A Roman physician Celsus, (about B.C. 30 to A.D. 38); was first present the coherent description of the phenomenon of inflammation enunciating four cardinal signs; rubor (redness), tumour (swelling), calor (heat) and dolar (pain). To these Galen added fifth sign functio loesa (loss of function), that was supported by John Hunter. Boerhaave laid much emphasis on the changed state of blood vessels, Haller and Spallanzane in 17th and 18th century established that the redness of the inflammed part was due to the passage of blood into tissues. Cohnheim in 1882 shared the view with Samnel, that the main feature of the reaction was an increased permeability of the vascular wall; a view which has been subsequently modified and extended. Metchnikoff put forward the theory of phagocytosis being the central phenomenon (Florey, 1970).

The whole phenomenon acquired a new meaning with notion of autoparmacology, introduced by Sir Henry Dale to describe the phenomenon that depend upon formation, synthesis or release of endogenous active substances, the so called mediators of physiopathological phenomenon. From a historical point of view, the histamine produced a typical flare in human skin, indistinguishable from that produced by insect bites and other irritating agents, including antigens or allergens in allergic individuals. The search for new mediators of the inflammatory reaction became a main concern. Kallidin was identified by Werle (1970) as mediator while and Ramwell and Pharris (1972) claimed that prostaglandins of E series are involved in cellular injury and inflammation. Paulus and Whitehouse (1972) mentioned some of the complements in this regard which together form approximately 10% (w/v) of human globulins.

The word inflammation is commonly used in medicine and it may be defined as series of change which takes place in living tissue following injury and ends with complete healing. The important idea at the outset in that inflammation is a process is a process and not a state (Floery, 1970).
For the alleviation of inflammation both acute and chronic as well as for the treatment of inflammatory diseases, many drugs like Indomethacin, Sulindac, Ibuprofen, Naproxen, Piroxicam, Nabumetone etc. are in clinical use. The corticosteroids have high anti-inflammatory activity and provide significant relief in many types of inflammation. But they have major disadvantage of equally harmful side-effects. Narcotic analgesics which are highly effective in relieving pain, lack the property to suppress inflammation. Thus the only drugs that are commonly used in inflammatory disorders are non-steroidal anti-inflammatory agents (NSAIDs) which have comparatively less side effects. These agents are a heterogenous group of compounds which have a carboxy group in their structure and are therefore acidic in nature. The important acidic non-steroidal compounds are aspirin, indomethacin, mefenamic acid, flufenamic acid, naproxen, sulindac, tolimetin, ibuprofen, Naproxen etc. Most of these acidic compounds are organic acids and non-selectively inhibit the COX-1 and COX-2 enzymes. Due to their modest selectivity of inhibition of COX-1, they exhibit these drugs possessed serious inherent side-effects like gastric haemorrhage, perforation, bone marrow depression and particularly gastric ulcer. On the contrary the recently developed non-steroidal, non acidic or weakly acidic anti-inflammatory agents like nabumetone are preferentially COX-2 isoform inhibitor. Since COX-2 is not normally present in tissues but is induced at the site of inflammation, the COX-2 inhibitors selectively inhibit the inflammation and are devoid of producing gastric ulceration which is due to suppression of COX-1, therefore they posses substantially lower incidence of gastric ulcer.

Many scientists have classified NSAIDs, which act by inhibiting COX-1 and COX-2 enzymes, is as follows-

1. **Non-selection COX inhibitors**
   - **Salicylic acid derivatives** : aspirin, sodiumsalicylate, cholins magnesium trisalicylate, salsalate, difluenisal, sulfasalazine, olsalazin.
   - **Para-aminophenol derivatives** : Acetaminopheno.
• **Indole and Indene acetic acids:** tolmetin, Ketarolac.
• **Arylpropionic acids:** ibuprofen, flurbiprofen, ketoprofen, fenoprofen, oxapozin.
• **Naphathalene derivatives:** Naproxen, nabumetone.
• **Anthranilic acids (fenamates):** Meclofenamic acid, mefenamic acid.
• **Enolic acids:** Oxicams (piroxicam, meloxicam).

2. **Selective COX-2 inhibitor**

• **Diaryl-substituted furanounes:** refecocib.
• **Diarylsubstituted pyrazoles:** celecoxib.
• **Indole acetic acids:** etodolac.
• **Sulphonanilides:** nimesulide.

**Pyrazolone and Pyrazole Derivatives**

![Phenylbutazone, Oxyphenbutazone, Celecoxib](image)

**Anthranilic Acid Derivatives:**

![Mefenamic acid, Meclofenamate Sodium](image)

**Indole Derivatives:**

![Indomethacin, Etodolac](image)
Naphthalene Derivatives:

Nabumetone

Naproxen

Propionic Acid Derivatives:

Ibuprofen

Fenoprofen

Diaryl Substituted Derivatives:

Rofecoxib

Salicylic Acid Derivatives:

Methyl Salicylate

Aspirin
INDOLES

Indole moiety is an essential component of different pharmacological and physiological active endogenous as well as exogenous substances. Compounds having indole as the parent moiety are associated with different medicinal chemistry like anti-inflammatory, anticonvulsant, hypnotic, antidepressant, antiparkinsonian, and cardiovascular etc. The discovery of indomethacin, sulindac, indole derivatives, as potent anti-inflammatory agents, has led to the exploration of indole nucleus. Moreover, large number of indole derivatives having substitution at 1, 2 and 3 positions by different heterocyclic moieties increases the anti-inflammatory potential of indole derivatives. In the light of these observations, scientists have synthesized several indole derivatives which possess potent anti-inflammatory activity. Some of these are as given below-

Synthesis of 1-benzoyl-β-carboline and 1-benzoyl-3-carboxyl-β-carboline derivatives have been synthesized by Mei-lim Yang et al. (2011).

Colucci et al. (2010) have been prepared new 4-{1-[(1-[4-(trifluoromethyl) benzyl]-1H-indol-7-yl] carbonyl} amino]cyclopropyl}benzoic acid derivatives as anti-inflammatory agents.
Sujatha et al. (2009) have been prepared of bis (indolyl) methane’s derivatives as anti-inflammatory agents, and the following compounds were found to possess good activity.

\[
\begin{align*}
\text{R=Hydrogen, 4-methylphenyl, 2-nitrophenyl, 4-chlorophenyl etc.}
\end{align*}
\]

The new series of novel-indolyl pyrimidine has been synthesized by Panda et al. (2008). Out of all compounds the following compounds were found to be most potent inflammation inhibitors.

A series of 1-(sulfanylphenyl)-3-trifluoromethyl-5-indolylpyrazolines were synthesized and evaluated as inhibitors of cyclooxygenase-II by Reddy et al (2008).

\[
\begin{align*}
\text{X=H, 5-F, 6-F, 5-Cl, 6-Cl, 7-Cl, 5-CN, 6-CN, 4-MeO, 6-NO}_2, 5-NH_2, 6-NH_2 \text{ etc.}
\end{align*}
\]
Kalaskar et al (2007) synthesized some new indole derivatives as anti-inflammatory agents, and the following compounds were found to possess good activity.

\[
\begin{align*}
R &= \text{H, } C_6H_5, \text{CH}_3(\text{CH}_2)_3, \text{CH}_2C_6H_5 \\
R^1 &= \text{CH}_3, C_6H_5;\text{ } R^2 = \text{H, } 6,7\text{-benz.}
\end{align*}
\]

Mohd. A. et al (2007) synthesized some new 3-substituted indole derivatives and which have been screened for their anti-inflammatory and analgesic activities.

\[
\begin{align*}
R &= \text{CH}_3, C_6H_5, C_2H_5\text{ etc.}
\end{align*}
\]


\[
\begin{align*}
R &= \text{H;}\text{ } R^1=\text{alkyl, aryl, heteroaryl.}
\end{align*}
\]

A new series of reverse ester/amide derivatives of indomethacin were synthesized and evaluated as selective COX-II inhibitors by Kalgutkar et al (2005).
Brown et al (2004), synthesize indolecarboxamides, which were found to be useful for treating inflammatory and respiratory diseases.

Some new 7-phenyl-5-(2'-phenylindol-3'-yl)-1,4-benzo[b] diazepines have been synthesized and screened by Biradar and Manjunath (2004) for their antiinflammatory, analgesic and locomotor activities.

