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A SYSTEMATIC REVIEW ON THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF HYDRAZIDE DERIVATIVES

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ABSTRACT

Plan: *A systematic review on the synthesis and biological activity of hydrazides and their derivatives.*

Preface: *The chemistry of hydrazide and its derivatives has obtained great interest in both organic chemistry and biological science with remarkable impact. The development of novel organic compounds with antimicrobial, antiviral, anti-inflammatory, anti-tubercular, antibacterial, antifungal activities have been of great interest and pharmaceutical importance. Hydrazides and hydrazones are possessing an $NHNH_2$ and NHN=CH- groups respectively. The availability of proton in hydrazides constitutes them as an important class of compound for new drug discovery. Therefore, researchers have showed great interest in developing these compounds as target structures for evaluating new biological activities.*

Outcome: *This review emphasizes on various methods of synthesis and several biological activities possessed by hydrazide and hydrazone derivatives, which may help the researchers for the design and development of novel hydrazides as potential candidate in pharmaceutical science.*

1. INTRODUCTION

Hydrazides are important class of functional groups in organic chemistry possessing$NHNH_2$ and NHN=CH- groups with the availability of proton that aids to their pharmaceutical importance. The remedial possibilities of acid hydrazides gained momentum after the innovation of Isonicotinic acid hydrazide (INH). The remarkable clinical value of INH [1] stimulated the study of other heterocyclic hydrazides possessing mono-cyclic nuclei like furan, pyrrole, thiophene and dicyclic nuclei like quinoline and isoquinoline.

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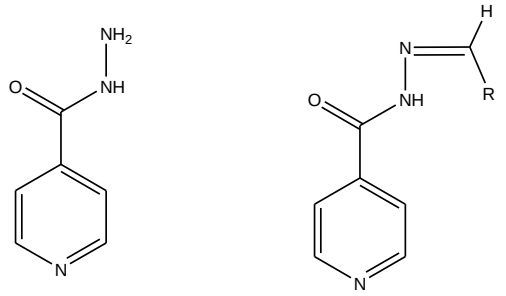
Many of such compounds have been prepared in pure form with wide spectrum of therapeutic effects. The synthesis is accomplished by 1 and 4 substituted pyridine derivatives correlated with INH and isonicotinoyl hydrazones of some aldehydes (Figure. **1**). These compounds were prepared by Yale *et al*.[2] to test the probable growth-inhibiting properties of the compounds (1) and (2) against *Mycobacterium. Tuberculosis.*



(1) **(2)**

Fig 1.Isonicotinoylhydrazones (INH) of substituted aldehydes.

The anti-tubercular activity of INH was not due to the pyridine nucleus but it stimulated the synthesis of a large number of hydrazides and other derivatives of similar structure. In addition to the activity against the *Tubercule bacilli*, their effect on other bacteria has also been studied. Some novel substituted 1, 3,4-oxadiazole and pyrazole synthesized from salicylic acid hydrazide and their derivatives evaluate for antitubercular activity[3], Synthesis and structure modification of salicylic acid hydrazides and modification of thiosemicarbazides of salicylic acid allow the preparation of the new derivatives of triazole and thiazole series and evaluate their various biological activity[4], analgesic[5], fungistatic[5] and diuretic[6] activities. Nasr *et al.*[7] synthesized a new series of coumarin bearing hydrazide–hydrazone moiety and evaluated them against human drug-resistant pancreatic carcinoma (Panc-1) cells and drug-sensitive (hepatic carcinoma; Hep-G2 and leukemia; CCRF) cell lines *in vitro*. Bromocoumarins were found to be the most active antitumor agent against drug-resistant pancreatic carcinoma cells. Two new acetyl pyridine hydrazones derived from cyano acetic acid hydrazide have been synthesized and evaluated at The National Cancer Institute, USA against full panel of 60 human tumor cell lines. Few compound demonstrated the most effect on prostate cancer cell line. Maleic acid hydrazide[9] was established as a growth regulator in plants. Some new benzylidene hydrazides[10] were reported as CNS active and anti-inflammatory agents (as shown in **(3)** Fig**2**). Synthesis and antimicrobial screenings of some new hydrazides were reported by Senguptaetal.[11] A new N'-Acetyl propane sulfonic acid hydrazide[12] and other acid hydrazides[13] showed potential antibacterial activity. Şenkardeş *et al.*[14] have designed a number of 2′,4′-difluoro-4-hydroxy-N'-(arylmethylidene)biphenyl-3-bohydrazide as anti-HCV and anticancer agents. Some hydrazides of (acridinyl-9-thio) acetic acid[15] proved to be moderately toxic and produced neurotropic, anti-inflammatory, analgesic, anti-microbial and fungi static effects. Certain 6-hydroxybenzofuran-5-carboxylic acid esters on treatment with diazomethane gave hydrazides [16] which were antifungal and possessed antiaflatoxinas shown in **(4)** & **(5)** Fig**2**.

