Chapter

16

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

1. INTRODUCTION

Inflammation may be defined as the series of changes that occur in living tissues following injury. The injury which is responsible for inflammation may be brought about by a variety of conditions such as : physical agents like mechanical trauma, ultra-violet or ionizing radiation ; chemical agents like organic and inorganic compounds, the toxins of various bacteria ; intracellular replication of viruses ; hypersensitivity reactions like reaction due to sensitized lymphocytes with antigenic material *viz.*, inhaled organic dusts or invasive bacteria ; and necrosis of tissues whereby inflammation is induced in the surrounding tissues.

Almost three decades ago, **steroids** namely : **prednisolone, dexamethasone, betamethasone, triamcinoline** and **hydrocortisone** were considered to be the **drug of choice as anti-inflammatory agents.** Owing to the several adverse effects caused by either short-term or long-term steroid therapy, these have been more or less replaced by much safer and better tolerated **non-steroidal anti-inflammatory drugs (NSAIDs).**

The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since the past three decades. A good number of these agents have been put into clinical usage widely and confidently thereby exhibiting positive therapeutic efficacy accompanied with fewer untoward reactions.

The mechanism of action principally responsible for most of the **NSAIDs** seems to be inhibition of prostaglandin synthesis by causing almost complete blockade of the activity of the precursor enzyme, *cyclogenase.* In fact, there are two *isozymes* that have been duly recognized for the **cyclo-oxygenase enzyme** (*viz.*, **COX-1** and **COX-2**). However, both **isozymes** practically perform the same reactions, but **COX-1** is the isozyme that is found to be *active* under normal healthy conditions. Importantly, in rheumatoid arthritis, **COX-2,** which is usually found to be quite dormant, gets duly activated and yields a substantial quantum of inflammatory prostaglandins. Based on these critical facts and observations a vigorous concerted effort is being geared up to develop such newer drug substances that are specifically selective for the **COX-2** isozyme, with a view to arrest particularly the production of the inflammatory prostaglandins.

In general, there exists virtually very little difference between the therapeutic efficacy of different **NSAIDs,** as certain patients would respond to one '**drug**' better than another. In reality, it is almost

difficult to predict the best suitable drug for a patient ; thus, it invariably necessitates to arrive at the **best-fit-drug** *via* trial and error only.

Keeping in view the innumerable adverse side effects caused by the **NSAIDs** their clinical usefulness are restricted drastically. Therefore, patients who are taking such drugs for a relatively longer periods should have periodic white-blood cell counts as well as determinations of serum creatinine levels, besides hepatic enzyme activities.

2. CLASSIFICATION

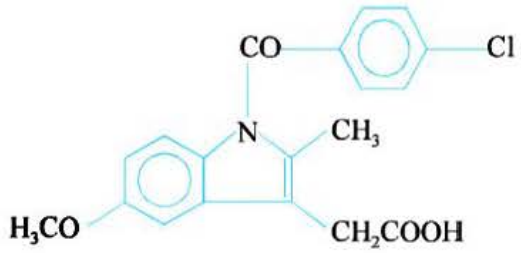
NSAIDs may be classified on the basis of their basic chemical structures as described below along with various classical examples belonging to each category, namely :

1. Heteroarylacetic acid analogues
2. Arylacetic acid analogues
3. Arylpropionic acid analogues
4. Naphthalene acetic acid analogues
5. Gold compounds
6. Miscellaneous anti-inflammatory drugs
7. Salicylic acid analogues and
8. Pyrazolones and pyrazolodiones.

2.1. Heteroarylacetic Acid Analogues

This constitutes an important class of **non-steroidal anti-inflammatory drugs** which have gained recognition in the recent past. A few classical examples of this group are, **indomethacin ; sulindac ; tolmetin sodium ; zomepirac sodium ;**

A. Indomethacin BAN, USAN, Indomethacin INN,

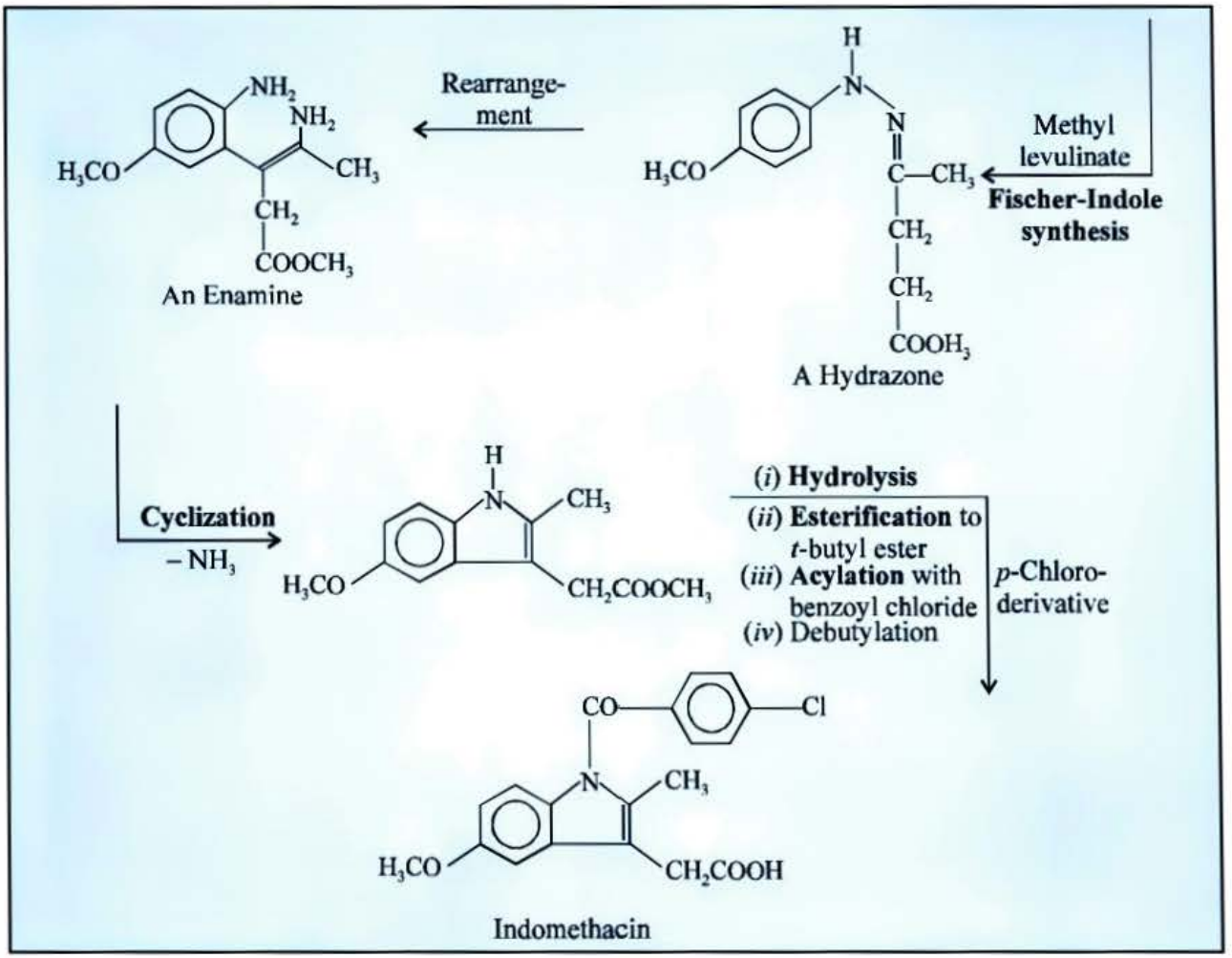


1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid ; 1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl- ; BP ; USP ;

