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Biological activities of hydrazide derivatives in the new millennium

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Abstract

Hydrazides and 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 hydrazide derivatives and screened them for their various biological activities viz. anticancer, anti-HIV, anthelmintic, antimycobacterial, anti-inflammatory, antidiabetic, antimicrobial, trypanocidal as well antimalarial activities.

Keywords: Hydrazides, hydrazones, biological activity.

Introduction

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

Biological activities of hydrazides/hydrazones in the new millennium

Hydrazides as antimicrobial agents

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. Sridhar et al. (2001) prepared Schiff bases and hydrazones of substituted isatin by reacting isatin and aromatic primary amines/hydrazines and determined their MIC values for antimicrobial activity against seven Gram positive and seven Gram negative standard and pathological strains by paper disk diffusion technique. The results of MIC values indicated that 3-(4-Bromo-phenylimino)-1-[(diphenylamino)-methyl]-5-nitro-1,3-dihydro-indol-2-one (**1**) and 3-(4-Bromo-phenylimino)-5-nitro-1,3-dihydro-indol-2-one (**2**) were found to be the most active compounds of the series.

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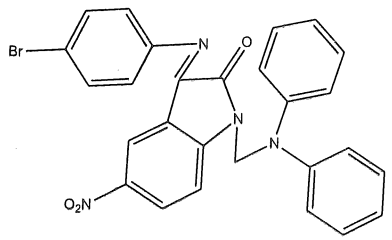

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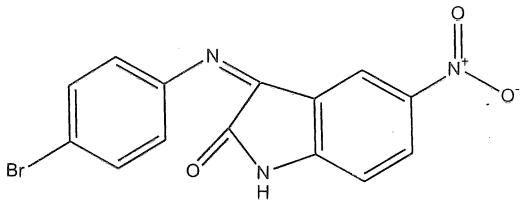

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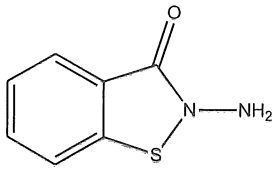
In a study of synthesis and antimicrobial evaluation of a series of 1,2 benzisothiazole hydrazides as well as their cyclic and acyclic 1,2 benzisothiazole parent hydrazides, 2-Amino-benzo[d]isothiazol-3-one (**3**) and 2-Amino-5-methyl-benzo[d]isothiazol-3-one (**4**) proved to be the most active compounds (Vicini et al. 2002).



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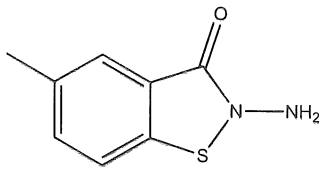

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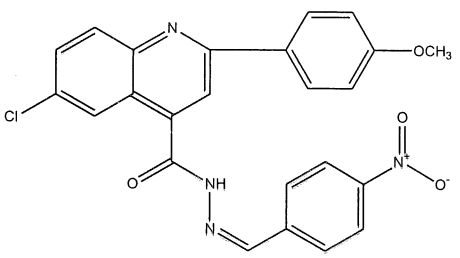
Metwally et al. (2006) synthesized a new series of 2-arylquinoline-4-carboxalic acid hydrazid-hydrazones and evaluated for their *in vitro* antimicrobial activity against *Staphylococcus aureus, Escherichia coli* and *Candida albicans*. Out of the synthesized compounds 6-chloro-2-(4-methoxyphenyl) quinoline-4-carboxylic acid (4-nitrobenzylidene)-hydrazide (**5**) was found to be most potent.

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 aureus* by Masunari *et al.* The results of antimicrobial study indicated that 4-Acetyl-benzoic acid [(5-nitro-thiophen-2-yl)-methylene]-hydrazide (**6**) was the most active compound (Masunari et al. 2007).



