



Analgesic and anti-inflammatory potential of hydrazones

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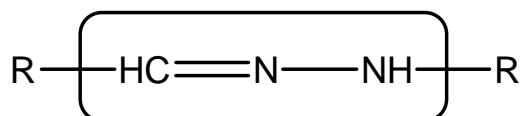
ABSTRACT

Hydrazide-hydrazone derivatives attracted the attention of medicinal chemists during the last few decades due to their diverse pharmacological activities. Great effort has been expended on the development of novel potent analgesic, anti-inflammatory agents with least side effects. Hydrazones constitute an important class of compounds for development of new drugs. This review highlights analgesic and anti-inflammatory activities shown by hydrazones.

Keywords: Analgesic, Anti-inflammatory, Hydrazones, COX

INTRODUCTION

Hydrazones possessing an azometine -NHN=CH- proton. Hydrazones constitute an important class of compounds for development of novel drugs. The researchers have shown intense interest to synthesize these compounds as target structures and evaluated their biological activities. Such kind of observations has been guiding for the development of new hydrazones that may possess varied biological activities.

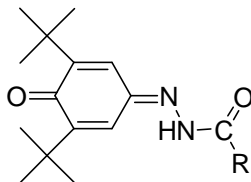


A number of hydrazone derivatives have been reported to various biological activities like analgesic, anti-inflammatory, antihypertensive, anticonvulsant, antimicrobial, anti-tubercular, antitumor, antimalarial and antiproliferative activities [1]. This review highlights synthesis of hydrazones and analgesic, anti-inflammatory activities shown by hydrazones.

Analgesic and Anti-inflammatory Activity:

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of pain and inflammation. These compounds non-selectively inhibit the two isoforms of the cyclooxygenase (COX-1 and COX-2) and thus prevent the metabolism of cellular arachidonic acid (AA) and the upregulation of prostaglandin formation, which otherwise lead to an increase of vascular permeability, edema, hyperalgesia, pyrexia and inflammation. Leukotrienes, produced through the 5-LOX enzyme pathway, may also contribute to both inflammation and NSAIDs induced side effects. For these reasons, compounds that are dual inhibitors of both COX and 5-LOX are being studied as potential analgesic and anti-inflammatory agents with an improved safety profile in comparison to NSAIDs [2]. Some evidences also suggested that the hydrazone moiety present in some compounds possess a pharmacophoric character for the inhibition of COX and LOX.

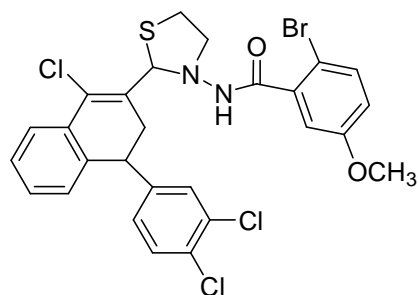
Hydrazone derivatives of 2, 6-di-*tert*-butyl-*p*-benzoquinone were synthesized. Molecular docking calculations were performed using AutoDock-Vina software for binding study with COX-2 and 5-LOX enzymes. All the synthesized compounds as well as standard dual COX-LOX inhibitor Darbufelone compound were docked. The best binding energy was exhibited by *N'*-(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)picolinohydrazide **1a**. The potential of all synthesized compounds to inhibit COX-1, COX-2 isoforms and 5-LOX was determined on pure enzymes. Phenyl and 4-pyridyl hydrazone derivatives of 2, 6-di-*tert*-butyl-*p*-benzoquinone (**1b** and **1c**) exhibited most potent 5-LOX and COX-2 inhibitory activities [3].



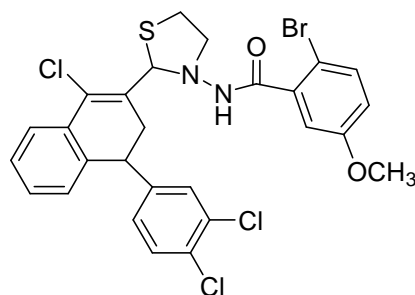
1a (R=3-Pyridyl), **1b**(R=Phenyl), **1c**(R=4-Pyridyl)

Some *N*-aryl hydrazones and their 2,3-disubstituted-4-thiazolidinone derivatives were synthesized and evaluated for antioxidant, anti-inflammatory and analgesic activities. The anti-inflammatory activity of seventeen newly synthesized thiazolidinone compounds were evaluated by applying carrageenan-induced paw edema bioassay using Diclofenac as a reference standard and the analgesic activity of the above mentioned compounds was also evaluated by applying tail flick method. The analgesic activity study revealed that the compounds **2**, **3g**, **3h**, **3i**, **3k**, **3l**, **3n** and **3p** having 4-chloro-1-(3,4-dichlorophenyl)-1,2-dihydronaphthalene, 4-nitro phenyl, phenyl, biphenyl, pyridyl, 4-fluoro phenyl, 2-hydroxy phenyl, and 4-hydroxy-3-methoxy phenyl substituent's showed good activity compared to the standard drug pentazocin.

The compounds **3g**, **3i**, **3j**, **3k**, **3m** and **3p** containing 4-nitro phenyl, biphenyl, 4-methyl phenyl, pyridyl, 6-methoxy-2-naphthyl, and 4-hydroxy-3-methoxy phenyl substituent's, respectively, are the most potent agents of this series against rat-foot inflammation [4].



2



Compound

R

3g 4-NO₂-C₆H₄

3h C₆H₅

3i C₁₂H₉

3j 4-Me-C₆H₄

3k C₆H₄N

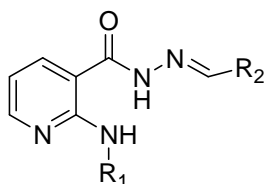
3l 4-F-C₆H₄

3m 6-OCH₃-2-naphthyl

3n 2-OH C₆H₄

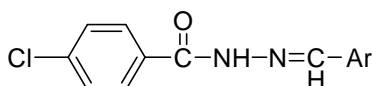
3p 4-OH-3-OCH₃-C₆H₃

A new series of niflumic acid-based *N*-acylhydrazone derivatives were synthesized and evaluated for their anti-inflammatory and analgesic activities. The anti-inflammatory activity of the compounds was studied using the carrageenan-induced rat paw edema assay. The analgesic activity of the compounds was studied using acetic acid-induced abdominal constriction test. Among them, 3-chlorophenyl **4d**, 3-pyridyl derivative **4o** and 4-pyridyl derivative **5f** exhibited the most potent anti-inflammatory activity relative to niflumic acid as the reference drug. Among substituted analog, 4-pyridyl (**4p** and **5f**) and 4-methoxyphenyl **4j** derivatives exhibited the most potent analgesic activity relative to the reference drug niflumic acid [5].



