

Exploring the Pharmacological Activities of Hydrazone Derivatives: A Review

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Abstract

The development of new potent chemical architectures, possessing anti-inflammatory, analgesic, antibacterial, antifungal, antiviral, anti-hypertensive, antidepressant, anticancer, antiplatelet, antimalarial and anticonvulsant etc. biological activities remain the main focus thought of many researchers. Among others, hydrazone derivatives acquire azomethine -NHN=CH- group gain considerable attention due to its diverse biological activities. A wide variety of hydrazone derivatives have been synthesized and their biological activities also been evaluated from time to time. The goal of present review is to highlight the diverse potential pharmacological activities of hydrazone derivatives as observations for new drug development.

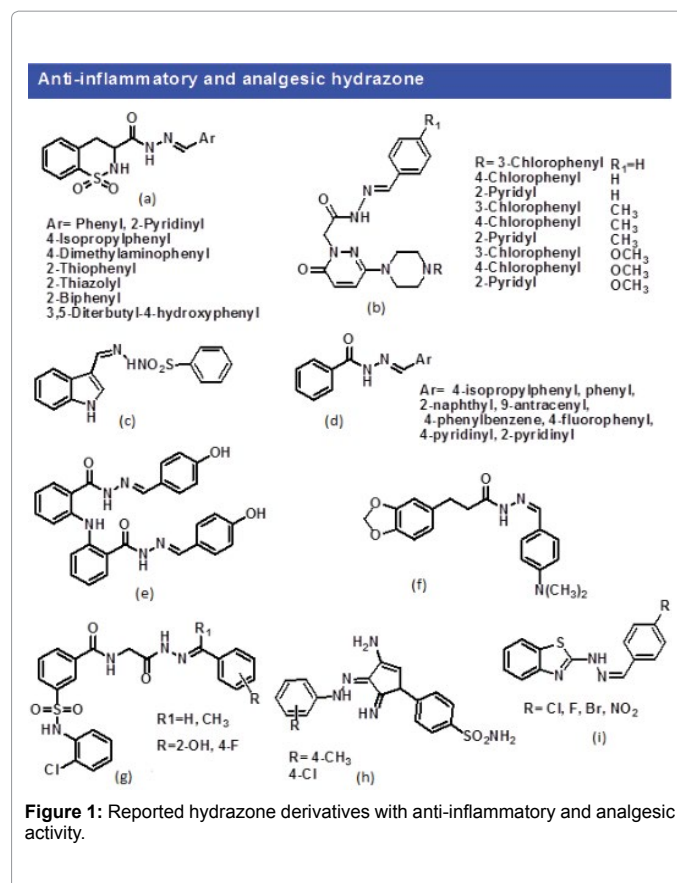
Keywords: Hydrazone derivatives; Azomethine; Pharmacological activities; Broad spectrum

Introduction

Hydrazone and its derivatives with azomethine -NHN=CH- group represents an important class of compounds with broad spectrum of pharmacological activities [1]. A variety of hydrazone derivatives have been synthesized with the potential pharmacological activities like antiinflammatory, antibacterial, analgesic, antifungal, antihypertensive, antiplatelet, anticancer, antimalarial, antidepressant, anticonvulsant and antiviral etc [2]. In addition to their extended biological properties they also combine with other functional groups to provide pharmacologically active molecules. The main theme of this study is to explore the biological and pharmacological importance of hydrazone derivatives for future development of new drug entities.

