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Recent Advances in Hydrazone Derivatives as Anti-Inflammatory Agents: A Comprehensive Review

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Abstract*—Hydrazone derivatives have emerged as promising candidates in the search for novel anti-inflammatory agents due to their structural versatility and broad biological activity. Inflammation, a key factor in the progression of various chronic diseases, is often managed with NSAIDs and corticosteroids, which are limited by significant side effects. Hydrazones offer an attractive alternative owing to their ability to modulate key inflammatory mediators such as cyclooxygenase (COX), lipoxygenase (LOX) and pro-inflammatory cytokines. Recent studies have explored a wide range of synthetic hydrazone derivatives, revealing valuable insights into their structure-activity relationships and mechanisms of action. This review summarizes recent advances in the synthesis, pharmacological evaluation and molecular targeting of hydrazone-based compounds with anti-inflammatory activity. Emphasis is placed on their therapeutic relevance and potential as safer, more effective anti-inflammatory agents, providing direction for future drug development efforts.*

***Keywords*—** *Hydrazone, Chemistry and Anti-inflammatory activity.*

I. INTRODUCTION

Inflammation is a complex physiological response to infection, injury or tissue damage, characterized by the release of pro-inflammatory mediators such as cytokines, prostaglandins and nitric oxide[1,2]. Although acute inflammation is essential for host defense and tissue repair, chronic inflammation is implicated in the pathogenesis of various debilitating disorders, including rheumatoid arthritis, cardiovascular diseases, neurodegenerative conditions and cancer[3]. Despite the widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in clinical practice, these therapies are frequently associated with adverse effects such as gastrointestinal irritation, renal impairment and immunosuppression, highlighting the urgent need for safer alternatives[4,5].

In this context, hydrazone derivatives have attracted increasing interest due to their diverse pharmacological properties and ease of chemical modification[6]. The hydrazone functional group, characterized by the –NH–N=CH– moiety, allows for extensive structural variation, enabling the fine-tuning of biological activity[7]. These compounds have shown significant anti-inflammatory potential through inhibition of cyclooxygenase (COX), lipoxygenase (LOX) and suppression of pro-inflammatory cytokines such as TNF-α and IL-6. Recent literature reports numerous hydrazone-based molecules exhibiting potent anti-inflammatory activity with improved safety profiles[8,9].

This review aims to present a comprehensive overview of recent developments in the design, synthesis and pharmacological evaluation of hydrazone derivatives as anti-inflammatory agents. Particular emphasis is placed on structure–activity relationships (SAR), mechanisms of action and molecular targets, with the goal of facilitating the rational design of novel therapeutic agents for inflammatory disorders.

CHEMISTRY:

Hydrazone derivatives are a versatile class of organic compounds characterized by the presence of the hydrazone functional group (–C=N–NH–), typically formed through the condensation reaction between hydrazines and aldehydes or ketones[10,11]. This reaction proceeds under mild acidic or neutral conditions, often yielding good to excellent product yields[12]. The structural simplicity and synthetic flexibility of hydrazones allow for the incorporation of a wide range of aromatic, heteroaromatic and aliphatic substituents, facilitating the development of structurally diverse analogs with improved pharmacological profiles[13].

The biological activity of hydrazones is highly influenced by the nature and position of substituents on both the hydrazine and carbonyl components[14]. Electron-withdrawing groups such as nitro, halogen or cyano groups generally enhance anti-inflammatory activity, likely due to improved binding affinity with inflammatory targets like cyclooxygenase (COX) enzymes[15]. Similarly, heterocyclic moieties such as thiazole, pyridine or indole rings have been frequently incorporated into hydrazone frameworks to improve selectivity, solubility, and metabolic stability[16].

Furthermore, hybrid molecules combining hydrazone linkages with known pharmacophores (e.g., NSAID scaffolds, chalcones or quinolines) have been synthesized to exploit synergistic effects. These molecular hybrids often display superior anti-inflammatory properties compared to their parent compounds[17].

Overall, the synthetic versatility and modular architecture of hydrazones make them ideal candidates for rational drug design, particularly in the development of novel anti-inflammatory agents with enhanced efficacy and safety.