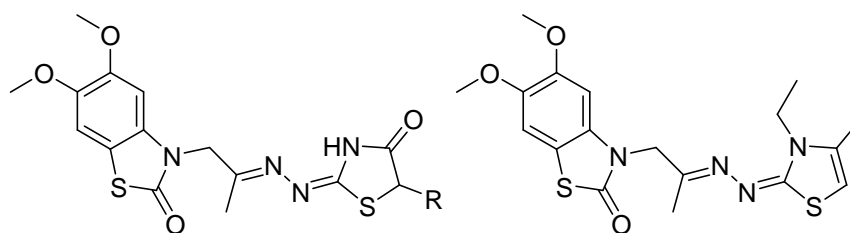
Compound	R ₁	R ₂
4d	3-CF ₃ -C ₆ H ₄	3-ClC ₆ H ₄
4j	3-CF ₃ -C ₆ H ₄	4-OMeC ₆ H ₄
4o	3-CF ₃ -C ₆ H ₄	3-Pyridyl
5f	CH ₃	4-Pyridyl
5p	3-CF ₃ -C ₆ H ₄	4-Pyridyl

A series of substituted-*N'*-[(*E*)-substituted phenylmethylidene] benzohydrazide analogs were synthesized and evaluated for their antioxidant, anti-inflammatory, and antimicrobial activity using different *in-vitro* models. The synthesized compounds were screened for anti-inflammatory activity using inhibition of albumin denaturation technique. It was found that **6a**, **6c**, **6d**, and **6e** compounds lead to considerable inhibition of denaturation. Out of these, **6e** was found as most active [6].



Compound	Ar
6a	2-OHC ₆ H ₄
6c	4-NO ₂ -C ₆ H ₄
6d	4-CH ₃ -C ₆ H ₄
6e	2-OHC ₁₀ H ₆

A series of benzothiazol-2-one derivatives was synthesized and screened for anti-inflammatory and analgesic agents. The carrageenan rat paw edema model of inflammation was used to evaluate the anti-inflammatory properties and the hot-plate test was performed on mice by using an electronically controlled hotplate of the synthesized compounds. The colorimetric COX (ovine) Inhibitor Screening Assay utilizes the peroxidase component of cyclooxygenase for *in-vitro* testing. The study revealed that the thiazolidinone derivative **7a** was the most potent anti-inflammatory agent. Compound **7b** exhibited the highest analgesic activity. The ulcerogenic effect of some active anti-inflammatory and analgesic derivatives was evaluated. The best result was exhibited by compound **7b** which showed comparable activity to the standard drug Indomethacin.

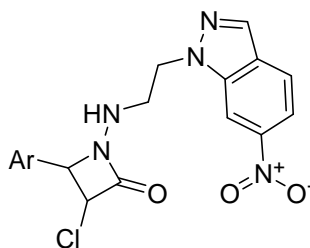


7a (R=H), **7b**(R=CH₃)

8b

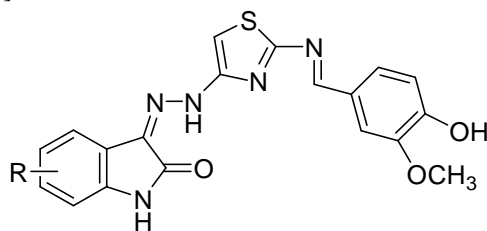
In-vitro inhibition of COX-1 and COX-2 enzyme experiment indicated that all compounds showed non-selective COX inhibitory activity. Among the tested compounds, the most interesting activity was found in compound **8b**: the percentage inhibition of COX-2 and COX-1 by compound **8b** is 73.47 and 42.63 %, respectively [7].

A new series of 3-chloro-1-((2-(6-nitro-1*H*-indazol-1-yl)ethyl)amino)-4-(substituted phenyl)-2-azetidinones was synthesized. All the compounds were screened *in-vitro* for their antibacterial, antifungal and anti-tubercular activities against some selected microorganism and for their anti-inflammatory activity (*in-vivo*) against albino rats. Compounds **9b**, **9d**, **9f**, **9g**, **9h**, **9i** and **9j** displayed higher activities than the other compounds of the series. Compound **9i** (3-Nitrophenyl substituted) was found most active compound and comparable to standard drug phenylbutazone [8].



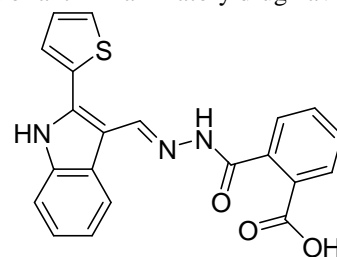
Compound	Ar	Compound	Ar
9b	4-ClC ₆ H ₄	9h	4-NO ₂ C ₆ H ₄
9d	2-ClC ₆ H ₄	9i	3-NO ₂ C ₆ H ₄
9f	3-BrC ₆ H ₄	9j	2-NO ₂ C ₆ H ₄
9g	2-BrC ₆ H ₄		

Venkateshwarlu, *et al.*, (2012) investigated a different isatin derivatives for their anti-inflammatory, analgesic and antipyretic activity. Some Isatin-3-[N²-(2-benzalaminothiazol-4-yl)]hydrazones were taken and their anti-inflammatory, analgesic and antipyretic activity was evaluated in animal models using indomethacin as a standard. Anti-inflammatory activity was determined by carrageenan induced rat paw edema model. Antipyretic activity was evaluated by Brewer's yeast induced pyresis model and measured reduction of rectal temperature. Eddy's hot plate method was employed for analgesic activity. All the compounds were screened, among the screened compounds **10D**, **10F**(5-methyl), **10H**(5-chloro) and **10J**(5-nitro) showed significant anti-inflammatory, analgesic and antipyretic activity when compared with the control group. These activities of isatin derivatives were found mainly due to substitution at 5th position [9].



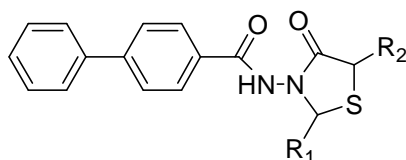
10D (R=H), 10F(R=5-CH₃), 10H(R=5-Cl) and 10J(R=5-NO₂)

A series of 2-thienyl-3-substituted indole derivatives were synthesized. The prepared compounds were evaluated for their anti-inflammatory activity (against carrageenan induced edema in albino rats using indomethacin as a standard drug) and ulcerogenic effect. After 4 hrs from administration of the tested compounds, Compound **11a** was found to be more potent as an anti-inflammatory agent than indomethacin with less ulcerogenic effect. Compound **11a** might be a promising lead drug for development of anti-inflammatory drug having less ulcerogenic effect [10].



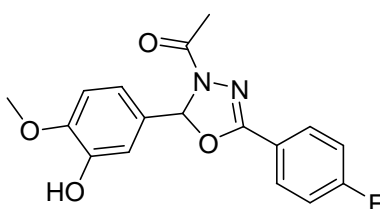
11a

2-(Aryl)-5-(arylidene)-4-thiazolidinone derivatives were synthesized and screened for analgesic and anti-inflammatory activity. Anti-inflammatory activity of all title compounds was carried out by carrageenan-induced rat paw edema test. Acetic acid-induced writhing model was employed to evaluate the analgesic activity. All synthesized 4-thiazolidinone derivatives were evaluated for anti-inflammatory activity and among them compounds **12l** and **12m** showed comparatively good percentage of inhibition of edema than the other synthesized compounds. The compounds **12h** and **12p** bearing two electron withdrawing groups i.e., chloro and nitro (**12h**) and fluoro and chloro (**12p**) were found to be most potent analgesic compounds [11].