New indole derivatives have been synthesized and evaluated for anti-inflammatory activity by Rani et al (2004). Out of the synthesized series some compounds have shown potent anti-inflammatory activity.
\[ R^1 = \text{OH, H, N, Me}_2; \quad R^2 = \text{H, OCH}_3 \text{ etc.}; \quad R^3 = \text{H, etc.} \]

Synthesis and anti-inflammatory, analgesic and COX-II inhibitory activities of indolylpyrazoline derivatives have been given by Kumar et al (2004).

\[ R = \text{CH}_3, \text{ C}_6\text{H}_5 \]

Stryapurina et al (2004) prepared some indole derivatives, and were found to be useful antiinflammatory agents as well as analgesics.

\[ R = \text{SCH}_3, \text{ C}_6\text{H}_5, \text{ CH}_2\text{COOC}_2\text{H}_5 \]

Seehra et al (2003) synthesized indole derivatives for the treatment of inflammatory conditions, such as arthritis and inflammatory bowel disease.

\[ R^1 = R^6 = \text{H, halo, CF}_3, \text{ alkoxy etc}; \quad R^2 = \text{H, halo, alkyl, OH, CF}_3, \text{ etc.}; \]
\[ R^3 = \text{COOH, SO}_3\text{H, etc}; \quad R^4 = \text{H, CF}_3, \text{ halo, CHO etc}; \quad R^5 = \text{alkyl, alkoxy etc.} \]
Some new indole derivatives have been synthesized and screened for their anti-inflammatory activity by Gadaginamath et al (2003).


\[ R^1=R^2=H, \text{ Halo, alkyl, alkoxy etc; } R^3=H \]

\[ X=H, F \text{ etc.} \]

\[
\begin{align*}
X= & \text{Cl, Br, etc; } R^1= \text{CH}_3, \text{Ph, etc; } R^2= \text{CH}_3, 4-\text{OCH}_3\text{C}_6\text{H}_4 \text{etc.}
\end{align*}
\]

Synthesis of some isatinoid compounds and reported promising anti-inflammatory, analgesic and antipyretic activities by Sridhar and Ramesh (2002).

\[
\begin{align*}
R= & \text{H, CH}_3, \text{NO}_2; \quad R^1= \text{1-Naphthyl, 4-Bromophenyl, 4-methoxyphenyl phenylhydrazino etc.}
\end{align*}
\]


\[
\begin{align*}
R^1= & \text{Me, Cl, OCH}_3; \quad R^2= \text{Me, Ph; } R^3= \text{Morpholino, 1-piperazinyl}
\end{align*}
\]

Sridhar et al (2001) reported anti-inflammatory and analgesic activities in following indole derivative.

\[
\text{R}=2\text{-OCH}_3\text{C}_6\text{H}_4, 4\text{-OCH}_3\text{C}_6\text{H}_4, \text{Ph etc.}; \text{R}^1=\text{H, 2-Cl etc.}
\]

Anti-inflammatory activity has been reported in following indole derivatives by Faull and Kettle (2000)

\[
\text{X}=\text{CH}_2, \text{SO}_2; \text{R}^1=\text{substituted aryl}; \text{R}^2=\text{COOH, COCH}_2, \text{OH etc.;}\]

\[
\text{R}^3=\text{H, alkenyl, aryl etc; R}^4=\text{OR}^{15} \text{ etc.}
\]

Bansal et al (1999) synthesized 1-(2'-hydroxy benzoyl)-5-(substituted phenyl)-3-(2'-methyl indolyl-2-pyrazolines) and found them potent anti-inflammatory agents.

\[
\text{R=H, 2-OMe, N(CH}_3)_2 \text{ etc.}
\]

3-(Thiazol-2-yl-methyl)-indoles have been synthesized by Woods et al (1998) as COX-II inhibitors.
A=halo, C₁₋₆ alkyl etc.; B=O₂, H₂; X=Br, Cl; L=5-7 membered heteroatom containing ring such as thiazole, oxazole etc.; R=substituted aryls.

Amir et al (1997) synthesized some indole and indazole derivatives and were found to possess promising anti-inflammatory activity.

R=H, alkyl etc.; X=H, halogen etc.

N-benzylindole and benzopyrazols were prepared and screened for anti-inflammatory, antiallergic and immunomodulating activities by Le Baut et al (1996).

Bajji et al (1994) synthesized some substituted-3-(4′-oxothiazolidin-2′-aryl/alkylimino)-indoles and screened for their anti-inflammatory and anticonvulsant activities.
Some novel indole derivatives were prepared and screened for their anti-inflammatory activity by Verma et al (1994).

Bhalla et al (1993) found that indolyl quinazolinones and their congeners exhibited significant anti-inflammatory and analgesic activities.

Substituted indole derivatives have been reported as anti-inflammatory agents by El-Diwani et al (1992).

Russo et al (1990) synthesize 6H-thiazolo (3',2':1,2-) -5-oxypyrimido [5,4-b]-indole derivatives as anti-inflammatory agents.
R=Me, Et etc.

1-Substituted-2-oxo-3-(2-chlorophenoxy)-4-(2-aryl-indole-3-yl)azetidins have been synthesized by Aggarwal (1989) and reported them to be anti-inflammatory and CNS active agents.

R=H, CH₃, Cl, OMe etc.; X=4-N, N-diphenylbenzamido etc.


R=N(R¹)₂ Morpholino etc; R¹=Pr, Me, CH₂Ph etc.


X=CH₂, SO₂; NRR¹=Piperidino, pyridinyl, α-naphthylamino, β-naphthylamino etc; Ar= C₁₀H₇ etc.

Teikoku (1986) synthesized 3-substituted-2-phenylindole derivatives and have been screened for their anti-inflammatory activity.
Some new derivatives of N-(indol-3-yl-glyoxyl)-amino acid were prepared by Da Sittimo et al (1984) and screened for their anti-inflammatory and analgesic activities.

Some new indolyl compounds were synthesized by Verma et al (1982) as potent anti-inflammatory agents.

Sen Gupta and Srivastava (1982) have synthesized 2-aryl-3-[(substituted hydrazino)-methyl]-indoles elicited potential anti-inflammatory, CNS and bactericidal activities.
Kameyama (1982) reported furoindole compounds as anti-inflammatory and analgesic agents.

Glamkowski and Fartunato (1980) synthesize some anti-inflammatory anti-depressant, analgesic agents of substituted-1,2,6,7-tetrahydroindolo (1,7-ab) (1,5)-benzodiazepines.

Some new indole derivatives with antiinflammatory, analgesic activities have been prepared by Sarbu et al (1980).
PHENOTHIAZINES

Phenothiazines possess a wide spectrum of pharmacological activities like anti-inflammatory, anti-psychotic, anti-parkinsonian, anti-convulsant activities etc. Furthermore, the introduction of different aryl, alkyl or heterocyclic moieties at 10-or 2-position of phenothiazine nucleus markedly enhances the anti-inflammatory properties. Various scientist have synthesized several 2- or 10-substituted derivatives of phenothiazine and reported the promising anti-inflammatory activity, which are given below-

A new class of 10H-phenothiazines have been prepared by Y.S. Sadandam et al. (2009).

(a) $R^1 = R^2 = R^3 = H$ (b) $R^1 = CH_3, R^2 = R^3 = H$ (c) $R^1 = Cl, R^2 = R^3 = H$
(d) $R^1 = H, R^2 = R^3 = Cl$ (e) $R^1 = OCH_3, R^2 = R^3 = H$ (f) $R^1 = R^2 = H, R^3 = OCH_3$
(g) $R^1 = H, R^2 = R^3 = OCH^2 - O$ (h) $R^1 = R^2, R^3 = NO_2$

Some new 2-chlorophenothiazinothiadiazol-2-oxo-azetidines have been synthesized by Srivastava et al (2000) and also reported anti-inflammatory, anti-microbial activities.

$Ar=2-ClC_6H_4, 3-ClC_6H_4, 2-BrC_6H_4, 2-OCH_3C_6H_4, 4-OCH_3C_6H_4$ etc.

Some newer derivatives of 10-substituted phenothiazine have been synthesized and evaluated for their anti-inflammatory activity, ulcerogenic liability and acute toxicity by Bansal and Kumar (1999). The compound 10-{2"-(3"-chloro-
2''-oxo-4''-methoxyphenyl-1''-azetidinyl) -4-oxazolyl]-phenothiazine was found to be most potent as compared to phenylbutazone.

A series of Schiff bases, thiazolidinones, $\Delta^2$-triazolines and formazans of 2-(chloro)-phenothiazines has been synthesized and screened for their anti-inflammatory activity by Kumar et al (1998). Out of all these compounds, 2-chloro- 10-(5'-substituted aryl-2'-oxo -4'-thiazolidin-1'-yl)-aminoacetyl phenothiazines have been found to possess prominent anti-inflammatory activity.

$$R = 2\text{-OCH}_3, 4\text{-OCH}_3, \text{H etc.}$$

Mishra et al (1997) synthesized 5-(arylidene-2'-aryl-3'-phenothiazino-acetamidyl)-1,3-thiazolidin-4-ones as anti-inflammatory, anti-convulsant, analgesic and antimicrobial agents.

$$\text{Het = Phenothiazine} ; R^1 = R^2 = R^3 = R^4 = \text{H}, \text{aryl, substituted aryl.}$$

Synthesis of novel N-substituted phenothiazines and piperazines and their anti-inflammatory, antifungal activities have been reported by Jain and Srivastava (1995).

$$R = 10\text{-Phenothiazine, Ph}_2\text{N etc., } R^1 = \text{H, Me.}$$
El-Said et al (1993) synthesized some new phenothiazine derivatives and reported their biological activities.

\[ \text{R} = \text{H, Cl, Br, Me, OH etc.} \]