Anti-inflammatory and Analgesic Activity

Inflammation refers to a commonly used broad term for a local response to cellular injury characterized by pain, capillary dilatation, edema, heat, redness and loss of function. To date, a number of hydrazone derivatives has been efficiently synthesized and evaluated for the analgesic and anti-inflammatory activities. It is important to mention that COX-I and COX-II have an important role in the inflammation. Structure modification of the parent bioactive molecule which is a common practice over the years may further enhance its biological importance. In this scenario, Barreiro et al. synthesized a series of novel hydrazone derivatives based on the structural modification of piroxicam (Figure 1a). The resulted compounds showed better anti-inflammatory and antinociceptive activity than the standard piroxicam drug [3]. A series of novel substituted hydrazone derivatives were also reported by Mehtap Gokce et al. that exhibit significant anti-inflammatory activity in comparison to the standard indomethacin drug (Figure 1b) [4]. Additionally, Sondhi et al. synthesized a number of amidine and hydrazone derivatives and its evaluation showed promising anti-inflammatory and analgesic activities. (Figure 1c) [5]. Pyrazine N-acylhydrazone derivatives synthesized by Lima et al. [6] showed anti-inflammatory and analgesic activity (Figure 1d). Similarly, Eissa et al. reported anthranilic acid based hydrazone derivatives [7] with good exhibition of anti-inflammatory activity (Figure 1e). Moreover, Barreiro et al. developed a series of novel N-acylhydrazone from the natural safole and were investigated for analgesic property. The compounds proved to have good analgesic activity (Figure 1f) [8].



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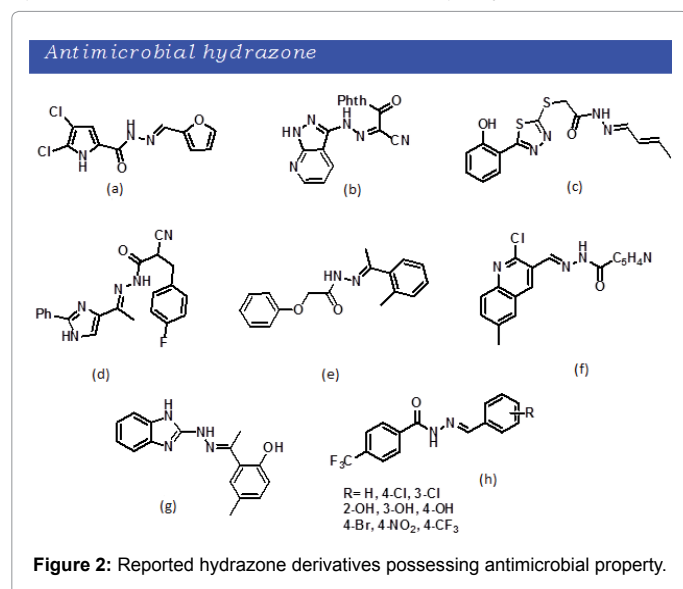
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Recently Korupolu et al. reported novel N-phenyl sulfonamide linked N-acylhydrazones [9]. The compounds are reported to have strong anti-inflammatory characteristic via inhibition of COX-2 enzyme (Figure 1g). Similarly Abdelgawad et al. demonstrated a series of new pyrazole bearing hydrazone derivatives and were tested for activity [10]. The novel hydrazone derivatives showed better anti-inflammatory property compared to the standard drug celecoxib (Figure 1h). Qin et al, synthesized a set of novel benzo[d]thiazole-hydrazones and investigated for biological activity [11]. Resulting new hydrazone derivatives displayed good anti-inflammatory character (Figure 1i).

Antimicrobial Activity

Rise in multi-drug resistance of bacterial infection in the last few decades cause increase risk of complications in antibiotic therapy [12] Therefore the development of new and effective antibiotics remains a challenging area for the researchers. Variety of hydrazone derivatives have been designed, synthesized and studied for antimicrobial characteristics. Chloropyrrole based aroyl hydrazone reported by Rane et al. (Figure 2a) Proven to have potential antimicrobial activity against gram negative and gram positive bacteria.[12] Additionally, Kalil et al. synthesized a series of novel hydrazone derivatives and reported to posse's potent antimicrobial activity (Figure 2b) [13]. Also, Wang et al reported a set of 5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-yl-sulfanyl acetyl hydrazones that showed a potent antimicrobial activity (Figure 2c) [14]. Abdel-Wahab et al. synthesized imidazole ring hydrazones that exhibit excellent antibacterial property (Figure 2d) [15]. Raja et al. developed 4-bromophenoxy acetic acid hydrazones and were investigated for antimicrobial activity (Figure 2e). The compounds were found to have good antibacterial property against gram positive, gram negative and mycobacterium [16]. Moreover, S. Kumar et al. demonstrated the synthesis of a series of 2-chloro-6-methylquinoline hydrazones and were investigated for pharmacological activity [17]. Most of the synthesized compounds were found to have maximum antibacterial activity (Figure 2f). Kale synthesized hydrazone Schiff's base derivatives and were subjected to biological screening [18]. Hydrazone derivatives revealed antibacterial activity against E-Coli and S-aureus (Figure 2g). Recently M. Krátky et al. reported a series of 4-(trifluoromethyl)benzohydrazone derived hydrazones and subsequent investigation of antibacterial activity [19]. Most of the new hydrazones exhibit better antibacterial activity (Figure 2h).