Compound	R ₁	R ₂
12h	3-NO ₂ C ₆ H ₄	4-ClC ₆ H ₄
12l	4-OCH ₃ C ₆ H ₄	3-NO ₂ C ₆ H ₄
12m	4-OCH ₃ C ₆ H ₄	4-ClC ₆ H ₄
12p	4-FC ₆ H ₄	4-ClC ₆ H ₄

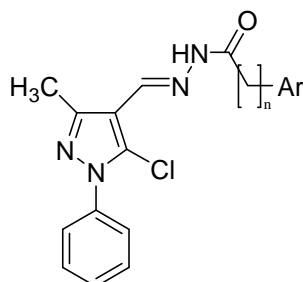
Hydrazide-hydrazones and their corresponding 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles were synthesized and screened for antifungal, Cytotoxic, anti-inflammatory and antioxidant activity .



Compound 13

Anti-inflammatory activity was carried out by inhibiting NF-κB. Of the tested compounds, **13** (*p*-Fluorophenyl substituted) showed a strong inhibition of NF-κB-dependent transcription in SW1353 cells induced by phorbol myristate acetate (PMA) with IC₅₀ values of 0.75 μg/ml, which was comparable with the activity of positive control, parthenolide (IC₅₀ of 0.68 μg/ml) [12].

Pharmacological screening for anti-inflammatory, analgesic activity of pyrazolyl derivatives were carried out along with molecular docking studies.



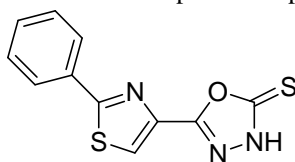
Compounds	Ar	n
14e	4-Chlorophenyl	1
14h	4-Chlorophenyl	0
14j	4-Fluorophenyl	0
14k	Phenoxy	1
14l	Isobutylphenyl	2
14m	Phenyl	1
14o	2,4-Dichlorophenyl	0

Analgesic and anti-inflammatory activity were evaluated using the tail immersion method and carrageenan-induced rat paw edema test respectively. Compounds **14e**, **14h**, **14j–m** and **14o** showed moderate but significant analgesic activity compared to the standard drug Diclofenac. In anti-inflammatory evaluation two pyrazole derivatives (**14h** and **14k**) were found to be almost equipotent with indomethacin throughout the study. The titled compounds were found to be non ulcerogenic indicated by their antiulcer activity. The docking studies of synthesised compounds in the active site of COX-2 was performed using dock simulation as incorporated in the MOE 2008.10. Docking studies of compound **14k** with a docked score of -11.192, which was found almost equal to indomethacin [13].

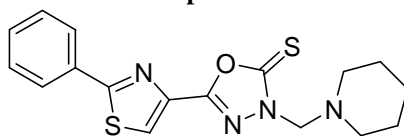
Docking, synthesis, and pharmacological investigation of novel substituted thiazole derivatives were carried out. Anti-inflammatory activity was evaluated by the carrageenan-induced paw edema test in rats and Analgesic activity was screened by acetic acid-induced writhing test.

Among all the synthesized compounds, those possessing 1, 3, 4-oxadiazole-2(3H)-thione (**15** and **16**) and pyrazole (**17** and **18**) at position 4 of thiazole exhibited more prominent and consistent anti-inflammatory activity than that of the standard drug diclofenac sodium. These compounds also showed significant analgesia in acetic acid-induced writhing test. The tested compounds showed one tenth of the ulcer index to that of reference diclofenac sodium at a dose of 25 mg/kg. These compounds exhibited quite less ulcerogenic index in the range of 0.44 to 0.62 whereas diclofenac sodium showed 4.67.

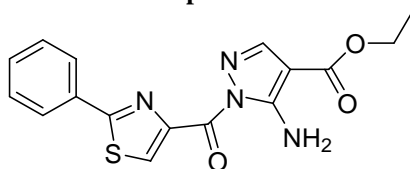
In order to find out the interactions of designed target molecules on COX-2 enzyme, the docking study was carried out on VLife MDS 4.0 software using grid analysis-based batch docking. The compounds **15** and **16** exhibited good activities both *in silico* (docking) and *in vivo* studies. Docking study and *in vivo* results showed that these series of compounds possess good potential and can be further developed into a potent lead [14].



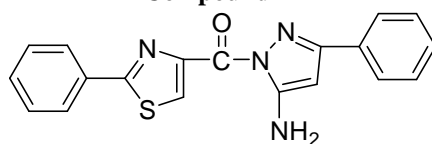
Compound 15



Compound 16

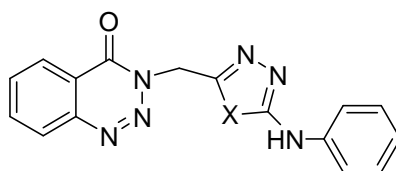


Compound 17



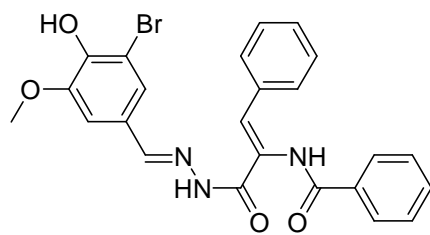
Compound 18

Synthesis, molecular modeling and anti-inflammatory screening of new 1,2,3-benzotriazinone derivatives were carried out. Some of the synthesized compounds were tested for anti-inflammatory activity using carrageenan-induced edema bioassay method in rats. Indomethacin was used as a reference standard in the assay. Celecoxib was additionally used as a second reference standard representing selective COX-2 inhibitor non-steroidal anti-inflammatory agents. Molecular docking of the synthesized compounds into COX-2 enzyme was carried out using the AutoDock 4.2 software package. Among the tested compounds, the benzotriazinones linked to either thiadiazole (**19**) or oxadiazole (**20**) evoked the highest anti-inflammatory activity as well as the best binding profiles into the COX-2 binding site [15].

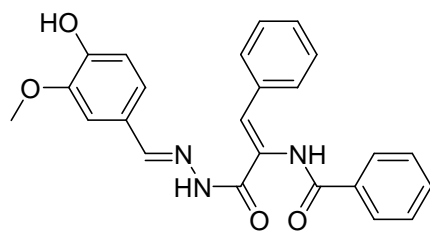


19 (X=S), 20 (X=O)

A series of novel N-(a-benzamido cinnamoyl) aryl hydrazone derivatives have been synthesized and screened for their anti-inflammatory and antioxidant activities. Of all the compounds screened, compound N'-(5-bromo-4-hydroxy-3-methoxybenzylidene)-2-(benzamido)-3-phenylacrylohydrazone (**21m**) shows anti-inflammatory activity (75%) which is equivalent to that produced by the same dose (100 mg/kg) of phenylbutazone (74%). Compound N'-(4-hydroxy-3-methoxy benzylidene)-2-(benzamido)-3-phenyl-acrylohydrazone (**21i**), shows good anti-inflammatory and antioxidant activity [16].

