

## Review Article

# Therapeutic Potential of Hydrazones as Anti-Inflammatory Agents

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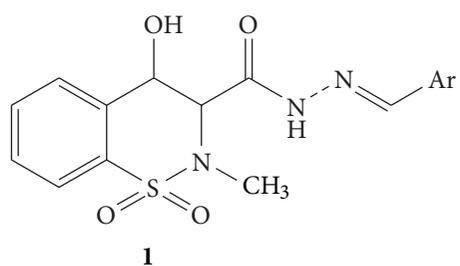
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Hydrazones are a special class of organic compounds in the Schiff base family. Hydrazones constitute a versatile compound of organic class having basic structure ( $R_1R_2C=NNR_3R_4$ ). The active centers of hydrazone, that is, carbon and nitrogen, are mainly responsible for the physical and chemical properties of the hydrazones and, due to the reactivity toward electrophiles and nucleophiles, hydrazones are used for the synthesis of organic compound such as heterocyclic compounds with a variety of biological activities. Hydrazones and their derivatives are known to exhibit a wide range of interesting biological activities like antioxidant, anti-inflammatory, anticonvulsant, analgesic, antimicrobial, anticancer, antiprotozoal, antioxidant, antiparasitic, antiplatelet, cardioprotective, anthelmintic, antidiabetic, antitubercular, trypanocidal, anti-HIV, and so forth. The present review summarizes the efficiency of hydrazones as potent anti-inflammatory agents.

## 1. Introduction

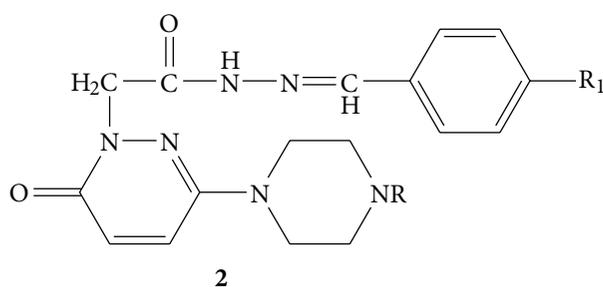
Inflammation is a physiological reaction which involves cellular and biochemical responses, which is not only symptom for common diseases but also known to be an early phase for some serious diseases such as Alzheimer's disease, cancer, heart vascular diseases [1] etc. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ketoprofen, ibuprofen, aceclofenac, and so forth under current clinical usage for the treatment of inflammation, algia and pyresis [2] are associated with major drawbacks of gastrointestinal disorders like dyspepsia, gastric ulcers, and so forth, due to the direct contact of free carboxylic group with the gastric mucosa [3, 4] and due to decrease in production of prostaglandins in tissue [5]. In order to overcome these drawbacks, there is an urgent need for design and synthesis of new chemical entities with excellent anti-inflammatory response and minimum side effects. Hydrazones are a class of organic compounds in the Schiff base family [6]. Hydrazones constitute a versatile compound of organic class having the basic structure  $R_1R_2C=NNR_3R_4$  [7, 8]. Two nitrogen atoms of hydrazone are nucleophilic but the amino type nitrogen is more reactive, whereas the carbon atom possesses both

characters, that is, nucleophilic and electrophilic. The active centers of hydrazine, that is, carbon and nitrogen, are mainly responsible for the physical and chemical properties of the hydrazones and, due to the reactivity toward electrophiles and nucleophiles, hydrazones are used for the synthesis of organic compound such as heterocyclic compounds [9, 10]. The general method for the synthesis of the hydrazones is the reaction of hydrazine with carbonyl compounds such as aldehydes or ketones in solvents like ethanol, methanol, butanol [11–13], and so forth. Hydrazones and their derivatives are known to exhibit interesting diverse biological activities like antioxidant [14], anti-inflammatory [15, 16], anticonvulsant [17, 18], analgesic [19, 20], antimicrobial [21–23], anticancer [24, 25], antiprotozoal [26], antiparasitic [27], cardioprotective [28], antidepressant [29], antitubercular [30, 31], anti-HIV [32], and trypanocidal etc. Hydrazones are also emerging as moiety of interest in medical biotechnology. Hydrazones are also used to couple with certain drugs and the bonds based on hydrazones are stable at the neutral pH [33]. The hydrazone Schiff bases of aryl, acyl, and heteroaryl compounds are known to have an additional donor site, that is, C=O, which make them more versatile and flexible. This versatility has led the hydrazones to emerge



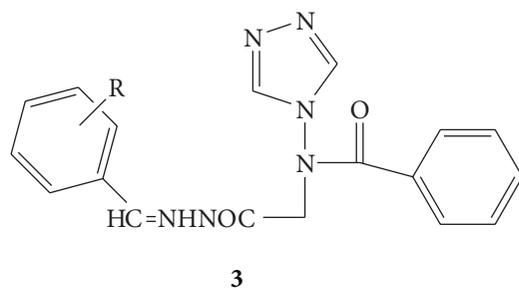
<b>1</b>	Ar
<b>a</b>	Phenyl
<b>b</b>	2-Pyridinyl
<b>c</b>	4-Isopropylphenyl
<b>d</b>	4-Dimethylaminophenyl
<b>e</b>	2-Thiophenyl
<b>f</b>	2-Thiazolyl
<b>g</b>	2-Biphenyl
<b>h</b>	3,5-Diterbutyl-4-hydroxyphenyl