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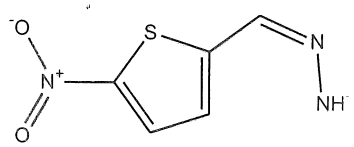

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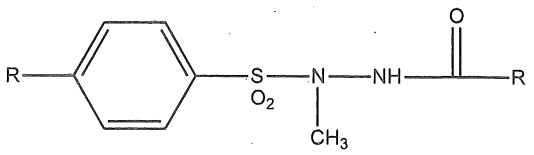
Zareef et al. (2008) synthesized derivatives of acylhydrazine such as substituted-2-mercapto-1,3,4-oxadiazoles, their corresponding ester, amide and benzenediasulfonamides and tested them for antimicrobial activity which showed that one of the acylhydrazine benzenediasulfonamide derivative (**7**) was having appreciable antimicrobial activity.



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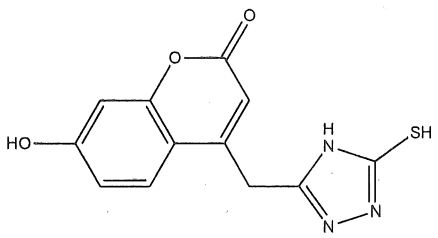
(7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid hydrazide derivatives were synthesized and screened for their antimicrobial activity against *Staphylococcus pneumoniae, Pseudomonas aeruginosa, Bacillus subtilis* and *Bacillus cereus* by Cacic et al. (2006). They found that 7-Hydroxy-4-[(5-mercapto-4H-1,2,4-triazol-3-yl)methyl]-2H-chromen-2-one (**8**) and 7-Hydroxy-4-[(5-mercapto-4H-1,3,4-oxadiazol-2-yl)methyl]-2H-chromen-2-one (**9**) were having good antimicrobial activity.



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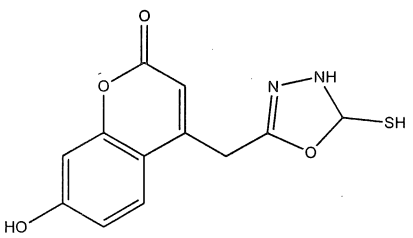
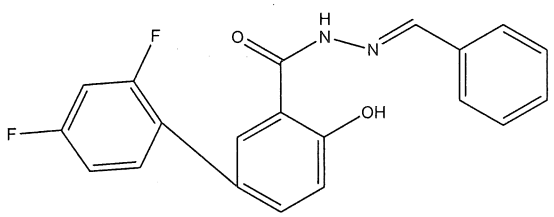


9

Hydrazides as antimycobacterial agents

Tuberculosis (TB) is the most prevalent infectious disease worldwide and a leading killer caused by a single infectious agent, that is, *Mycobacterium tuberculosis*. Patients develop resistance to 1st and 2nd line drugs. This stimulated researchers to search for new effective antitubercular agents. Kucukguzel et al. (2003) synthesized several diflunisal hydrazide-hydrazone derivatives namely 2',4'-difluoro-4-hydroxybiphenyl-3-carboxylic acid [(5-nitro-2-furyl/substitutedphenyl) methylene]-hydrazide. All the compounds were screened for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA). The results showed that 2',4'-difluoro-4-hydroxy-biphenyl-3-carboxylic acid benzylidene-hydrazide (**10**) exhibited appreciable antimycobacterial activity.



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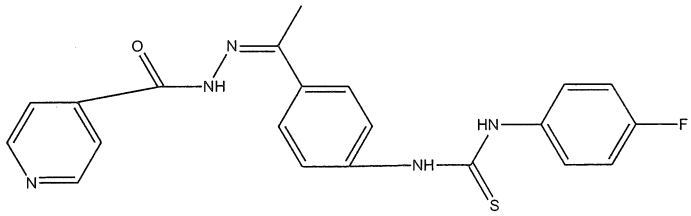
Sriram et al. (2006) synthesized various isonicotinyl hydrazones by reacting isonicotinyl hydrazide [INH] with 1-(4-acetylphenyl)-3-[(4-sub)phenyl]thiourea and tested for their antimycobacterial activity *in vitro* against *Mycobacterium tuberculosis* H37Rv and INH-resistant *M. tuberculosis* using the BACTEC 460 radiometric system. The results indicated that

1-(4-fluorophenyl)-3-(4-{1-[(pyridine-4-carbonyl)-hydrazono]ethyl}phenyl)thiourea (**11**) was found to be the most potent compound with a minimum inhibitory concentration of 0.49 μM.