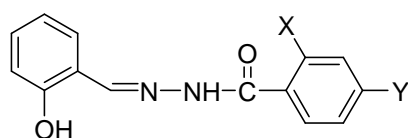


21m



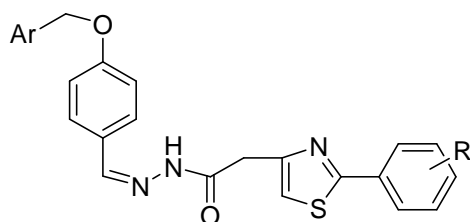
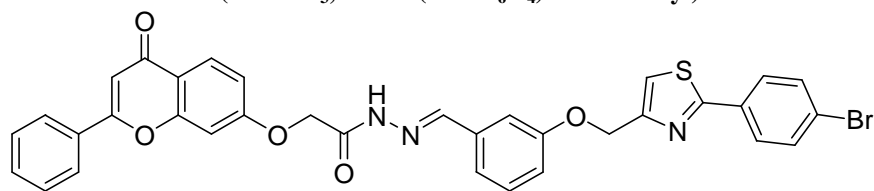
21l

Salicylaldehyde 2-chlorobenzoyl hydrazone (**22**), salicylaldehyde 4-chlorobenzoyl hydrazone (**23**) and their complexes with zinc were evaluated in animal models for peripheral and central nociception and acute inflammation. It was studied that all compounds significantly inhibited acetic acid-induced writhing response. All compounds showed levels of inhibition of zymosan-induced peritonitis which is comparable or superior to indomethacin, indicating an expressive anti-inflammatory profile [17].



22 (X= Cl, Y= H) and 23 (X= H, Y= Cl)

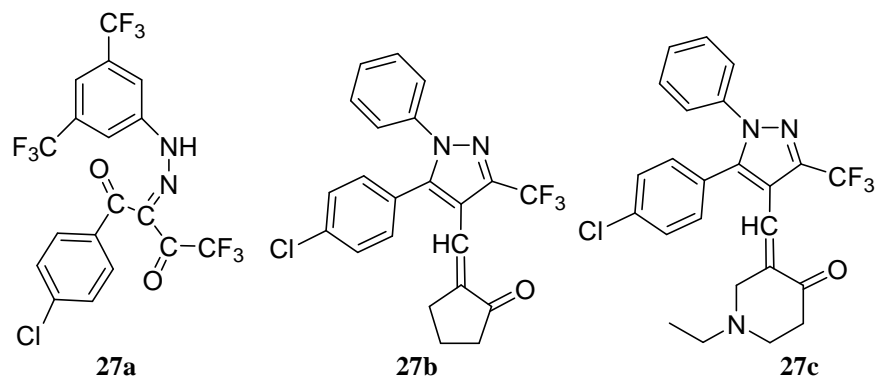
A series of novel acyl-hydrazones bearing 2-aryl-thiazole moiety were synthesized by the condensation between derivatives of 4-[2-(4-methyl-2-phenyl-thiazole-5-yl)-2-oxo-ethoxy]-benzaldehyde and 2, 3 or 4-(2-aryl-thiazol-4-ylmethoxy)-benzaldehyde, respectively and different carboxylic acid hydrazides. Various substituted 2-aryl-thiazole hydrazone derivatives were synthesized and screened for their anti-inflammatory potential. Compounds **23**, **24**, **25**, **26** showed 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 **23**, which has 2-phenyl-thiazole and [2-(4-methylphenyl)-4-methylen]-thiazole hydrazine moieties in its structure, proved to be a more active inhibitor of the marrow acute phaseresponse than Meloxicam [18].

23 (R=4-CH₃, Ar= 2-C₆H₅-Thiazol-4-yl)24 (R=4-CH₃, Ar= 2-(4-BrC₆H₄)-Thiazol-4-yl)25 (R=4-CF₃, Ar= 2-(4-BrC₆H₄)-Thiazol-4-yl)

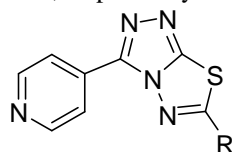
26

New arylhydrazone derivatives and a series of 1,5-diphenyl pyrazoles were designed and synthesized from 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione. The newly synthesized compounds were investigated *in vivo* for their

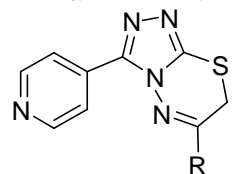
anti-inflammatory activities using carrageenan-induced rat paw oedema model. Moreover, they were tested for their inhibitory activity against ovine COX-1 and COX-2 using an *in-vitro* cyclooxygenase (COX) inhibition assay. Some of the new compounds (**27a**, **27b** and **27c**) showed a reasonable *in vitro* COX-2 inhibitory activity. A virtual screening was carried out through docking the designed compounds into the COX-2 binding site to predict if these compounds have analogous binding mode to the COX-2 inhibitors. Docking study of the synthesized compounds **27a**, **27b** and **27c** into the active site of COX-2 revealed a similar binding mode to SC-558, a selective COX-2 inhibitor [19].



Some triazole, triazolothiadiazole, and triazolothiadiazine derivatives were synthesized and screened for Anti-inflammatory, Analgesic and Antibacterial activity. The anti-inflammatory activity of final compounds was determined according to the paw induced edema method. Indomethacin was used as a comparator and reference drug. The analgesic activity was determined in mice using the hot-plate method, in comparison with indomethacin as a reference drug. Compounds **28a**, **28b**, **28d**, **28e**, and **28f** were the most active anti-inflammatory agents with a long duration of action. In the analgesic activity, compounds **28c**, **28d** and **28e** were the most active compounds when they contained *p*-Cl, *p*-Br, or *p*-OMe moieties, respectively in their structures [20].

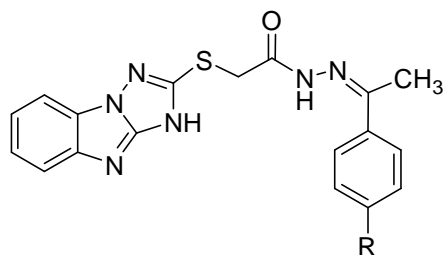


28a (R= -CH₃) and **28b** (R= -C₆H₅)

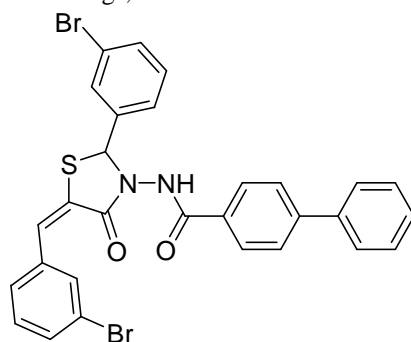


Compounds	R
28c	4-Cl-C ₆ H ₅
28d	4-Br-C ₆ H ₅
28e	4-CH ₃ O-C ₆ H ₅
28f	4-F-C ₆ H ₅

Benzimidazo-1,2,4-triazole derivatives were synthesized and evaluated for antimicrobial and anti-inflammatory activity. Three new series of *N*'-(aryl or heteroarylmethylidene)-2-(1*H*-1,2,4-triazolo[2,3-*a*]benzimidazol-2-ylsulfanyl) acetohydrazides, *N*'-(α -arylethylidene)-2-(1*H*-1,2,4-triazolo[2,3-*a*]benzimidazol-2-ylsulfanyl) acetohydrazides and 2-([5-(alkyl or aralkylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl)sulfanyl)-1*H*-1,2,4-triazolo[2,3-*a*]benzimidazoles were synthesized. The anti-inflammatory activity of the synthesized compounds was evaluated according to the carrageenan induced paw edema method in comparison to indomethacin as a reference drug. Compounds **29a**, **29c** and **29d** were found to be more active than indomethacin giving 107-113% anti-inflammatory activity at 5 hrs. Docking studies of the inhibitor were performed by MOE (Molecular Operating Environment) using COX enzyme. The molecular modeling studies of the examined compound **29c** indicated that the compound was probably non selective anti-inflammatory agent [21].