Indocin$^{(R)}$ (MSD)

Synthesis

(*Contd...*)

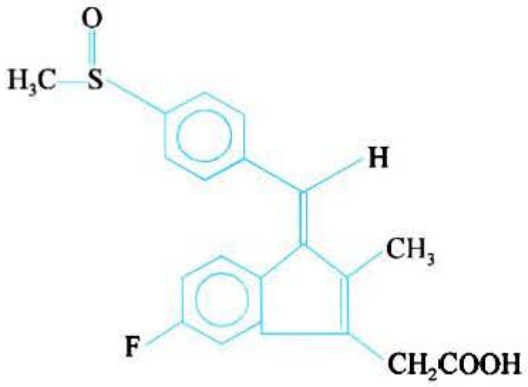


p-Methoxy phenyl diazonium chloride is obtained by the diazotization of *p*-anisidine which on reduction with sodium sulphite yields *p*-methoxy phenyl hydrazine. The resulting product undergoes the Fischer-indole synthesis in the presence of methyl levulinate to form a hydrazone which on intra-molecular rearrangement gives an enamine. This on cyclization loses a molecule of ammonia and forms an intermediate compound. It is then hydrolysed to the corresponding acid which is re-esterified *via* the anhydride to give the tert-butyl ester. Finally acylation with *p*-chlorobenzoyl chloride followed by debutylation gives rise to the official compound.

It is a non-steroid drug possessing anti-inflammatory, antipyretic and analgestic properties. *It is usually used for the treatment of rheumatoid arthritis, ankylosing (rheumatoid) spondylitis, gouty arthritis and osteoarthritis.* It is not an ordinary simple analgesic and owing to its reasonaly serious untoward effects should be used with great *caution.*

Dose : *In gout, usual, adult, oral, 100 mg initially, followed by 50 mg 3 times daily until pain is relieved ; As antirheumatic, oral, 50 mg 2 or 3 times daily ; As antipyretic, oral, 25 to 50 mg 3 times daily.*

B. Sulindac INN, BAN, USAN,



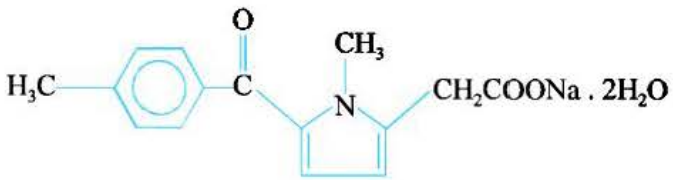
cis-5-Fluoro-2-methyl-1-[(*p*-methylsulfinyl) benzylidene] indene-3-acetic acid ; 1H-Indene-3-acetic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl) phenyl] methylene]-, (Z)-; USP ;

Clinoril(R) (MSD).

It is a fluorinated indene with a structural resemblance to indomethacin. It has anti-inflammatory, analgesic and antipyretic properties. *It is usually employed in the treatment of rheumatic and musculoskeletal disorders ; and also for severe and long-term relief of signs and symptoms of acute painful shoulder, acute gouty arthritis and osteoarthritis.*

***Dose** : Usual, adult, oral, 150 mg twice a day with food.*

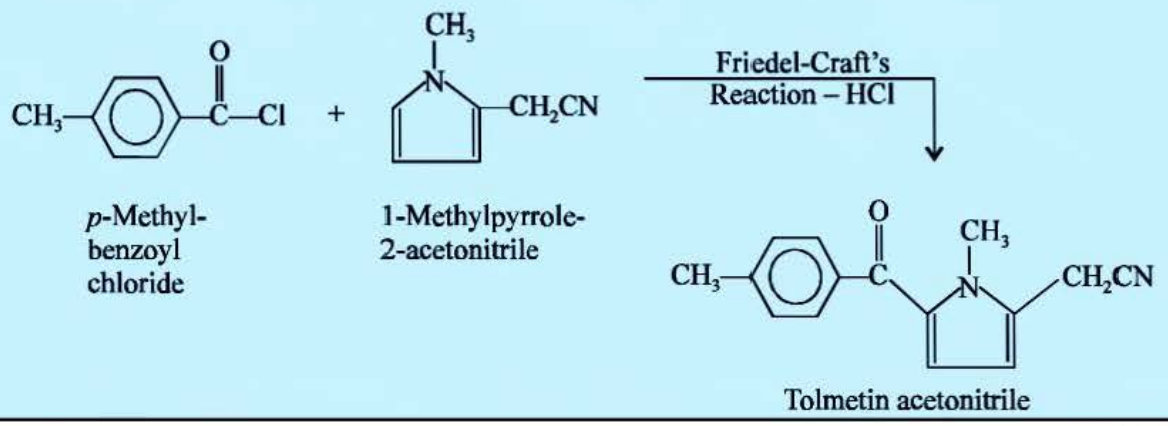
C. Tolmetin Sodium BAN, USAN, Tolmetin INN,



Sodium 1-methyl-5-*p*-toluoylpyrrole-2-acetate dihydrate ; 1H-Pyrrole-2-acetic acid, 1-methyl-5-(4-methylbenzoyl)-, sodium salt, dihydrate ; USP ;

Tolectin(R) (McNeil).