Herman's *et al.*[17] marked that transformation efficiency of *Mycobacterium aurum* was increased tenfold by using the much renowned INH. Certain N-aryl glycylhydrazides[18] inhibited the growth of *Mycobacterium smegmatis*. Hydrazide also possess anti-helmintic[19-20] anti-diabetic [21] and anti-tumor[22] activities. A new radio iodinated hydrazide[23] showed good localization in tumor tissues when injected into mice bearing human cancer zero graft. The aroylhydrazone chelator 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone showed greater antimalarial agent activity than desferrioxamine against chloroquine-resistant and sensitive parasites [24]. Murtaza *et al.*[25] synthesized new sulfonyl hydrazide their novel derivatives and they also have investigated the biological activities such as antioxidant, antibacterial, enzyme inhibition and study, recently Islam *et al.* reported the design, synthesis, and biological evaluation of phenolic hydrazide hydrazones as potent Poly(ADP-ribose) polymerase (PARP) inhibitors[26]. A series of bis (indolyl) hydrazide–hydrazones were synthesized and evaluated for their cytotoxicity against selected human cancer cell lines [27]

1.1. Condensation Products of Hydrazides

The condensation products of a large number of hydrazides with various aldehydes and ketones were being reported by Buu Hoi *et al* [28]. The condensation products- hydrazones were found to be less toxic than the parent hydrazides due to blocking of the free-NH_2 group. Sunidhi *et al*. 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) benzenesulfono hydrazide and N'-(1H-indol-3-yl)methylene)-4-methyl-benzenesulfono hydrazide were exhibited good anti-inflammatory and analgesic activities respectively[29]. Hydrazides were also found to possess antitumor and anti-diabetic activities [30]. A survey of literature reveals that extensive work has been done on hydrazones which show a wide range of biological activity variations. Hydrazones were found to possess antibacterial properties [31-35]. In addition, they have also been reported to possess antifungal [36-38], antiviral [39-40] as well as insecticidal activity [41-42].

Hydrazones of isoniazide with dicarbonyl compounds such as methyl and dimethyl glyoxals, acetyl acetone and succinic aldehyde were synthesized by Hofmann *et al.*[43]. Hydrazones of INH with various aldehydes like acrolein, acetonal, anisaldehyde and 4-nitro salicylaldehyde were prepared by Libermann *et al*.[44] but none of these derivatives were found to be as active as INH itself. Supniewski *et al*.[45] synthesized the hydrazides of pyridine carboxylic acid and their hydrazones with different aromatic aldehydes. The hydrazones were found to inhibit partially or completely the growth of *S. aureus, E. coli* and *B. subtilis*. Also quinoline-8-thioglycollyl hydrazones[46-48] too possesses antimicrobial properties (as shown in **(6)** Figure **2**). Shah *et al.*[49] has reported the antimicrobial property of formazans from Mannich base of 5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole which synthesized from hydrazide 3-amino methyl-5-(4-chloro phenyl amino)-2-mercapto-4′-(2′,6′-dinitro phenoxy)-acetyl hydrazide. Maximo da Silva and coworkers[50] have observed that galloyl hydrazides derivatives possess antiproliferative Activity. In addition to this pyruvic acid hydrazones are used as cardiovascular drugs[51] and synthesis of series of 5-methylpyrazine-2-carbohydrazide derivatives.

In vitro anti-tubercular activity was evaluated against Mycobacterium tuberculosis (H37Rv) in Middle brook 7H-9 broth medium. Amongst synthesized compounds, seven compounds showed remarkable anti-tubercular activity [52].

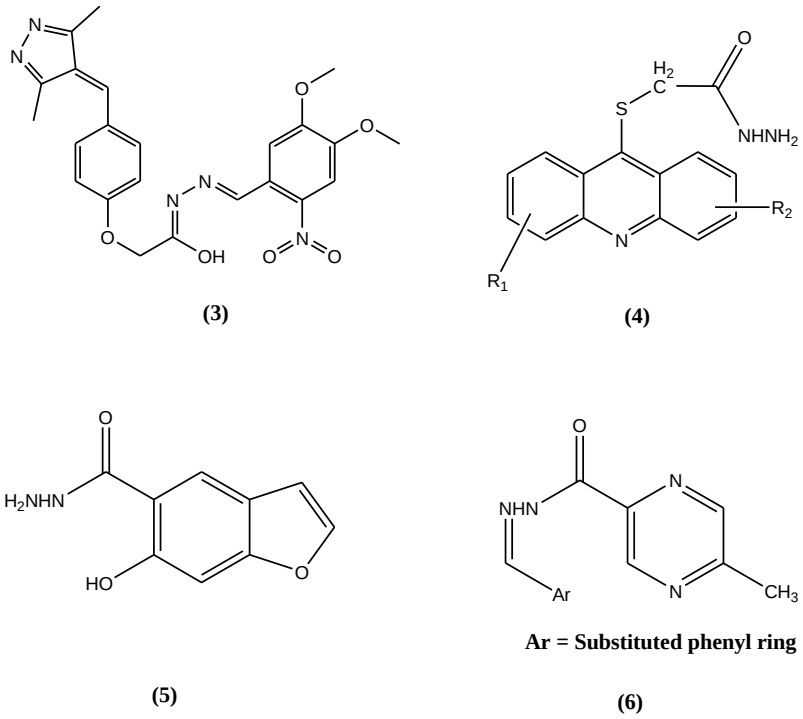


Fig 2. Hydrazides and Hydrazones with anti-inflammatory and antimicrobial activity.

