, phenytoin and carbamazepine. Compounds with the electron withdrawing chloro substituent at the orthopositionto the amino group led to considerable increase in the activity but were relatively moretoxic. The presence of a bulkier electron donating methoxy group at paraposition of theamino group resulted in an increase in activity. This may be due to the increase in lipophilicityof the compound. The effect of the methyl group was found to be different inthe three groups of compounds. In the case of triazole derivatives, the activity was asfollows: o ~ m >p, with no effect on toxicity. In the case of oxadiazole derivatives, onlyp-substituted compound was active, and in thiadiazole derivatives it followed the orderofo ~ p >mIt shows that hydrazone-indole based heterocyclic derivatives were found to have encouraging anticonvulsant activity[11]

JegadeesanVaigundaRagavendran *et al* (2007) designed and synthesized anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore and evaluated by using intraperitoneal (i.p.) maximal electroshock-induced seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and intraperitoneal

picrotoxin (ipPIC)-induced seizure threshold tests. All of the compounds were ineffective in the MES test. Most of the compounds were found to be effective in the scSTY and ipPIC models and very few compounds showed protection in the sc PTZ model. The study reported that the synthesis of pharmacophoric combinations of phthalimide-GABA-anilide/hydrazones as candidate anticonvulsants. Of the two series of pharmacophorichybrids, the phthalimideGABA-anilides were found to be more effective than the corresponding phthalimide-GABA-hydrazone derivatives[12].

DarpanKaushik *et al* (2010) synthesized and evaluated the anticonvulsant activity of N'- [(5-chloro-3- methyl- 1- phenyl- 1H -pyrazol-4-yl) methylene] 2/4-substituted hydrazides. They tried to develop aryl acid hydrazidehydrazones as new congeners to join this, as this group mimics the cyclic ureide group of semicarbazone. Among the compounds, the aryl derivative 5a exhibited activity against both the MES and scPTZ models. When the C-4 position i.e. paratothe aryl ring was substituted with electron withdrawing group the compounds were found to be more potent and active in both themodels as compared to electron donating group, while compound with p-methoxy group was found to be weakly active in the MES model only and shows no activity in the scPTZ model. With increasing electronegativity, the compound was found to be more potent [13Ravi Kulandasamy*et al (2009)* evaluate the anticonvulsant activity of thirty nine new 3,4-di(substituted)oxy-N2,N5-bis(substituted)thiophene-2,5-dicarbohydrazide, by using intraperitoneal (ip) administration in three seizure models, which include maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and 6 Hz screens. [13]

2.2 Antidepressant Activity: Iproniazide, isocarboxazide and nialamide, which are hydrazide derivatives, exert their action byinhibiting the enzyme monoamine oxidase (MAO). Inhibition results in increased levels of norepinephrine, dopamine, tyramine and serotonin in brain neurons and in various other tissues. There have been many reports on the antidepresant / MAO-inhibiting the activity of hydrazones derived from substituted hydrazides and reduction products. Ten new arylidenehydrazides which were synthesized by reacting 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide with various aldehydes, evaluated for their antidepresant activity. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid 3,4-methylenedioxy / 4-methyl / 4-nitrobenzylidene-hydrazide showed antidepresant activity at 100 mg/kg [14]



arylidenehydrazides (vi)

R. M. Mohareb *et al* (2010) Synthesized of hydrazide-hydrazone derivatives and evaluated for antidepressant activity. The reaction of cyanoacetylhydrazine with ω-bromo(4-methoxyacetophenone) gave the hydrazidehydrazone derivative. This compound reacted with either potassium cyanide or potassium thiocyanide to give thecyanide or thiocyanide derivatives. The reaction of compound with either hydrazine hydrate or phenyl hydrazine gave the hydrazine derivatives. The latter compounds underwent a series of heterocyclization when react with different reagents to give 1,3,4-triazine and pyridine derivatives. Evaluations of synthesized compounds was done for antidepressant activity by using Porsolt's forced-swimming test After 60 min of i.p. administration, some compounds shown below showed mild non-significant antidepressant activity at high doses and were active, compared with the control group, using saline as negative control. The rest of compounds failed to display antidepressant properties in the swimming test[7].

