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Hydrazone: A promising pharmacophore in medicinal chemistry

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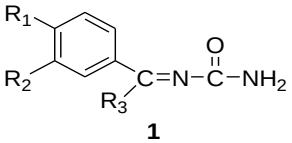
Abstract
Hydrazone is a privileged moiety and has significant position in the field of medicinal chemistry. Due to its worthy chemotherapeutic potential hydrazone receives much attention of today's researchers in the field of drug discovery and development. These observations may be helpful for the development of new hydrazones with potent biological activities.

Keywords: hydrazone; biological activity; importance

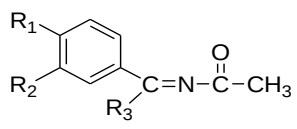
Introduction
Hydrazone moiety acquires a significant position in synthetic and medicinal chemistry. Hydrazone moiety constitute an "azomethine" R-C (H)=N-N(H)-Ar group which may be derivatives of aldehydes and ketones by replacement of oxygen atom with the $=NNH_2$ group. Hydrazones also act as intermediate for development of novel drugs [1]. The literature studies on hydrazones have shown that this class of compounds possess diverse biological and pharmacological properties such as anticonvulsant, antimycobacterial, antidepressant, anticancer, analgesic, anti-inflammatory, antiviral, antiplatelet, antimalarial, antimicrobial, cardio protective/vasodilator, anti-HIV, antihelmintic, antidiabetic, antiprotozoal, anti‑trypanosomal, antischistosomiasis [1-6] etc. Due to the synthetic flexibilities, selectivity as well as sensitivity toward the transition metal ions, hydrazone have been studied by the chemists for years [7]. Their metal complexes have potential applications as catalysts, luminescent probes, and molecular sensors [8-10]. The hybrids of hydrazones with other functional groups lead to compounds with unique physical and chemical character [11].
Owing to their chemotherapeutic value in the development of novel pharmacologically activities compounds, hydrazones have received much attention of synthetic chemist in the last few decades and still study is going on. This review is an attempt to study the synthetic as well as chemotherapeutic potential of hydrazones in biology and medicine.

Biological activity
Anticonvulsant activity
Dimmock *et al.* [12] have reported the synthesis and biological screening of various acetylhydrazones (1a-g) and semicarbazones (2a-l) found to afford good protection against convulsions.



1

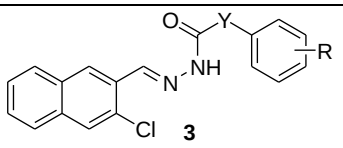
a) $R_1 = R_2 = R_3 = H$, b) $R_1 = Cl$, $R_2 = R_3 = H$,
c) $R_1 = R_2 = Cl$, $R_3 = H$, d) $R_1 = CH_3$, $R_2 = R_3 = H$,
e) $R_1 = OCH_3$, $R_2 = R_3 = H$ f) $R_1 = Br$, $R_2 = R_3 = H$,
g) $R_1 = R_2 = H$, $R_3 = CH_3$



2

a) $R_1 = R_2 = R_3 = H$, b) $R_1 = Cl$, $R_2 = R_3 = H$,
c) $R_1 = R_2 = Cl$, $R_3 = H$, d) $R_1 = CH_3$, $R_2 = R_3 = H$,
e) $R_1 = OCH_3$, $R_2 = R_3 = H$ f) $R_1 = Br$, $R_2 = R_3 = H$,
g) $R_1 = R_2 = H$, $R_3 = CH_3$, h) $R_1 = Cl$, $R_2 = H$, $R_3 = CH_3$,
i) $R_1 = R_2 = Cl$, $R_3 = CH_3$, j) $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$,
k) $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_3$, l) $R_1 = Br$, $R_2 = H$, $R_3 = CH_3$

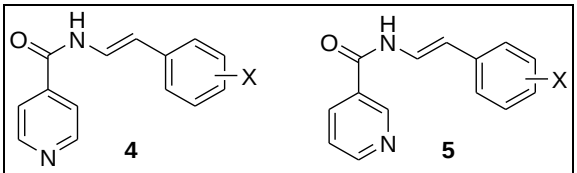
In another study, a series of differently substituted 2-chloroquinolinyl hydrazones 3a-l were synthesized and screened *in vivo* against electrical and chemical model of convulsions. Synthesized compounds were found very effective Anticonvulsant agent but activity decreases with introduction of spacer like CH_2 or CH_2O [13].