Some benzophenothiazines and their hydrogenated derivatives have been synthesized and screened for their anti-inflammatory, antiallergic and cardiovascular activities by Fortin et al (1985).

\[ \text{X} = \text{O, S, SO}_2 \text{ etc.; R}^1 = \text{H, alkyl etc., R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H, alkyl, alkenyl etc.} \]

10- [(3, 5-Diaryl-2-pyrazolin-1-yl)- acetyl]- phenothiazines were prepared by Jaiswal et al (1981) and also reported their anti-inflammatory as well as anticonvulsant activities.

\[ \text{R} = \text{NO}_2, \text{NO, Cl, OH etc., R}^1 = \text{H, 4-NO}_2, \text{4-Cl etc.} \]
NAPHTHALENES

Naproxen and nabumetone, substituted naphthalene derivatives, are one of the most widely used NSAIDs other than aspirin, and have been found to possess potent anti-inflammatory activity. Heterocyclic/aliphatic functionalized systematic variations at α- or β-position of naphthalene nucleus markedly modulate the anti-inflammatory activity. Some of the naphthalene derivatives exhibiting various biological activities especially anti-inflammatory, are given below-

Synthesis and pharmacological evaluation of heterocyclic-6-substituted -1,2,4-triazole [3,4-b]-1,3,4, thiadiazole derivatives have been reported by Mohd. Amir et al (2007).

\[
\text{R=R}^1 = 2\text{ClC}_6\text{H}_4, 2\text{-BrC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 2\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-CH}_3\text{C}_6\text{H}_4 \text{ etc.}
\]

Anti-inflammatory activity has been reported in 1,3,4-oxadiazoles linked to naphtho [2,1-b] furan by Ravindra et al. (2006).

\[
\text{R=C}_6\text{H}_5, \text{m-Cl-C}_6\text{H}_4, \text{p-Cl-C}_6\text{H}_4, \text{p-OCH}_3\text{-C}_6\text{H}_4 \text{ etc.}
\]

2-substituted-1-naphthol derivatives have been prepared by Kongkathip et al (2005) as COX-I & COX-II inhibitors.
Some new $\alpha$-amino naphthalene derivatives have been prepared by Sharma et al (2003) and screened for their anti-inflammatory activity.


1-acetyl-5-substituted-aryl-3-(β-aminonaphthyl)-2-pyrazoline derivatives as inflammation inhibitors have been synthesized by Bansal et al (2001).

Better anti-inflammatory activity has been reported in 6-methoxy-a-methyl-naphthalene acetic acid derivatives by Mohammad et al (1999) and were found to be more potent than reference drug naproxen.
Hodges (1998) synthesized some naphthoquinones as anti-inflammatory as well as antibacterial agents.

\[ R=H, \text{ alkyl}; \ R^1=\text{side chain cont.-COOH}; \ R^2=H, \text{ org-substituent}. \]

Carganico et al (1997) synthesized the following compound and found to possess anti-inflammatory and antiallergic activity.


\[ R^1=\text{Ph, lower alkyl etc.}; \ R^2=H, \text{ lower alkyl etc}; \ R^3=R^4=\text{lower alkoxy}; \ R^5=R^6=H, \text{ OH, halogen, alkoxy}. \]

Anti-inflammatory and other biological activities have been reported by Girard and Hamel (1994) in 3-(hydroxymethyl)-4-phenyl-7-[5-\{4-(4-hydroxy tetrahydropyron-4-yl)-3-pyridinyl\}-methoxy]-2-naphthalencarboxylic acid (lactone).

Singh et al (1993) reported anti-inflammatory activity in \( \alpha-\text{aryl-amido-alkyl-methyl})-\beta-(\text{diphenylimino})-\text{naphthyl ethers.} \)
Potent anti-inflammatory activity have been reported by Akubue et al (1991) in 2-naphthol derivatives.

Nohira and Teraguchi (1986) have synthesized and reported the anti-inflammatory, analgesic, antipyretic activities in the following compound.

Anti-inflammatory, analgesic and anti-pyretic activities in 2-(carboxy methoxy)-1-naphthalene sulphonamide derivatives have been reported by Onesu et al (1981).

Kita and Yamada (1980) synthesized some 2-(6-methoxy-2-naphthyl)-propanoic acids and the following compound has been found to possess promising anti-inflammatory and analgesic activities.
QUINAZOLINONES

Quinazolinones are the versatile nitrogen heterocyclic compounds displaying a wide-variety of biological and pharmacological activities like anti-inflammatory, anticonvulsant, hypnotic, sedative, tranquilizers, antidepressant and anti-parkinsonian in animals as well as in human system. The chemistry and pharmacology of quinazolinones have been of great interest to medicinal chemists. Recently several scientists have elucidated that quinazolinone system possess the various variable sites like position 2 and 3, which can be suitably modified by the introduction of different heterocyclic moieties to yield the potent anti-inflammatory agents. Various derivatives of quinazolinone have been synthesized and evaluated for anti-inflammatory activity.

Amin et al. (2010) have been prepared a series of spiro [(2H, 3H) quinazoline-2,1′- cyclohexan]-4(1H)- one derivatives as anti-inflammatory and analgesic agents.

\[
\begin{align*}
\text{Ar} & = \text{H, 4-N(CH}_3)_2, 4\text{-OCH}_3, 2\text{-OCH}_3 \\
\end{align*}
\]

Srivastava et al. (2009) reported synthesis and anti-inflammatory activity of some novel 3-(6-substituted-1, 3 benzothiazole-2-yl)-2{{4-substituted phenyl} amino} methyl quinazidines-4 (3H)-ones.

\[
\begin{align*}
\text{R} & = \text{CH}_3, \text{OCH}_3, \text{Cl, F; R'=}\text{H, CH}_3, \text{OCH}_3, \text{Cl, NO}_2\text{C}_6\text{H}_4, 2\text{-Cl C}_6\text{H}_4, 2\text{-Cl C}_6\text{H}_4 \\
\end{align*}
\]

R = CH\textsubscript{3}, CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}, CH (CH\textsubscript{3}) CH\textsubscript{2}CH\textsubscript{3}, C\textsubscript{9}H\textsubscript{3}N; X=H, I

Some novel 3-phenyl-2-substituted-3H-quinazolin-4-ones were synthesized by Alagarsamy et al (2007) and screened for their anti-inflammatory analgesic and ulcerogenic activities.

R\textsuperscript{1}=H, CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, C\textsubscript{6}H\textsubscript{5} etc.; R\textsuperscript{2}=H, CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, C\textsubscript{3}H\textsubscript{7}, C\textsubscript{6}H\textsubscript{5}, 2-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}, 4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}, 2-ClC\textsubscript{6}H\textsubscript{4}, 4-ClC\textsubscript{6}H\textsubscript{4} etc.

Alagarsamy et al (2004) synthesized a series of novel 2-methylthio-3-substituted quinolin-4-(3H)-ones and the compounds synthesized were investigated for analgesic, anti-inflammatory and antibacterial activities.

R\textsuperscript{1}=R\textsuperscript{2}=CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, Ph etc.

Some new thiazolyl and thiadiazolyl derivatives of 4(3H) quinazolinone have been synthesized by Bekhit et al (2004). Some of these derivatives possess potent anti-inflammatory and anti-microbial activities.
Kumar et al (2003) prepared some new 2,3,6-trisubstituted quinazolinones and screened for their anti-inflammatory, analgesic as well as ulcerogenic activities.


Kumar et al (2003) given the synthesis of novel quinazolinyl-Δ²-pyrazolines and these were tested for their anti-inflammatory, analgesic, ulcerogenic and cyclooxygenase activities.
Synthesis and anti-inflammatory activity of some new 2,3-disubstituted-6-monosubstituted-quinazolin-4(3H)-ones have been done by Rani et al (2002).

\[
X=\text{H, Br}; \ R=\text{o-Cl, o-OCH}_3, \text{ H, m-Cl}
\]

\[
R^1=\text{m-OCH}_3, \text{ p-OH, H, p-N (CH}_3)_2, \text{ p-OCH}_3 \text{ etc.}
\]

Alagarsamy et al (2002) synthesized a series of novel 2-phenyl-substituted quinazolin-4(3H)-ones and also reported their anti-inflammatory analgesic activities.

\[
R=\text{N-CH}_3, -(\text{CH}_3)_2\text{N, -(C}_2\text{H}_5)_2\text{N, Ph}_2\text{N etc}
\]

Adams et al (2001) synthesized some 3,4-dihydro-(1H)-quinazolin-2-ones and screened for their anti-inflammatory activity.

\[
X=\text{O, S}; \ R^1=\text{naphthyl, heterocyclyl or heteroaryl, (un) substituted phenyl.}
\]

\[
R^2=(\text{un) substituted alkyl, heterocyclyl (alkyl) or heteroaryl (alkyl).}
\]


\[
R=\text{H, 4-N(CH}_3)_2, \text{ 4-OCH}_3, \text{ 2-OCH}_3
\]
Synthesis and anti-inflammatory activity of some newer quinazolinones have been reported by Tyagi et al. (1999).

