Review Article

Analgesic, Anti-Inflammatory, and Antiplatelet Profile of Hydrazones Containing Synthetic Molecules

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Hydrazones are present in many of the bioactive compounds with wide interest because of their diverse pharmacological applications. Hydrazones possess wide variety of biological activities such as anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimicrobial, antitumor, anti-HIV, anthelmintic, antidiabetic, antiparasitic, and other anticipated activities. This created an interest for researchers towards synthesized variety of hydrazone derivatives for different biological activities. Therefore many researchers have synthesized hydrazone derivatives as target structures for their biological activities. This paper focuses on the analgesic, anti-inflammatory, and antiplatelet activities of hydrazones.

1. Introduction

Hydrazones constitute an important class of biologically active drug molecules which has attracted the attention of medicinal chemists due to their wide range of pharmacological properties. These compounds are being synthesized as drugs by many researchers in order to combat diseases with minimal toxicity and maximal effects. These predictions have provided a therapeutic pathway to develop new effective biologically active hydrazones. A number of hydrazine derivatives have been reported to exert notably biological activities [1, 2].

Hydrazones possess an azomethine –NHN=CH group which are considered as derivatives of aldehydes and ketones in which the oxygen atom has been replaced by the =NNH₂ group. Hydrazones are of wide interest because of their diverse biological applications such as anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antitumour, anticancer, vasodilator, antiviral, anti-HIV, anthelmintic, antidiabetic, and trypanocidal activities [2–10].

The hydrazones are used as hole transporting agents in organic layer photoconductors, as quantitative analytical reagents, especially in colorimetric and fluorometric determination of metal ions [11–13]. Furthermore, some hydrazones have also been used as herbicides, insecticides, nematocides, rodenticides, and plant growth regulators as well as plasticizers and stabilizers for polymers. The metal complexes of hydrazones have potential applications as catalysts, luminescent probes, and molecular sensors [1, 14, 15]. A class of N-arylsulfonyl hydrazones has been developed as novel inhibitors of IMP-1, a metallo-β-lactamase. As a requirement for bulky aromatic substituents on each side of the sulfonyl hydrazine backbone, these compounds may serve as efficient inhibitors of IMP-1. Molecular modeling has provided structural basis for the anti-metallo-β-lactamase activity of hydrazonelone compounds [16]. A series of hydrazones were evaluated as potential inhibitors of anthrax lethal factor. There were significant differences in the types of inhibition observed with the different assays [17]. Kinetic analysis of the dipeptidyl disulfides and dipeptidyl benzoylhydrazones indicated that these inhibitors act as irreversible inhibitors of Cathespins S, and benzoylhydrazones were shown to be potent inhibitors of Cathespins S [18]. Hydrazones and phenyl hydrazones of different aryl aldehydes showed an effect on endogenous proteolysis in liver. It was observed
that p-nitro benzaldehyde hydrazone exhibited maximum inhibitory effect [19]. The effect of hydrazones and phenyl hydrazones of simple aryl aldehydes along with their semicarbazones and thiosemicarbazones on the activity of liver alkaline and acid phosphatase [20, 21].

Hydrazones are an important class of compounds for new drug development. This created an interest to 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 analgesic, anti-inflammatory, and antiplatelet properties of hydrazone derivatives. Hydrazones are not only intermediates but also very effective organic compounds when they are used as intermediates and coupling products that can be synthesized by using the active hydrozen component of –CONHN=CH–azomethine group. Many effective compounds, such as iproniazid and isocarboxazid, are synthesized by the reduction of hydrazide-hydrazones. Iproniazid, like INH, is used in the treatment of tuberculosis. It has also displayed a antidepressant effect, and patients appear to have a better mood during the treatment. Another clinically effective hydrazide-hydrazones is nifuroxazid, which is used as an intestinal antiseptic [22–25]. Hydrazones are a class of organic compounds which possess the structure R$_2$N$\equiv$C$\equiv$NNH$_2$. They are related to ketone and aldehyde in which oxygen has been replaced with NNH$_2$ group. These azometine –NHN=CH–protons constitute an important class of compounds for drug development. Hydrazones are formed by the reaction of hydrazine or hydrazide with aldehydes and ketones. Hydrazones are widely used in organic synthesis. Many effective compounds, such as iproniazide and isocarboxazid, are synthesized by the reduction of hydrazide-hydrazones. Another effective hydrazide-hydrazone is nifuroxazid, which is used as an intestinal antiseptic [26–30]. This review highlights analgesic, anti-inflammatory, antipyretic, and antiplatelets activities shown by hydrazones.