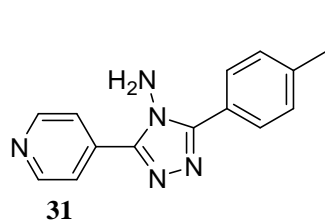
29a (R=H), 29c (R=Cl) and 29d (R= OCH₃)

Some new biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides have been synthesized and evaluated for anti-inflammatory activity. All compounds were screened for anti-inflammatory activity employing carrageenan test at the dose of 10 mg/kg and exhibited significant activities. The compound **30i**, with a substitution of bromine on both the aromatic rings, was found to be the most potent anti-inflammatory agent [22].

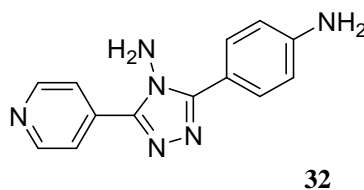


Compound 30i

5-Substituted-3-pyridine-1, 2, 4-triazoles were synthesized and tested for antibacterial, antifungal and anti-inflammatory activity. In *in-vivo* antiinflammatory activity, among the selected synthesized compounds **31** and **32** showed good activity. They also screened all selected compounds for ulcerogenic adverse effect at 200mg/kg dose level. After microscopic examination, no ulceration risk was seen in selected compounds which have triazole moiety in their structure [23].

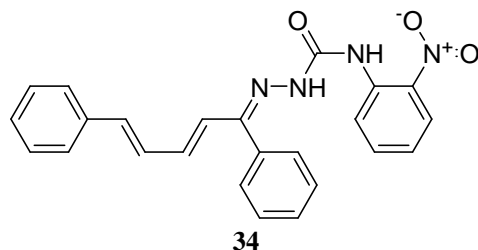


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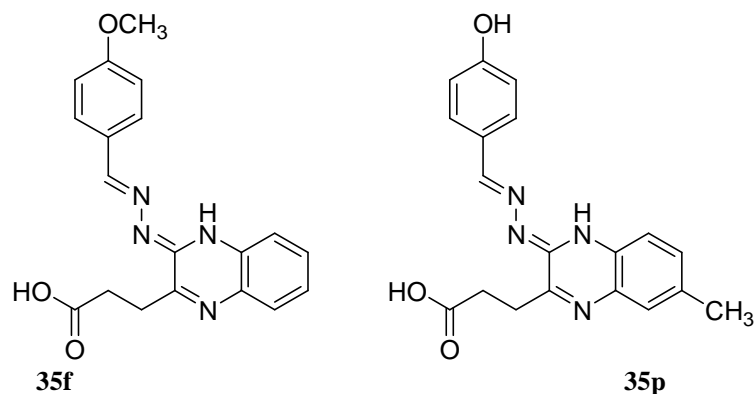
A series of novel 'chalconylsemicarbazide' derivatives was synthesized. The synthesized compounds were evaluated for their analgesic and anti-inflammatory activities. Most of the compounds were found to be more or comparable potent than the reference standard drugs. Based on the pharmacological screening results 1-(1,5-diphenylpenta-2,4-dienylidene)-4-(2-nitrophenyl) semicarbazide (**34**) was the most active lead compound [24].



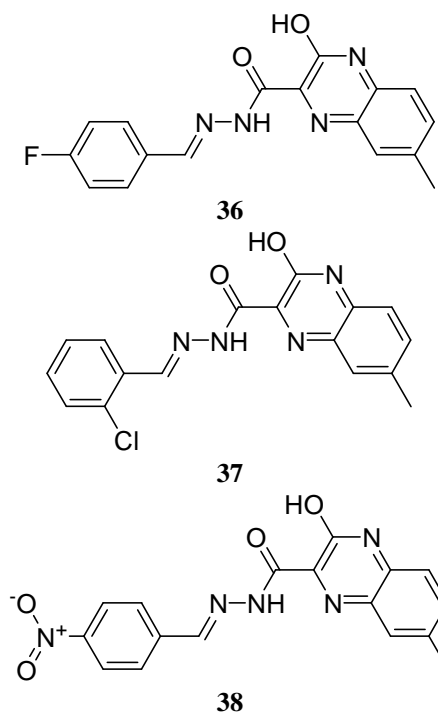
34

Hydrazone derivatives of quinoxalinone were synthesized and evaluated for antimicrobial and anti-inflammatory activity. Quinoxalinone derivatives were synthesized by the condensation of 1,2-diaminobenzene with α -ketoglutaric acid to yield 3-(3-oxo-3,4-dihydroquinoxalin-2-yl) propionic acid and then treated with hydrazine hydrate to yield its hydrazones. This was further reacted with substituted aromatic aldehydes to produce hydrazone derivatives of quinoxalinone. These hydrazones derivatives were evaluated for antiinflammatory activity, and among them only compounds having the methoxy group at the para position, i.e. **35f** and **35p**, showed

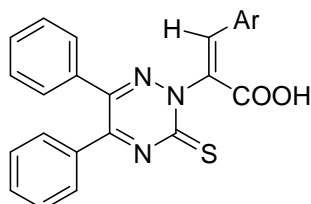
comparatively good percentage of inhibition of edema than the other synthesized compounds. Compounds **35f** and **35p** were further tested for ulcerogenic activity and found to have 'zero' ulcerogenic index [25].



A series of substituted Hydrazone and Quinoxaline derivatives have been synthesized and have been screened for their antibacterial activity. Some of the compounds have been screened for anti-inflammatory activity against the carageenan induced rat paw edema in albino wistar rats. Compound **36**, **37** and **38** exhibited highly significant anti-inflammatory activity [26].

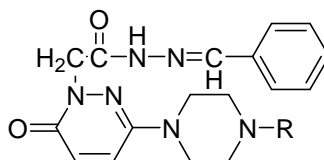


A series of 1,2,4-triazine derivatives were synthesized and evaluated for their anti-anxiety and anti-inflammatory activities. All the compounds were evaluated for anti-inflammatory activity by carageenan induced rat paw edema method. The study revealed that among all compounds only **39**, **40** and **41** were found to be the most potential derivatives with % inhibition of 88.23, 84.88 and 91.28, respectively, while the reference drug indomethacin showed 79.28% inhibition [27].