FIGURE 1



<b>2</b>	R	R
<b>a</b>	3-Chlorophenyl	H
<b>b</b>	4-Chlorophenyl	H
<b>c</b>	2-Pyridyl	H
<b>d</b>	3-Chlorophenyl	CH <sub>3</sub>
<b>e</b>	4-Chlorophenyl	CH <sub>3</sub>
<b>f</b>	2-Pyridyl	CH <sub>3</sub>
<b>g</b>	3-Chlorophenyl	OCH <sub>3</sub>
<b>h</b>	4-Chlorophenyl	OCH <sub>3</sub>
<b>i</b>	2-Pyridyl	OCH <sub>3</sub>

FIGURE 2



<b>3</b>	R
<b>a</b>	H
<b>b</b>	4-Methyl
<b>c</b>	4-Methoxy
<b>d</b>	3,4-Dimethoxy
<b>e</b>	2-Chloro
<b>f</b>	4-Chloro
<b>g</b>	4-Dimethylamino
<b>h</b>	4-Hydroxy
<b>i</b>	3-Nitro
<b>j</b>	4-Nitro

FIGURE 3

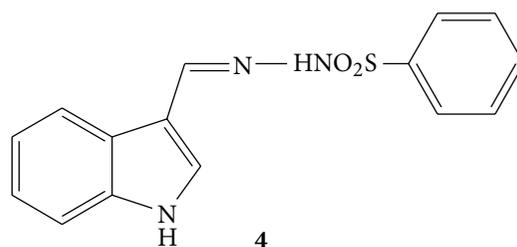


FIGURE 4

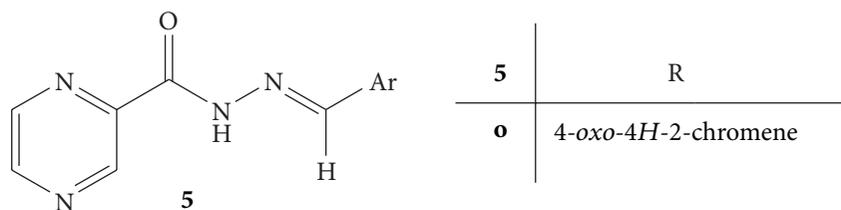


FIGURE 5

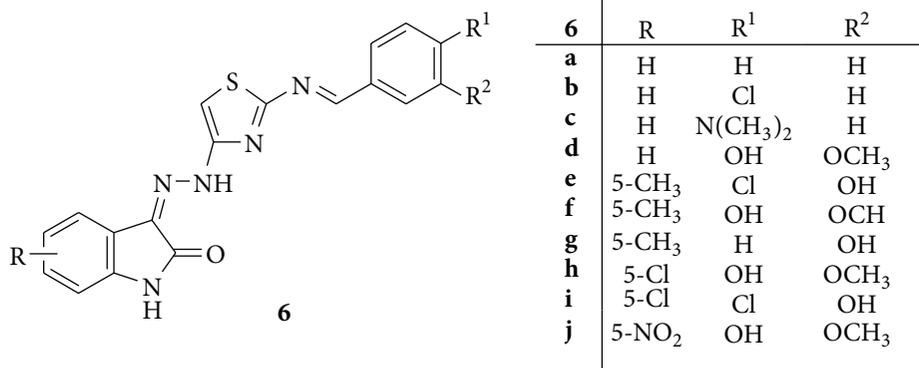


FIGURE 6

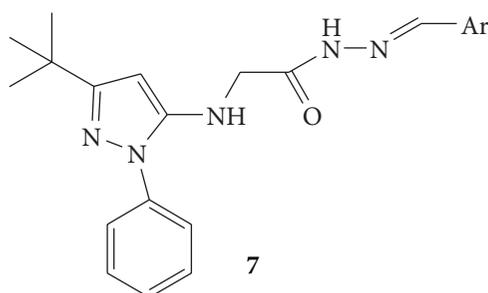


FIGURE 7

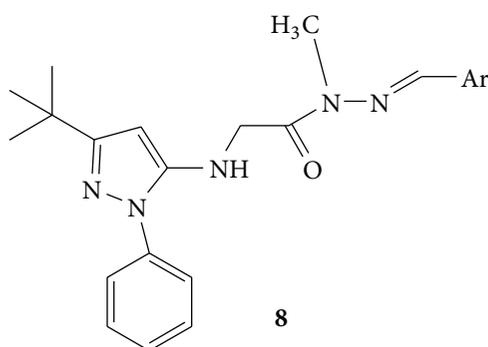


FIGURE 8

as good chelating agents that can form a variety of complexes with different transition metals [6]. Some hydrazones have been introduced by the researchers as potent drugs, such as nifuroxazide, an intestinal antiseptic [34, 35], dihydralazine as hypertensive, and gyromitrin, a toxin.