R=2-F, 2,4-Cl₂

Saravana et al. (1998) synthesized some 6-bromo-2,3-di-substituted-4-(3H)-quinazolinones as potential anti-inflammatory agents.

R=2-CH₃, 4-F, 3-OCH₃, 3-NO₂; R¹=H, C₂H₅

Preparation of 2,8-disubstituted quinazolinones have been reported by Heiker et al. (1996) and these were found to be anti-inflammatory as well as cardiovascular agents.

Synthesis and anti-inflammatory, anti-convulsant and hypnotic activities of 6-bromo-2,3-disubstituted-4(3H)-quinazolinones have been reported by Abdel-Alim et al. (1994).

R=PhCH₂S; R¹=Et; R²=H
Ethyl-1-methyl-5-[2-substituted-4-oxo-3(4H)-quinazolinyl]-1H-pyrazole-4-acetates have been synthesized by Daidone et al (1994) and anti-inflammatory, analgesic activities have also been reported.

\[
\text{R}=\text{H, Me, Et, Ph.}
\]


\[
\text{R}=\text{H, OH; R}^1=\text{alkyl; R}^2=\text{Ph, carboxyalkyl, etc.}
\]

Singh et al (1992) synthesize some 2-aryl-3-(acylhydrozonomethyl phenyl) quinazolin-4(3H)-ones and were found to possess anti-inflammatory and CNS activities.

\[
\text{R}=\text{aryl; R}^1=\text{Ph, CH:CHPh.}
\]

The series of 6,8-substituted-3-[3]-4-2-hydroxy-3-substituted pyroxyphenyl-2-methyl-4-[3H]-quinazolinones were prepared and screened for their anti-inflammatory activity by Saxena et al (1991).

\[
\text{R}=\text{4-phenyl, piperazinyl, morpalinyl; R}^1=R^2=\text{H, Br}
\]
5-Substituted 8-oxo-8H-phthalazino-[1,2-b]-quinazolines possessing pronounced anti-inflammatory activity have been reported by Razvi et al (1990).

\[ R = \text{H, CH}_3, \text{C}_6\text{H}_5, 4\text{-Cl}-\text{C}_6\text{H}_4, 4\text{-OCH}_3\text{-C}_6\text{H}_4, 4\text{-CH}_3\text{-C}_6\text{H}_4 \]
\[ R^1 = R^2 = R^3 = \text{H, Cl} \]

Kumar et al (1990) reported that quinazolinyl pyrazolines possessed potent anti-inflammatory activity.

\[ X = \text{H, Br}; R = 2\text{-F}, 2\text{-OCH}_3, \text{H}; 4\text{-NMe}_2 \text{ etc.} \]

Farghaly et al (1990) synthesized and reported pyrazole derivatives of 4-(3H)-quinazolinones as potent inflammation inhibitors.

Some anti-inflammatory and CNS depressant agents 2-phenyl-3-[4-(N,N-disubstituted carbonyl)-phenylamino]-8-substituted-4(3H)-quinazolones have been synthesized by Nigam et al (1989)

\[
\begin{align*}
\text{R}=\text{H, Br; } \text{NR}^1\text{R}^2=\text{Marpholino, piperidino}
\end{align*}
\]

A new series of substituted quinazolinones derivatives by incorporating pyrimidinediones moiety at 3-position of quinazolinones have been synthesized and reported their anti-inflammatory activity by Kumar et al (1988).

\[
\begin{align*}
\text{R}=\text{H, Br, I; } \text{R}^1=\text{H, Br; } \text{R}^2=\text{CH}_3, \text{C}_2\text{H}_5; \text{R}^3=\text{H, 4-OCH}_3; \text{R}^4=\text{C}_6\text{H}_5, \\
2-\text{Cl-C}_6\text{H}_4, 2,4-\text{Cl}_2-\text{C}_6\text{H}_3
\end{align*}
\]

Sadanandev et al (1987) synthesized some substituted 2,3-dihydro-1-(β-phenylethyl)-2-aryl and 3-diaryl-4-(1H)-quinazolinones and reported their anti-inflammatory activity.

\[
\begin{align*}
\text{R}=\text{R}^1=\text{R}^2=\text{R}^3=\text{H, OMe etc.}
\end{align*}
\]

Anti-inflammatory, analgesic, anti-fungal and anti-bacterial activities have been reported by Rao et al (1986) in 3-(5-aryl-1,3,4-oxadiazole-2-yl-methyl)-2-methyl-4-(3H)-quinazolinones.
37

R=R^1=H, Br; R^2=Ph, substituted Ph etc.

Agarwal et al (1985) synthesized 1-(2-arylindol-3-yl)-2-[3-(p-morpholino-phenyl)-6,8-disubstituted quinazolin-4-(3H)-on-2-yl]-ethenes as anti-inflammatory activity.

R=H, Cl, Me, OMe; R^1=H, Br, I; R^2=H

The anti-inflammatory, analgesic and anti-pyretic activities of 3-isooxazolyl-substituted-4-(3H) quinazolinones were reported by Plescia et al (1984).

R=Ph, Pr, furyl, Me etc.

Singh et al (1984) have reported the synthesis and potential anti-inflammatory activity of 2-substituted phenethyl-3-substituted phenyl-4-(3H)-quinazolinones.

R=Cl, Me; R^1=3-Cl, 2-OH, 2-OCH_3, R^2=4-Phenyl, Piperazino, Morpholino etc.

5-aryl-12H-quinazolo-[3,2 a]quinazolin-12-ones were prepared and found to be inflammation inhibitors by Kamal and Sattur (1983).

Verma et al (1981) synthesized some quinazolinones and reported their anti-inflammatory activity.
ANTHRANILIC ACIDS

The fenamates are a family of non-steroidal anti-inflammatory drugs (NSAIDs), which are derivatives of N-phenylanthranilic acid. This family includes mefenamic, meclofenamic and flufenamic acid etc., which are useful agents for clinical treatment of inflammatory disorders. The fenamates have anti-inflammatory, analgesic and anti-pyretic properties. Considerable amount of work has been done on structural variation of this sub-class of NSAIDs. It has been observed that the best known NSAIDs are acidic in nature. Furthermore, substitution pattern at N-position of anthranilic acid plays a pivotal role in delineating the anti-inflammatory activity of these agents. Structural variations, as given by various scientist, which prove that anthranilic acid derivatives have potent anti inflammatory activity, are as follows-

A new series of substituted anthranilic acid derivatives by incorporating thiazolidin-4-one moiety at N-position of anthranilic acid have been synthesized by Goel et al (1999). The compound 3-(4'-bromo-2'-carboxyphenyl)-2-(fluorophenyl)-5-methyl-4-thiazolidinone has been found to possess better anti-inflammatory activity than reference drug.

4-\{[(9H-fluroenyl)-ethoxycarbonyl]-amino\}-benzoic acid as potent inflammation inhibitor has been synthesized by Perumattam (1996).

\[
\text{R}=\text{H, CH}_3 \text{ etc.; } \text{R}^1=\text{H, OH, CH}_3, \text{COOC}_2\text{H}_5 \text{ etc.}
\]

Aboukull et al (1994) synthesized and reported the anti-inflammatory as well as analgesic activities of some anthranilic acid derivatives.

\[
\text{R}=\text{H, 3-Cl, 4-Cl etc.; } \text{R}^1=\text{H, Me etc.}
\]

A series of 1-(2-carboxyphenoxy)-3-chloro-4-arylazetidin-2-ones of anti-inflammatory agents have been synthesized by Kumar et al (1990).

\[
\text{R}=2-\text{OCH}_3, \ 4-\text{OCH}_3, \ 4-\text{N (CH}_3)_2, \text{ H etc.}
\]

2-(phenylamino)-benzoic acid derivatives have been synthesized by Francisco et al (1987) and also screened for their anti-inflammatory and analgesic activities.

\[
\text{R}^1=\text{H, CH}_3 \text{ etc; } \text{R}^2=\text{Cl, COOC}_2\text{H}_5 \text{ etc.}
\]
N-Acetylamophenol-N-(p-substituted phenylalkyl) anthranilates were prepared and found to possess potent anti-inflammatory and analgesic activities by Unidistributers Pvt. Ltd. India (1984).

![Structural formula of N-Acetylamophenol-N-(p-substituted phenylalkyl) anthranilates](image)

**R=H, halo, NO2, alkyl, alkoxy; R1=H, halo, alkoxy, alkyl; Z=alkylene**

Some new anti-inflammatory and analgesic agents of anthranilic acid derivatives have been prepared by Khalifa et al. (1982).

![Structural formula of some new anti-inflammatory and analgesic agents of anthranilic acid derivatives](image)

**R=H, Br etc.; R1=H, Br, CH3 etc.**

Ferrini et al (1980) synthesized some substituted anthranilic acid amides as inflammation inhibitors.

![Structural formula of some substituted anthranilic acid amides as inflammation inhibitors](image)

**R=H, aliph etc.; R1=H, (cyclo) aliph etc.;
R2=H, alkyl, halogen etc.; n=m=2,3 etc.**

p-substituted-N-benzenesulfonyl anthranilic acids as inflammation inhibitor have been synthesized by Borne et al. (1974).