Hydrazine derivatives are reported to be potent inhibitors of mono-amine oxidase enzyme showing appreciable anti-convulsant activity [53]. A new series of 2-arylquinoline-4-carboxylic acid hydrazide–hydrazones was synthesized using an appropriate synthetic route. All the target compounds were evaluated for their in vitro antimicrobial activity. Verma *et al.*[55] reported the virucidal activity of certain hydrazones. Utku *et al*.[56] synthesized and evaluated the acetylcholinestearase inhibitory activity of some substituted hydrazones. The reaction of the aryl sulphonyl hydrazide **(7)** with the acetylenic ester in the presence of triphenyl phosphine gives the corresponding derivatives of hydrazine **(8)** in good yield[57] as shown in Figure 3. Decyclization of 5-aryl-2,3-dihydrofuran-2,3-diones under the action of p-toluenesulphonyl hydrazides **(9)** in anhydrous dioxane afforded β-N-(4-methylphenylsulphonyl) hydrazides **(10)** of aroylpyruvic acid which showed anti-inflammatory and antimicrobial activity[58].

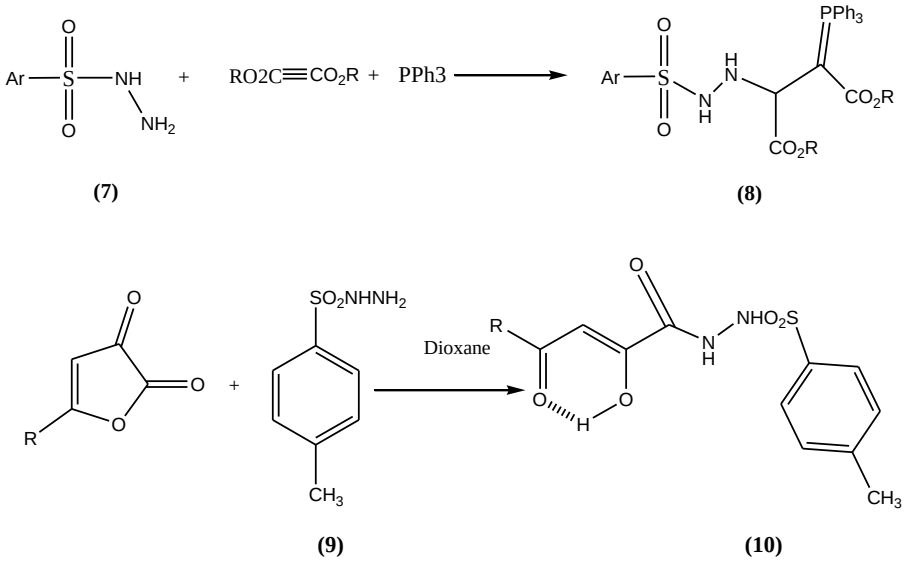


Fig 3. Decyclization action of Sulphone hydrazides.

1.2. Pyrazine Based Hydrazide Derivatives

Ozdemir *et al.*[59] synthesized some new imidazo[1,2-a]pyrazines based hydrazide derivatives **(11)** and assessed its antifungal and antibacterial activity. The chemical reaction of imidazo[1,2-a]pyrazine-2-carboxylic acid hydrazides with several arylaldehydes gave compounds like **(11)** with various substitutions at R1, R2, R3 and R4 as shown in Figure **4**. Kaplancikli *et al*[60] synthesized new hydrazide derivatives of the series of compounds and evaluated comparatively for their anti-inflammatory, antifungal and cytotoxic activities. The evaluation of anti-inflammatory activity was done in terms of inhibition of NF-κB, Reactive oxygen species (ROSs) generation and inducible nitric oxide synthase (iNOS) enzyme activity. Several derivatives inhibited NF-κB and iNOS, but there was no effect observed on intracellular ROS generation and no cytotoxicity was observed. Furthermore, the antifungal activity of hydrazide derivatives was evaluated by bio autography and a broth micro dilution assays against plant pathogens. In-depth dose response studies at micro molar concentration showed that hydrazide derivatives were more active against *Phomopsisobscurans* and *P. viticola* than other tested fungi. The results of the biological evaluations compared with the chemistry suggested that groups substituted on the phenyl ring influenced the physicochemical properties and thus contributed to the biological activity as shown **(12)** and **(13)** Figure **4**. Abdel-Aziz *et al.*[61] optimized and identified a series of pyrazine-2-carboxylic acid hydrazide derivatives **(14)** and determined their biological activity against *M. tuberculosis* in BACTEC 12B medium by broth microdilution assay.

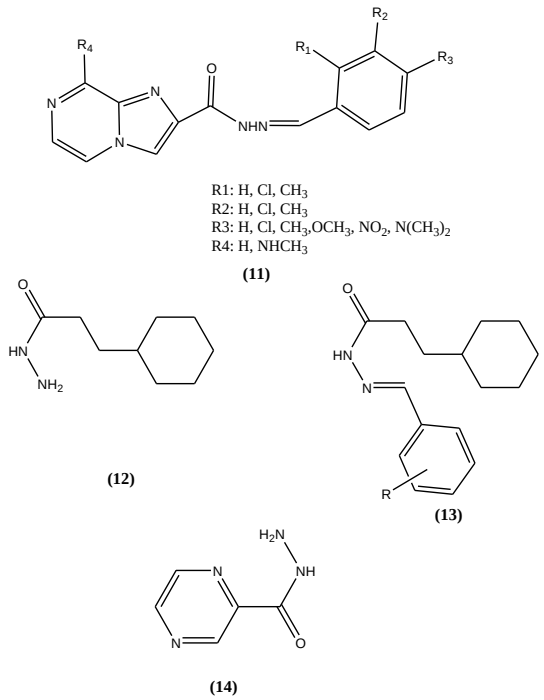


Fig 4. Carboxylic acid substituted hydrazides (12) & (13) and Pyrazine Based Hydrazide Derivatives (11) & (14).