2.3 Antimalarial Activity: Keeping the above facts in mind, Gemma *et al*. (2006) synthesized a new series of N1-arylidene-N2- quinolyl- and N2-acrydinylhydrazones and tested in vitro for their antimalarial properties against a series of Plasmodium falciparum strains, namely the chloroquine-sensitive D10 and 3D7, and the CQ-resistant W2 and K1. The results indicated that N-(7-Chloro-quinolin-4-yl)- N'-(4-pyrrolidin-1-ylmethyl-benzylidene)-hydrazine was the most active compound of the series [15].

A series of N1-arylidene-N2-quinolyl and N2-acrydinylhydrazoneswere synthesized and tested for their antimalarial properties. The new synthesized compounds showed an antiplasmodial activity against the chloroquine-sensitive D10 strain in the same range of chloroquine(CQ)[16].

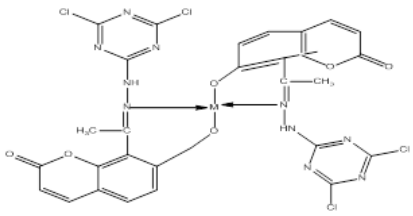
2.4. Antimicrobial Activity: The resistance of bacteria against antimicrobial agents has become a widespread medical problem especially as nosocomial pathogens. Treatment options for these infections are often limited, especially in

debilitated and immunocompromised patients. The search for new antimicrobial agentswillconsequently always remains as an important and challenging task for medicinal chemists.

Olayinka O. Ajani *et al* (2010)developed a simple and efficient method for the synthesis of various 2-quinoxalinone-3-hydrazonederivatives using microwave irradiation technique and evaluated fortheir antimicrobial activities against the organisms B. cereus (NCIB6349), B. stearothermophilus (NCIB 8222), B. subtilis (NCIB 3610), B.anthracis (LIO), Bacillus polymyxa (LIO), Corynebacteriumpyogenes (LIO), Streptococcus faecalis (NCIB775), S. aureus (NCIB 8588), Clostridiumsporogenes (LIO), E. coli (NCIB 86), P. fluorescence (NCIB3756), K. pneumonia (NCIB 418), S. dysenteriae (LIO), P. aeruginosa(NCIB 950) and C. albican (LIO) by usig agar diffusion technique The most active antibacterial agent was 3- {2- [1-(6- chloro- 2-oxo-2H-chromen-3-yl)ethylidene] hydrazinyl} quinoxalin-2(1H)-one, 7 while 3-[2-(propan-2-ylidene)hydrazinyl]quinoxalin-2(1H)-one, 2 appeared to be the most active antifungal agent[17].

Madalina Veronica Angelusiu*et al* (2010) prepareda new aroyl- hydrazone, N-(2-pyridinecarbaldehyde)- N0-[4-(4-chloro-phenylsulfonyl) benzoyl]- hydrazone (L) and its Cu(II), Co(II) and Ni(II) complexes and antibacterial activity were studied againstgram-positive bacteria: Staphylococcus aureus, Bacillus subtilis and gram-negative bacteria: *Pseudomonas aeruginosa*, Escherichia coli by using minimum inhibitory concentrations (MICs) method. The obtained results show that the ligand (L) has a weak action on all the tested microorganisms. The activity of N-(2-pyridinecarbaldehyde)-N0-[4-(4-chloro-phenyl sulfonyl) benzoyl]-hydrazone (L) becomes more pronounced when coordinated to the metal ions.[18].

Ummuhan Ozdemir Ozmen *et al* (2008) synthesized new sulfonylhydrazone derivatives and their nickel complexes and evaluated their antibacterial activity against gram-positive bacteria (*staphylococcus aureus, bacillus subtilis, bacillus magaterium*) and gram-negative bacteria (*salmonella enteritidis*, *Escherichia coli*) by using minimum inhibitory concentration (MICs) method. The antibacterial result showed that the sulfonyl hydrozone compounds posses a broad spectrum of activity against the tested bacteria at MIC values between 145 and 683µg/ml.The presence of electron densities on donor atoms (as O, S, N, etc.)in ligands contributes positively to the increase of the activity of compound against bacteria. But the decrease of the electron densities by the coordination through the donor atoms causes the lower activities of complexes than ligand's [19].



hydrazones and its chelates

Aakash Deep *et al* (2010) desigened biphenyl-4-carboxylic acid hydrazide- hydrazone and evaluated for their in vitro antimicrobial activity against two gram negative strain (*Escherichia coli and Pseudomonas aeruginosa*) and two Gram positive strain (*Bacillus subtilis* and *staphylococcus aureus*) and fungle strain (*Candida albicans* and *Aspergillusniger*).The structural requirements for antibacterial and antifungle activity are different for substituted hydrazides. Most antibacterial compound compounds showed the least antifungle activity and compounds being the most active antifungle compounds have shown the least antibacterial activity. The presence of electron withdrawing groups (-NO2, -Cl, Br) on aromatic ring improved the antimicrobial activity of compounds[20].