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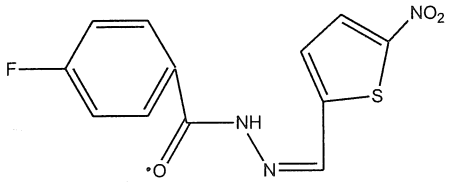
Bedia et al. (2006) synthesized a series of hydrazide–hydrazones, based on a series of 4-substituted benzoic acid and screened for their antituberculosis activity against *Mycobacterium tuberculosis* H37Rv with the help of the BACTEC 460 radiometric system. In this series, 4-fluorobenzoic acid [(5-nitro)thiophen-2yl)-methylene]hydrazide (**12**) showed the highest inhibitory activity with percentage inhibition of 99 %.

In a study of substituted isonicotinyl hydrazide derivatives as antimycobacterial agents against *Mycobacterium tuberculosis, Mycobacterium avium* and *Mycobacterium interacellulare* using agar dilution method, pyrazine-2-carboxylic acid N'-(4-chloro-benzylidene)-N-(pyridine-4-carbonyl)-hydrazide (**13**) showed maximum activity against tested organisms (Sinha et al. 2005).



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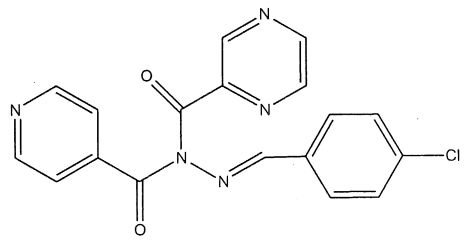

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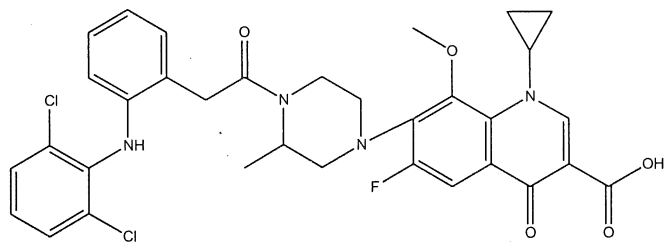
Various diclofenac acid hydrazones and amides were synthesized and evaluated for *in vitro* and *in vivo* antimycobacterial activities against *Mycobacterium tuberculosis* (Sriram et al. 2006).

The results showed that 1-cyclopropyl-6-fluoro-8-methoxy-7-[[N^4-(2-(2-(2,6-dichloro phenylamino)phenyl)acetyl)-3-methyl]-N^1-piperazinyl]-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**14**) was found to be the most active compound *in vitro* than first line antitubercular drug isoniazid. In the *in vivo* animal model, **14** decreased the bacterial load in lung and spleen tissues (Sriram et al. 2006).



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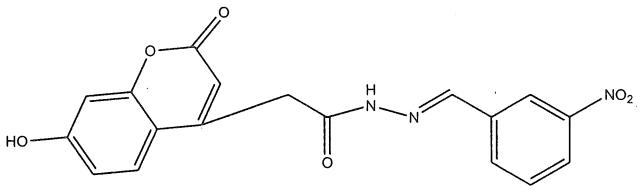
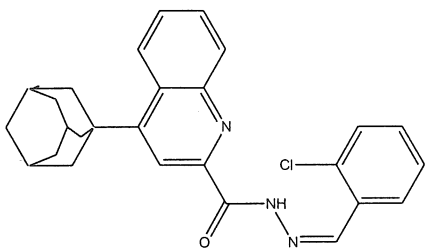
During the coumarin-4-acetic acid benzylidene hydrazides as anti-tubercular agents against *Mycobacterium tuberculosis* H37Rv strain using the BACTEC 460 system, (7-Hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid (3-nitro-benzylidene)-hydrazide (**15**) was found to be most potent with MIC and percentage inhibition of 6.25 μg/mL and 93 % respectively (Manvar et al. 2008).



15

In an effort to optimize previously identified lead, 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 (**16**) inhibited drug-sensitive *Mycobacterium tuberculosis* H37Rv at 1.00 μg/mL (99 % inhibition) and was equipotent to standard drug isoniazid.