1.3. Acyl Hydrazone Derivatives

Bonacorso. *et al*.[62] reported the reactivity study on 6-hydrazinonicotinic acid hydrazide hydrate **(15)** and to prove it as a versatile precursor for some new interesting heterocycles **(16).** Thus, attempting to demonstrate the reactivity differentiation between the two dinucleophilic centers in the hydrazide hydrate. Moldovan. *et al*.[63] synthesized a series of novel acyl-hydrazine**(17), (18)** and **(19)** bearing 2-aryl-thiazole moiety formed by the condensation of 4-[2-(4-methyl-2-phenyl-thiazole-5-yl)-2-oxo-ethoxy]-benzaldehyde derivatives and 2, 3 or 4-(2-aryl-thiazol-4-lmethoxy)-benzaldehyde and different carboxylic acid hydrazides. The formed products were studied for their *in vivo* anti-inflammatory activity and in an acute experimental inflammation. The phagocytic activity of bone marrow response at acute phase and NO synthase (iNOS) inhibitors were evaluated. Three compounds **(17), (18)** and **(19)** inhibited NO (iNOS) synthesis stronger than meloxicam which is commonly used as reference drug for anti-inflammatory activity as shown in Figure **5**.

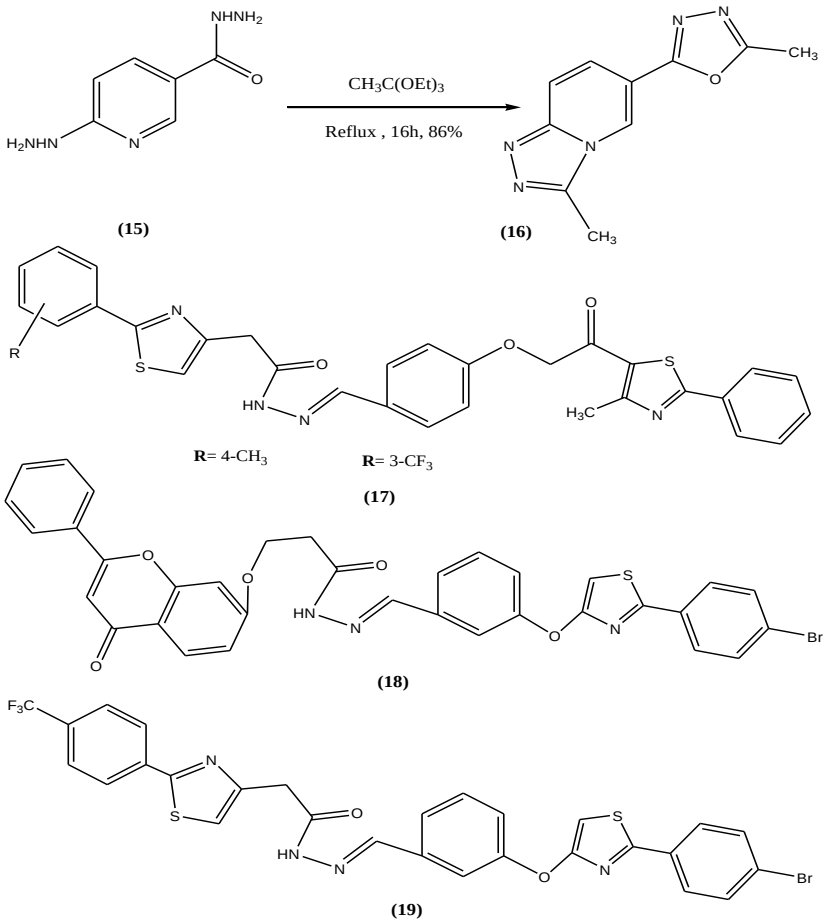


Fig 5.Hydrazinonicotinic acid hydrazide (16) Acyl-hydrazones bearing 2-aryl-thiazole moiety*1.4.*

Carbohydrazides Derivatives

Number of alicyclic, aliphatic, aromatic and heterocyclic carbohydrazides and their derivatives are reported which present a number of biological activities [64-77]. Hence, different carbohydrazides prepared were found to be useful in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, haemorrhage and sepsis[73]. Carbohydrazides and related compounds **(20)** and **(21)** exhibited anti-fungal[64], anti-viral[76], bacteriostatic[64,69,71,76], anti-parasite[64-72], anti-tuberculous[65-68], psychotropic[64] and insecticidal[77] activities. Abdel-Zaher *et al*.[77] studied the chemistry of carbofunctionally substituted hydrazones **(22)** and **(23)**.

Rollas *et al*.[78] studied various biological activities of hydrazone derivatives **(24)** like anti-convulsant, anti-depressant, analgesic, anti-inflammatory, anti-platelet, anti-malarial, anti-microbial, anti-mycobacterial, anti-tumoral, vasodilator, anti-viral and schistosomiasisas shown in Figure **6**.