3

a) Y = H, R = H, b) Y = H, R = 2-CH_3, c) Y = H, R = 4-OCH_3, d) Y = H, R = 4-Cl, e) Y = H, R = 2,4-Cl_2, f) Y = H, R = 4-Br, g) Y = H, R = 4F, h) Y = H, R = 4-NO_2, i) Y = H, R = 3-CH_3, j) Y = CH_2, R = H, k) Y = CH_2, R = 4-Cl, l) Y = CH_2,O R = H

A series of aryl acid hydrazones 4 -5 of substituted aromatic acid hydrazides have also screened for their anticonvulsant potential by Sinha *et al.* [14] and found that Aryl acid hydrazones of nicotinic acid hydrazide were very effective in the MES test.



4 **5**

a) X = 4-Cl, b) X = 2-Cl, a) X = 2-Br b) X = 2-Cl,

Ulloora *et al.* [15] investigated twenty seven derivatives of 1, 4-dihydropyridin-4-yl-phenoxyacetohydrazones (6) for their anti-convulsant activity by MES, scPTZ and 6 Hz tests but compounds were found very effective against MES test

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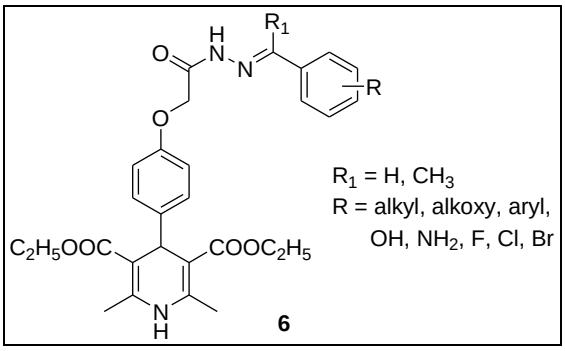
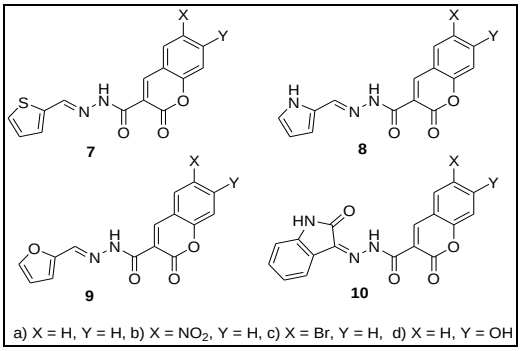


6

Anticancer activity

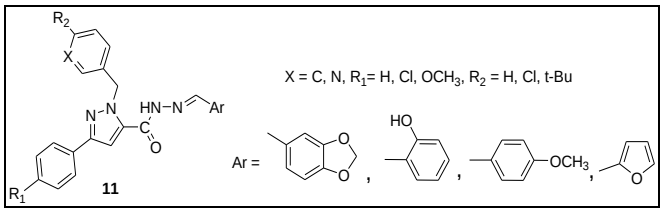
Sixteen coumarins bearing hydrazide-hydrazone moiety 7-10 were synthesized and evaluated *in vitro* against human drug-resistant pancreatic carcinoma (Panc-1) cells and drug-sensitive (hepatic carcinoma; Hep-G2 and leukemia; CCRF) cell lines using doxorubicin (DOX) as positive control. The 6-brominated coumarin hydrazide-hydrazone derivatives were found to be more potent against DOX [16].