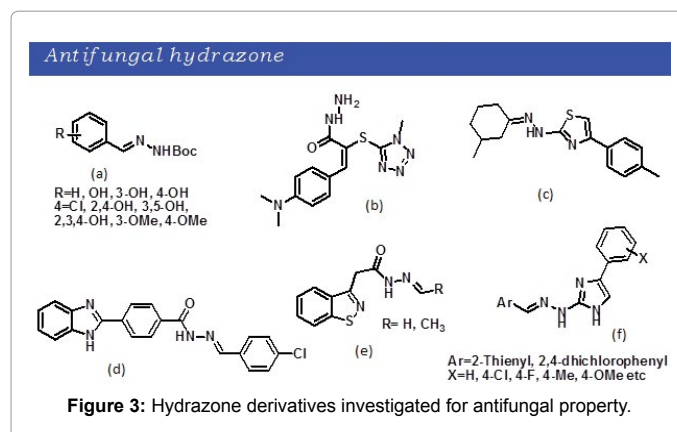


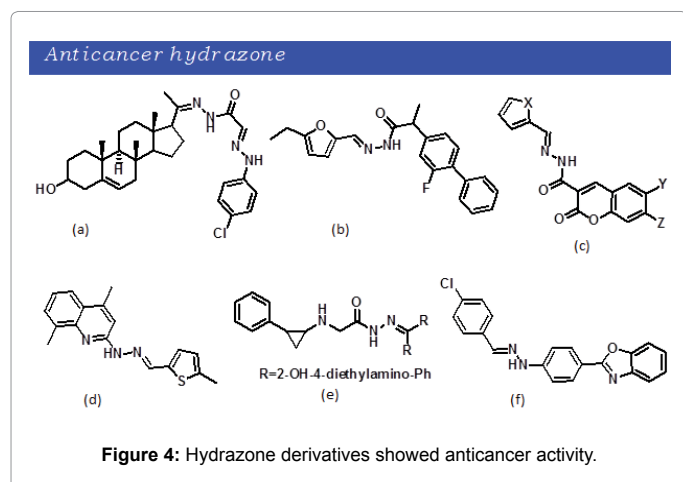
Antifungal Activity

The increasing mortality rate in systemic fungal infection is attributed due to the high antifungal drug resistance. Such scenario creates the urge for developing safe and effective antifungal drugs for clinical use. A series of hydrazones were synthesized from the coupling of aldehydes with tert-butyl carbazate by Casanova et al. [20]. The resulting hydrazones were subjected to antifungal screening and promising activity was observed for most of the compounds (Figure 3a). Altintop et al. synthesized novel hydrazone derivatives through the addition-elimination reaction of 2-[(1-methyl-1H-tetrazol-5-yl)thio]] aceto-hydrazone and aromatic aldehydes/ketones [21]. Compounds were subsequently investigated and were observed to have significant antifungal potential (Figure 3b). A series of 2-thiazolylhydrazones were developed by Chimenti et al. that exhibit potent antifungal activity against various *Candida* species (Figure 3c) [22]. Ozkay et al. synthesized benzimidazole based hydrazone derivatives and were subjected to antifungal and antibacterial studies and significant antifungal and antibacterial activity was observed [23]. Interestingly, one of the compound showed more activity than the standard antifungal ketoconazole (Figure 3d). Paola Vicini et al. reported the synthesis of a number of hydrazones of 1,2-benzisothiazole hydrazides [24]. The series of compound was tested against bacteria and yeast and were reported as good antibacterial agent as well as most of the hydrazone derivatives were active against yeast (Figure 3e). This year S. Kauthale et al. synthesized a set of thiazolyl hydrazones through one pot synthesis [25]. The resulting compounds were observed to possess moderate to good antifungal activity (Figure 3f).