## 2. Anti-Inflammatory Activity

A series of benzothiazine N-acylhydrazones **1(a-h)** was designed by structural modification of piroxicam and synthesized and evaluated for the anti-inflammatory and antinociceptive activities (Figure 1). The pharmacological screening revealed that compounds **1(a-h)** have exhibited better activity than standard drug piroxicam. Compounds **1f** and **1g** were identified as new anti-inflammatory and antinociceptive agents which were capable of inhibiting cell recruitment by 70% and 80%, respectively, at dose of 100  $\mu\text{mol/kg}$ , p.o in zymosan- and carrageenan-induced peritonitis [36].

A novel series of 6-substituted-3(2H)-pyridazinone-2-acetyl-2(p-substituted/nonsubstituted benzal)hydrazine **2(a-i)** was synthesized and evaluated for their analgesic and anti-inflammatory activity (Figure 2). The activity was evaluated by using carrageenan-induced paw oedema assay and indomethacin was employed as standard for comparison of results. The results revealed that 6-substituted-3(2H)-pyridazinone-2-acetyl-2(nonsubstitutedbenzal)hydrazones, that is, **2a**, **2b**, and **2c**, were found to be most potent anti-inflammatory agents. Compound **2a**, 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 [37].

A novel series of N-(substituted benzylidene)-2-(N-(4H-1,2,4-triazole-4-yl) benzamido)acetohydrazide derivatives **3(a-j)** was synthesized and evaluated for the anti-inflammatory and antimicrobial activity (Figure 3). Indomethacin was used as standard drug and carrageenan-induced paw oedema method was employed for the anti-inflammatory screening of the test compounds. It was found

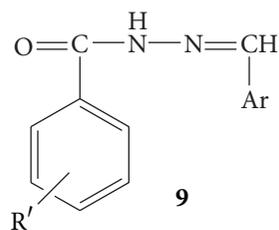


FIGURE 9

9	R'	Ar
c	4-Cl	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
d	4-Cl	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
e	4-Cl	2-OHC <sub>10</sub> H <sub>6</sub>

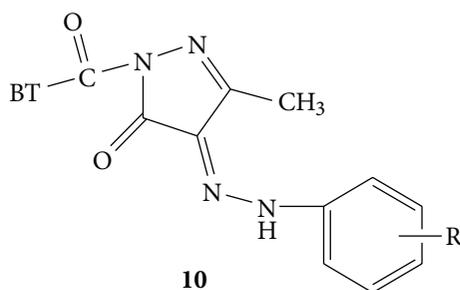


FIGURE 10

10	R
a	H
b	2-Nitro-4-methyl
c	2,5-Dichloro
d	4-Chloro-2-methyl
e	2,5-Dimethyl

that compounds **3f**, **3g**, and **3j** substituted with 4-chloro, 4-dimethylamino, and 4-nitro exhibited 66.7, 61.7, and 63.2% inhibition, respectively, at 50 mg/kg, oral dose, whereas standard drug indomethacin had shown 64.2% inhibition at 10 mg/kg, oral dose [38].

Synthesis of a novel series of some amidine and hydrazone derivatives **4** was reported (Figure 4). The synthesized compounds were further subjected to evaluation of anti-inflammatory and analgesic activities. Anti-inflammatory activity evaluation was carried out using carrageenan-induced rat paw oedema assay and compound **4a** was found to have good anti-inflammatory activity [39].

A series of nineteen pyrazine N-acylhydrazone (NAH) derivatives **5(a-s)** was (Figure 5) designed by molecular simplification of the prototype (LASSBio-1018), a nonselective cyclooxygenase inhibitor. Synthesis of the designed compounds was carried out and they were evaluated for their anti-inflammatory and analgesic activities in several animal models of pain and inflammation like writhing test, formalin test, hot plate test, zymosan-induced peritonitis, capsaicin-induced ear edema, and Freund's adjuvant-induced arthritis model. Thalidomide (TNF- $\alpha$  inhibitor), celecoxib (COX-2) inhibitor, and indomethacin (selective COX-1 inhibitor) were employed as standard drugs. Results enlightened that compound **5o** (2-N'-[(E)-(3,4,5-trimethoxyphenyl)methylidene]-2-pyrazinecarbohydrazide, LASSBio-1181, had better pharmacological activities and can be used as a lead compound for development of new analgesic and anti-inflammatory agents [40].

A novel series of isatin derivatives, that is, isatin-3-[N2-(2-benzalaminothiazol-4-yl)]hydrazones **6(a-j)**, was synthesized and evaluated for anti-inflammatory, analgesic, and antipyretic activities (Figure 6) [41].

Carrageenan-induced rat paw oedema model was used for evaluation of anti-inflammatory activity and indomethacin was employed as standard drug. It was found that the compounds **6f**, **6h**, and **6j** substituted at fifth position with methyl, chloro, and nitro groups, respectively, exhibited significant anti-inflammatory activity [41].