7 **8** **9** **10**

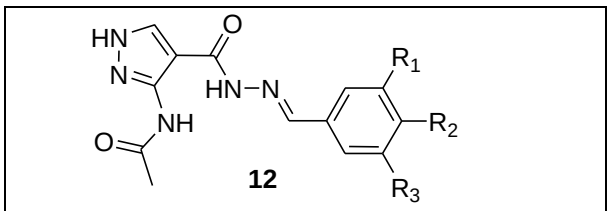
a) X = H, Y = H, b) X = NO_2, Y = H, c) X = Br, Y = H, d) X = H, Y = OH

Xia *et al.* [17] reported the synthesis and potent proliferation activity of twenty 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide hydrazones 11 against A549 lung cancer cell.



11

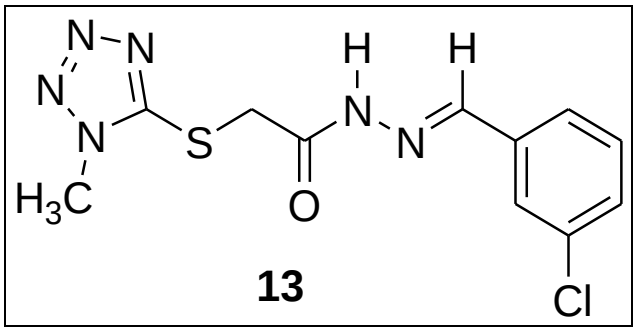
In another report, Hassan *et al.* [18] investigated the proliferation potential of some pyrazole hydrazones 12a–d against human breast adenocarcinoma MCF-7 cell line.



12

a) R_1 = R_2= R_3 = H, b) R_1 = H, R_2= OCH_3,R_3 = H, c) R_1 = R_2= OCH_3, R_3 = H, d) R_1 = R_2= R_3 = OCH_3

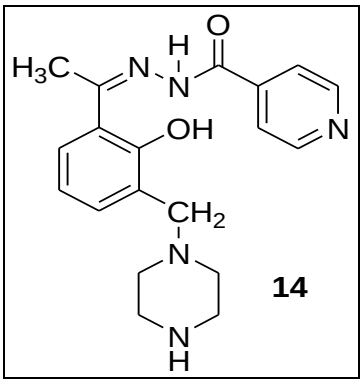
Altintop *et al.* [19] synthesized and screened thirty three hydrazones derivatives of tetrazoles against A549 cancer cell and found compound 13 as most promising anticancer agent.



13

Antitubercular activity

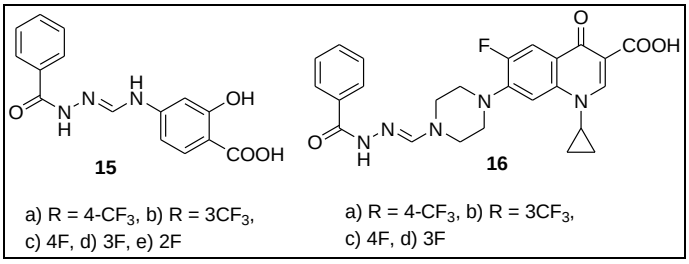
Sriram *et al.* [20] reported the synthesis fifteen derivatives of isonicotinoyl hydrazone and evaluate them for antimycobacterial activity against Mycobacterium tuberculosis. Compound N'-{1-[2-hydroxy-3-(piperazin-1-ylmethyl) phenyl] ethylidene} isonicotinohydrazide 14 was found to be more potent than the reference compound.



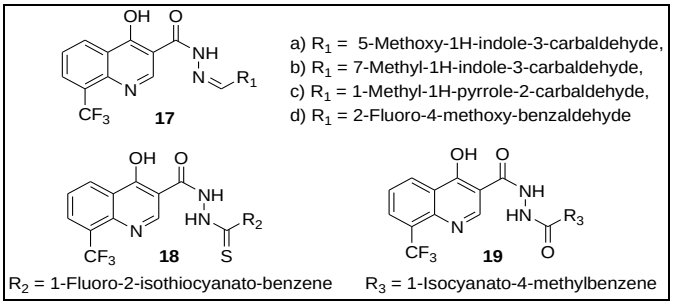
14

A series of fluorine-containing hydrazones with antimycobacterial properties were prepared and investigated. All synthesized were found to be non-toxic in MIC concentrations for human hepatocytes, PBMC cells and human SH-SY5Y neuroblastoma cells. Compounds 15 and 16 have shown remarkable activity against MDR-tuberculosis

and were found to be more potent to inhibit MDR-TB infection then references [21].