Anticancer Activity

Cancer is a burning issue under investigation which refers to the uncontrolled and rapid abnormal cell division that can invade nearby tissue. In 2015 about 90.5 million people were cancer carrying and even its number is increasing every year. A number of hydrazone derivatives have been developed with anticancer properties. R. M. Mohareb et al. reported the synthesis of a number of hydrazone-hydrazone derivatives from ring D modification of pregnenolone [26]. These compounds were evaluated for anticancer activity and were reported highly effective against breast cancer, lung cancer and CNS cancer compared to the reference drug doxorubicin (Figure 4a). Similarly, Küçükgülzel et al. synthesized a series of hydrazone-hydrazone derivatives using Flurbiprofen as template [27]. The compounds were shown to have significant activity against leukemia cancer cell line and ovarian cancer cell lines (Figure 4b). Nasr et.al developed coumarin based hydrazone-hydrazone derivatives and bromocoumarins (Figure 4c) were reported





to have good antitumor activity against pancreatic carcinoma and hepatic carcinoma [28]. Savini et al. synthesized a series of new 3- and 5-methylthiophene-2-carboxaldehyde a-(N)-heterocyclic hydrazones and were investigated for anticancer activity [29]. Compound N-(4,8-dimethyl-quinolin-2-yl)-N'-(5-methylthiophen-2-ylmethylene)-hydrazine was found to be the most active antitumor agent (Figure 4d). Recently Sun et al. reported a set of phenylalanyl hydrazones that were evaluated for anticancer activity [30]. Novel hydrazones were found effective against gastric cancer (Figure 4e). Very recently a set ofazole bearing hydrazone derivatives were reported by Labib et al. and were subjected to testing for anticancer activity [31]. The synthesized hydrazones were found effective against breast cancer and hepatic cancer cell lines (Figure 4f).

Antidepressant Activity

According to WHO (world health organization), depression is a mental disorder characterized by persistent sadness and a loss of interest in daily activities. Depression affected 300 million people around the globe and is considered as a leading cause of suicide. A number of hydrazone derivatives are reported to have antidepressant activity. de Souza et al. synthesized a set of sulphonamides and sulphonylhydrazones of maleimide [32]. Upon evaluation, the compounds were found to have promising antidepressant activity. Interestingly, sulphonyl-hydrazone was found to be the most active compound than imipramine (Figure 5a). A series of hydrazone derivatives were developed and investigated for antidepressant property by Gokhan-Kelekci et al. [33]. Most of the compounds showed MAO inhibition activity (Figure 5b). Ergec et al. demonstrated a series of ten arylidenehydrazides and were tested for antidepressant activity [34]. The resulting compounds showed good antidepressant property (Figure 5c). Pandeya reported the synthesis of a series of phenylacetic acid hydrazones [35]. All of the compounds exhibit promising antidepressant activity when compared with tranlycypromine (Figure 5d).