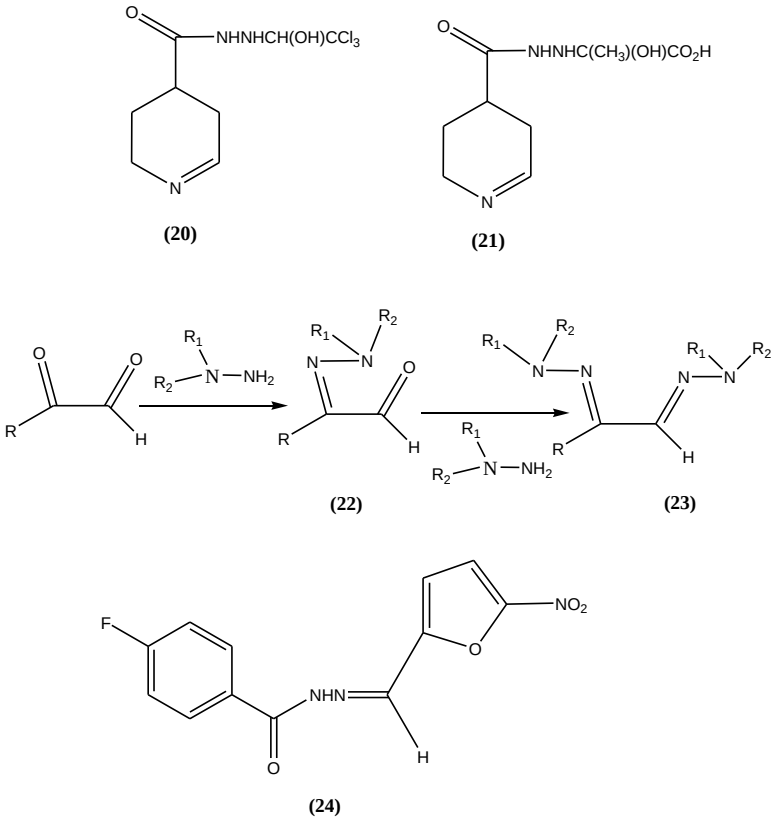


Fig 6. Some carbofunctional derivatives of hydrazides.

1.5. Coumarin and Indole Based Hydrazone

Kotali *et al*.[79-81] synthesized some 7-Hydroxy-8-acetylcoumarin substituted hydrazones and the anti-leucemic activity of 7-Hydroxy-8-acetylcoumarin benzoylhydrazone**(25)** was studied**.** Gurkok *et al*.[82] investigated antimicrobial activities of Indole-3-Aldehyde hydrazide/hydrazone derivatives **(26)** and **(27).** Küçükgüzel *et al*.[84] synthesized diflunisal hydrazide-hydrazone derivatives. 2,4-Difluoro-4-hydroxybiphenyl-3-carboxylic acid [(5-nitro-2-furyl)methylene] hydrazide **(28)** has shown activity against *S. epidermis* HE-5 and *S. aureus* HE-9 at 18.75 µg/mL and 37.5µg/mL, respectively. 2,4-Difluoro-4-hydroxybiphenyl-3-carboxylic acid [(2,4,6-trimethylphenyl)methylene]hydrazide has shown biological activity against *Acinetobacter calcoaceticus*IO-16 at a concentration of 37.5 µg/mL.

Cefepime which was used as the standard drug was found to show less activity against the same microorganism as shown in Figure **7**.

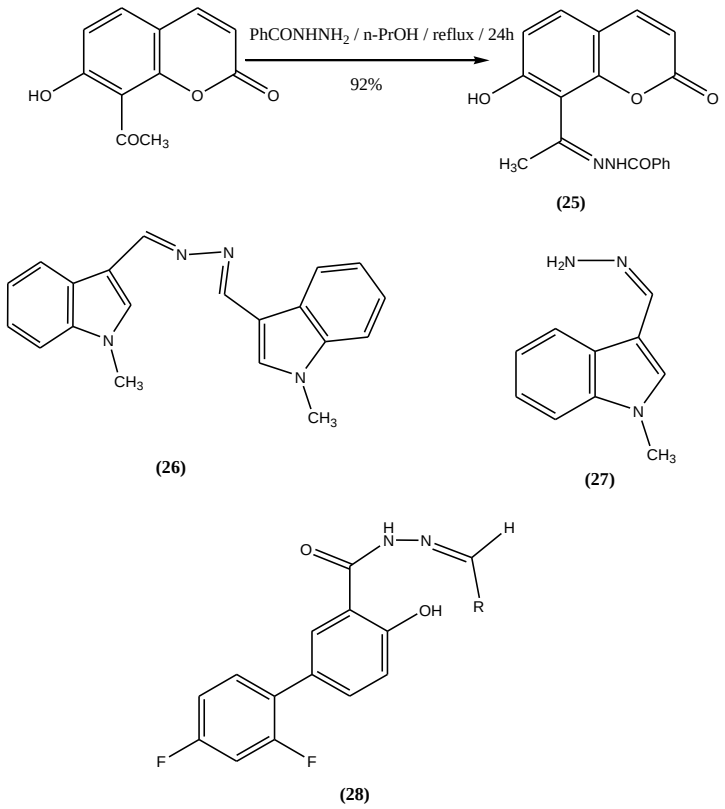


Fig 7. Coumarin and indole based hydrazone derivatives

Sudha *et al.*[85] synthesized coumarin-oxadiazole compounds **(29)** and all compounds derived from 2-oxo-2H-Chromene-3-Carbohydrazides **(30)** which showed good *in vitro* antihelmintic activity as shown in Figure **8**.