### 2. Analgesic and Anti-Inflammatory Activites

Nonsteroidal anti-inflammatory drugs (NSAIDs) are largely used in the treatment of pain and inflammation. Hydrazones that are dual inhibitors of both cyclooxygenase (COX) and 5-lipoxygenase (5-LO) are being studied as potential analgesic and anti-inflammatory agents in comparison to NSAIDs [31]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammation, pain, rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections, and fever. The two isoforms of COX are poorly distinguishable by most of the classical NSAIDs, and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal (GI) injury, suppression of TXA2 formation, and platelet aggregation. The combination of these interactions is probably the reason for GI bleeding which is the most serious complication of these drugs. Some evidence suggests that the hydrazones moiety present in some compounds possesses a pharmacophoric character for the inhibition of COX. In fact, some evidence suggests that the hydrazone moiety present in derivative possesses a pharmacophoric character for the inhibition of COX [32]. The results showed that pyridine ring at the aryl moiety of the arylhydrazone is having good analgesic activity in comparison to mefenamic acid. Compounds possessing the 4-tolyl or 4-fluorophenyl moiety are more active than 4-bromophenyl and 4-N,N-dimethylaminophenyl. The anti-inflammatory evaluation showed that the replacement of carboxylic acid group of mefenamic acid with N-arylhydrazone moiety cannot produce any advantage in the anti-inflammatory property [33]. Analgesic activity of some (4Z)-3-methyl-1-[(2-oxo-2Hchromene-4-yl)carbonyl]-1H-pyrazole-4,5-dione-4-(4-substituted phenyl)hydrazone, some of them showed significant analgesic activity. 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 increased analgesic activities [34]. Hydrazones derivatives of quinoxalinone and evaluated for anti-inflammatory activity showed that compounds having methoxy group at the para-position showed comparatively good percentage of inhibition of edema than the other compounds [35]. Treatment of 3-cyano acetylindole with diazonium salts of 3-phenyl-5-amino pyrazole and 2-amino pyrazole gave the corresponding hydrazones. Compound 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 [36]. The anti-inflammatory derivative 2-(2-formylfuryl) pyridylhydrazone (I) presented a 79% inhibition of pleurisy at a dose of 80.1$\mu$mol/kg. The results concerning the mechanism of the action of these series of N-heterocyclic derivatives in platelet aggregation suggest a Ca$^{2+}$ scavenger mechanism. Compound 2 was able to complex Ca$^{2+}$ in in vitro experiments at 100$\mu$M concentration, indicating that these series of compounds can act as Ca$^{2+}$ scavenger depending on the nature of the aryl moiety present at the imine subunit [37]. A series of analgesic compounds that belong to the N-acylarylhydrazone class were synthesized from natural saffrole. [(4'-N,N-Dimethylaminobenzylidene-3-(3',4-methylenedioxyphenyl)propionyl hydrazine] (2) was more potent than dipyrone and indomethacin [38]. Analgesic and anti-inflammatory activity of furoxan-N-acylhydrazones (3, 4) [39]. The anti-inflammatory activity of some aryl hydrazones (5) got good results [40]. Various hydrazine derivatives (6) reported them to have promising in vivo anti-inflammatory activity [41]. Hydrazone derivatives (7) with selective COX-2 inhibition. The compound is reported to have an ED$_{50}$ value of 0.2 mmol/Kg [42]. Benzothiophene derivatives (8) with inhibition of 50.2% have been developed [43]; see Figure 1.

Fifteen different isatin[N-(2-alkylbenzoxazole-5-carbonyl)] hydrazones (9) were screened for analgesic, anti-depressant, and H1-antihistaminic activities [44]. These compounds were also studied for their effect on pentobarbitone-induced narcosis. Three compounds bearing a methyl substituent at 7-position of the benzoxazole system exhibit good analgesic activity. Schiff bases and phenyl hydrazone of isatins, prepared from isatin and appropriate aromatic primary
amine/hydrazines were screened for analgesic, anti-inflammatory, and antipyretic activity \([45]\). 1-Diphenylaminomethyl-3-(1-naphthylimino)-1,3-dihydroindol-3-one, 3-(1-naphthylimino)-5-bromo-1,3-dihydroindol-2-one (10), and 1-diphenylaminomethyl-3-(4-methylphenylimino)-1,3-dihydroindol-3-one exhibited the highest analgesic, anti-inflammatory, and antipyretic activity respectively. Few 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal)hydrazide derivatives exhibited analgesic and anti-inflammatory agents. None of the compounds was found to show gastric ulcerogenic effect in comparison with reference NSAIDs [46]. 2-(2-Formylfuryl)pyridylhydrazone possessed anti-inflammatory activity and showed 79% inhibition of pleurisy at a dose of 80.1 \(\mu\)mol/kg. The results indicated that these series of compounds can act as \(\text{Ca}^{2+}\) scavenger and platelet aggregation [37]; see Figure 2.