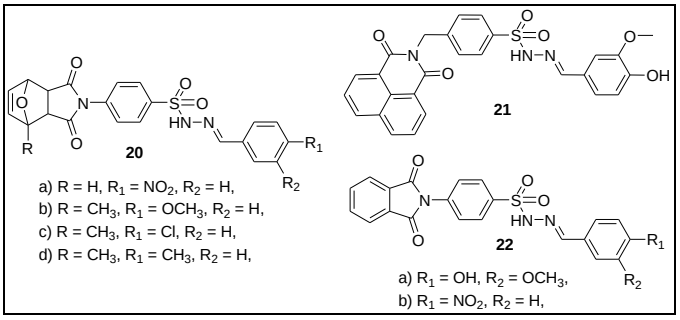


Thomas *et al.* [22] have reported the synthesis of three series of 4-hydroxy-8-trifluoromethyl-quinoline derivatives and were evaluated for their antimicrobial activities including antimycobacterial activity against ant imycobacterial activity against *Mycobacterium. tuberculosis* H37Rv, *Mycobacterium. smegmatis* (ATCC 19420), *Mycobacterium. fortuitum* (ATCC 19542) and MDR-TB strains compounds 17a-d, 18 and 19 displayed promising potential inhibit the antimycobacterial activity.

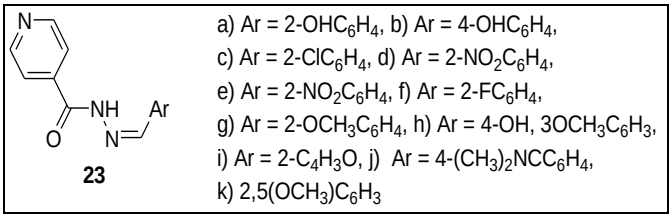


Antidepressant activity

A synthesis of a series of sulphonamides and sulphonyl hydrazones of maleimide, naphthalimide and phthalimide derivatives was accomplished and were further screened for their antipressent potential in mice. An investigation result that compounds 20-22 were found effective antidepresents and compound 20c was most active among them [23].

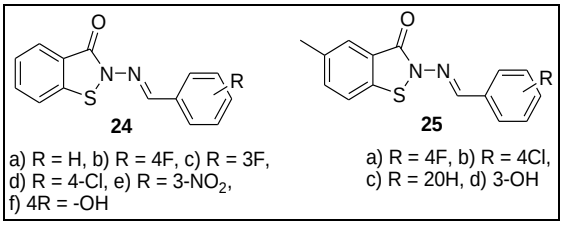


Thomas *et al.* [24] described the synthesis and CNS activity of N'-[(1Z)-aryl methylidene] pyridine-4-carbohydrazides 23a–k. Synthesized compounds were found to have significant *in vivo* antidepressant potential in the animal models.