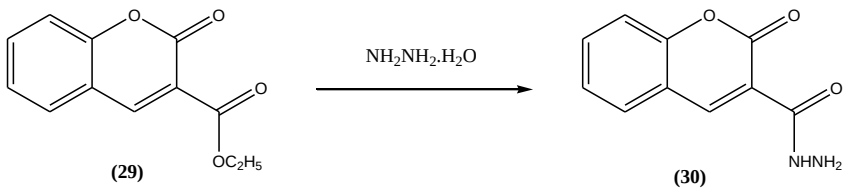


Fig 8. Chromene-3-carbohydrazide obtained from chromene-3-carboxylate*1.6. Derivatives of Hydrazides of Benzotriazole:*

Tiwari *et al.*[86] reported microwave synthesis of pyrazole containing benzotriazole moeities which is achevied by cyclocondesation of substituted chalcones with hydrazide of benzotriazole in presence of galcial acetic acid. The hydrazide based synthesized compounds were analyzed for their antibacterial and antifungal activities against various microbes as shown in Figure **9**.

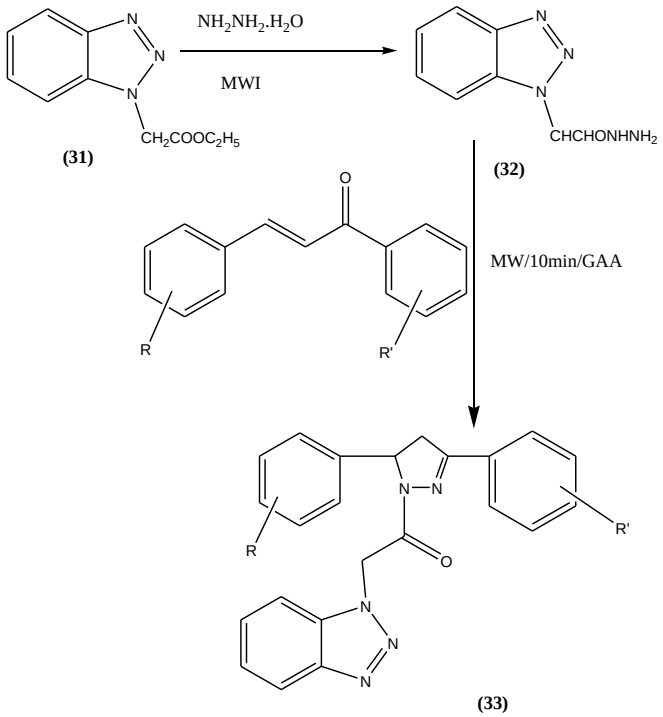


Fig 9.Cyclocondesation of substituted chalcones with hydrazide of benzotriazole

1.7. Substituted Derivatives of Hydrazides

Kumar *et al.*[87] synthesized some new 2,5-disubstitued 1,3,4-oxadiazoles from (3-arylsulfonyl) propane hydrazides **(34)** and **(35).** Two new series of 2,5-disubstitued 1,3,4-oxadiazoles from [3-(4-chlorophenyl)sulfonyl] propane hydrazide and [3-(4-methylphenyl)sulfonyl] propane hydrazide **(36)** have been synthesized and tested for antimicrobial activities as shown in Figure **10**.

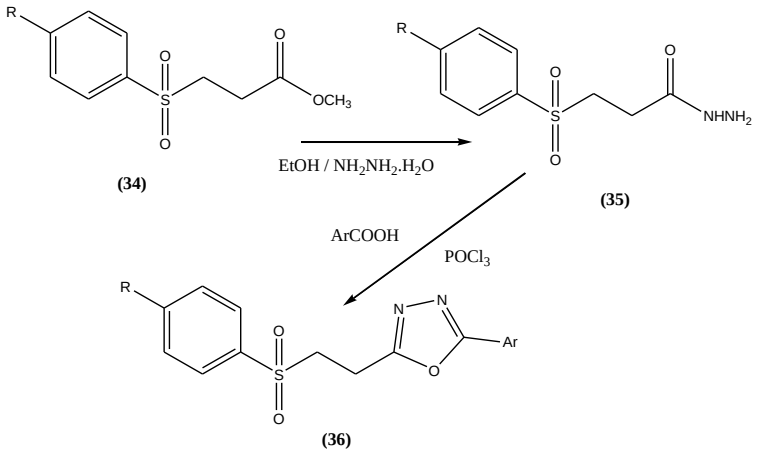


Fig 10. Substituted oxadiazoles from 3-arylsulfonyl propane hydrazides.

Maddela *et al.*[88] reported ten new N'-subtituted-2-methylquinoline-3-carbohydrazide **(38)** and screened for in vitro antimicrobial and antioxidant activities. The results clearly revealed that all ten compounds possess in vitro antioxidant activity at the tested dose as compared to the standard drug, ascorbic acid as shown in Figure **11**.