Synthesis of a novel series of orally active N-phenylpyrazolyl-N-glycinyldihydrazone derivatives, **7a-g** (Figure 7) and **8** (Figure 8), was carried out. Synthesized compounds were evaluated for their *in vivo* analgesic and anti-inflammatory activities and *in vitro* inhibition of TNF- $\alpha$  (tumor necrosis factor). Compounds **7a**, (E)-2-(3-tert-butyl-1-phenyl-1H-pyrazol-5-ylamino)-N'-((4-(2-morpholinoethoxy)naphthalen-1-yl)methylene)acetohydrazide, and **7f**, (E)-2-(3-tert-butyl-1-phenyl-1H-pyrazol-5-ylamino)-N'-((4-chlorobenzylidene)acetohydrazide, were known to possess anti-inflammatory activities when compared to the standard drug used, that is, SB-203580 [42].

Synthesis of a novel series of substituted-N'-[(1E)-substituted phenylmethylidene]benzohydrazide analogs, **9(a-n)** (Figure 9) was reported and evaluated for their *in vitro* anti-inflammatory, antimicrobial and antioxidant activities. Albumin denaturation studies were carried out in order to evaluate the anti-inflammatory activity by employing diclofenac sodium as standard. Compounds **9c**, **9d**, and **9e** were reported to have good anti-inflammatory activity due to presence of 4-nitro, 4-methyl, and 2-hydroxy groups, respectively, whereas **9e** was found to be the most active anti-inflammatory agent [43].

Synthesis and biological evaluation of some new benz[b]-thiophene derivatives like thiaziazole, pyrazoline, oxadiazole and diaryl pyrazoles was carried out. N<sup>1</sup>-(3-chloro-

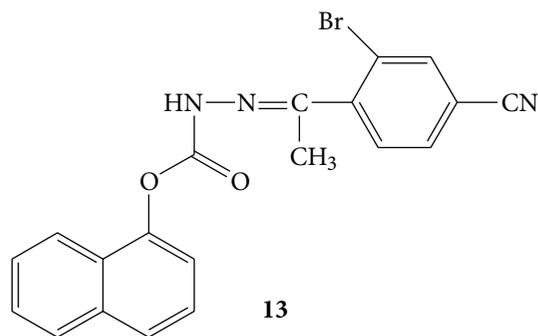


FIGURE 11

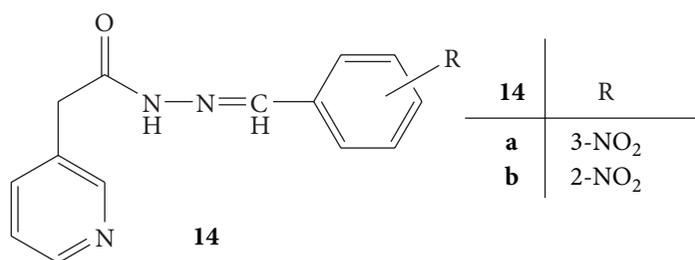


FIGURE 12

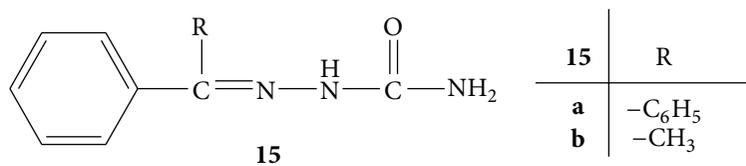


FIGURE 13

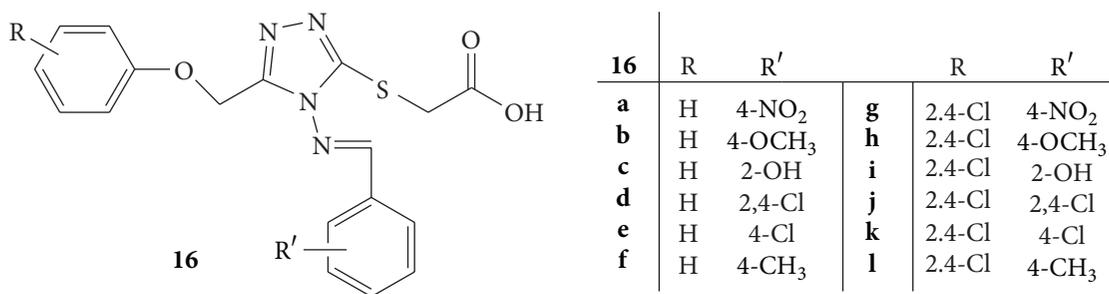


FIGURE 14

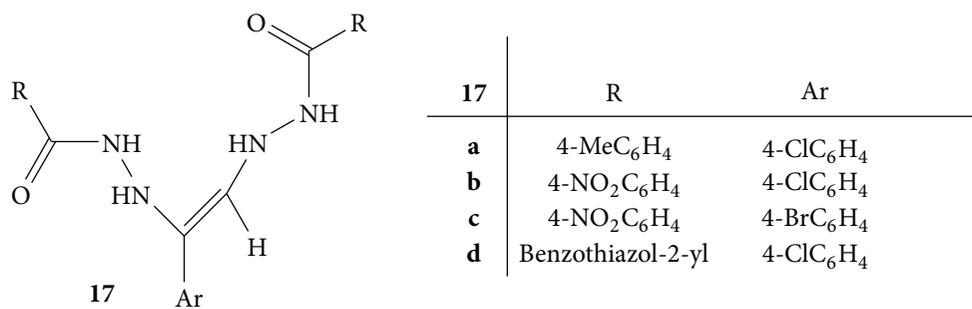
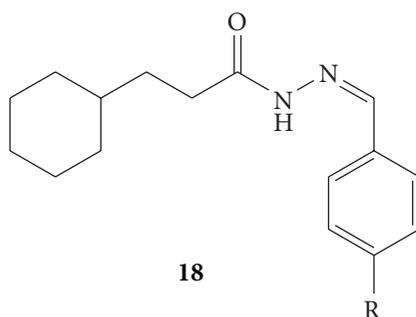