![Structural formula of p-substituted-N-benzenesulfonyl anthranilic acids as inflammation inhibitor](image)

**R=Br, Cl, I, H, F etc.**

N-arylanthranilic acid esters were prepared by Synthelabo (1974) and also reported their anti-inflammatory activity.
Aries (1972) have prepared anthranilic acid derivatives as anti-inflammatory agents.

Fujihira et al. (1971) synthesized and reported promising anti-inflammatory activity in N-phenylanthranilic acid.

N-(pyridyl or pyrimidinyl)-anthranilic acid derivatives were synthesized by Aries (1970) and these showed anti-inflammatory, antipyretic and analgesic activities.
THIAZOLES

Substitution pattern in thiazol nucleus plays a pivotal role in delineating the biological activity. Moreover, substitution by different heterocyclic moieties at position 2 and 4 either imparts biological activity or enhances it. Scientists have synthesized several indole derivatives which possess potent anti-inflammatory activity. Some of these are given below-

Anti-inflammatory evaluation of some new acylhydrazone bearing 2-aryl-thiazole have been synthesized by Moldovan et al. (2011).

Some new 2-Amino-5- thiazolyl motif have been synthesized and screened for anti-inflammatory activity by Franklin et al (2008) out of all compounds these two were found to be most active.

$R^1 = 6$-Cl, 7-Cl, 8-CH$_3$, 6-Cl 7-Cl, 8-CH$_3$ $R^2 = 6$ Br, 6-Br, 6 Br, 6,8-Br

Synthesis of acridinyl-thiazolino derivatives as inflammation inhibitors have been reported by Sondhi et al (2005) and also reported their analgesic activity.

$R^1 - R^5 = H, \text{CH}_3, \text{OCH}_3, \text{Cl}, \text{etc.}$

2-Arylamino-4-phenylthiazol-5-acetic acid and esters as Non-Steroidal anti-inflammatory drugs have been synthesized by Mohan and Attimarad (2004).

\[
\text{R}=4\text{-F, 2-Cl, 3-methoxy, 4-Cl, etc.}
\]


\[
\text{R=H, CH}_3, \text{ Cl, NO}_2; \text{ R}^1 = \text{CH}_3, \text{COOC}_2\text{H}_5; \text{ R}^2 = \text{H, CHO, OCH}_2\text{CH}_3
\]

Holla et al (2003) synthesized some new 2,4-disubstituted thiazoles and reported their anti-inflammatory and analgesic activities.

\[
\text{R}^1 = 4\text{-Br, -C}_6\text{H}_4 \quad \text{R}^2=3,4\text{-}(\text{CH}_2\text{OCH}_2)\text{C}_6\text{H}_3
\]

New substituted 1-H-pyrazolyl-thiazolo-[4,5-d]-pyrimidines have been synthesized as anti-inflammatory and anti-microbial agents by Bekhit et al (2003).
Some new thiazoles as inflammation inhibitors have been prepared by Fujiware et al (2002).

![Chemical structure](image)

Sharma et al (1998) synthesized some 3-(2-thiazolyl)-1,2-benzisothiazoles and reported their anti-inflammatory activity.

![Chemical structures](image)

$R = CH_3, C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4$ etc.

$R^1 = H, COCH_3$

Some ethyl-2-arylamino-5-phenyl thio-thiazole-4-carboxylates and their sulphones as potential analgesic, anti-inflammatory and anti-microbial agents have been synthesized by Baddi and Mahajanshetti (1997).

![Chemical structures](image)

$R = H, p-CH_3, p-OCH_3, p-Cl, p-Br, 2-CH_3, 4-Cl$

The series of 5,6-diaryleidazo-[2,1-b]-thiazole compounds were prepared and their inhibitory potencies against COX-II and COX-I enzymes were measured by Michel et al (1997).
\[ R^1 = \text{H, Me, Cl etc}; \quad R^2 = \text{H, Me, Cl etc}; \quad R^3 = 4\text{-MeSO}_2, \text{H}; \]
\[ R^4 = \text{H, 4-MeSO}_2, \text{F, Cl}; \quad R^5 = \text{H, F etc.} \]

Synthesis of 2-(4'-carboxymethyl-3'-methyl-5'-oxo-2'-pyrazolin-1'-yl)-4-arylthiazoles have been given by Sawhney et al (1982) as inflammation inhibitors.

\[ R = \text{H, Cl, Br etc.} \]
AZETIDINONES

Kumar et al. (2009) have been prepared newer quinazolin-4-one derivatives as anti-inflammatory activity.

\[
\begin{align*}
R &= \text{H, Cl, Br etc.}
\end{align*}
\]

3-\{(4'-\text{p-chlorophenyl})-thiazol-2'-yl\}-2-\{(\text{substituted azetidinone/thiazolidine})-\text{aminomethyl}\}-6\text{-bromoquinazolin-4-ones as anti-inflammatory agents prepared by Kumar et al. (2007).}

\[
\begin{align*}
R &= \text{H, p-\text{CH}_3, p-\text{OCH}_3, p-\text{Cl, p-Br}}
\end{align*}
\]

Some new azetidinoyl derivatives have been synthesized by Bhati et al. (2008) and the following compound was found to be most active anti-inflammatory agent.

\[
R = 4\text{-N(\text{CH}_3)C}_6\text{H}_4
\]
Srivastava et al (2002) synthesized some new 1,2,4-triazolo-thiadiazoles and its 2-oxoazetidines and were also screened for their anti-inflammatory, antibacterial, antifungal and anti-convulsant activities.

\[
\text{Ar} = 2-\text{Cl-C}_6\text{H}_4, 3-\text{Cl-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 2-\text{Br-C}_6\text{H}_4, 3-\text{Br-C}_6\text{H}_4, 2-\text{OCH}_3\text{-C}_6\text{H}_4 \text{ etc.}
\]

Synthesis of β-lactam compounds as inflammation inhibitors have been reported by Bisacchi et al (2002).

\[
\text{R} = \text{COOH, acyl, etc; X=acyl, SO}_2\text{-alkyl etc; n=1-6}
\]

Some derivatives of substituted azetidinyl thiazolyl/oxazolyl benzidine have been synthesized by Bansal et al (2000) and screened for their anti-inflammatory activity.

\[
\text{R=2-OCH}_3\text{-C}_6\text{H}_4 \text{ etc.}
\]

Some new substituted β-amino naphthalene derivatives as inflammation inhibitors were prepared by Bansal et al (2000)

\[
\text{R} = 4\text{-N(CH}_3)_2\text{C}_6\text{H}_4
\]
10-Substituted phenothiazine have been synthesized and screened for their anti-inflammatory activity, ulcerogenic liability and acute toxicity by Bansal and kumar (1999).


Some substituted azetidinones as inflammation inhibitors have been synthesized by Amato et al (1997).


\[ R^1=R^2=\text{H, alkyl}; R^3=\text{H, alkyl etc}; W=O, \text{CONH, etc}; Y=O, \text{CO, bond}; Z=\text{diphenylamino etc.}; n=0-6 \text{ integer}, m=0-6 \text{ integer}. \]

\[
\begin{array}{c}
\text{M} = H, \text{C}_{1-6} \text{ alkenyl etc.; } \text{R} = \text{C}_{1-6} \text{ alkyl; } \text{R}^1 = \text{alkoxyalkyl etc.}
\end{array}
\]

\[
\begin{array}{c}
\text{R}^2 = \text{R}^3 = H, \text{COOH, Ph etc.; } \text{R}^4 = (\text{un}) \text{ substituted carbonylconty.}
\end{array}
\]

\[
\begin{array}{c}
\text{substituted; } \text{R}^5 = \text{R}^6 = H, \text{COOH, Ph, OH etc.}
\end{array}
\]

A series of 1-(2-carboxyphenyl) -3 chloro-4- arylazetidin-2- ones have been synthesized by kumar et al (1990) and reported their anti-inflammatory activity

\[
\begin{array}{c}
\text{R=H, 2-OCH}_3, 4\text{-OCH}_3, 4\text{-N (CH}_3)_2 \text{ etc.}
\end{array}
\]

Some new 1-substituted -2-oxo-3-chloro/3-(2-chlorophenoxy)-4- (2-arylindol-3-yl)-azetidines as anti-inflammatory agents have been synthesized by Agarwal (1989).

\[
\begin{array}{c}
\text{R=H, Cl, CH}_3 \text{ etc.;}
\end{array}
\]

Osaka Soda Co. (1985) synthesized 3,4-diphenyl-1-(arylmethyl) -2-azetidinone derivatives as anti-inflammatory agents.

\[ R = \text{Halo, alkoxy etc.} \]

Tandon et al (1983) synthesized some azetidinones as inflammation inhibitors and analgesic agents.

\[ X = \text{H, OH; } R = 2F, 2-\text{Cl, 2-OH etc.} \]

\[ R = \text{H, 4- (CH}_3\text{)_2N etc.} \]