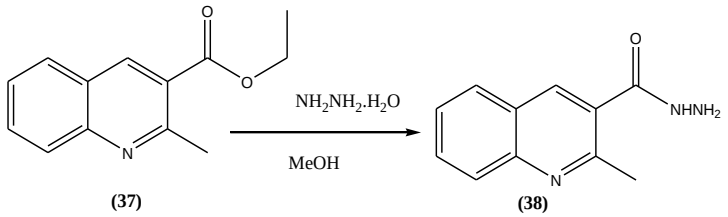
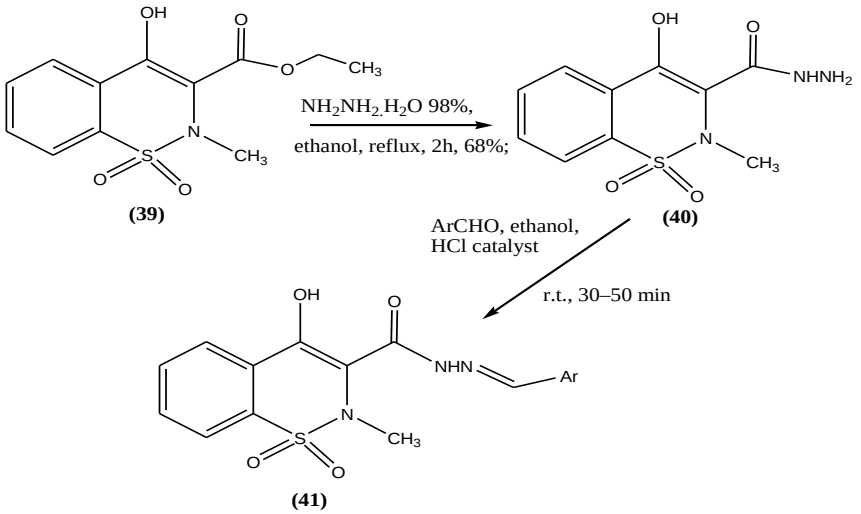


Fig 11. Reaction of substituted quinolone carboxylate with hydrazine hydrate.

Miranda *et al.*[89] synthesized a chain of N-acylhydrazones**41(a–h)** from commercially available compound **(39)** ethyl 4-hydroxy-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide in subsequent two steps, as given in Figure **12**. The main intermediate hydrazide (**40)** in 68% yield was obtained by treating with ethanol solution of compound **(39)** with 98% hydrazine monohydrate for 02 hours under reflux condition. Finally, condensation of compound **(40)** with suitable aromatic and heteroaromatic aldehydes at room temperature, in the presence of acid catalysis provided the target compounds **41(a–h)** with 48–63% overall yield of targeted compounds. The compound series were evaluated for the anti-inflammatory and anti-nociceptive activities. The pharmacological screening revealed that series of hydrazones exhibited better activity than standard drug piroxicam.



[(a-h) Ar = Phenyl, 2-pridinyl, 4-Isopropylphenyl, 4-Dimethylaminophenyl, 2-Thiophenyl, 2-Thiazolyl, 2-Biphenyl, 3,5-Diterbutyl-4-hydroxyphenyl)]

Fig 12.Reaction of hydroxylbenzothiazine-3-carboxylate1, 1-dioxide with hydrazine hydrate.

Kaushik *et al.*[90] synthesized a series of N'-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene] 2/4-substituted hydrazides **(42).** The anti-convulsant activity of the synthesized compound was analysed against maximal electroshock induced seizure (MES) and subcutaneous pentylenetetrazol (scPTZ) induced seizure modelsin mice. The neurotoxicity check was done using the rotorod method. Bala *et al.*[91] gave the synthesis of a novel series of substituted-*N*'-[(1E) substituted phenyl methylidene] benzo hydrazide **(43)** and evaluated for their *in vitro* anti-inflammatory, antioxidant and antimicrobial activities. Anti-inflammatory activity by employing diclofenac sodium as standard. Compounds **43c, 43d** and **43e** were reported to have good anti-inflammatory activity due to the presence of 4-nitro (c), 4-methyl (d), and 2-hydroxy groups (e), respectively, whereas **43e** was found to be the most active anti-inflammatory agent. Narang *et al.*[92] analyzed that the nicotinic acid hyrazide derivatives substituted with the nitro group at *meta* and *para* position **(44)** and **(45)**, respectively, were found to be the most active anti-inflammatory agents. The conclusion revealed that the substitution of nitro group and halogens group contributed to anti-inflammatory activity. Hamdy *et al.*[93] synthesized a series of (4-substituted phenyl) ethene-1,2-diyl) bis(4-substituted benzhydrazide), **(46)** by reaction of 2-chloro-1-(4-chloro phenyl)ethanone or 2-bromo-1-(4-bromophenyl)ethanone **(47)** with acid hydrazides. All the synthesized compounds were evaluated for the anti-inflammatory, analgesic, and ulcerogenic activities. Formalin induced 'rat paw oedema model' was selected and ketoprofen was employed as standard drug. All compounds were found to exhibit good anti-inflammatory property.