II. ANTI-INFLAMMATORY ACTIVITY

Mingxia Song *et al*., reported a series of hydrazone derivatives of pyrazole-4-carboxaldehydes were designed, synthesized and screened for *In-vitro* LPS-induced TNF-α model and *in-vivo* xylene-induced ear-edema model was used to evaluate their anti-inflammatory activity. Among those Compound 1 showed potent activity with IC_{50} value of 5.56μM at 10μg/ml and also the same compound showed

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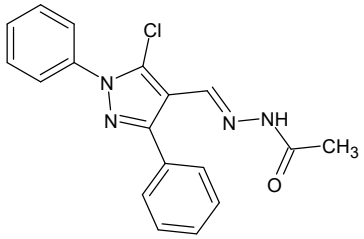
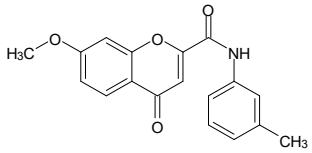
potent activity for markedly inhibited the ear edema at the doses of 20 mg/kg when compared with the reference drug dexamethasone at the same dose[18].



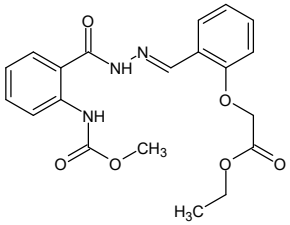
Compound 1

Tao Xing *et al*., they reported a series of novel hydrazones derivatives, Characterized using spectroscopic methods and screened for *in-vitro* anti-inflammatory activity by Cell inhibitory activity. Among those Compounds 2 exhibited good anti-inflammatory activity with EC50 value of 5.326µM at 10µg/ml concentration when compared with diclofenac as a references drug[19].



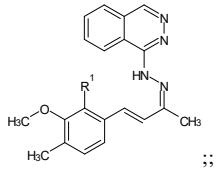
Compounds 2

Halil Senol *et al.,* reported a series of twenty-nine compounds were synthesized using ethyl chloroacetate with salicylaldehyde and 4- hydroxybenzaldehyde, Characterized and evaluated for *in-vitro* cytotoxicity studies by COX-II inhibition activity. According to the results of new target hydrazones, 6–9 (a–e), were synthesized with good yields (95–85%), the Compound 3 showed more potent anti-inflammatory activity with IC50 value of 6.83 µM at 20µg/ml concentration when compared with diclofenac as a references drug[20].



Compound 3

Maria Alice Miranda Bezerra Medeiros *et al.,* reported a series of novel hydrazones derivatives, characterized by spectroscopic methods and examined for anti-inflammatory activity using the acetic acid-induced nociception test. They reported that Compound 4a attenuated the nociceptive activity, reducing the number of writhing's by 83.87% and 78.78% at the both tested doses (20 mg/kg and 40 mg/kg) and Compound 4b reduced the nociceptive effect of acetic acid, reducing the number of writhing's by 96.00% and 89.93% at both tested doses (20 mg/kg and 40 mg/kg. when compared with diclofenac as a standard drug[21].



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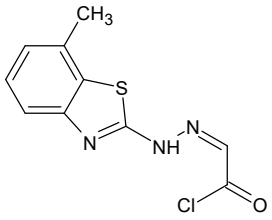
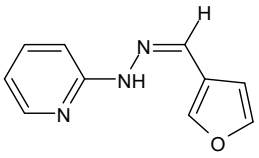
Compound 4a, R^1=H
Compound 4b, R^1=CH_3

Shi-Meng Wang *et al*., (2017) reported a series of new benzo[d]thiazole-hydrazones were synthesized, characterized by analytical and spectroscopic techniques. The synthesized compounds were all tested in vitro for their anti-inflammatory properties and ability to block H+/K+ ATPase. Among that Compound 5 shows potent activity with IC50 value of 5.83µg/ml when compared with the Standard drug Ibuprofen[22].



Compound 5

Todeschini AR et al. discovered that the most significant anti-inflammatory derivative, 2-(2-formylfuryl)pyridyl hydrazone, exhibited a 79% suppression of pleurisy at a dosage of 80.1 µmol/kg. The findings related to the mechanism of action of these series of N-heterocyclic derivatives in platelet aggregation, which points to a Ca2+ scavenger mechanism, were explained. In vitro experiments at a concentration of 100 µM showed that compound 6 was able to complex Ca2+, indicating that, depending on the nature of the aryl moiety present at the imine subunit[23], these series of compounds can act as Ca2+ scavengers.