β-lactams and their intermediates as anti-inflammatory agents have been reported by Bose (1981)

\[ R = \text{H, acyl, etc.; } R^1 = \text{H, SMe; } R^2 = \text{H, furyl, CH: CH Ph etc.} \]


\[ X = \text{bond, CH}_2\text{-CH}_2\text{ etc.; } Z = \text{C}_2\text{-5 alkylene (CH}_2\text{), R = alkyl, aryl etc.; } R^1 = \text{dialkylamino, Me}_2\text{N etc.} \]
Anti-inflammatory and antihypertensive activities in azetidinol derivatives have been reported by Castaigne et al. (1976).

\[
\begin{align*}
\text{R} &= \text{H, CH}_2\text{NMe}_2 \text{ etc.}; \\
\text{R}^1 &= \text{R}^2 = \text{Me, Et etc.}; \\
\text{R}^3 &= \text{H, Ac etc.}
\end{align*}
\]

Okutani et al. (1974) synthesized and reported anti-inflammatory activity of 3-substituted azetidine derivatives.

\[
\begin{align*}
\text{R} &= \text{OH; R}^1 = \text{Me, CH, PhCHMe etc.; R}^2 = \text{H.}
\end{align*}
\]

Pifferi and Testa (1970) have been reported anti-inflammatory activity in azetidin-2-ones.

\[
\begin{align*}
\text{R} &= \text{R}^1 = \text{Pr, NR}^2\text{R}^3 = 5 \text{ Nitro -2- thienylidene amino}
\end{align*}
\]
PYRAZOLINE AND PYRAZOLE CONGERNERS

Pyrazolines and pyrazolones are the most important representatives of hydrazine in both the synthetic and theoretical respect. Compounds of these classes are widely used as photographic developers, dyes, herbicides and medicinal agents with potent analgesic and anti-inflammatory activities. The most important, From the therapeutic point of view, are phenylbutazone and oxyphenbutazone. These potent anti-inflammatory drugs have been prescribed by clinicians for the treatment of rheumatoid arthritis and other inflammatory disorders. They act by inhibiting both cyclooxygenase-1 and cyclooxygenase-2 enzymes. Moreover, other important drugs of this pharmacodynamic family are anti-pyretic like aminopyrine, pipyrone and apazone. In addition, a large number of pyrazolines have been synthesized by several scientists which are summarized below:

Sauzem et al (2008) synthesize some novel pyrazoles and reported as anti-inflammatory as well as analgesic agents.

\[
\begin{align*}
\text{R}^1 & = \text{H, Et}; \quad \text{R}^2 = \text{H, Me.}
\end{align*}
\]

Some indole and pyrazole derivatives as potent anti-inflammatory agents have been synthesized by Patten et al (2007).

\[
\begin{align*}
\text{R} & = \text{p-Cl, p-Br etc.}
\end{align*}
\]
Bhaskar et al (2007) synthesized and reported the anti-inflammatory activity of some 4,5 disubstituted -3- methyl-1,3a,4,5- tetrahydropyrazolo [3,4-c] pyrazoles, and out of all compounds these were found to be most active.

\[
\begin{align*}
\text{R} &= \text{Cl}; \text{R}^1 = \text{H}; \text{R}^2 = \text{H, Cl}; \text{R}^3 = \text{H}
\end{align*}
\]

Amir and Kumar (2005) synthesized and screened some 3,5-dimethyl pyrazoles, 3-methyl pyrazol-5-ones and 3,5-disubstituted pyridoxines for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities.

\[
\begin{align*}
\text{R} &= \text{4-OCH}_3, \text{2-OH, 3-OCH}_3, \text{4-OH, 4-Cl etc.}
\end{align*}
\]

Synthesis of some new pyrazolo pyrimidines have been reported by Reddy et al (2004) and were screened for COX-II inhibitory activity.

\[
\begin{align*}
\text{R}^1 &= \text{H, CH}_3; \text{R}^2 = \text{CH}_3, \text{H}; \text{R}^3 = \text{CH}_3, \text{OCH}_3, \text{Cl, Br}
\end{align*}
\]

Potent anti-inflammatory activity was reported in isoxazolinyl derivatives of anthranilic acid by Rani et al (2003).

\[
\begin{align*}
\text{X} &= \text{H, I}; \text{R} = \text{m-OCH}_3, \text{p-OH etc.}; \text{R}^1 = \text{o-Cl, o-CH}_3 \text{ etc.}
\end{align*}
\]
1-(10-Bromo-7H-indolo[2,3-C]-isoquinoline-5-yl)-3-(p-methoxy-phenyl)-5-(Phenyl)-pyrazoline has been synthesized by Hiremath et al (2002) found to possess significant anti-inflammatory activity.


Some new 1,5-diphenylpyrazoles as COX-II inhibitors have been synthesized by Katsuya et al. (1999).

Some new anti-inflammatory, analgesic and antimicrobial agents of pyrazoline derivatives have been synthesized by Udupi et al. (1998).

Matsuo et al (1997) synthesized 1,3,5-trisubstituted pyrazoles as inflammation inhibitors.
Synthesis of 1,5-diarylpyrazoles selective COX-II inhibitors were reported by Bertenshaw (1996).


5-arylhydrazonyl-N-phenylpyrazole derivatives have been synthesised by Freitas et al (1995) and also screened for their anti-inflammatory and analgesic activities.
New pyrazolylbenzenesulfonamides and its derivatives have been prepared by Talley et al (1995) and were also screened for their anti-inflammatory activity.

\[
R^1 = \text{substituted (hetero) aryls; } R^2 = \text{H, cyano, alkyl haloalkyl, alkoxy carbonyl, NO}_2; R^3 = \text{H, NO}_2, \text{formyl alkyl, cyano etc.; } R^4 = \text{Cycloalkyl, aryl, heterocycl etc.}
\]

Daidone et al (1994) reported anti-inflammatory as well as analgesic activities in ethyl-1-methyl-5-[2-substituted-4-oxo-3(4H)-quinazolinyl]-H-pyrazole-4-acetates.

\[
R=\text{H, Me, Et, Ph etc.}
\]

Substituted pyrazolines and pyrimidines exhibited potent anti-inflammatory activity which was reported by Andotra et al. (1993).

\[
R=\text{Me, Et etc.; } Ar=\text{Ph etc.}
\]

Mann et al (1992) synthesized the N-acetyl pyrazoline derivatives and have screened for their anti-inflammatory, analgesic and antipyretic activities.

\[
R=\text{H, 2-Cl etc; } R^1=\text{H, 2-Cl, 3-Cl, 4-Cl, 2-Br etc.}
\]

\[
\text{R}=\text{H, CH}_3\text{CO etc.}
\]

Indolylthiazolidinyl pyrazolines have been reported potent inflammation inhibitors by Kumar et al. (1990).

\[
\text{R}=2\text{-CH}_3, \text{C}_6\text{H}_5 \text{etc; R}^1=\text{H, 2-OCH}_3, 2\text{-F etc.}
\]


\[
\text{Kumar et al (1990) reported that quinazolinylpyrazolines possessed potent anti-inflammatory activity.}
\]
X=H, Br; R=2-F, 2-OCH₃, H, 4-N (CH₃)₂ etc.

3-Amino and 3-trifluoracetamino-4,5-dihydro-1H-pyrazoles as anti-inflammatory agents, have been synthesized by Sawhney et al. (1989).

R=C₆H₅NSR¹; R¹=H, Cl etc.

Some new glycosilated-3-methylpyrazolin-5-(4H)-one-4-benzylidenes have been synthesized and screened for their anti-inflammatory activity by Jain et al. (1988).

R¹=H, etc; R²=H, OCH₃, OC₂H₅ etc; R³=OCH₃, H etc.

Vaid et al (1986) reported promising anti-inflammatory and analgesic activities in the following compound.