Metwally *et al*. (2006) synthesized a new series of 2-arylquinoline-4-carboxalic acid hydrazid-hydrazones and evaluated for 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)-hydrazidewas found to be most potent[21]

Masunari *et al*. (2007), fourteen p-substituted benzoic acid [(5-nitro-thiophen-2-yl)-methylene]-hydrazides were synthesized and tested in vitro for antimicrobial activity against standard (ATCC 25923) and multi drug-resistant (3SP/R33) strains of Staphylococcus aureusby Masunari *et al*. The results of antimicrobial study indicated that 4-Acetyl-benzoic acid [(5-nitro-thiophen-2-yl)-methylene]-hydrazide was the most active compound [22].

Zareef *et al*. (2008) synthesized derivatives of acylhydrazine such as substituted-2-mercapto-1,3,4-oxadiazoles, their corresponding ester, amide and benzenediasulfonamides and tested

them for antimicrobial activity which showed that one of the acylhydrazinebenzene diasulfonamide derivative was having appreciable antimicrobial activity [23]

2.5. Antimycobacterial Activity: Tuberculosis is a serious health problem that causes the death of some three million people every year worldwide. In addition to this, the increase in M. tuberculosis strains resistant to front-line antimycobacterial drugs such as rifampin and INH has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of tuberculosis.

Sriram *et al*.(2006), various diclofenac acid hydrazones and amides were synthesized and evaluated for in vitro and in vivo antimycobacterial activities against Mycobacterium tuberculosis. The results showed that 1-cyclopropyl-6-fluoro-8-methoxy-7-[[N4-(2-(2-(2,6-dichloro phenylamino)phenyl)acetyl)-3-methyl]-N1-piperazinyl]-4-oxo-1,4-dihydro-3-quinoline carboxylic acidwas found to be the most active compound in vitro than first line antitubercular drug isoniazid. In the in vivo animal model, decreased the bacterial load in lung and spleen tissues[24].

Nayyar *et al*. (2007) synthesized two new series of 2- substituted quinolines 4-(adamantan-1-yl) group and evaluated in vitro for their antimycobacterial activities against drug-sensitive M. tuberculosis H37Rv strain. Compound 4-adamantan-1-yl-quinoline-2-carboxylic acid (2-chloro benzylidene) hydrazide inhibited drug-sensitive Mycobacterium tuberculosis H37Rv at 1.00 µg/mL (99 % inhibition) and was equipotent to standard drug isoniazid[25].

Manvar *et al*.(2008)During the coumarin-4-acetic acid benzylidenehydrazides as anti-tubercular agents against Mycobacterium tuberculosis H37Rv strain using the BACTEC 460 system, (7-Hydroxy-2-oxo- 2H-chromen-4-yl)-acetic acid (3-nitro-benzylidene)-hydrazide**(30)** was found to be most potent with MIC and percentage inhibition of 6.25 µg/mL and 93 % [26].

AhmetOzdemir *et al* (2010) synthesized some novel hydrazone derivatives by the reaction of (5,6,7,8-tetrahydronaphalen-1-yl) acetic acid hydrazide with various benzaldehydes which gave 5,6,7,8-tetrahydronaphthalen acetic acid benzylidenehydrazide derivatives and evaluated their antituberculosis activity which showed that compounds having –OH and –NO2 in ortho and meta position of aromatic ring having high antituberculosis activity and low cytotoxicity [27].

SrivsatavaRitu *et al* (2010) synthesized twelve aryl acetic acid hydrazonesand tested first time for their activity against mycobacterium. The compounds showed moderate activity against H37 RV strain of Mycobacterium tuberculosis at a concentration of 10µM [28].