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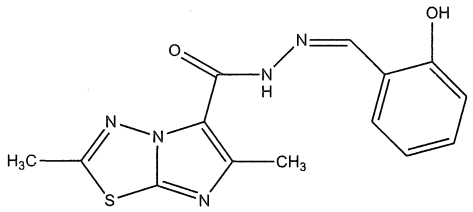
Hydrazides as antitumour agents

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.

Terzioglu et al. synthesized some novel 2,6-dimethyl-N-substituted phenylmethylene-imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazides from 2,6-dimethyl imidazo-[2,1-b][1,3,4]-thiadiazole-5-carbohydrazide and screened them for anticancer activity. 2,6-Dimethyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carboxylic acid (2-hydroxy-benzylidene)-hydrazide (**17**) showed the most favorable anticancer activity among the tested compounds (Perziogle et al. 2003). Vicini et al. (2006) synthesized several benzo[d]isothiazole hydrazones and evaluated for their potential antiretroviral activity. Among the synthesized compounds benzo[d]isothiazole-3-carboxylic acid (4-methoxy-benzylidene)-hydrazide (**18**) was 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.



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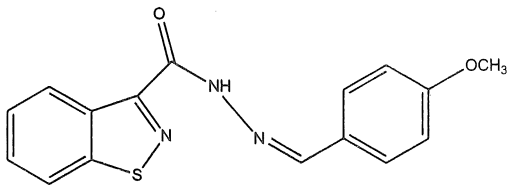

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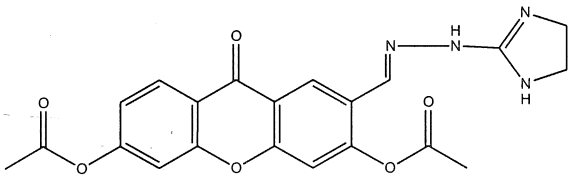
In order to explore the antiproliferative effect associated with the xanthone framework, several aryl hydrazonomethyl derivatives were synthesized from various isomeric 1,3-dihydroxyxanthone carbaldehydes by Lembege et al. (2007). The synthesized compounds were tested for their *in vitro* antiproliferative activity using the MTT colorimetric method against two human cancer cell lines (MCF-7, breast adenocarcinoma, and KB 3.1, squamous cell oral carcinoma) for two time periods (24 h and 72 h). Among the series, 6-((2-(4,5-dihydro-1H-imidazol-2-yl)hydrazono)-methyl)-9-oxo-9H-xanthene-1,3-diyl diacetate (**19**) was having highest antiproliferative activity.

Sztanke et al. (2007) synthesized novel fused 1,2,4-triazine aryl derivatives containing the ethoxycarbonyl and carbohydrazide formations. The *in vitro* anticancer evaluation of these compounds using BrdU method for human LS180, SiHa and T47D carcinoma cells indicated that 8-(3-Chloro-phenyl)-4-oxo-4,6,7,8-tetrahydro-imidazo[2,1-c][1,2,4] triazine-3-carboxylic acid hydrazide (**20**) exhibited remarkable effect against SiHa and LS180 tumour cells.



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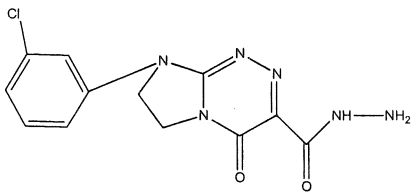

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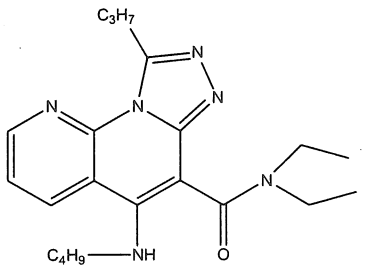
Hydrazides as analgesic and anti-inflammatory agents

Roma et al. (2000) synthesized substituted heterocycles by the reaction with hydrazides and screened for their anti-inflammatory activity using carrageenin induced paw edema assay in rat. Among these 5-Butylamino-1-propyl-2,3,9,9b-tetraaza-cyclopenta[a]naphthalene-4-carboxylic acid diethylamide (**21**) and 5-Ethylamino-1-propyl-2,3,9,9b-tetraaza-cyclopenta[a]naphthalene-4-carboxylic acid diethylamide (**22**) were found to be most active.