Synthesis



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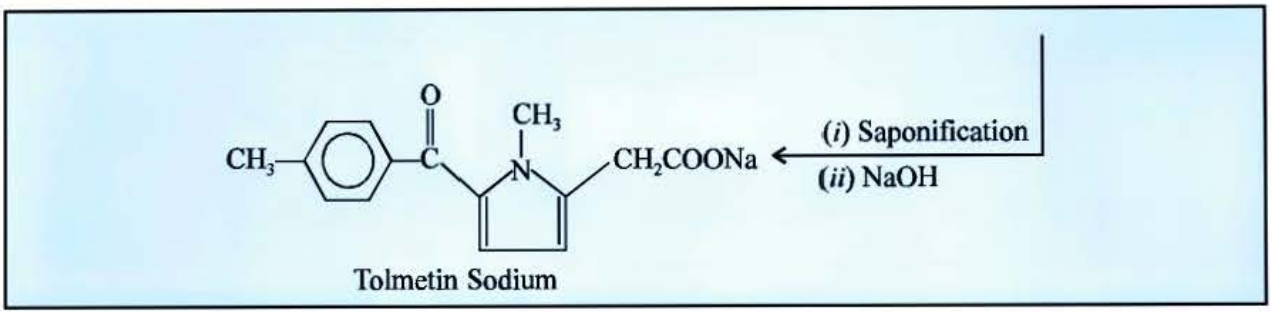


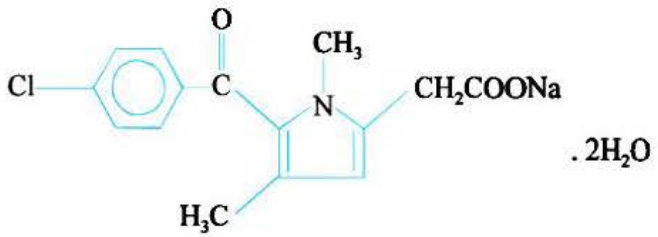
Tolmetin Sodium

Tolmetin acetonitrile may be prepared by the Friedel-Craft's reaction between *p*-methylbenzoyl chloride and 1-methylpyrrole-2-acetonitrile with the elimination of a mole of hydrochloric acid. The resulting product after appropriate separation from its 4-aroyl isomer is finally subjected to saponification followed by conversion to its sodium salt.

It has antipyretic, analgesic and anti-inflammatory actions. It is employed in the *treatment of rheumatic and other musculoskeletal disorders.* The drug is, however, comparable to indomethacin and aspirin in the control and management of disease activity.

Dose : *(Equivalent to tolmetin) Adult, oral, initial, 400 mg 3 times per day, subsequently adjusted to patient's response.*

D. Zomepirac Sodium BAN, USAN, Zomepirac INN,



Sodium 5-(*p*-chlorobenzoyl)-1, 4-dimethylpyrrole-2-acetate dihydrate ; 1H-Pyrrole-2-acetic acid, 5-(4-chlorobenzoyl)-1, 4-dimethyl-, sodium salt, dihydrate ; USP ;

Zomax(R) (McNeil).

It is an analgesic and anti-inflammatory drug structurally very similar to tolmetin sodium. It is normally used in mild to moderate pain, including that of musculoskeletal disorders.

Dose : *(Zomepirac sodium 1.2 g is approximately equivalent to 1g of zomepirac) ;* 400 to 600 mg of zomepirac daily.

2.1.1. Mechanism of Action

The **mechanism of action** of drugs discussed under Section 16.2.1. are as under :

2.1.1.1. Indomethacin

The **'drug'** exerts its pharmacologic activity by inhibiting the **enzyme *cyclo-oxygenase.*** It has been observed that this aforesaid enzyme specifically involved in the biosynthesis of prostaglandins that are solely responsible for the pain and inflammation of rheumatoid arthritis ; and, therefore, inhibiting the **'enzyme'** decreases the prostaglandin levels and eases the apparent symptoms of the disease. Besides, it has been proved beyond any reasonable doubt that the *'drug'* also inhibits the synthesis of useful prostaglandins both in the GI-tract and kidney.

Indomethacin, is invariably absorbed quite rapidly after oral administration ; peak plasma levels are accomplished in just 2 hours ; and almost 97% of the drug is protein bound. It has a half-life of 2.6 to 11.2 hours ; and only 10-20% of the drug gets excreted practically unchanged in the urine.

Caution. The high potential for dose-related adverse reactions both restrains as well as makes it imperative that the smallest effective dosage must be determined for each individual patient carefully and meticulously.

2.1.1.2. Sulindac

The precise mechanism of action of the **'drug'** is still unknown. However, it is believed that the **'sulphide metabolite'** may perhaps inhibit the prostaglandin synthesis. Interestingly, it exerts appreciably much less effect on the platelet function and bleeding time in comparison to *'aspirin'*, it must be used with great caution in such patients who could be affected quite adversely by this sort of action.

The **'drug'** gets absorbed invariably to the extent of 90% after the oral administration. The peak plasma levels are usually accomplished in about 2 hour in the fasting patient and may be extended between 3-4 hours when given with food. It has been duly observed that the mean half-life of sulindac is 7 = 8 hours ; and the mean half-life of the corresponding sulphide-metabolite is 16.4 hour (almost double than the parent drug).

2.1.1.3. Tolmetin Sodium

The exact mechanism of action of the **'drug'** is not yet established, although inhibition of prostaglandin synthesis most probably contributes heavily to its anti-inflammatory activity. It has been observed adequately that in such patients having rheumatoid arthritis different types of manifestations of its anti-inflammatory and analgesic actions do occur, but there exists little distinct proof of alteration of the progressive course of the prevailing disease.

The **'drug'** is usually absorbed not only rapidly but also completely having peak-plasma levels being attained within a span of 30-60 minutes after an oral therapeutic after a dosage regimen (40 mcg. mL^{-1}) after a 400mg dosage). Besides, it gets bound nearly to 99% to the plasma proteins ; whereas, the mean plasma-life is almost 1 hour. Importantly, all of a dose gets excreted in the urine within 1 day, either as conjugates of the parent drug *'tolmetin'* or as an **inactive oxidative metabolite**.

2.1.1.4. Zomepirac Sodium

The **'drug'** happens to be the *chloro*-derivative of tolmetin ; and, therefore, it predominantly shows appreciably longer plasma levels nearly 7 hours*, thereby attributing much lesser dosing frequency. It has been demonstrated adequately that a dose ranging between 25-50mg of this *'drug'* gives relief almost equivalent to that produced by aspirin, 650mg. Interestingly, in advanced cancer subjects, oral doses of 100-200mg were as effective the moderate parenteral doses of morphine.**

Note. The *'drug'* is presently not marketed because of its severe anaphylactoid reactions.***

2.2. Arylacetic Acid Analogues

It has been observed that organic compounds which bear some sort of resemblance either with respect to their structural features or functionally often display similar biological actions. However, it may be noted with interest that by contrast there exists no such common goals between arylacetic and arylpropionic acids.

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*O' Neill PJ *et al. J Pharmacol Exp Therap.*, **209**, 366, 1979.