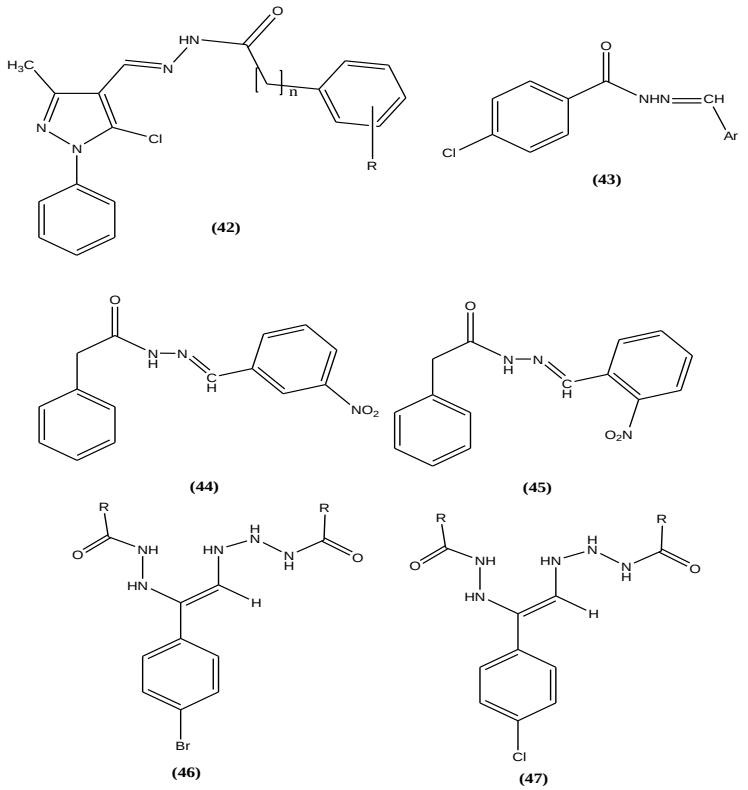
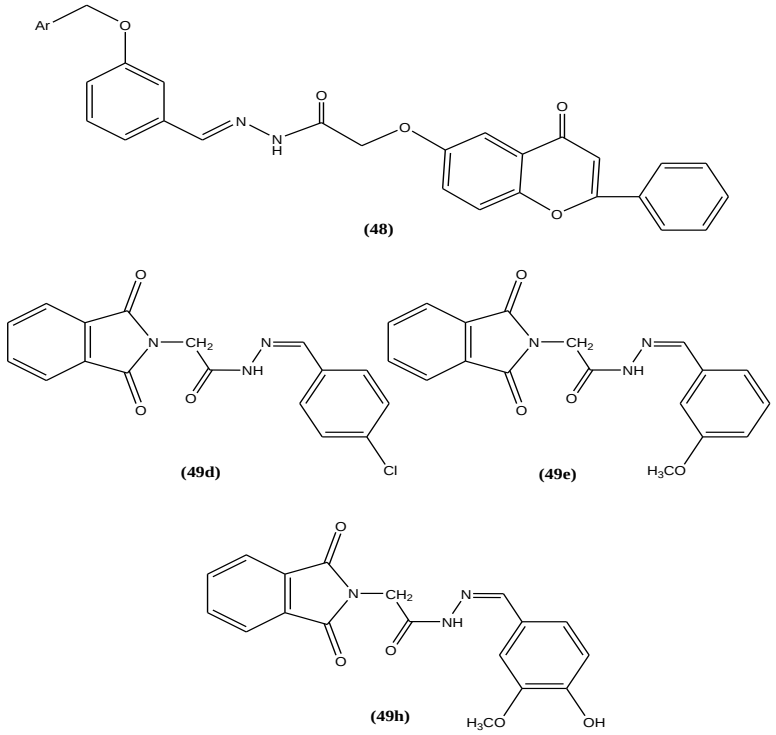


Fig 13. Substituted hydrazone derivatives.

Moldovan *et al.*[94] synthesized few novel acyl hydrazones possessing 2-aryl-thiazole moiety and found their NO inhibition property. During synthesis of NO, its % increases significantly in acute inflammation due to the expression of iNOS. The NO synthesis was significantly reduced by **48a,** and **48b** and except for **48a** all displayed a stronger inhibitory activity than meloxicam. Kajal*et al.*[95] synthesized a novel series of phthalic anhydride based substituted benzylidene-hydrazide derivatives, **49a–i**. All the synthesized derivatives were assessed for *in-vivo* anti-inflammatory and analgesic activities by carrageenan-induced 'rat paw edema' and 'tail immersion' methods using diclofenac sodium as standard drug. The results revealed that derivatives **49d, 49e**, and **49h** have shown potent anti-inflammatory activity with percentage inhibition of 58.6%, 61.4%, and 64.0%, respectively, which is comparable with standard drug diclofenac sodium, that is, 68.0%.



[(d-h) Ar = 2-C_6H_5-thiazol- 4-yl, 2-(4-Br-C_6H_5)-thiazol-4-yl)]

Fig 14. Some new acyl hydrazones bearing 2-aryl-thiazole moiety.

2. CONCLUSION

Hydrazide is a simple molecule and many of its derivatives have been known for more than a century. The literature review reveals that different substitued hydrazides and their derivatives possess potential biological activity which may range from anticonvulsant, antidepressant, analgesic, anti-inflammatory, anti-platelet, antimalarial, antimicrobial, anticonvulsant, anti-mycobacterial, anticancer, vasodilator, antiviral, anti-schistosomiasis, anti-HIV, anthelmintic, antidiabetic, and trypanocidal activities. The reported work shows the synthesis of biologically active heterocyclic hydrazide and their derivatives and their remarkable biological and clinical applications. This database in the form of review will help the researcher and academicians to develop new hydrazide and hydrazones derivatives.

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Mohd.Shahnawaz Khan*, Saba Parveen Siddiqui and Nazia Tarannum. A systematic review on the synthesis and biological activity of hydrazide derivatives. *Hygeia.J.D.Med* **2017**; 9(1):61-79. Available from http://www.hygeiajournal.com , DOI: 10.15254/H.J.D.Med.9.2017.165