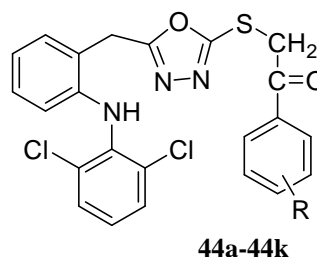
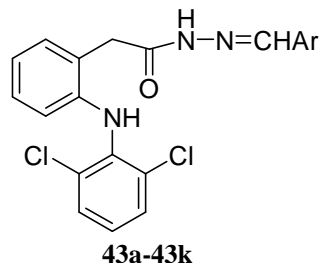
39 (Ar=4-OH-C₆H₄), **40**(Ar=4-OCH₃-C₆H₄) and **41**(Ar=3,4,5-(OCH₃)₃-C₆H₂)

New 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(*p*-substituted benzal)hydrazone derivatives were synthesized as analgesic and anti-inflammatory agents. Analgesic activity evaluation was carried out using phenylquinone-induced writhing assay. 6-[4-(3-Chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-benzal hydrazone **42a**, 6-[4-(4-chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-benzal hydrazone **42b** and 6-[4-(pyridyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-benzal hydrazone **42c** derivatives have been shown better analgesic activity than reference compound ASA. The anti-inflammatory activity evaluation was carried out using carrageenin-induced paw oedema assay, and compounds **42a**, **42b** and **42c** exhibited good anti-inflammatory activity. Anti-inflammatory activity of 6-[4-(3-chlorophenyl)piperazine]-3(2*H*)-pyridazinone-2-acetyl-2-benzal hydrazone **42a** has been found slight superior to that of indomethacin although it was tested at a dosage much higher than indomethacin.

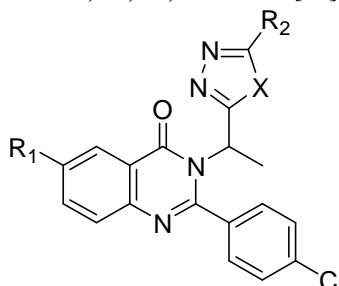


42a (R=3-Chlorophenyl), 42b(R=4-Chlorophenyl) and 42c(R=2-Pyridyl)

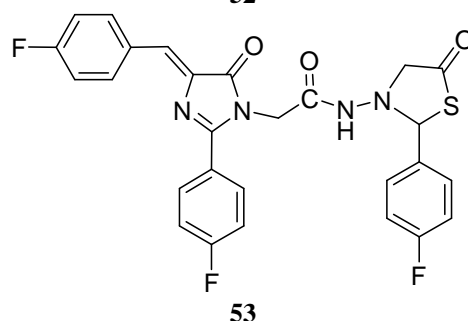
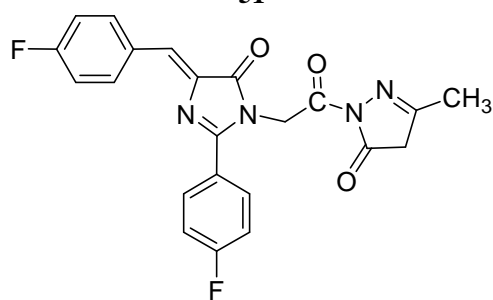
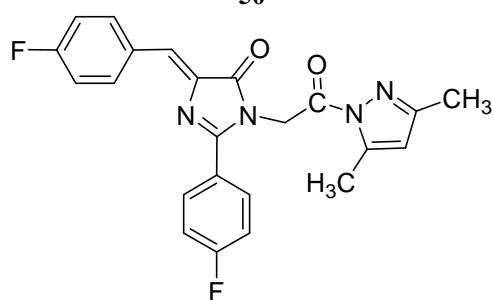
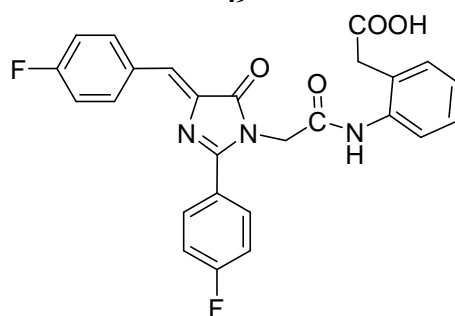
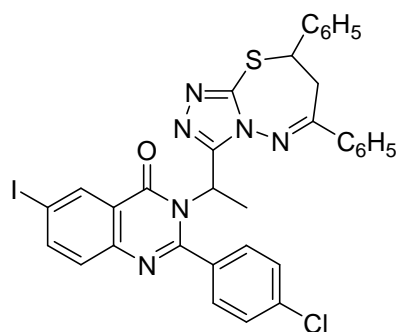
Synthesis and pharmacological screening of a series of *S*-substituted phenacyl 1,3,4-oxadiazoles and Schiff bases derived from 2-[(2,6-dichloroanilino)phenyl] acetic acid (diclofenac acid) are described. The 1,3,4-oxadiazoles and diclofenac moieties are important because of their versatile biological actions. In the present studies, the oxadiazole system has been functionalized onto the diclofenac acid moiety and 18 compounds in this series were synthesized. These compounds were tested *in vivo* for their anti-inflammatory activity. The compounds, which showed significant activity (comparable to the standard drug diclofenac sodium), were screened for their analgesic activity and to check their ability to induce ulcers by ulcerogenicity and histopathology studies. Eight new compounds, out of 18, were found to have significant anti-inflammatory activity in the carrageenan induced rat paw oedema model, with significant analgesic activity in the acetic acid induced writhing model with no ulcerogenicity. The compounds, which showed negligible ulcerogenic action, also showed promising results in histopathology studies, that is, they were found to be causing no mucosal injury [28].



A series of 3*H*-quinazolin-4-ones was synthesized in order to obtain new compounds with potential analgesic and anti-inflammatory activity. Some compounds were evaluated for their analgesic and anti-inflammatory activities by writhing and carrageenan-induced rat paw edema tests, respectively. The best dual analgesic / anti-inflammatory relative activity was observed with compounds **45**, **46**, **47**, **48** and **49** [29].



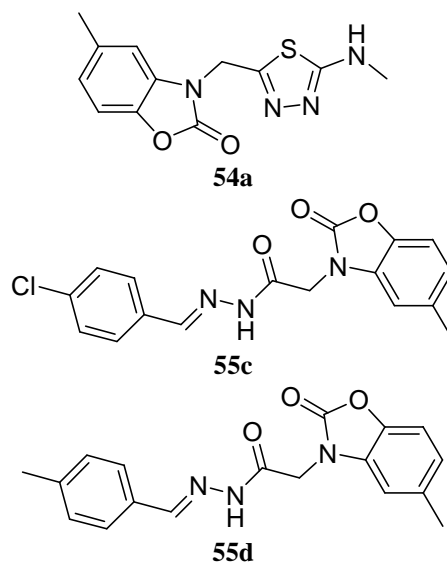
Compounds	X	R ₁	R ₂
45	-O-	-I	-SCH ₂ C ₆ H ₅
46	-O-	-I	-C ₆ H ₅
47	-O-	-CH ₃	-NHC ₆ H ₅
48	-S-	-I	-NHC ₆ H ₅



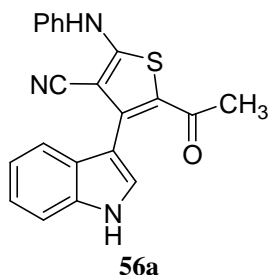
New imidazolyl acetic acid derivatives were synthesized and screened for antiinflammatory and analgesic activities. Synthesized compounds were evaluated for their anti-inflammatory activity against carrageenan induced rat paw edema and their analgesic activity using the writhing test in albino mice. Compounds **50**, **51**, **52**, **53** exhibited

maximum anti-inflammatory activity, and all the compounds inhibited writhing, with **52** and **53** being two times more effective than the reference standard [30].