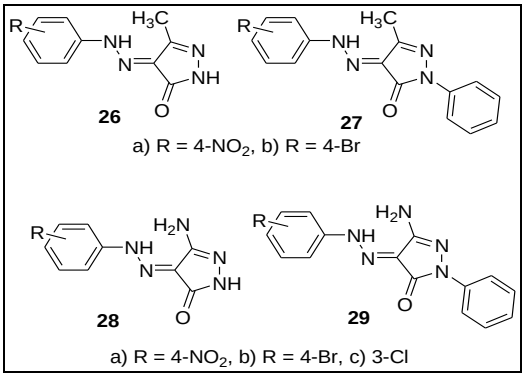


Anti-human immunodeficiency virus (HIV) activity

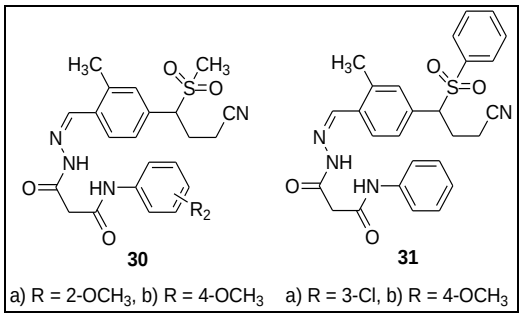
Vicini *et al.* [25] have reported the synthesis and the anti-HIV properties of novel benzo [*d*] isothiazole hydrazones against wild type HIV-1 and EFVR mutant. Compound 24a and 24b showed good activity against wild type HIV-1 and compounds 24a, c, d, e, f, and 25a-d showed good potential against the EFVR mutant.



Singh *et al.* [26] have reported the synthesis and screening of some phenyl hydrazone bearing pyrazole hybrid compounds 26-29 for anti HIV potential using TZM-*bl* cell lines and synthesized compounds were shown good activities.

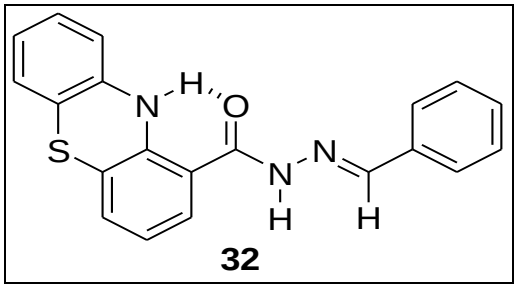


Dingra *et al.* [27] also reported the synthesis and anti HIV activity of some 2-methyl-4-N-20-cyanoethyl-N-methane / benzene sulphonyl aminobenzaldehyde hydrazones 30-31.

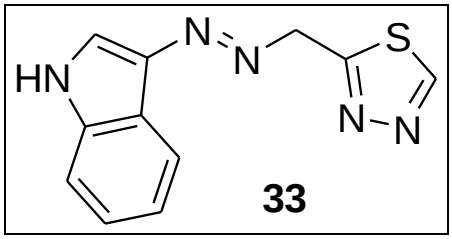


Antiplatelet activity

Silva *et al.* [28] synthesized and screened some phenothiazine-attached acylhydrazones for their antiplatelet activity and reported a new potent antiplatelet compound 32 for inhibition of *platelet COX-1 enzyme.*

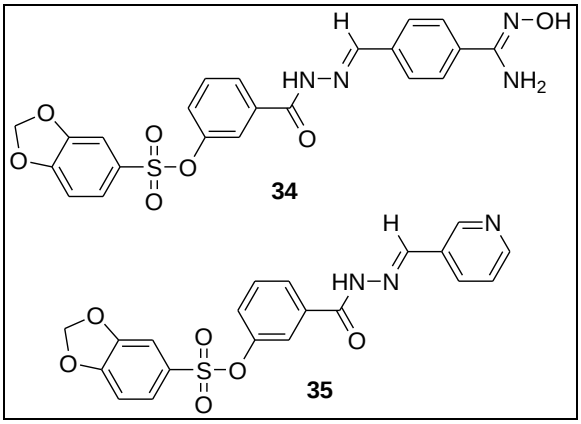


Mashayekh *et al.* [29] investigated the synthesis and antiplatelet aggregation activity of some indole hydrazone derivatives and reported compound 33 as potent agent to inhibit antiplatelet aggregation.



33

In another study, Lima with her group [30] reported synthesis and antiplatelet activity of some arylsulfonate–Acylhydrazone derivatives and found compounds 34-35 as good antiplatelet agents.



Conclusion

This present article highlights the significant role of hydrazones as lead for the development of novel compounds.

Acknowledgements

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Conflict of Interest: The author has declared no conflict of interest.

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