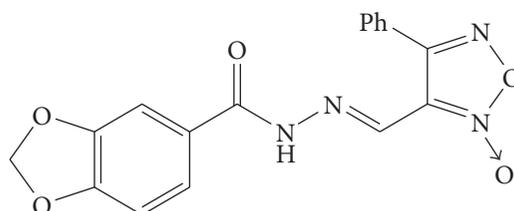
FIGURE 15



18

18	R
a	H
b	NO <sub>2</sub>
c	CH <sub>3</sub>
d	Br
e	F
f	OH
g	OCH <sub>3</sub>
h	Cl
i	CH(CH <sub>3</sub> ) <sub>2</sub>
j	N(CH <sub>3</sub> ) <sub>2</sub>

FIGURE 16



19

FIGURE 17

robenzo[b]thiophene-2-carbonyl)-3-methyl-4-9 substituted phenylhydrazono pyrazolin-5-one **10(a-e)** were subjected to anti-inflammatory and antimicrobial evaluation (Figure 10). Compound **10b** substituted with 2-nitro-4-methyl was found to have 50.25 % inhibition which is near about the standard drug diclofenac sodium i.e. 51.88% [44].

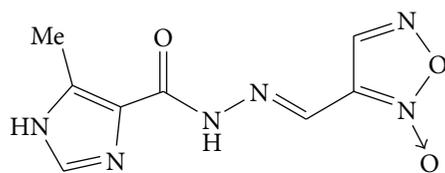
Synthesis of zinc complexes **11**, [Zn(LASSBio-466)H<sub>2</sub>O]<sub>2</sub> of salicylaldehyde 2-chlorobenzoyl hydrazone (H<sub>2</sub>LASSBio-466), and **12**, [Zn(HLASSBio-1064)Cl]<sub>2</sub> salicylaldehyde 4-chlorobenzoyl hydrazone (H<sub>2</sub>LASSBio-1064), was carried out. The complexes were further subjected to evaluation for peripheral and central nociception and acute inflammation in animal models. Both of the complexes exhibited anti-inflammatory activity. Complex **11** has shown activity in both phases of formalin test like indomethacin and indicated its ability to inhibit nociception associated with the inflammatory response, whereas H<sub>2</sub>LASSBio-466 was active only in first phase of formalin test. H<sub>2</sub>LASSBio-1064 inhibited both phases but no improvement was indicated by the complex [45].

Synthesis of some new hydrazide derivatives of 2-naphthoxy acetic acid [46], nicotinic acid [47, 48] and naphthalene-1-acetic acid [49] has been reported. Out of these hydrazide derivatives most active antimicrobial compounds were selected and subjected to evaluation of the anti-inflammatory activity. Carrageenan induced rat paw oedema model was employed for the evaluation of these active compounds using diclofenac sodium as standard drug. Results

revealed that naphthalen-1-yloxy)-acetic acid [1-(2-bromo-4-cyano-phenyl)-ethylidene]-hydrazide **13** (Figure 11) has shown percent inhibition of 20.90% at a dose of 50 mg/kg [50].

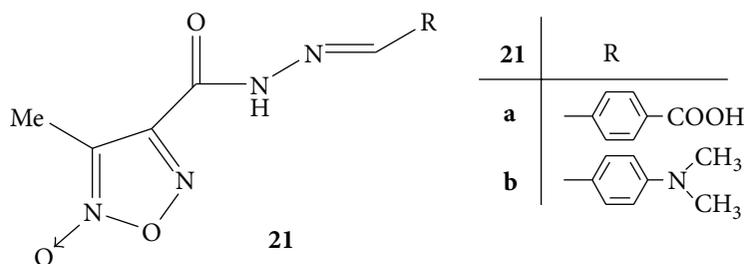
The nicotinic acid hydrazide derivatives, **14a** and **14b**, substituted with nitro group at *meta* and *ortho* positions, respectively, were found to be the most active anti-inflammatory agents (Figure 12). The percent inhibition of compounds **14a** and **14b** was found to be 37.29% and 35.73%, respectively, at the dose of 20 mg/kg and 34.17% and 25.12%, respectively, at the dose of 50 mg/kg, whereas percent inhibition of diclofenac sodium was found to be 38.85%. The conclusion drawn from the results was that the substitution of nitro group and halogens contributed to anti-inflammatory activity [50].