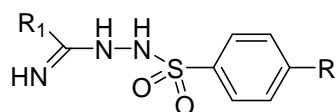
1-Acylthiosemicarbazides, 1,2,4-triazole-5(4*H*)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazinones were prepared and screened for analgesic-anti-inflammatory and antimicrobial activities. The analgesic activity of the compounds was studied by using both the acetic acid-induced writhing test and hot plate test in mice. The analgesic effects of **54a**, **55c** and **55d** were higher than those of both morphine and aspirin. Additionally, these studies showed that the most potent analgesic agent **55d** carries methyl substituent at the phenyl ring of the hydrazone group [31].



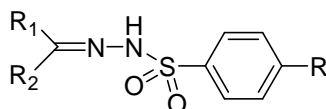
Synthesis of new 3-substituted indole derivatives was carried out and evaluated for anti-inflammatory and analgesic activity. The activity of the newly synthesized compounds compared to indomethacin as a reference was measured before and 4h after carrageenan injection. The analgesic activity (antinociceptive) of the synthesized compounds was also investigated. It was assessed by two different models: the acetic acid-induced writhing test and the hot-plate test. 3-(3-Indolyl)thiophene derivative **56a**, analogue of tenidap, was the most potent anti-inflammatory compound [32].



A number of amidine derivatives (3a-i) were synthesized by condensation of cyanopyridine and cyanopyrazine with sulfonylhydrazides in the presence of sodium methoxide. 2-Acetylpyridine and 4-acetylpyridine were condensed with sulfonylhydrazides by microwave irradiation in solid phase to give corresponding hydrazones. Anti-inflammatory activity evaluation was carried out using carrageenin-induced paw oedema assay and compounds **57e**, **57f** and **58e** exhibited good anti-inflammatory activity i.e. 52%, 37% and 38% at 50 mg/kg po, respectively. Analgesic activity evaluation was carried out using acetic acid writhing assay and compounds **57a**, **57c**, **57e** and **58f** showed good analgesic activity, that is, 50%, 50%, 50% and 60% at 50 mg/kg po, respectively [33].

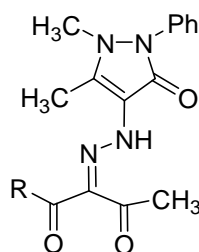


- 57a** R= -H, R₁= 2-pyridyl
57c R= -OCH₃, R₁= 2-pyridyl
57e R= -CH₃, R₁= 4-pyridyl
57f R= -OCH₃, R₁= 2-pyridyl



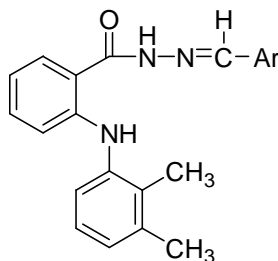
58e R= -H, R₁= 2-pyridyl, R₂= 3-indolyl
58f R= -CH₃, R₁= 2-pyridyl, R₂= 3-indolyl

Synthesis, analgesic and antipyretic activity of 2-(antipyrin-4-yl)hydrazones of 1,2,3-triketones and their derivatives were carried out. The analgesic activity was studied using conventional test for acetate-induced convulsions. The antipyretic properties were studied in a group of male white mongrel rats with a model fever induced by the intravenous injections of pyrogenal. It was established that 1,2,3-triketone 2-(antipyrin-4-yl)hydrazones (**59a** and **59b**) exhibit analgesic activity comparable with that of analgin [34].



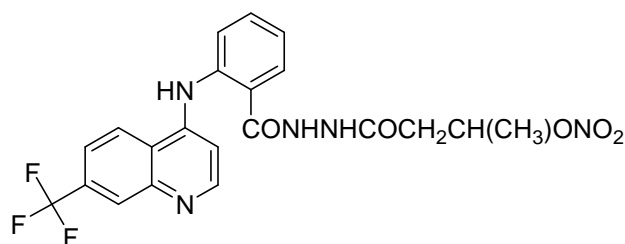
59a (R=-CH₃) and **59b**(R=-H(CF₂)₂)

A series of N-Arylhydrazone derivatives of mefenamic acid were synthesized in order to obtain new compounds with potential analgesic and anti-inflammatory activity. Most of the synthesized compounds induced significant reduction in the writhing response when compared to control. Among them, compounds **60**, **61**, **62**, **63**, **64**, **65** and **66** were significantly more potent than mefenamic acid in the writhing test. The anti-inflammatory activity of these seven compounds were evaluated and compounds **60**, **61**, **62**, **63** and **64** showed significant anti-inflammatory activity in comparison to control but their effect was weaker than mefenamic acid [2].



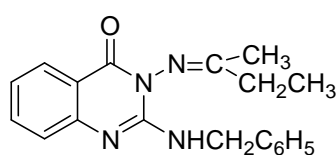
Compound	Ar
60	4-tolyl
61	4-fluorophenyl
62	4-hydroxyphenyl
63	4-pyridyl
64	3-pyridyl
65	2-pyridyl
66	4-Bromophenyl

Six derivatives of the general formula 2- or 4-(7-trifluoromethylquinolin-4-ylamino) benzoic acid N0-(nitroxyacetyl or propionyl) hydrazide and an oxime of the formula 1-[4-(7-trifluoromethylquinolin-4-ylamino)phenyl]ethanone oxime were synthesized and tested for their in vivo anti-inflammatory, analgesic, and ulcerogenic properties. Compound 2-(7-trifluoromethylquinolin-4-ylamino)benzoic acid N'-(2-nitroxy propionyl)hydrazide (**67**) showed an anti-inflammatory activity comparable to that of indomethacin in the carrageenan-induced rat paw edema test, and equipotency to glafenine in the acetic acid mice induced writhing model at 100 mg/kg p.o., respectively [35].

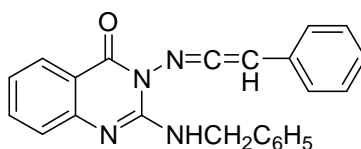


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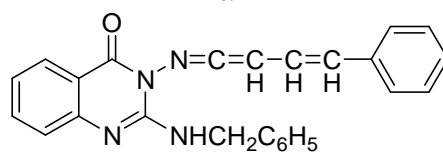
A series of novel 2-benzylamino-3-substituted quinazolin-4(3*H*)-ones have been synthesized by treating 3-amino-2-benzylamino quinazolin-4(3*H*)-one, with different aldehydes and ketones. The starting material 3-amino-2-benzylamino quinazolin-4(3*H*)-one was synthesized by nucleophilic substitution of thiomethyl group of 3-amino-2-methylthio quinazolin-4(3*H*)-one by benzylamine. The title compounds were investigated for analgesic and anti-inflammatory activities. The compounds **68**, **69** and **70** showed more potent anti-inflammatory activity than diclofenac sodium. All the test compounds exhibited significant analgesic activity, whereas the compound **70** is equipotent with diclofenac sodium [36].