2.1. Antiplatelet Activity. The antiplatelet activity of tricyclic acylhydrazone derivatives (11) 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-OH-8-CH\(_3\)-6-phenylpyrazolo[3,4-b]thieno-[2,3-d]pyridine-2-carbohydrazide was evaluated at 10 \(\mu\)M, presenting, respectively, 10.4 and 13.6% of inhibition of the PAF-induced platelet aggregation [37]. The evaluation of platelet antiaggregating profile led to the identification of a new potent prototype of antiplatelet derivative, that is, benzylidene 10H-phenothiazine-1-carbohydrazide (IC\(_{50}\) = 2.3 \(\mu\)M), which acts in the AA pathway probably by the 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, possessing selective peripheral or central mechanism of action [47]. The evaluation of platelet antiaggregating profile led to the identification of a new potent prototype, that is, benzylidene 10H-phenothiazine-1-carbohydrazide (IC\(_{50}\) = 2.3 \(\mu\)M) (12), which acts in the arachidonic acid (AA) pathway probably by the inhibition of platelet COX-1 enzyme. Change in para-substituent group of acylhydrazone framework permitted to identify a hydrophilic carboxylate derivative and a hydrophobic bromo derivative as two analgesics that are more potent than dipyrone, possessing selective peripheral or central mechanism of action [48]. Hydrazones containing 5-methyl-2-benzoazoline, the analgesic effects of 2-[2-(5-methyl-2-benzoazoline-3-yl)acetyl]-4-chloro-/4-methyl benzylidene hydrazine (13a) and (13b)
were found to be higher than morphine and aspirin. In addition, 2-[(5-methyl-2-benzoxazoline-3-yl)acetyl]-4-methoxy benzylidine hydrazine at 200 mg/kg dose possessed the anti-inflammatory activity [49]. N’-(3,5-Di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1,3-benzodioxole-5-carbohydrazine (14) as an anti-inflammatory compound [50]. Antiplatelets decrease platelet aggregation and prevent the formation of thrombus. Hydrazone derivatives (15, 16, 17) exhibited an in vitro antiplatelet activity; see Figure 3.

3. Synthetic Approach for the Novel Hydrazonone and Its Biological Activity

A number of organic compounds obtained by chemical synthesis as model compounds have useful analgesic, anti-inflammatory, antipyretic, and antiplatelets activities. Many of hydrazonones its derivatives possess interesting biological activities, such as analgesic, anti-inflammatory, antimicrobial, and antitumor activities. The biological activity of synthesized hydrazonone derivatives was characterized and detailed study is in progress to modify the synthetic route, structural activity, and toxicological barriers for the enhanced pharmacological efficiency of synthetic hydrazones [37, 45–49].

4. Development of New NSAIDs

The NSAIDs preparations are among the most commonly prescribed drugs. NSAIDs are sometimes known as the aspirin-like drugs because they have an activity profile that is broadly similar to that of aspirin; that is, they all possess analgesic, anti-inflammatory, and antipyretic properties to some degree and produce characteristic side effects, including gastric intolerance and depression of blood clotting through inhibitory action on platelet function. Two closely related
forms of the cyclooxygenase have been identified which are now known as COX-1 and COX-2. Both isoenzymes transform arachidonic acid (AA) to prostaglandins (PGs) but differ in their distribution and their physiological roles. Meanwhile, the responsible genes and their regulation have been clarified. COX-1, the predominantly constitutive form of the enzyme, is expressed throughout the body and performs a number of homeostatic functions such as maintaining normal gastric mucosa and influencing renal blood flow. Simmons also recently codiscovered COX-3 in 2002 and analyzed this new isozyme's relation which acetaminophen (paracetamol), arguably the most widely used analgesic drug in the world. The clinical ramifications and knowledge of COX isozymes are therefore rapidly expanding and could perhaps offer significant hope for future treatments of pain, inflammation, and fever [37, 45–49].

5. Discussion

Hydrazones, possessing an azomethine –NHN=CH– group, constitute an important class of compounds as target structures for their biological activities. These observations guide us for the development of new hydrazones that possess varied biological activities. The literature studies on hydrazones have shown that these derivatives possess a wide variety of biological activities such as antitumor, antibacterial, antiviral, anti-hypertensive, anticonvulsant, anti-inflammatory, analgesic, antipyretic, antipatelets, vasorelaxant, anticoagulant, and antiprotozoal activities. There has been considerable interest in the development of novel compounds with wide varieties of biological activities. These molecules are easily prepared and have diverse pharmacological potential. This encourages the researchers to synthesize different new compounds bearing hydrazones with low toxicity. Differently substituted hydrazones have been developed and found to be active against different pharmacological targets. These observations have been guiding the development of new hydrazones that possess varied biological activities. Hydrazone derivatives of carbonyl compounds constitute an important class of biologically active compounds [50–57].

6. Conclusion

Hydrazonone nucleus exhibited immense pharmacological activities. The simple hydrazonone nucleus is present in compounds are evaluating for new products that possess some remarkable pharmacological activities, such as analgesic, anti-inflammatory, antipyretic, antipatelet aggregation, cardiotonic, anti-hypertensive, analgesic, vasodilatory, antidiabetic, and anticonvulsant activities. The present review focuses on hydrazonone which possesses potential analgesic, anti-inflammatory, antipyretic, and anti-platelet aggregation activities that are new in development.

References