**Wallenstein SL, *Unpublished Report.*

***An agent producing anaphylactic reactions.

The early 1970s have withnessed the introduction of arylacetic acids into numerous beneficial antiarthritic-analgesic agents ; however, their various structural parameters are still being explored exhaustively. A few **salient features** are enumerated below :

- Indole and pyrrole acetic acid, that are also aromatic in character, are regarded as a subgroup.
- Acidic heterocyclic sulphonamide compounds also afford clinically important **NSAIDs**.

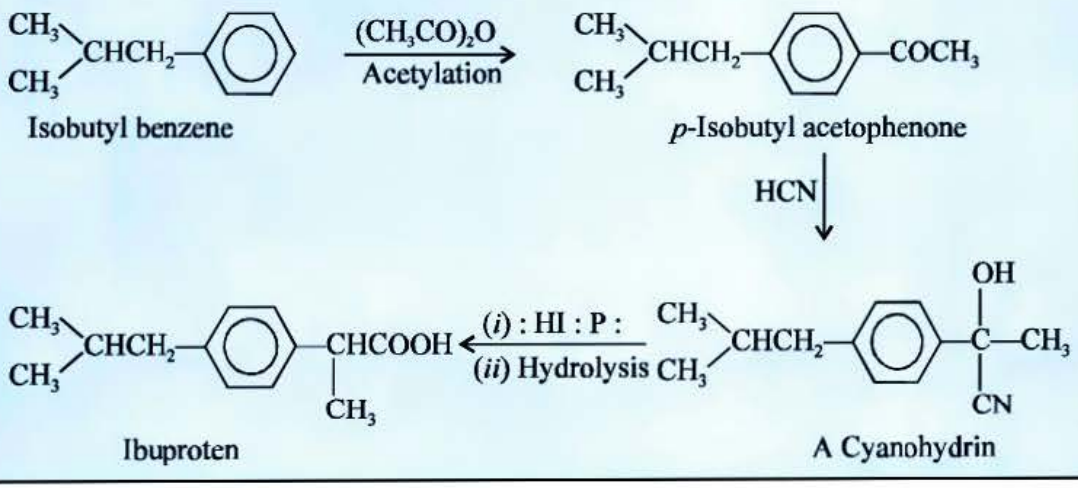
Interestingly, all these compounds additionally show useful antipyretic activities. They all share a more or less common mechanism of action.

A few potent analogues belonging to this class of compounds are described below : **ibuprofen** ; **ibufenac** ; **diclofenac sodium**.

A. Ibuprofen INN, BAN, USAN,

(±)-*p*-Isobutylhydratropic acid ; Benzeneacetic acid, α-methyl-4-(2-methyl-propyl), (±)-; BP ; USP ; Motrin(R) (Upjohn) ; Brufen(R) (Boots) ; Nuprin(R) (Bristol-Myers) ; Advil(R) (American Home Prod.).

Synthesis



p-Isobutyl acetophenone is prepared by the acetylation of isobutyl benzene which upon treatment with hydrocyanic acid yields the corresponding cyanohydrin. This on heating with hydrogen iodide in the presence of red phosphorous helps to reduce the benzylic hydroxyl moiety ; further hydrolysis of the nitrile groups gives the official compound.

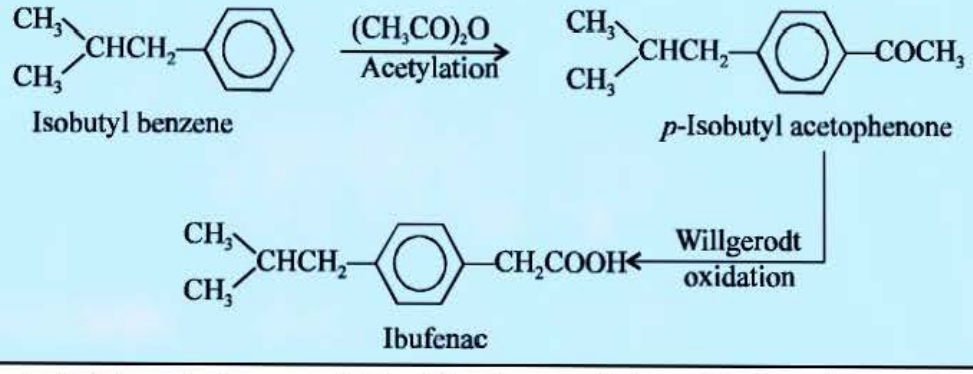
It is an anti-inflammatory drug that possesses anti-pyretic and analgesic actions. It is indicated for the *treatment of rheumatoid arthritis and osteoarthritis.* It is also recommended *to arrest acute flares and in the long-term management of these diseases.*

Dose : *Usual, oral adult, analgesia (dysmenorrhea), 200 to 400mg 4 to 6 times per day ; in rheumatoid arthritis, osteoarthritis, 300 to 400mg 3 or 4 times daily.*

B. Ibufenac INN, BAN, USAN,

(*p*-Isobutyl-phenyl) acetic acid ; Benzeneacetic acid, 4-(2-methylpropyl);
Dytransin(R) (Boots).

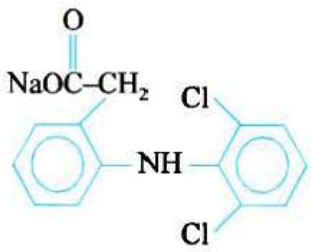
Synthesis



The *p*-isobutyl acetophenone obtained by the acetylation of isobutylbenzene is subjected to Wilgerodt oxidation to yield **ibufenac**.

It has anti-inflammatory, analgesic and antipyretic actions. It was formerly employed in the rheumatic conditions but was found to cause hepatotoxicity.

C. Diclofenac Sodium BAN, USAN, Diclofenac INN,



Sodium [*o*-(2, 6-dichloroanilino) phenyl] acetate ; Benzene-acetic acid, 2-[(2, 6-dichlorophenyl) amino]-, monosodium salt ; Dichlorophenac sodium ;
Voltaren(R) (Ciba-Geigy) ;

It is a phenylacetic acid derivative which has analgesic, antipyretic and anti-inflammatory actions. It is mostly employed in the *treatment of rheumatoid arthritis and other rheumatic disorders.*

Dose : *20 to 50 mg 3 times day. It is also given as a suppository.*

2.2.1. Mechanism of Action

The **mechanism of action** of compounds described under section 16.2.2 shall be dealt within the sections that follows :

2.2.1.1. Ibuprofen

The **'drug'** seems to be fairly comparable to *'aspirin'* in the control, management and treatment of rheumatoid arthritis having a distinct and noticeable lower incidence of side effects.* It has been amply proved and established that the pharmacologic activity of this **'drug'** exclusively resides in the S–(+)-isomer not only in **ibuprofen** but also throughout the arylacetic acid series. Nevertheless, these strategic isomers are exclusively responsible for causing more potent inhibition of the prostaglandin synthetase.