68

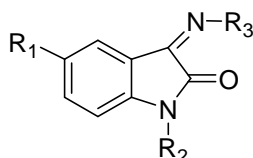


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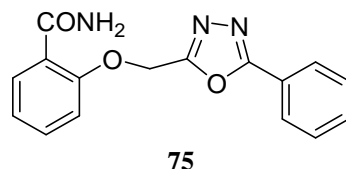
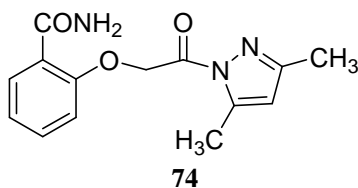
Schiff bases and phenyl hydrazone of isatins were prepared by reacting isatin and the appropriate aromatic primary amine/hydrazines. A new series of the corresponding N-mannich bases were synthesized by reacting them with formaldehyde and diphenylamine. The compounds were screened for analgesic, anti-inflammatory and antipyretic activity. 1-Diphenylaminomethyl-3-(1-naphthylimino)-1,3-dihydroindol-3-one (**71**), 3-(1-naphthylimino)-5-bromo-1,3-dihydroindol-2-one (**72**) and 1-diphenylaminomethyl-3-(4-methylphenylimino)-1,3-dihydroindol-3-one (**73**) were found to exhibit the highest analgesic, anti-inflammatory and antipyretic activity respectively. 1-Diphenylaminomethyl-3-(4-methylphenylimino)-1,3-dihydroindol-3-one (**73**) was found to be the most active compound of the series [37].



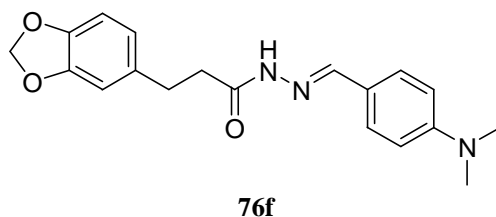
Compounds	R ₁	R ₂	R ₃
71	H	-CH ₂ N(C ₆ H ₅) ₂	Naphthyl
72	Br	H	Naphthyl
73	H	-CH ₂ N(C ₆ H ₅) ₂	4-CH ₃ C ₆ H ₄

Synthesis and evaluation of the Analgesic and Antiinflammatory activities were carried out of *O*-Substituted Salicylamides. The antiinflammatory activity of the synthesized compounds was evaluated using carrageenan-induced paw edema method. Analgesic activity of the compound was studied by applying electric current as a noxious stimulus and the minimum voltage that causes the rats to emit a cry was determined. The some of the tested

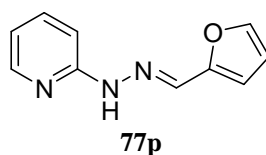
compounds were found to have significant analgesic activity. Compound **74** showed activity superior to salicylamide in respect to the % oedema. The ulcerogenic activity of the compounds in comparison with salicylamide clearly showed that compound **75** induce no ulcerogenic effect and it showed activity superior to salicylamide itself in respect to the volume of the pleural fluid & analgesic activity [38].



A new series of antinociceptive compounds belonging to the N-acylarylhydrazone (NAH) class were synthesized from natural safrole. The analgesic activity was determined *in vivo* by the abdominal constriction test induced by acetic acid in mice. The most analgesic derivative represented by **76f**, [(4'-N,N-dimethylaminobenzylidene-3-(3',4'-methylenedioxyphenyl)- propionylhydrazone], was more potent than dipyrone and indomethacin, used as standards [39].

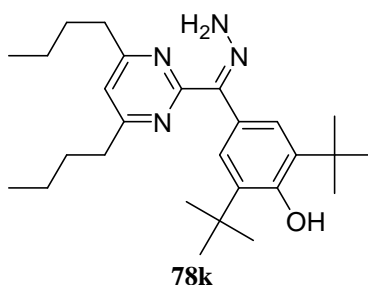


Synthesis new functionalized 2-pyridylarylhydrazone derivatives was carried out and evaluated for analgesic, anti-inflammatory and anti-platelet activity. The pharmacological results here in disclosed, suggested that the anti-inflammatory and analgesic activities of these new pyridine hydrazone derivatives observed in the carrageenan pleurisy model and acetic acid writhing test, respectively, are probably due to an interference on the arachidonic acid (AA) metabolism. The most important anti-inflammatory derivative 2-(2-formylfurane) pyridylhydrazone **77p** presented a 79% inhibition of pleurisy [40].

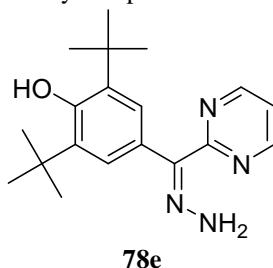


The results concerning the mechanism of action of this series of N-heterocyclic derivatives in platelet aggregation suggested a Ca^{2+} participation, probably by a complexation scavenger mechanism. *In vitro* experiments revealed the ability of compound 2-(2-formylfurane) pyridylhydrazone (**77p**) to complex Ca^{2+} at 100 μM concentration, indicating that this series of compounds can act as Ca^{2+} scavenger depending on the nature of the aryl moiety present at the imine subunit [40].

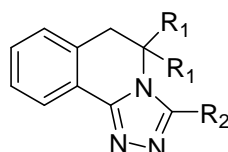
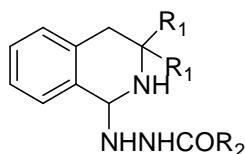
2,6-Di-*tert*-butylphenol hydrazones were synthesized and evaluated for 5-lipoxygenase inhibiting activity. The compounds initially synthesized for testing as 5-LOX inhibitors were the hydrazones, in which various heterocycles were linked to a phenolic moiety through a hydrazone. The activity of the products is expressed as IC_{50} , calculated as the concentration of test compound required to cause 50% inhibition of LTB_4 (5-LOX) formation, as measured on rat peritoneal neutrophils (PMNL). Investigations into this new series have resulted in the identification of several compounds, such as **78k**, as potent inhibitors of 5-LOX activity.



The *in-vivo* efficacy of **78e** was evaluated in Arachidonic Acid-induce Ear inflammation in mice (AAE). Comparison of **78e** with standard anti-inflammatory compound indicated that **78e** had a good profile of activity [41].



1-Hydrazino-3,3-dialkyl-3,4-dihydroisoquinoline derivatives were synthesized and screened for anti-inflammatory and analgesic activity. The antiinflammatory activity of the synthesized compounds was studied on white rats using model of carrageenan- induced paw edema. The analgesic activity was studied using the "hot plate" test. It was found that the attachment of a 5-bromofuroyl radical (**79d** and **79e**) gives rise to certain antiinflammatory effect. The cyclization of **79e** with the formation of a triazolo[3,4-a]isoquinoline (**80c**) gives rise to moderate analgesic activity, but eliminates the antiinflammatory action [42].



CONCLUSION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs in inflammatory disease, since they are effective in management of pain, fever, redness, edema arising as a consequence of inflammatory mediator release. Currently available nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit gastric toxicity. Long-term use of these drugs has been associated with gastrointestinal (GI) ulceration, bleeding, ototoxicity, nephrotoxicity, inhibition of platelet function, limitation of renal blood flow, asthma and anaphylactoid reactions in susceptible individuals. So there is greater need for newer NSAIDs devoid of such side effects.

Hydrazones constitute an important class of compounds for development of newer Nonsteroidal anti-inflammatory drugs (NSAIDs) which may have lower side effects as compare to conventional drug because it lacks carboxylic acid group which is mainly responsible for gastric and other kind of toxicities.

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