***2.6* Antiviral Activity:** HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Current treatment regimens are based on the use of two or more drugs that belong to group of inhibitors termed as highly active antiretroviral therapy (HAART). Some thiourea compounds were reported to be non-nucleoside inhibitors (NNIs) of the reverse transcriptase (RT) enzyme of the human immunodeficiency virus (HIV). Such hydrazones have been reported to be the potent inhibitors of ribonucleotidereductase activity. N-Arylaminoacetylhydrazones and O-acetylated derivatives of sugar N-arylaminoacetylhydrazones were synthesized and evaluated for their antiviral activity against Herpes simplex virus-1(HSV-1) and hepatitis-A virus (HAV). Some compounds revealed the highest antiviral activity against HAV-27 and HSV-1.[29]

Al-Macrosaur *et al*.(2007), HIV-1 integrase (IN) is a critical enzyme for viral replication. This intiatedMasawi *et al*. to screen salicylhydrazide class of compounds for their potent HIV-1 integrase inhibitory activity. The results of screening showed (4-Phenyl-5-pyridin-4-yl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetic acid (2-hydroxy-benzylidene)-hydrazide,displayed weak HIV-1 integrase inhibitory activity [30].

***2.7* Antischistosomiasis:** Schistosomiasis causes debilitating nutritional, hematologic and cognitive deficits, with substantial morbidity and mortality in populations. There are five species of flatworms that cause schistosomiasis. Schistosomamansoni, S. intercalatum, S. haematobium, S. japonicumand S. mekongi. Schistosomamansoniand S. intercalatum, S. japonicumand S. mekongicause intestinal and Asian intestinal schistosomiasis, respectively. S. haematobiumresides in the venous plexus, which causes urinary schistosomiasis[31]

9-Acridanone hydrazones have been developed by Hoffmann-La Roche (Basel-Switzerland). One of these compounds (RO 15-5458/000) was administered at two dose levels 25 mg and 15 mg/kg body-weight to *S. mansoniinfected* vervet-monkeys[32].

In addition, same compounds were found to be effective against S. mansoniin mice, killing

almost all the skin schistosomules, when administered at the dose of 100mg/kg. In experiments carried out with Cebus monkeys, the compound RO 15-5458 / 000 was shown to be fully effective at 25 mg/kg.[33]

2.8 Antianthrax Activity: Inhalation of Bacillus anthracisspores is often fatal if not appropriately treated in a timely fashion. Inhaled spores in the lung alveoli are phagocytes by alveolar macrophages and transported to the lymph nodes, where the spores germinate and multiply. The bacteria release a toxin that kills host macrophages, disabling the host immune system and thereby allowing the bacteria to escape the lympho node defense barrier to reach the blood system causing bacteraemia and toxaemia, which rapidly kills the host. Anthrax toxin consists of three proteins: protective antigen (PA), edema factor (EF) and lethal factor (LF). The inhibition of LF proteolytic activity is a promising method for treating exposure to Bacillus anthracisspores.

In light of above facts, Hanna *et al*. (2007) generated series of hydrazones and analyzed them for their potential anthrax lethal factor inhibition. The study showed thatshowed an appreciable activity.[34]

2.9 Trypanocidal Activity: African trypanosomes are the causative agent of sleeping sickness in human and Nagana in cattle. Chemotherapy of African trypanosomiasis still relies heavily on drugs developed decades ago and some of them are toxic. In addition, the emergence of drug resistant trypanosome stains in animals has been widely reported. Therefore, the development of new antitrypanosomal drugs is urgently required. Keeping this in mind, Caffery *et al*. (2002) screened a non-peptidyl acyl hydrazide proteinase inhibitory library of 500 compounds for inhibition of brucipain (major cystein proteinase). The compounds with IC50 values <40 μM were tested for their efficacy against blood stream forms of Trypanosomabruceiin cell culture. Some of the synthesized acyl hydrazides showed 50% or more inhibition of trypanosome replication at <1 μM. The trypanocidal activity of most effective compound 4-Nitro-benzoic acid [4-(4-nitro-phenyl)-cyclopenta-1,3-dienylmethylene]-hydrazidewas comparable to those of commercial drugs sumarin and diminazineaceturate.[35]

This stimulated Leite *et al*. (2006) to synthesize a novel series of thiosemicarbazone and aminoacyl-thiazolidones derivatives. Biological evaluation of synthesized compounds indicated that 2-{N'-[2-(4-Chloro-phenylsulfanyl)-ethylidene]-hydrazino}-5-methyl-thiazol-4-one exhibited significant in vitro activity against epimastigotTrypanosomacruzi[36]

2.10 Leishmanicidal Activity: According to the World Health Organization (TDR, 2005), leishmaniasis, caused by species of the genus Leishmania (Sarcomastigophora, Kinetoplastida) an emerging and uncontrolled Category I diseases, constitutes a major public health problem, causing significant morbidity and mortality in Africa, Asia and the Americas. The present treatments available for leishmaniasis are far from ideal.