Synthesis of benzophenone semicarbazone (BSC) **15a** and acetophenone semicarbazone (ASC) **15b** was carried out (Figure 13). The anti-inflammatory activity was determined on Swiss albino mice by using carrageenan-induced mice paw oedema model. Both of the compounds were screened at two different doses, that is, 25 mg/kg and 50 mg/kg (p.o.). Compound **15a** showed 36.6% and 46.6% of inhibition at 25 mg/kg and 50 mg/kg, respectively, whereas compound **15b** showed 34.6% and 41.5% inhibition. Diclofenac sodium was used as standard drug which showed 70.29% inhibition at 10 mg/kg (p.o.). From the above observations, it was concluded that both of the test compounds possessed anti-inflammatory activity [51].



20

FIGURE 18



21

FIGURE 19

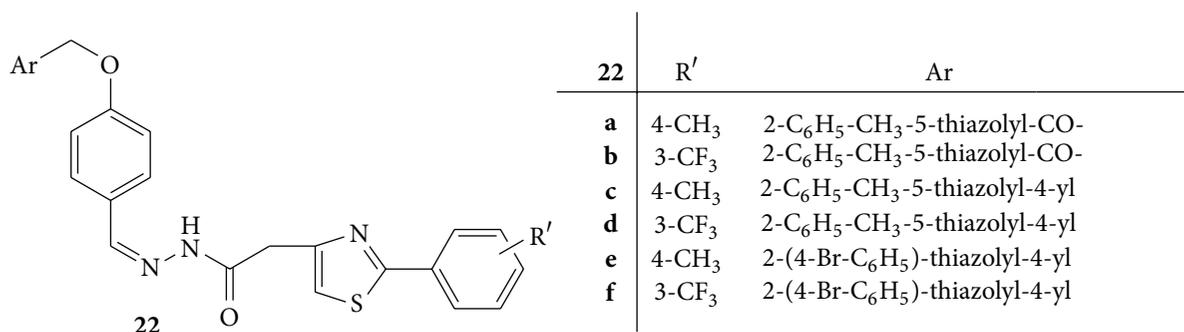


FIGURE 20

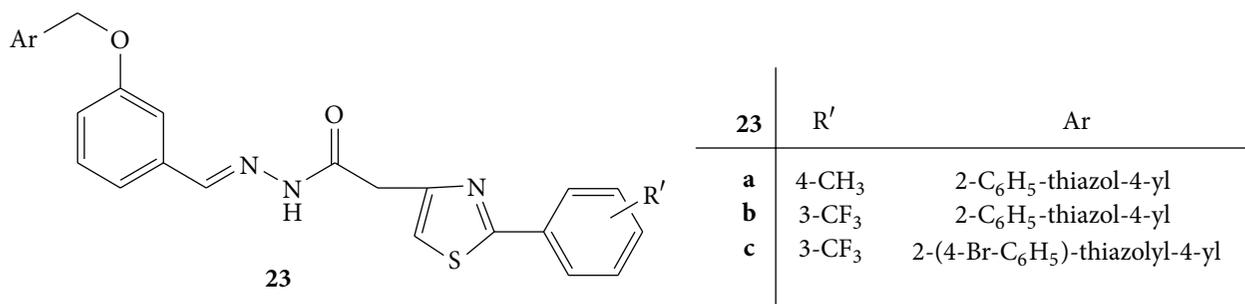


FIGURE 21

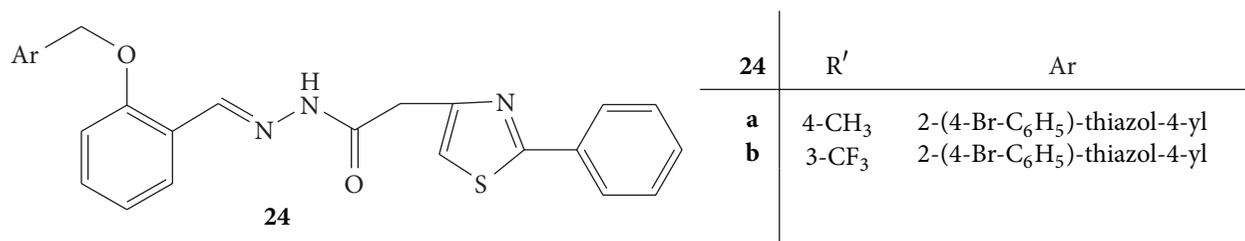
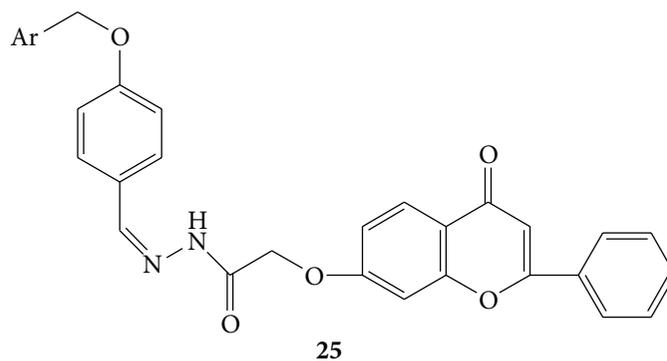