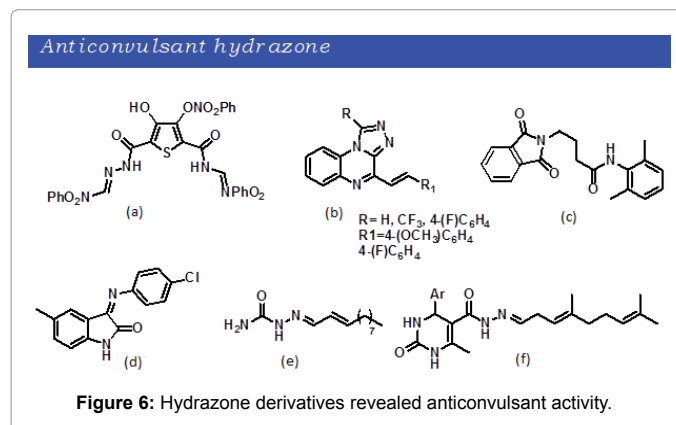
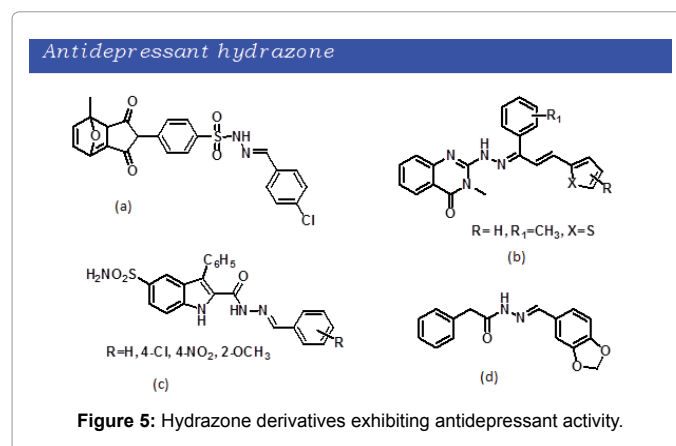
Anticonvulsant Activity

According to epilepsy foundation, epilepsy is a chronic disorder characterized by recurrent unpredictable and unprovoked seizures. It is the fourth most common neurological disorder affecting people of all ages. Verity of hydrazone derivatives are reported possessing anticonvulsant activity. Kulandasamy et al. showed a series of new hydrazones and bishydrazones and were screened for anticonvulsant activity [36]. The compounds showed significant antiepileptic activity

(Figure 6a). Wagle et al. demonstrated the synthesis and anticonvulsant investigation of hydrazone derivatives and found that the compounds exhibit potential anticonvulsant activity with respect to reference diazepam drug (Figure 6b) [37]. Ragavendran et al. prepared two sets of phthalimide-GABA anilides/hydrazones and were subsequently tested for neurotoxic and anticonvulsant activities [38]. The compounds possess anticonvulsant property. Notably, the most active compound was found to be the 4-(1,3-dioxo-1,3-dihydro-2H-isindol-2-yl)-N-(2,6-dimethylphenyl)butanamide (Figure 6c). Sridhar et al. synthesized and screened hydrazone, Schiff and Mannich bases for anticonvulsant activity [39]. The compounds showed significant anticonvulsant property but the most active compound observed was 3-(4-Chlorophenylimino)-5-methyl-1,3-dihydro-indol-2-one (Figure 6d). Dimmock et al. synthesized a series of oxamoylhydrazones, acetylhydrazones, and semicarbazones [40]. Upon their pharmacological investigation it was observed that acetylhydrazones, and semicarbazones (Figure 6e) afford promising anticonvulsant activity as compared to the oxamoylhydrazones. Similarly in recent year Sanchit et al. reported the synthesis of pyrimidine hydrazones Schiff bases [41]. The newly synthesized hydrazone derivatives exhibit good anticonvulsant activity (Figure 6f).