The **'drug'** gets absorbed quite fast after the oral administration ; and evidently the peak plasma serum levels generally are attainable within a span of 1 to 2 hour. It is usually metabolized rapidly and eliminated in the urine. The serum half-life is quite transient ranging between 1.8 and 2.0 hour.

Note. The inclusion of '*ibuprofen*' as an OTC-drug (*i.e.*, non prescription drug) in the United States is solely based on its lack of any serious untoward problems stretched over a decade of meticulous clinical observation and experience.

2.2.1.2. Ibufenac

The **'drug'** is a precursor in which the α-methyl benzeneacetic acid (ibuprofen) is replaced with simple benzeneacetic acid function, that was abandoned on account of its severe hepatotoxicity and was found to be less potent.

2.2.1.3. Diclofenac Sodium

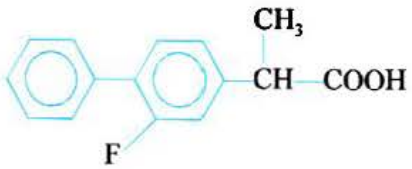
The **'drug'** is believed to exert a wide spectrum of its effects as a consequence of its ability to inhibit the prostaglandin synthesis noticeably. However, its anti-inflammatory activity is very much akin to other members of **NSAIDs** having a potency, *on weight basis*, which is nearly 2.5 times that of **indomethacin.** Likewise, *on weight basis*, its analgesic potency is about 8-16 times than that of **ibuprofen.**

Note. The corresponding potassium salt (Voltaren$^{(R)}$; Cataflam$^{(R)}$, which is proved to be faster acting, is invariably indicated for the management of acute pain and primary dysmenorrhea. It is also specifically recommended for patients having a history of high BP.

2.3. Arylpropionic Acid Analogues

Like the arylacetic acids the arylpropionic acid analogues also exhibit potent anti-inflammatory properties besides usual antipyretic and analgesic characteristics. A few examples of this category of compounds are discussed here, **flurbiprofen** ; **ketoprofen** ; **indoprofen** ; **fenoprofen calcium**.

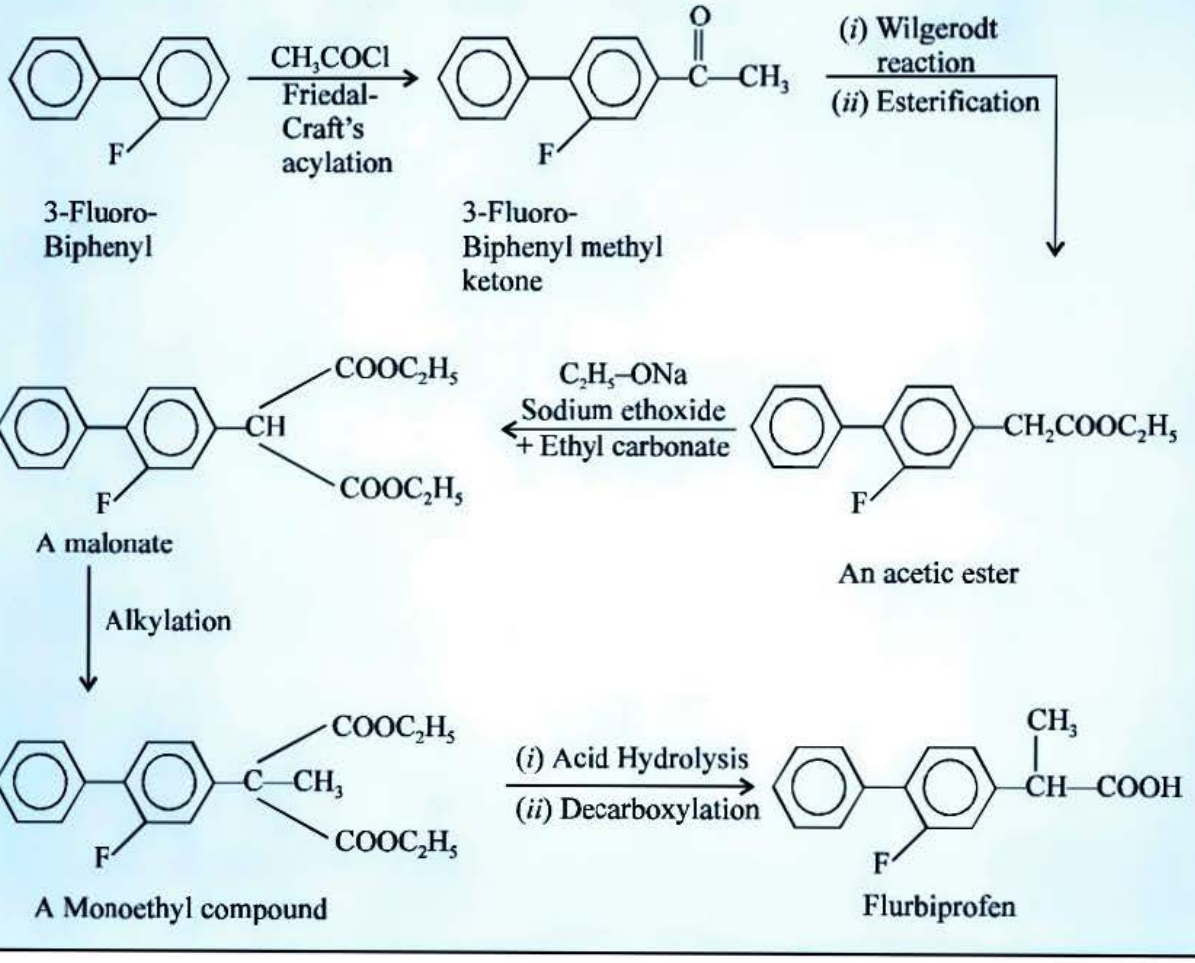
A. *Flurbiprofen* INN, BAN, USAN,



2-(2-Fluorobiphenyl-4-yl) propionic acid ; [1, 1′-Biphenyl]-4-acetic acid, 2-fluoro-α-methyl-, (±)-; (±)-2-Fluroro-α-methyl-4-biphenylacetic acid ; (±)-2-(2-Fluoro-4-biphenylyl) propionic acid ; Ansaid$^{(R)}$ (Upjohn).

*Dorman J *et. al. Can Med. Assoc J.* **110**, 1370, 1974.