FIGURE 22



Ar = 2-C<sub>6</sub>H<sub>5</sub>-thiazol-4-yl

FIGURE 23

A novel series of 2-[4-(substituted benzylideneamino)-5-(substituted phenoxy)methyl]-4H-1,2,4-triazol-3-yl thio] acetic acid, **16(a-l)**, was synthesized (Figure 14). All the newly synthesized compounds were evaluated for *in vivo* anti-inflammatory and analgesic activities. Among the series **16d**, **16e**, **16j**, and **16k** showed significant activity with 63.4%, 62.0%, 64.1%, and 62.5% edema inhibition, respectively, as compared to standard drug diclofenac 67.0% after the third hour. Compounds **16g**, **16h**, **16i**, and **16l** showed good anti-inflammatory activity, whereas compounds **16a-c** and **16f** were found to be the least active. The results enlightened the effect of electron withdrawing moiety, that is, chloro group on the anti-inflammatory activity [52].

A series of bis-hydrazone derivatives, that is, (Z)-N',N''-(1-(4-substituted phenyl)ethene-1,2-diyl)bis(4-substituted benzhydrazide), **17(a-d)**, was synthesized by reaction of 2-chloro-1-(4-chloro phenyl)ethanone or 2-bromo-1-(4-bromophenyl)ethanone with acid hydrazides (Figure 15). 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 activity with percent inhibition of 68.4% and 61.4% of compounds **17b** and **17c**, respectively, after three hours [53].

Synthesis of a series of hydrazone derivatives, that is, N-(substituted benzylidene)-3-cyclohexylpropionic acid hydrazide, **18(a-j)**, was carried out (Figure 16). The synthesized compounds were evaluated for anti-inflammatory activity and cytotoxicity. Inducible nitric oxide synthase (iNOS) and NF- $\kappa$ B were selected for determination of anti-inflammatory activity. Inhibition of iNOS activity was also observed in LPS-induced RAW 264.7 cells. Compounds **18c**, **18e**, and **18i** were more active than the other synthesized compounds which proved that there is a positive correlation between the inhibitions of iNOS activity and functional groups, that is, methyl, fluoro, and isopropyl, on phenyl ring [54].

Inhibition of NF- $\kappa$ B mediated transcription was seen in human chondrosarcoma (SW1353) cells and compounds **18a**, **18c**, and **18h** have shown inhibition with IC<sub>50</sub> values of 6.9,

7.7, and 6.4  $\mu$ g/mL, respectively (Figure 17). This observation correlated that methyl and chloro groups have a considerable influence on the inhibition of NF- $\kappa$ B mediated transcription. The other compounds **18d**, **18e**, **18g**, and **18i** inhibited the NF- $\kappa$ B activity to a lesser extent with IC<sub>50</sub> values in the range of 10–14  $\mu$ g/mL. Compounds **18b**, **18d**, and **18j** were found to be comparatively less active than other compounds. From the results, it was concluded that substitutions at *para* position of phenyl ring had significant influence on anti-inflammatory activity [54].

By application of molecular hybridization approach design, and synthesis of thirty two furoxanyl N-acylhydrazones (furoxanyl-NAH) was carried out. Synthesized compounds were evaluated for their *in vitro* as well as *in vivo* analgesic and anti-inflammatory activities. The *in vitro* anti-inflammatory activity was evaluated by decrease in NF- $\kappa$ B activation and interleukin-8 inhibition by using a human pathway-specific reporter cell system (HT-29-NF- $\kappa$ B-hrGFP) whereas carrageenan induced paw oedema was used for *in vivo* evaluation of anti-inflammatory activity. Furoxanyl-NAH **19** (Figure 17) and benzofuroxanyl-derivative **20** (Figure 18) were reported to have orally anti-inflammatory and analgesic activities without interleukin-8 inhibition. Furoxanyl-NAH derivative **21a** (Figure 19) was emerged as a structural lead to develop new lipoxygenase (LOX) inhibitors. The active derivatives **19**, **21a** and **21b** were found to be less mutagenic and were proposed as candidates for the further clinical studies [55].

Synthesis of a series of novel acyl-hydrazones bearing 2-aryl-thiazole moiety was carried out. The synthesized compounds were screened for *in vivo* anti-inflammatory activity by evaluating three parameters, that is, nitric oxide synthesis, phagocytes activity, and acute phase bone marrow response, in acute experimental inflammation [56].