In the search for new rational chemotherapeutic alternatives, Visbal *et al*. (2008) synthesized two novel trans [Pt(Hpy1)2(Cl)2] and trans [Pt(Hpy2)2 (Cl)2] complexes by the reaction of K2PtCl4 with sterol hydrazone ligands 20-hydrazone-pyridin-2-yl-5a-pregnan-3b-ol (Hpy1) and 22-hydrazone-pyridin-2-yl-chol-5-ene-3b-ol (Hpy2). These organic compounds are specific inhibitors of sterol methyl transferase (SMT). Promastigotes of Leishmania (L.) mexicanawere treated for 48 h with 10 μM of the sterol hydrazones Hpy1 or Hpy2 alone or coordinated to Pt. Hpy1 produced higher leishmanistatic activity than Hpy2 (39% growth inhibition vs. 16%), which significantly increased (71%, $p < 0.001$) when the complex trans- [Pt(Hpy1)2(Cl)2] was used [37].

2.11Analgesic, Antiinflammatory and Antiplatelet Activity: In the 1980's, hydrazone type containing compounds such as BW 755c and CBS 1108 were described as dual COX\5-LO inhibitors which present analgesic and anti-inflammatory activities. In fact, some evidences that the hydrazone moiety present in derivative possess a pharmacophoric character for the inhibition of COX.

Ali Almasirad *et al* (2005) a series of N-Arylhydrazone derivatives o mefenamic acid (a known non steroidal anti-inflammatory) synthesized by replacement of carboxylic acid moiety of mefenamic acid with an N-arylhydrazone group and evaluated their analgesic and anti-inflmmatory activity by using abdominal constriction test (writhing test) and carrageenan-induced rat pow edema test. The pharmacological results showed that pyridine ring at the aryl moiety of the arylhydrazone having good analgesic activity in comparision to mefenamic acid. Compounds possessing the 4-tolyl or 4-flurophenyl moiety are more active then 4-bromophenyl and 4-N, N –dimethyl-aminophenyl. The anti-inflammatory evaluation of seven most potent compounds showed that replacement of carboxylic acid group of

mefenamic acid with N-arylhydrazone moiety cannot produce any advantage in the anti-inflammatory property of this drug [38].

K.K Sivakumar *et al* (2010) worked on analgesic activity of some (4Z)-3-methyl-1-[(2-oxo-2H-chromene-4-yl)carbonyl]-1H-pyrazole-4,5-dione 4-[(4-substitutedphenyl) hydrazone] some of them showed significant analgesic activity compared with the standard drug (indomethacin 5mg\kg) at the dose level of 50 mg\kg on oral administration. Pharmacological evaluation was done by using Acetic acid-induced writhing model in mice which showed that the presence of 4-chloro, 4-bromo, 3,4-dichloro, 3,4-dibromo and 4-methyl group in the aromatic ring of 4-position of the pyrazole-hydrazono nucleus gave rise to an increased analgesic activities [39].

SuroorA.Khan *et al* (2009) synthesized hydrazone derivatives of quinoxalinone and evaluated for anti-inflammatory activity by using carageenan induced rat powedema method which showed that compounds having methoxy group at the para position showed comparatively good percentage of inhibition of edema than the other synthesized compounds[40]. Treatment of 3-cyano acetylindole with diazonium salts of 3-phenyl-5-amino pyrazole and 2- amino pyrazole gave the corresponding hydrazones. Out of the synthesized compounds, 3-(1H-Indol-3-yl) -3-oxo-2- [(5-phenyl -2H- pyrazol- 3 -yl)- hydrazono]-propionitrile was found to possess appreciable analgesic and anti-inflammatory activity.[41]