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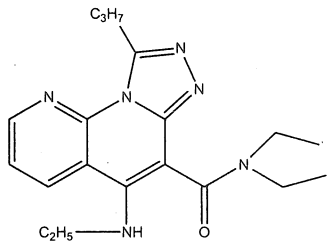

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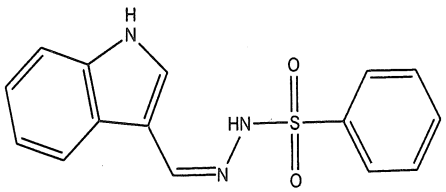
Sunidhi et al. (2006) synthesized a number of substituted hydrazides and screened them for their anti-inflammatory activity using carrageenan induced paw edema assay and observed that N'-((1H-indol-3-yl)methylene)benzenesulfonohydrazide (**23**) and N'-((1H-indol-3-yl)methylene)-4-methyl-benzenesulfono hydrazide (**24**) were exhibited good anti-inflammatory and analgesic activities respectively.



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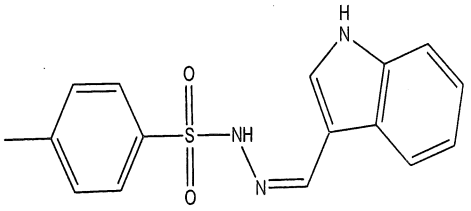

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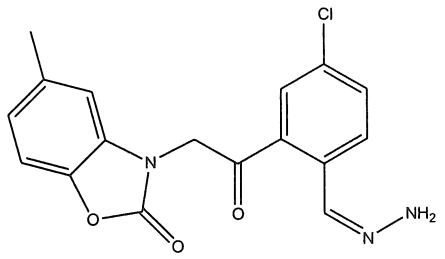
Salgin-Goksen et al. (2007) synthesized arylidene hydrazides as cis–trans conformers and evaluated for their analgesic, anti-inflammatory and antimicrobial activities. Among the synthesized compounds, 2-[2-(5-Methyl-2-benzoxazolinone-3-yl)acetyl]4 chlorobenzylidene hydrazine (**25**) showed good analgesic activity. They have also observed that good anti-inflammatory activity was exhibited by 2-[2-(5-Methyl-2-benzoxazolinone-3-yl)acetyl]-4-methoxybenzylidene hydrazine (**26**) in carrageenin induced paw edema model.



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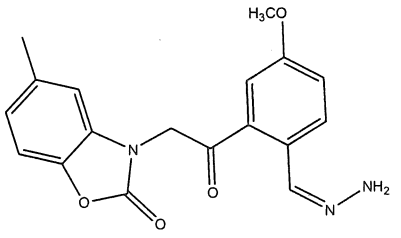

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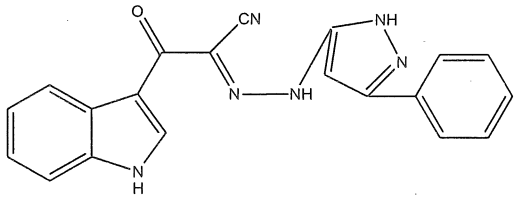
Treatment of 3-cyano acetylindole with diazonium salts of 3-phenyl-5-amino pyrazole and 2-amino pyrazole gave the corresponding hydrazones. Out of the synthesized compounds, 3-(1H-Indol-3-yl)-3-oxo-2-[(5-phenyl-2H-pyrazol-3-yl)-hydrazono]-propionitrile (**27**) was found to possess appreciable analgesic and anti-inflammatory activity (Radhwan et al. 2007).



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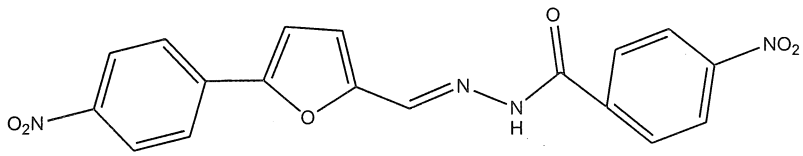
Hydrazides as trypanocidal agents

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 IC_{50} values <40 μM were tested for their efficacy against blood stream forms of *Trypanosoma brucei* in 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]-hydrazide (**28**) was comparable to those of commercial drugs sumarin and diminazine aceturate.