Compounds **22c**, **22e**, **22f**, **24b**, and **26b** were found to have a good inhibitory effect on the acute phase marrow response by reducing the absolute leukocytes count due to the lower neutrophils percentage. Compound **22c** (Figure 20) with 2-phenyl-thiazole and [2-(4-methylphenyl)-4-methylen]-thiazole hydrazine moieties was proved to be a more potent inhibitor of the acute phase bone marrow

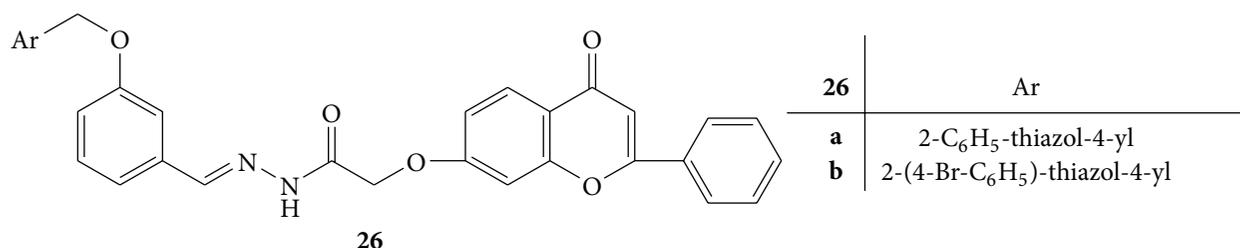


FIGURE 24

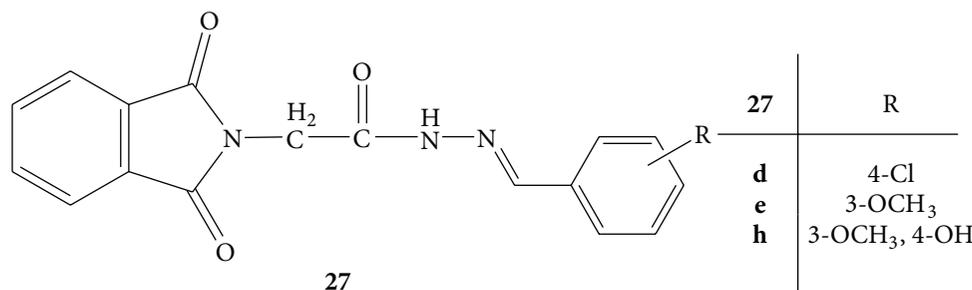


FIGURE 25

response than meloxicam, the anti-inflammatory standard drug [56].

Phagocytic activity was assessed by calculating phagocytic index (PI) and the phagocytic activity (PA). All the newly synthesized compounds reduced PI significantly and compounds **22a** (Figure 20), **22b** (Figure 20), **22d** (Figure 20), **23b** (Figure 21), **24b** (Figure 22), **25** (Figure 23) and **26b** (Figure 24) were observed as more potent inhibitors than meloxicam. PA was significantly reduced by the compounds **22a**, **22d**, **23b**, **24b**, **23c**, **25** and **26b** from which **22a**, **22d**, **20** and **26b** were found to be more potent inhibitors than meloxicam [56].

Synthesis of NO increases significantly in acute inflammation due to the expression of iNOS. The NO synthesis was significantly reduced by **22a**, **22b**, **23c**, **26a**, and **26b** and they all, except for **26a**, displayed a stronger inhibitory activity than meloxicam [56].

Synthesis of a novel series of phthalic anhydride based substituted benzylidene-hydrazide derivatives, **27a-i**, was carried out. All the synthesized derivatives were screened for *in vivo* anti-inflammatory and analgesic activities by carrageenan-induced rat paw oedema and tail immersion methods, respectively, using diclofenac sodium as standard drug. The results revealed that derivatives **27d**, **27e**, and **27h** (Figure 25) 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%. The reaction time of derivatives **27d** and **27h** that was found to be  $8.91 \pm 0.21$  and  $9.09 \pm 0.03$ , respectively, after 90 minutes which is comparable with reaction time of diclofenac sodium ( $10.93 \pm 0.01$ ) after 90 minutes has shown analgesic potency of these derivatives [57].

### 3. Conclusion

Hydrazone derivatives are well known to have various important pharmacological activities and are used for synthesis of a wide variety of medicinally active compounds. This review paper summarizes the anti-inflammatory potential of hydrazone derivatives and the effect of substitutions of different groups on the anti-inflammatory activity. This summarized study is an attempt to bring about the anti-inflammatory activity for awakening the safe use of this important chemical moiety with minimal or no ulcerogenic effects in future.

### Conflict of Interests

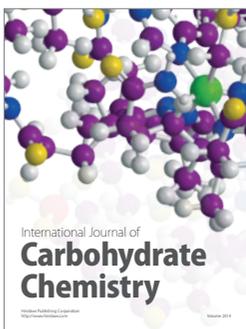
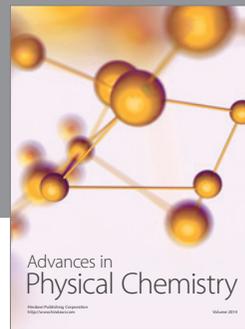
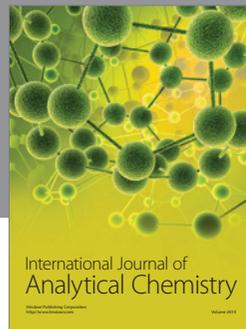
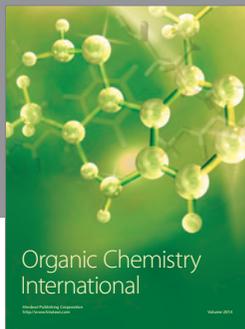
The authors declare that there is no conflict of interests regarding the publication of this paper.

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