Synthesis

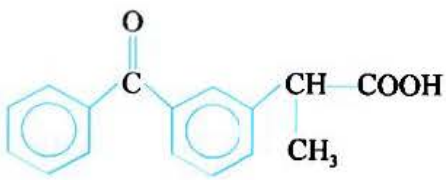


3-Fluoro biphenyl methyl ketone may be prepared by the Friedal-Craft's acylation of 3-fluorobiphenyl with acetyl chloride which upon Wilgerodt reaction followed by esterification yields the corresponding acetic ester. This on treatment with sodium ethoxide and ethyl carbonate yields a malonate which on alkylation forms a monoethyl compound. The resulting product on subsequent hydrolysis and concomitant decarboxylation yields **flurbiprofen**.

It is a phenylpropionic acid analogue which *possesses analgesic, anti-inflammatory and antipyuretic actions.* It is generally employed in the *treatment of rheumatoid arthritis and other rheumatic disorders.*

Dose : *Usual, adult, 150 to 200mg per day in 3 to 4 divided doses.*

B. Ketoprofen INN, BAN, USAN,



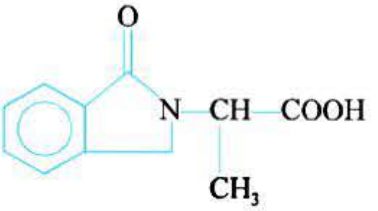
2-(3-Benzoylphenyl) propionic acid ; *m*-Benzoylhydratropic acid ; Benzeneacetic acid, 3-benzoyl-α-methyl- ; BP ;

Alrheumat(R) (Bayer, U.K.) ; Orudis(R) (May & Baker, U.K.)

It is used in the *treatment of rheumatoid arthritis and osteoarthritis.*

Dose : *50 to 100 mg twice daily with food.*

C. Indoprofen INN, BAN, USAN,



2-[4-(1-Oxoisoindolin-2-yl) phenyl] propionic acid ; *p*-(1-Oxo-2-Isoindolinyl) hydratropic acid ; Benzeneacetic acid, 4-(1, 3-dihydro-1-oxo-2H-isoindol-2-yl)-α-methyl- ;

Endyne(R) (Adria).

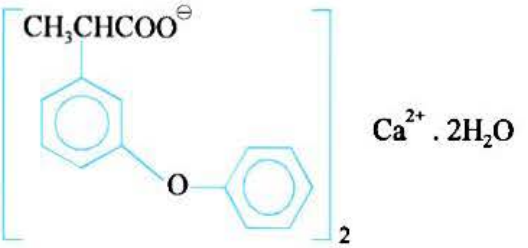
It is generally used for the relief of various types of pain. It is also employed in the treatment of rheumatoid arthritis and osteoarthrosis.

Dose : *600 to 800 mg per day in divided doses.*

D. Fenoprofen *Calcium* BAN, USAN, Fenoprofen INN,

Calcium (±)-2-(3-phenoxyphenyl) propionate dihydrate ; Calcium (±)-*m*-phenoxyhydratropate dihydrate ; Benzeneacetic acid, α-methyl-3-phenoxy-, calcium salt dihydrate, (±)- ; BP ; USP ;

Nalfon(R) (Lilly).



Fenoprofen calcium has *anti-inflammatory, (antiarthritic), and analgesic properties.* It has been shown to inhibit prostaglandin synthetase. It is known to *reduce joint-swelling, decrease the duration of morning stiffness and relieve pain.* It is also indicated *for acute flares and exacerbations and in the long-term management of osteoarthritis and rheumatoid arthritis.*

Dose : *(Fenoprofen equivalent) Usual, adult, oral, rheumatoid arthritis, 600mg 4 times daily ; osteoarthritis, 300 to 600mg 4 times per day.*

2.3.1. Mechanism of Action

The mechanism of action of the compounds discussed under Section 16.2.3. shall now be dealt with in the sections that follows :

2.3.1.1. Flurbiprofen

The '**drug**' is structurally and pharmacologically related to **fenoprofen**, **ibuprofen** and **ketprofen**. It is used for its specific ocular effects ; and therefore, is administered topically to the eye just before

certain ocular surgeries so as to prevent any intra operative miosis. However, the exact mechanism for the prevention and management of the postoperative ocular inflammation is yet to be established.

2.3.1.2. Ketoprofen

The **'drug'** is closely related to fenoprofen in its structure and properties. Besides, it has shown a very low incidence of side-effects and hence, has been approved as an OTC-drug in US.

2.3.1.3. Indoprofen

It is a **NSAID** now rarely used because of its adverse reactions. The **'drug'** shows carcinogenicity in *animal* studies ; and, therefore, it has been withdrawn from the market completely.

2.3.1.4. Fenoprofen Calcium

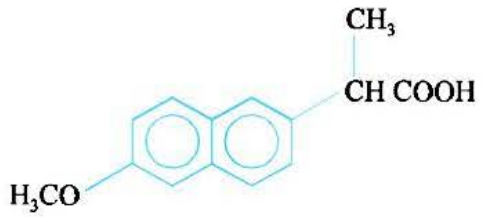
It is a propionic acid structural analogue closely related to **ibuprofen** and **naproxen**. The mechanism of action most probably relates to its inhibition of prostaglandin synthesis. The **'drug'** gets rapidly absorbed after the oral administration. Peak plasma-levels (of about 50 mcg. mL^{-1}) are attained within 2 hour after oral administration of a 600 mg dosage. The plasma half-life is nearly 3 hour. It is highly bound to albumin upto 90%.

It has been observed that nearly 90% of a single oral dosage gets eliminated within a span of 24 hours mostly as **fenoprofen glucoronide** and **4'-hydroxy fenoprofen glucuronide**, the obvious major-urinary metabolites of the **'drug'**.

2.4. Naphthalene Acetic Acid Analogues

The recent intensive quest for non-steroid anti-inflammatory drugs and arylacetic acids in particular offer a brighter scope that the naphthalene acetic acid analogues might turn out to be the leading compounds of an extensive series of promising clinical agents. **Example : Naproxen.**