The antiplatelet activity of novel tricyclic acylhydrazone derivatives was evaluated by their ability to inhibit platelet aggregation of rabbit platelet-rich plasma induced by platelet-activating factor (PAF) at 50 nM. Benzylidene- / 4′-bromobenzylidene 3-hydroxy-8-methyl-6-phenylpyrazolo [3,4-b]thieno-[2,3-d]pyridine-2-carbohydrazide were evaluated at 10 μM, presenting, respectively, 10.4 and 13.6% of inhibition of the PAF-induced platelet aggregation[42]. The evaluation of platelet antiaggregating profile let to identification of a new potent prototype of antiplatelet derivative, that is benzylidene 10H-phenothiazine-1-carbohydrazide (IC50=2.3 μM), which acts in the arachidonic acid pathway probably by inhibition of platelet COX-1 enzyme. Additionally, the change in para-substituent group of acylhydrazone framework permitted to identify a hydrophilic carboxylate derivative and a hydrophobic bromo derivative as two new analgesics that are more potent than dipyrone, which is the standard, possessing selective peripheral or central mechanism of action[43].

2.12. Antitumoral Activity: Cancer remains a major public health issue at the beginning of the 21st century. Chemotherapy is one of the ways to fight against cancer. Therefore, the need for accelerated development of new, more effective as well as less toxic chemotherapeutic agents has appeared.

Liang-Wen Zheng *et al* (2009) synthesized a series of substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovered a potent apoptosis inducer in A549 lung cancer cells. The results showedthat (E)-1-(4-tert-butylbenzyl)-N0-(1-(5-chloro-2-hydroxyphenyl)ethylidene)-3-(4-chlorophenyl)-1H-pyrazole- 5-carbohydrazide possessed the highest growth inhibitoryeffect and induced apoptosis of A549 cells[44].

Vicini *et al*. (2006) synthesized several benzo[d]isothiazolehydrazones and evaluated for their potential antiretroviral activity. Among the synthesized compounds benzo[d]isothiazole-3-carboxylic acid (4-methoxy-benzylidene)-hydrazidewas found to be the most potent antiproliferative compound and the fragment –CO−NH−N=CH−2- hydroxyphenyl was identified as being very important for biological activity, suggesting intramolecular hydrogen bond formation or favorable mutual disposition between two important centers in the pharmacophore[45].

2.13. Vasodilator Activity: Conventional therapy to treat hypertension often involves arterial vasodilation. It is important to find new vasodilators with a potential for clinical use. A new bioactive compound of the N-acylhydrazone class, 3, 4-methylenedioxybenzoyl-2-thienylhydrazone, named LASSBio-294, and was shown to have inotropic and vasodilatory effects. New derivatives of LASSBio-294 were designed and tested on the contractile responses of rat vascular smooth muscle in vitro. Phenylephrine-induced contractions of aorta was inhibited by the derivatives N-methyl-2-thienylidene-3,4-methylenedioxy-benzoyl hydrazine, named LASSBio-785 and N-allyl-2- thienylidene-3,4-methylenedioxy-benzoyl hydrazine, named LASSBio-788. The concentrations necessary to cause 50% reduction in maximum contractions (IC50) were 10.2 +/- 0.5 and 67.9 +/- 6.5 μM. Vasodilation induced by both derivatives is likely to be mediated by a direct effect on smooth muscle because it was not dependent on the integrity of vascular endothelium. LASSBio-785 was seven times more potent than the reference compound LASSBio-294 (IC50 = 74 μM) in producing an endothelium-independent vasodilator effect[46].

2.14 Antidiabetic Activity: Glycogen synthase kinase-3 (GSK-3), a protein in the serine/threonine kinase family, is broadly expressed and serves many functions within the human body. Among some of the diseases that GSK-3 may affect are Alzheimer's disease, diabetes, various cancer types and neurological disorders. One function of GSK-3 is to mediate the conversion of glycogen to glucose and is regulated in part by insulin signaling. In patients with insulin resistance, GSK-3 is constituently active, which leads to an increase in plasma glucose levels and hyperglycemia. Inhibitors of GSK-3 could reduce glucose levels by mimicking the effect of insulin signaling on GSK-3 and thus could be used as anti-diabetic treatments. In view of above, Smalley *et al*. (2006) synthesized a set of novel heterocyclic pyrimidylhydrazonesas inhibitors of glycogen synthase kinase-3 (GSK-3) with the most active compound exhibiting low nanomolar activity. Quantum mechanical calculations indicate that of the conformational factors that could determine binding affinity, the planarity of the phenyl ring in relation to the central core and the conformation of the hydrazone chain are the most influential[47].

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