R=H, Cl, F etc.
Kamal et al (1985) reported potent anti-inflammatory activity in 4-aryl-2-(3'-5'-dimethylpyrazolyl) quinazolines.

\[
\text{X=H, Cl etc.; X}^1=\text{H, Cl etc.}
\]

Singh et al (1984) synthesized some inflammation inhibitors of 6-fluoro-2-(3'-methyl-5'-oxo-2'-pyrazolin-1'-yl)-benzothiazole and its 4-substituted analogs.

\[
\text{R=CH}_2\text{OOEt etc.; R}^1=\text{H, F etc.}
\]

Anti-inflammatory and CNS depressant activities of some fluorine containing pyrazolo-[5,1-C][1,2,4]-triazines have been reported by Joshi et al (1983).

\[
\text{R=Me, CF}_3, \text{Ph etc.; R}^1=4-\text{FC}_6\text{H}_4, 3,4-\text{F(MeO)} \text{ C}_6\text{H}_3 \text{ etc.}
\]

2-(4'-carboxymethyl-3'-methyl-5'-oxo-2'-pyrazolin-1'-yl)-benzothiazoles and 2-(4'-carboxymethyl-3'-methyl-5'-oxo-2'-pyrazolin-1'-yl)-4-arylthiazoles have been reported as potent anti-inflammatory agents by Sawhney et al (1982).

\[
\text{R=H, Cl, Br etc.; R}^1=\text{H, Cl, NO}_2, \text{Me etc.}
\]
Jaiswal et al (1981) synthesized some 10-[3,5-Diaryl-2-pyrazolin-1-yl)acetyl]-phenothiazines and reported their anti-inflammatory as well as anticonvulsant activities.

\[
\text{R=NO, NO}_2, \text{Cl, OH etc; } R^1=\text{H, 4-Cl, 4-NO}_2 \text{ etc.}
\]
THIADIAZOLES

El Shehry, et al. (2010) have been prepared 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo(thiadiazoles and thiadiazines) as anti-inflammatory and molluscicidal agents.

\[
\text{Ar} = \text{CH}_3, \text{C}_6\text{H}_5, \text{C}_2\text{H}_5 \text{ etc.}
\]

Sadaf, et al. (2010) have been synthesized 6-substituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid as anti-inflammatory agents.

\[
\text{R} = \text{CH}_2 \text{ CH}_2 \text{ CH}_3 \text{ etc.}
\]

Sherif et al. (2009) possessed some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents.

\[
\text{R} = \text{H, Cl, CH}_3, \text{ OCH}_3, \text{ OC}_2\text{H}_5 \text{ etc.}
\]

Karegoudar et al (2008) synthesized some thiadiazole derivatives. All the synthesized compounds were screened for their anti-inflammatory as well as antimicrobial activities. Some of the compounds exhibited promising antimicrobial and anti-inflammatory activities and the following compound showed maximum anti-inflammatory activity.
The Various derivatives of thiadiazolothienopyrimidinones were synthesized by Jyothi et al. (2007). The synthesized compounds were evaluated for anti-inflammatory activity.

Some 3-alkyl/aryl-6-(1-chloro-1,3,4-dihyronaphth-2-yl)-5,6-dihydro-1,3,4-triazolo [3,4-b] [1,3,4]-thiadiazoles have been prepared by Kamotra et al. (2007) and reported their anti-inflammatory activity.

Manna et al. (2005) reported 5-substituted arylimino-3-(2,4-diethoxy arylimino)-1,2,4-dithiazolidines as anti-inflammatory, antifungal, antitumor agents.

The new 3-alkyl-6-aryl-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles have been synthesized by Ghate and Sreenivasa et al (2002) and reported their anti-inflammatory, antifungal and antibacterial activities.

Srivastava et al (2002) synthesized some new 1,2,4-triazolo-thiadiazoles and 2-oxoazetidines as anti-inflammatory, antimicrobial, anticonvulsant agents.

Srivastava et al (1999) synthesized some inflammation inhibitors of 1-[5’-(N-carbazolylmethyl)-1’,3’,4’-thiadiazol-2’-yl]-4-substituted phenyl-3-chloro-2-oxo-azetidines and also reported these as antimicrobial and anti convulsant agents.
Song et al (1999) has reported the following compound as cyclooxygenase-II inhibitor.

Some substituted -5-triazole [3.4-b] [1,3,4]-thiadiazole derivatives have been prepared by Gupta et al (1998) and these compounds were found to possess promising anti-inflammatory activity.

\[ R = \text{Cl, OCH}_3, \text{Br etc., } R^1 = \text{4-OMe C}_6\text{H}_4, \text{CH}_3, \text{C}_2\text{H}_5 \text{ etc.} \]

New anti-inflammatory, antibacterial and antifungal agents of 2-substituted phenyl-3-(3-alkyl/aryl)-5,6-dihydro-5-triazolo [3,4b] [1,3,4]-thiadiazol-6-yl indoles have been synthesized by Gupta et al (1997).

\[ R = \text{H, OMeC}_6\text{H}_4, \text{CH}_3, \text{C}_2\text{H}_5 \text{ etc., } R^1 = \text{H, CH}_3, \text{CH}_3\text{Cl} \]

Rani et al (1990) synthesized 5-(Benzothiazol-2-thiometyl) -2-phenylamino 1,3,4-thiadiazol as inflammation inhibitor.
Russo et al (1987) synthesized 5H-benzothieno [3,2-d] [1,3,4]-thiadiazolo [3,2-a]-pyrimidin-5-one derivatives and these were examined for analgesic, ulcerogenic and anti-inflammatory activities. The following compounds have shown potent anti-inflammatory activity.

\[
\begin{array}{c}
\text{R} = \text{SEt, SMe, Et etc.}
\end{array}
\]

2-(Aryloxyalkyl)-5- (3,4-methylenedioxy phenyl) -5- triazolo [3,4-b]- 1,3,4-thiadiazoles were prepared by Prasad et al (1986), and screened for their anti-inflammatory activity.

\[
\begin{array}{c}
\text{R} = \text{Ph, Substituted Ph etc., R}^1 = R^2 = \text{H, Me etc.}
\end{array}
\]

Some new 4-(2-alkyl-1,3-quinazolin-4-yl-oxymethyl)-2-(p-substituted phenylamino)-1,3,4-thiadiazoles as anti-inflammatory agents have been synthesized by Mohan et al (1985).

\[
\begin{array}{c}
\text{R} = \text{Me, Et etc.; R}^1 = 2-\text{OMe, 4-OMe, H etc.}
\end{array}
\]

Deshmukh et al (1984) observed mild anti-inflammatory and CNS depressant activities in 1,3,4-thiadiazole congeners.

\[
\begin{array}{c}
\text{R} = \text{H, Cl, OMe etc.; R}^1 = \text{H, Cl, etc., Z = Bond, CH}_2, \text{CH}_2-\text{CH}_2 \text{ etc.}
\end{array}
\]

\[
\begin{array}{c}
Z^1 = \text{Bond, CH}_2.
\end{array}
\]
Mazzone et al (1982) synthesized and screened some 5-aryl-2-amino-1,3,4-oxo (thia) diazoles for their anti-inflammatory, antifungal and anti pyretic activities.

\[ R = \text{substituted Ph}; R^1 = \text{H, C}_{1-3} \text{ alkyl or Ph.} \]
OXADIAZOLE

Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecular, 1,3,4-oxadiazole derivatives have played an vital role in the medicinal chemistry. There are large number of synthetic compounds with oxadiazole nucleus used for antibacterial antifungal, analgesic and antiinflammatory.

Nagalakshmi G. (2008) synthesized some 2, 5- disubstituted -1,3,4, oxadiazoles as anti-inflammatory and antimicrobial agents. The following were found to be better anti-inflammatory agents.

\[ \text{Ar} = 3, 5-(\text{NO}_2)_2 \text{C}_6\text{H}_3, \text{C}_6\text{H}_5 \text{CONHC}_6\text{H}_4. \]

A new series of 2-[3-(4-methoxyphenyl) propan-3- one]-5- (substituted phenyl)-1,3,4- oxadiazoles was synthesized by Husain A (2008). These compounds were tested for their anti-inflammatory and ulcerogenic actions and the following were found to have very good anti-inflammatory activity.

\[ \text{R} = 4-\text{NO}_2\text{C}_6\text{H}_4, \text{C}_6\text{H}_5-\text{CH}_2, \text{C}_6\text{H}_5-\text{OCH}_2 \]

Synthesis of some new 1,3,4-oxadiazole derivatives as anti-inflammatory agents have been given by Amir et al (2007).

\[ \text{R} = \text{C}_6\text{H}_5, 2-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2,4-\text{Cl}_2\text{C}_6\text{H}_3, 2-\text{acetoxyphenyl, 1-(4-}
\]
\[ \text{isobutylphenyl) ethyl, 1-(6-methoxynaphth-2yl) ethyl etc.} \]
Frank et al (2007) synthesized oxadiazoles containing imidazole moiety and reported their anti-inflammatory and antifungal activities.

\[
R = \text{C}_6\text{H}_5, \ 4-\text{CH}_3\text{C}_6\text{H}_4, \ 4-\text{OCH}_3\text{C}_6\text{H}_4, \ 4-\text{ClC}_6\text{H}_4, \ 2-\text{CH}_3\text{C}_6\text{H}_4 \text{ etc.}
\]

Ravindra et al (2006) synthesized some inflammation inhibitors of 1,3,4-oxadiazoles linked to naphtho [2,1-b] furan, and the following compound was found to be most active.