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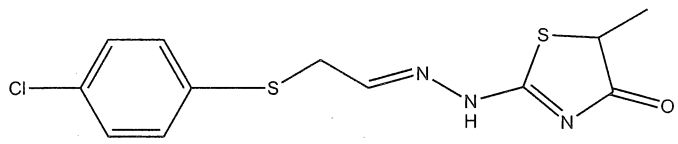
Chagas disease is a serious health problem that affects around 20 million people in Central and South Americas. The protozoan *Trypanosoma cruzi* is the causative agent of this disease. Current therapy is based on nifurtimox and benznidazole, drugs capable of eliminating parasitaemia and reducing serological titers in the acute phase of infection but not effective for all *Trypanosoma cruzi* strains, especially in the chronic phase of infection. 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 (**29**) exhibited significant *in vitro* activity against epimastigot *Trypanosoma cruzi*.



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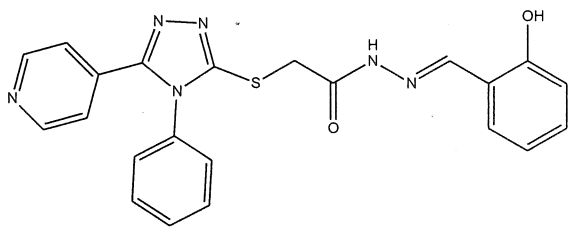
Hydrazides as leishmanicidal agents

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] (**30**) and trans [Pt(Hpy2)2 (Cl)2] (**31**) 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.) mexicana* were 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.

Hydrazides as anti-HIV agents

HIV-1 integrase (IN) is a critical enzyme for viral replication. This intiated Masawi 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 (**32**), displayed weak HIV-1 integrase inhibitory activity (Al-Macrosaur et al. 2007).



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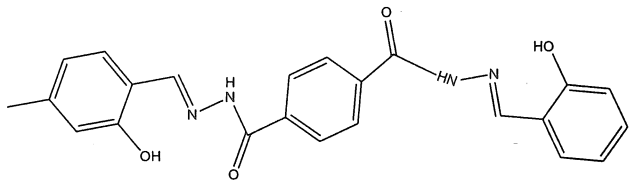
Hydrazides as inhibitor of anthrax lethal factor

Inhalation of *Bacillus anthracis* spores 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 lymphonode 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 anthracis* spores.

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 that **33** showed an appreciable activity.



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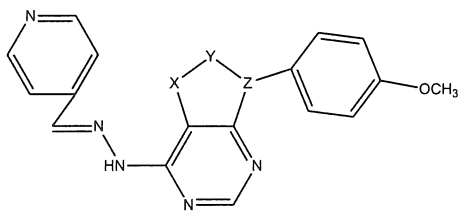
Hydrazides as antidiabetic agents

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 pyrimidyl hydrazones (**34**) as 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.

Hydrazides as antimalarial agents

Malaria is a disease caused by parasitic protozoa of the genus *Plasmodium* which afflicts more than 500 million people worldwide, causing approximately 2 million deaths each year. For decades, chloroquine (CQ) provided reliable prophylaxis for travelers and therapy for those with established infection. However, the emergence in the early 1960s and subsequent spread of CQ-resistant parasites created a tremendous therapeutic void. As a result, there is an urgent need for the rapid development of effective, safe and affordable chemotherapeutics. 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 **35** was the most active compound of the series.



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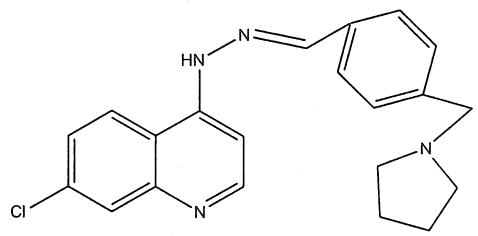

35

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