A. Naproxen INN, BAN, USAN,

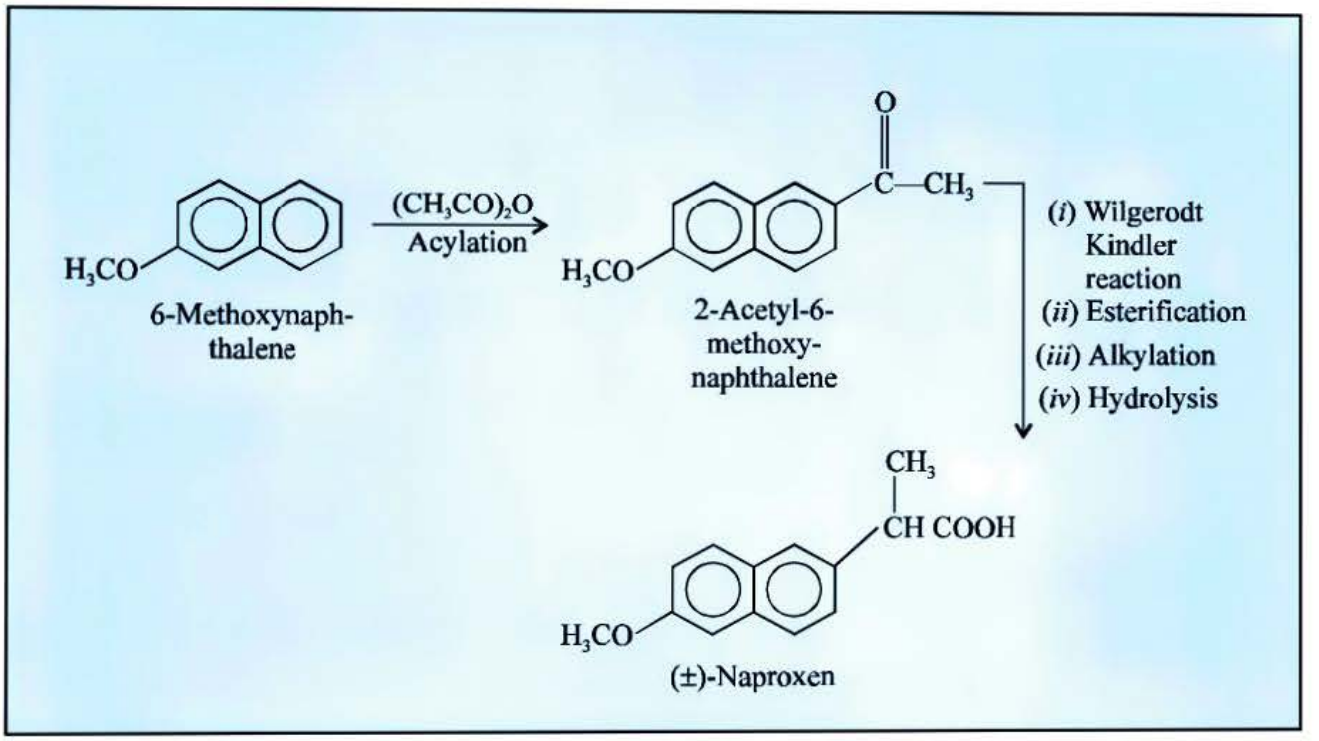


(±)-2-(6-Methoxy-2-naphthyl)-propionic acid ; (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid ; 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (+)- ; BP ; USP ;

Naprosyn(R) (Syntex).

Synthesis

2-Acetyl-6-methoxy-naphthalene may be prepared by the acylation of 6-methoxynaphthalene. The resulting product is then subjected to a series of reactions, namely ; **Wilgerodt-Kindler reaction**, esterification, alkylation and hydrolysis ultimately yields *DL*-Naproxen. Resolution of the resulting racemic mixture is caused through precipitation of the more potent *D*-enantiomer as the cinchonidine salt.



It possesses analgesic, anti-inflammatory and anti-pyretic actions. It is normally used in the *treatment of rheumatic or musculoskeletal disorders, rheumatoid arthritis, dysmenorrhea, and acute gout.* However, the sodium salt is mostly employed as an analgesic for a variety of other painful conditions.

Dose : *Adult, in rheumatoid arthritis, 250 to 375mg as initial dose 2 times per day ; in acute gout, 750mg as loading dose followed by 250mg 3 times a day until relieved.*

2.4.1. Mechanism of Action

The **mechanism of action** of **naproxen** is described below :

2.4.1.1. Naproxen

It is a naphthalene acetic acid structural analogue available commercially as the acid and its sodium salt and is sold OTC. The **'drug'** is fairly comparable to **aspirin** both in the management and control of disease symptoms. Nevertheless, it has relatively lesser frequency and severity of nervous system together with milder GI-effects.

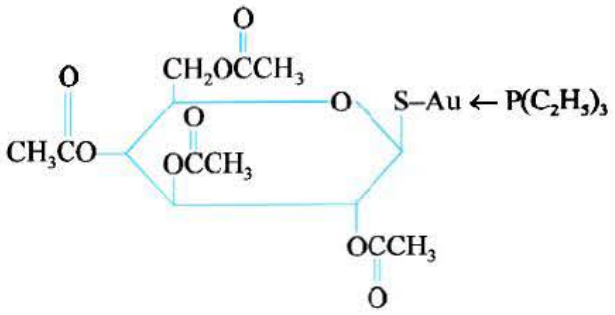
It is absorbed almost completely from the GI tract after an oral administration. Peak plasma levels ($\simeq$ 55 $mg.mL^{-1}$) are accomplished after 4 to 5 doses at an internal of 12 hours. It has been observed that more than 99% gets bound to serum albumin. The mean plasma half-life is nearly 13 hour. About 95% of a dose gets excreted in the urine, largely as **conjugates of naproxen** and its corresponding **inactive metabolite 6-demethyl-naproxen**.

2.5. Gold Compounds

In general, gold compounds either suppress or prevent, but do not cure arthritis and synovitis. The use of organic gold derivatives for the treatment of rheumatoid arthritis was first reported in 1927.

However, the monovalent gold compounds bring symptomatic relief to rheumatoid arthritis in patients. A few classical examples of this class of compounds are discussed below. **Examples : auranfin ; aurothioglucose ; aurothioglycanide ; sodium aurothiomalate.**

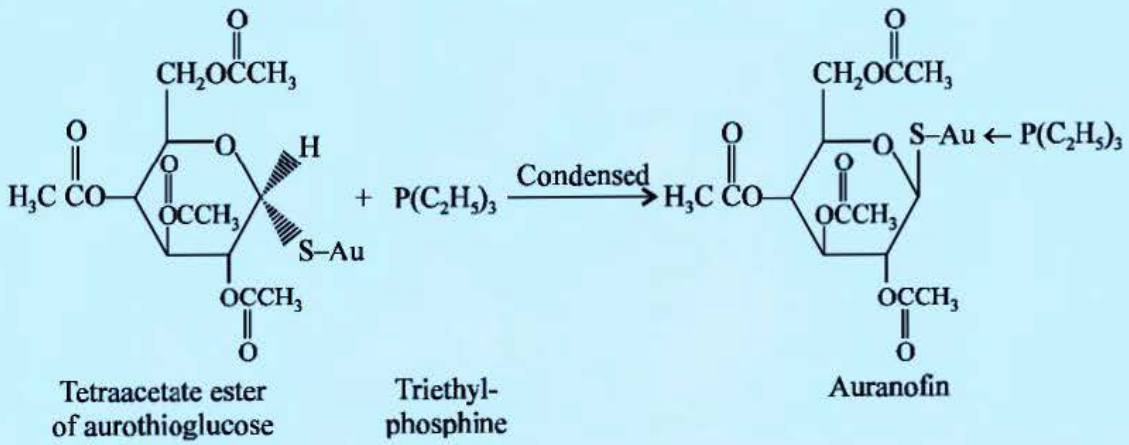
A. Auranofin INN, BAN, USAN,



(1-Thio-β-D-glucopyranosato) (triethylphosphine) gold 2, 3, 4, 6-tetra-acetate ; Gold, (2, 3, 4, 6-tetra-*o*-acetyl-1-thio-β-D-glucopyranosato-S) (triethylphosphine)- ;

Ridaura(R) (SK & F).