Antihypertensive Activity

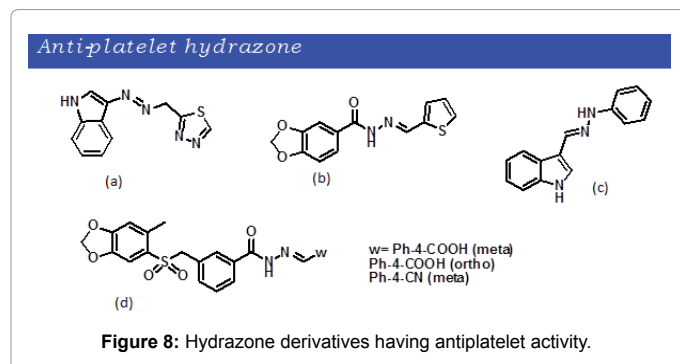
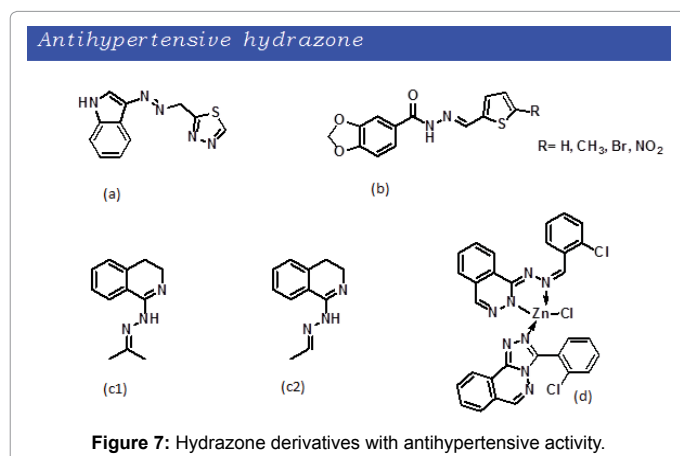
According to the WHO, hypertension also known as elevated blood pressure, is a condition in which the blood vessels have a persistent high pressure. In majority of the cases the cause is nonspecific/unknown. Long term hypertension is considered one of the major risk factor for cardiovascular diseases. To overcome this rapidly increasing health



problem, a number of researchers have paid attention to developed verity of hydrazone derivatives for the management of hypertension. Leal et al. reported the synthesis of saffrole based N-acylhydrazones [42]. The compounds were evaluated and found to have antihypertensive characteristic (Figure 7a). As vasodilatation is one of the factors that reduces elevated blood pressure, Silva designed and synthesized new acylhydrazone derivatives and subjected to vasodilator screening [43]. The new compounds showed vasodilator effect by directly acting on smooth muscle endothelium (Figure 7b). Diana et al. synthesis a series of 1-substituted 3,4-dihydroisoquinolines [44]. The resulted compounds were tested and were declared that 1-hydrazino homologue and the corresponding acetaldehyde and acetone hydrazones show significant antihypertensive activity (Figures 7c1 and 7c2). Bakale demonstrated the synthesis of ligand zn(II) complex of 2-chlorobenzaldehyde, hydralazine and hydrazine [45]. The complex was evaluated for antihypertensive activity and was found to exhibit promising activity through *in situ* generating 1,2,4-triazole moiety (Figure 7d).

Antiplatelet Activity

Platelet aggregation has a pivotal role in blood clotting and thrombosis. Thrombosis is a leading cause of cardiovascular diseases that are considered as the major cause of natural death [46]. A number of hydrazone derivatives has been synthesized and evaluated for antiplatelet property. A series of Indole moiety bearing hydrazones derivatives were reported by Mashayekhi et al. that showed antiplatelet aggregation character (Figure 8a) [47]. Brito et al. demonstrated the synthesis and antiplatelet activity of a set of thienylacylhydrazone derivatives [48]. The most active compound reported was ((2-thienylidene)3,4-methylenedioxybenzoyl)hydrazine (Figure 8b). A series of new hydrazones consisting of three families



of arylsulfonate-acylhydrazone derivatives were synthesized through structural modification of known thrombin inhibitors by Lima et al. [49]. All of the three classes of compounds indicated antiplatelet aggregation activity (Figure 8c). Mohebbi et al. has demonstrated the synthesis of a range of indole-based aryl(aroyl)hydrazone derivatives [50]. Among the resulting compounds, Phenylhydrazone derivatives exhibit significant antiplatelet activity (Figure 8d).

Conclusion

In summary hydrazone and its derivatives represent an exciting group of compounds with broad spectrum of pharmacological and biological activities. A verity of hydrazone derivatives have been designed synthesized and screened for its biological activities. The present review aim on exploring pharmacological potentials of hydrazone derivatives. In the current scenario of demand and search for potent chemical architectures, appropriate designing, synthesis, SAR and docking studies of novel hydrazone derivatives can lead to the development of new drugs molecules with diverse therapeutic activities.

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