Compound 6

Lima PC *et al*., reported a new series of antinociceptive compounds that belong to the N-acyl arylhydrazone class were synthesized from natural safrole. [N,N-Dimethylaminobenzylidene-3-methylenedioxyphenyl) propionylhydrazine] Compound 7 was more potent than dipyrone and indomethacine are used as standard anti-inflammatory/antinociceptive drugs[24].

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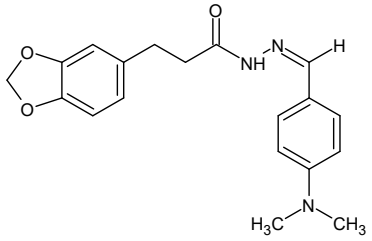
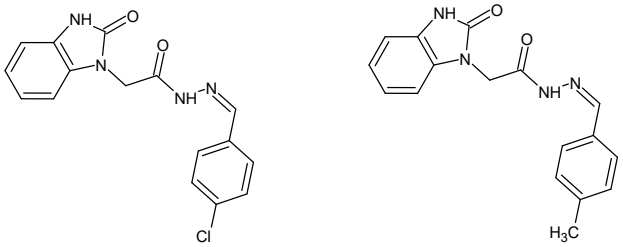


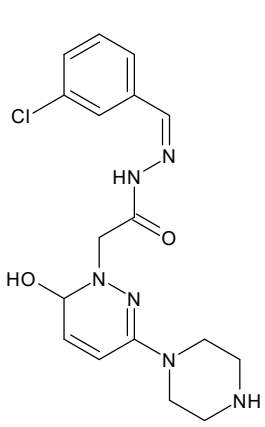
Compound 7

Gokhan-Kelekci *et al* synthesized hydrazones containing 5-methyl-2-benzoxazoline. The analgesic effects of 2-[2-(5-methyl-2-benzoxazoline-3-yl)acetyl]-4-chloro-/4-methyl benzylidene hydrazine Compound 8a and 8b were found to be higher than those of morphine and aspirin. In addition, 2-[2-(5-methyl-2-benzoxazoline-3-yl)acetyl]-4-methoxybenzylidene hydrazine at 200 mg/kg dose possessed the most anti-inflammatory activity[25].



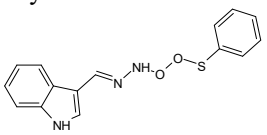
Compound 8a and 8b

Mehtap G *et al*., reported a novel series of 6-substituted-3(2H)-pyridazinone-2-acetyl-2(p-substituted/nonsubstituted benzal) hydrazine was synthesized and evaluated for their analgesic and anti-inflammatory activity. The carrageenan-induced paw edema assay was used to assess the activity, and indomethacin was used as the standard for comparing the results. Compound 9, or 6-substituted-3(2H)-pyridazinone-2-acetyl-2(non-substitutedbenzal) hydrazones, was shown to be the most effective anti-inflammatory drug, according to the data. Compound 9, 6-[4-(3-chlorophenyl) piperazine]-3(2H)-pyridazinone-2-acetyl-2(p-substituted/nonsubstituted benzal) hydrazine, was found to be slightly better than standard drug indomethacin[26].



Compound 9

Sondhi SM *et al*., synthesis of a novel series of some amidine and hydrazone derivatives was reported. The produced chemicals underwent additional testing for analgesic and anti-inflammatory properties. Compound 10 was discovered to have significant anti-inflammatory effects in the carrageenan-induced rat paw edema assay used to assess anti-inflammatory activity[27].



Compound 10

III. Conclusion

Hydrazone derivatives have demonstrated significant promise as anti-inflammatory agents due to their structural versatility, ease of synthesis and broad spectrum of biological activity. Numerous studies have highlighted their ability to modulate key inflammatory pathways, including COX, LOX and pro-inflammatory cytokines. Structure-activity relationship analyses have facilitated the design of more potent and selective analogs with improved safety profiles. Continued exploration of hydrazone-based compounds, particularly through hybridization strategies and target-specific modifications, holds great potential for the development of next-generation anti-inflammatory drugs. Future research should focus on *in-vitro* and *in-vivo* evaluations, toxicity profiling and clinical translation to advance these compounds into therapeutic use.

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