Some new 2,5-disubstituted-1,3,4-oxadiazole derivatives have been synthesized and evaluated for their anti-inflammatory activity by Amir and Kumar (2004).

\[
R = \text{aryl, amino, N-alkyl, N-aryl etc.}
\]


\[
R = \text{H, halo, alkyl etc.; } X = \text{N,CH etc.; } Y = \text{CR, N}
\]

\[
L = \text{O,S, NH etc.; } Z = \text{NH}_2, \text{NPh}_2, \text{ etc.; } n = \text{O-6}
\]
Synthesis and anti-inflammatory activity of substituted 1,3,4-oxadiazole derivatives have been reported by Ladva et al (1996).

\[ R = \text{C}_6\text{H}_5, \text{3-COOH-4-ClC}_6\text{H}_3, \text{3-COOH 4-OHC}_6\text{H}_3, \text{3-COOH, 4OCH}_3\text{C}_6\text{H}_3 \text{ etc.} \]

Omar et al (1996) synthesized some new 1,3,4-oxadiazole derivatives, and were also screened for their anti-inflammatory as well as analgesic activities.

\[ R = \text{p-pyridyl etc.}; R^1 = \text{ethyl, phenyl etc.} \]

[(4-Acetamidophenoxy)-methyl]-2-(p-substituted phenylamino)-1,3,4-oxadiazoles have been synthesized by Narqund et al (1994). These compounds have been screened for inflammatory activity.

\[ R^1 = \text{ph, 4-BrC}_6\text{H}_4 \text{ etc.; } X = \text{bond etc.} \]

Anti-inflammatory derivatives of 1,3,4-oxadiazole have been synthesized by Abbas et al (1993), and also reported their anti-pyretic activities.

\[ R^1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{allyl, Bu, mannich base etc.} \]
Rani et al (1990) synthesized some oxadiazoles and compound 5-(benzothiazol-2-ylthiomethyl-phenylamino)-1,3,4-oxadiazole reported as inflammation inhibitor.

![Chemical structure of oxadiazole](image)

Anti-inflammatory, analgesic and antibacterial agents of 2-substituted-6-carbethoxy-5(H)-oxo-oxadiazolo [4,5a]-pyridines have been synthesized by Murty et al (1988).

![Chemical structure of oxadiazole](image)

\[ \text{R}^1 = \text{ph, ClC}_6\text{H}_4 \text{etc.} \]

Some newer quinazolinyl-oxadiazoles have been synthesized by Mohan et al (1985) and were screened for their anti-inflammatory activity.

![Chemical structure of oxadiazole](image)

\[ \text{R} = \text{Me, Et etc.}; \text{R}^1 = \text{H, ph etc.}; \text{R}^2 = \text{Me, substituted ph etc.} \]

2,5-disubstituted 1,3,4-oxadiazoles have been reported as anti-inflammatory agents by Mazzone et al (1984).

![Chemical structure of oxadiazole](image)

\[ \text{R} = \text{R}^1 = \text{trimethoxy phenyl, dioxymethyleneophenyl etc.} \]

Heterocyclic comounds [5-H-1,2,4-oxadiazolo-(2-3a) pyridine] have been found to possess anti-inflammatory and analgesic activities by Yamanouch Pharmaceutical (1981).

![Chemical structure of oxadiazole](image)

\[ \text{R} = \text{Ph, alkyl etc.} \]
THIAZOLIDINONES

Thiazolidinones are the derivatives of thiazolidine which belongs to an important group of heterocyclic compound. Thiazolidinones with a carbonyl group at position 2,4 or 5 have been subject of extensive study in the recent past. Furthermore, diverse biological activities like anti-inflammatory, bactericidal, fungicidal, insecticidal anti-convulsant, tuberculostatic, antithyroidal, potentiation of phenobarbital, induced sleeping time, cardiovascular etc. have been found to be associated with thiazolidinone derivatives. Several thiazolidinone derivatives have been synthesized and evaluated for their anti-inflammatory activities. Such as-

Certain thiazolidinones have been prepared by Taranalli et al (2008) and were also screened for anti-inflammatory, analgesic and antipyretic activities.

\[ R = H, CH_3; R^1 = OCH_3, Cl, NO_2, F; R^2 = H, OH \]

3-[4′-(p-chlorophenyl)-thiazol-2′-yl]-2-[(substituted azetidinone/thiazolidinone)-amino-methyl]-6-bromo quinazolin-4-ones have been synthesized by Kumar et al (2007) and also screened for their anti-inflammatory activity.

\[ R=H, O-Cl, p-Cl, p-OCH_3, o-OCH_3, p-CH_3 \] etc.
Pattan et al (2006) synthesized some new benzylidene thiazolidinone derivatives and were also tested for their anti-inflammatory activity.

\[
\begin{align*}
R &= 4\text{-fluorobenzene, 4\text{-}nitrobenzene, 4\text{-}methylbenzene. 4\text{-}methoxybenzene} \\
\text{Some thiazolidinone derivatives of naphtho } [2,1\text{-}b] \text{ furan as anti-inflammatory agents have been synthesized by Vagdevi et al (2006).} \\
R &= \text{C}_6\text{H}_5, 2\text{-OHC}_6\text{H}_4, 2\text{-OCH}_3\text{C}_6\text{H}_4, 4\text{-OCH}_3\text{C}_6\text{H}_4, 4\text{-OH} 3\text{-OCH}_3\text{C}_6\text{H}_3, 4\text{-ClC}_6\text{H}_4 \text{ etc.} \\
\text{Ottana et al (2005) synthesized 5\text{-}arylidene\text{-}2\text{-}imino\text{-}4\text{-}thiazolidinones as potent inflammation inhibitors.} \\
R &= 3\text{-OCH}_3, 4\text{-OCH}_3, 4\text{-Cl etc.; } R^1 = 3\text{-OCH}_3, 4\text{-OCH}_3 \text{ etc.} \\
\text{A series of 5\text{-}arylidene\text{-}2\text{-}aryl\text{-}3\text{-}[(2\text{-benzothiazolythio})\text{-}acetamidyl]1\text{-}3\text{-}thiazolidin\text{-}4\text{-}ones have been synthesised by Srivastava et al (2004). These have been screened for their antifungal, antibacterial and anti-inflammatory activities.}
\end{align*}
\]
Roman et al. (2003) synthesized some 2-arylamino-2-thiazolin-4-ones and reported their anti-inflammatory activity.

Bansal et al. (2001) synthesized a series of thiazolidinyltriazino-quinazolines as inflammation inhibitors. The most potent compound of the series was 5-(5'-p-dimethylaminophenyl-2'-oxo-4'-thiazolidin-1'-yl)-amino-4-phenyl-2-methyl-10-bromo-[1,2,4]triazino-[2,3-C]-quinazolines.

A series of substituted thiazolidinone derivatives has been synthesized by Goel et al. (1999) and the compound 3-(4'-bromo-2'-carboxyphenyl)-2-(fluorophenyl)-5-methyl-4-thiazolidinone has been found to better anti-inflammatory agent than reference drug phenylbutazone.

Walsh and Uwaydah (1992) synthesized 2-aryl-5-alkyl-4-thiazolidinones as cyclooxygenase and 5-lipoxygenase inhibitors.
Some newer Indolylthiazolidinones as inflammation inhibitors have been synthesized by Singh et al (1986).

Revesz and Petcher (1985) reported anti-inflammatory and analgesic activities in acylaminophenyl-thiazolidine carboxylates.

Promising anti-inflammatory and analgesic activities have been shown in some compounds of a series of thiazolidinone derivatives by Sempuku (1983).

Okuda (1982) synthesized a series of 4-thiazolidinones and some compounds of the series have been reported as inflammation inhibitors.
NATURAL PRODUCTS

Research in the field of phytochemistry has led to discovery of efficacy of a number of plant products for the treatment of inflammatory disorders. The studies have resulted in the discovery of following products:

A. Curcumin: The rhizome of plant Curcuma Longa has used for the treatment of inflammatory disorders since ancient time. Its active principle curcumin (diferulcyemethane) (I) was isolated from Curcuma Longa. The detailed pharmacological evalution of its activity and mode of action has been done by Ghatak and Basu (1972). It has been reported that it inhibits prostaglandin synthesis as well as platelet prostaglandin production (Thattle and Dahanukar, 1986).

B. Tomatine: The alkoloid tomatine (Lycopersicin) (II), Present in wild tomato plant, has been extracted, which inhibits oedema induced by carrageen an impregnated cotton pallets in rats Filderman and Kovacs, (1986).

C. Griseofulvin: Griseofulvin (III) was isolated from *Pencillium Griseofulvin*. It possessed moderate anti-inflammatory activity with low toxicity.
D. 18 \( \beta \) Glycyrrhetic acid: 18-\( \beta \)-Glycyrrhetic acid (IV) was isolated from the roots of Liquorice. It has anti-inflammatory property. Its methyl as well as diacetate derivatives were also synthesized and were found to possess anti-inflammatory activity Krans, (1960).

E. Cryogenini: Nucifora and Malone (1971) reported anti-inflammatory properties in cryogenine (V), which was isolated from plant *Heimia Salicifolia*.

Gold

Gold in elemental form, has been employed for centuries as an antipruritic to relieve the itching palm. In more modern times, the observation by Robert Koch in 1890 that gold inhibited Mycobacterium tuberculosis in vitro led to trials in arthritis and lupus erythematosus, thought by some to be tuberculosis manifestations. At present, gold derivatives are used in the treatment of rheumatoid arthritis. These derivatives such as Aurothioglucose (I), Gold sodium thiomalate (II) and auranofin (III) are used for the treatment of inflammatory disorders or rheumatoid arthritis (William and Kenneth; 1996) when NSAIDs do not show a satisfactory response.
In all the gold derivatives, possessing potent anti-inflammatory activity, it is important to notice that gold is attached to sulfur.