Synthesis

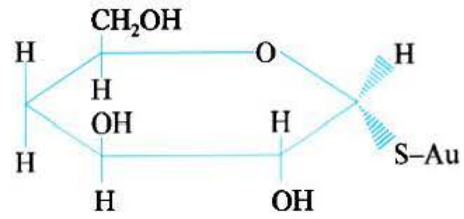


It may be prepared by the condensation of the tetraacetate ester of aurothioglucose with triethylphosphine to yield the co-ordination complex, auranofin.

Auranofin is administered orally and is used chiefly for its *anti-inflammatory action in the cure of rheumatoid arthritis.*

Dose : *Usual, adult, oral 3mg 2 times daily.*

B. Aurothioglucose BAN, USAN,

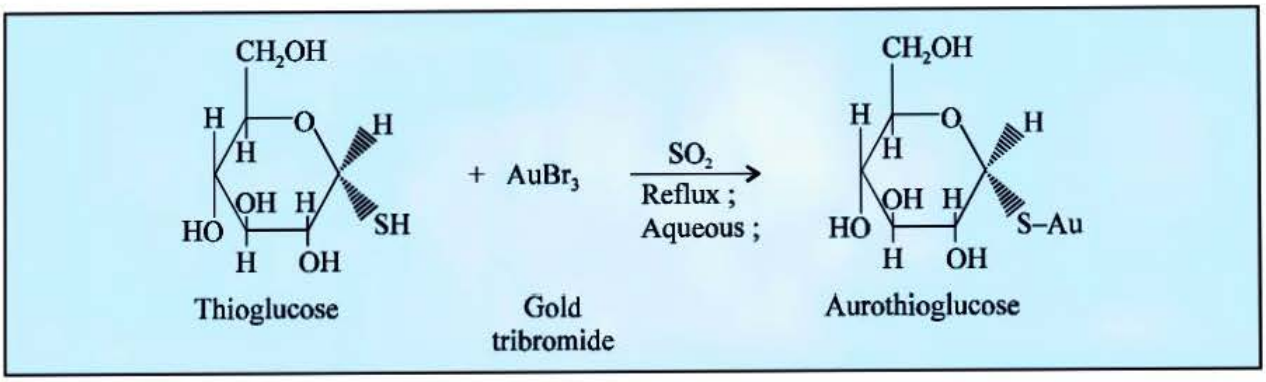


(1-Thio-D-glucopyranosato) gold ; Gold, (1-thio-D-glucopyranosato)- ; Gold Thioglucose ; (D-Glucosylthio) gold ; USP ;

Solganal$^{(R)}$ (Schering-Plough).

Synthesis

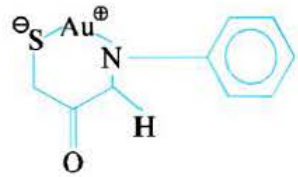
Aurothioglucose is prepared by refluxing together an aqueous solution of thioglucose and gold tribromide in the presence of sulphur dioxide. The resulting compound is precipitated, and is purified by dissolving in water and after which it is reprecipitated by the addition of alcohol.



It is an antirheumatic drug employed for *treatment of active and progressing rheumatoid arthritis and nondisseminated lupus erythematosus. It has been reported that no other antirheumatic drug possesses the capability of arresting the progression of the disease, as gold can do in some cases.*

Dose : *Intramuscular, administration as a suspension in oil for adult in an usual weekly dose of 10mg increasing gradually to 50mg ; children between 6 to 12 years, may be given one quarter the usual dose.*

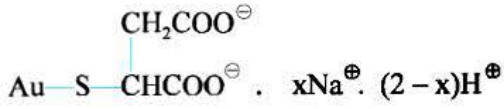
C. Aurothioglucanide INN, BAN, USAN,



S-Gold derivative of 2-mercaptoacetanilide ; α-Auromercaptoacetanilide ; 2-Aurothio-N-phenylacetamide ;

It is used mainly for its *anti-inflammatory effect in the treatment of rheumatoid arthritis.* Being practically insoluble in water it is more gradually released and subsequently absorbed than the other water-soluble gold compounds.

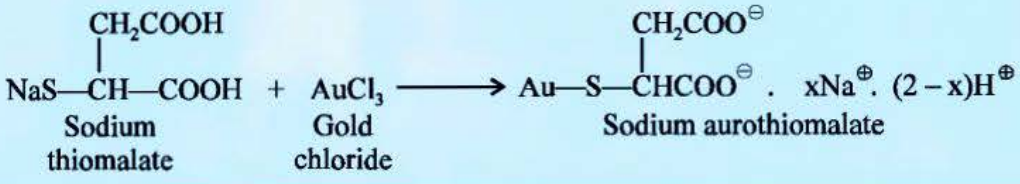
D. Sodium Aurothiomalate INN, BAN, Gold Sodium Thiomalate USAN,



Mercaptosuccinic acid, monogold (1+) sodium salt ; Butanedioic acid, mercapto-, monogold (1+) sodium salt ; (A mixture of the mono- and di-sodium salts of gold thiomalic acid) ; Gold Sodium Thiomalate USP ;

Myochrysine(R) (MSD).

Synthesis



It may be prepared by the interaction of sodium thiomalate with gold chloride.

It possesses anti-inflammatory actions and is used chiefly for the treatment of rheumatoid arthritis. It is extremely *effective in active pregressive rheumatoid arthritis.* It is, however, ineffective against other types of arthritis.

Dose : *Adult, intramuscular, initially, 10mg 1st week, 25mg in second week, 50mg per week for 20 weeks, and for maintenance 50mg every 2 weeks for 4 days.*

2.5.1. Mechanism of Action

The mechanism of action of compounds described under section 16.2.5 shall be dealt within the sections that follows :

2.5.1.1. Auranofin

The value of gold salts in the rheumatoid arthritis is fairly well established ; except for this drug, all available gold preparations should be IM administered. Nearly 25% of the gold content in the *'drug'* gets absorbed. The mean terminal body half-life varies between 21 to 31 days. It has been observed that nearly 60% of the **'absorbed gold'** gets excreted in the urine ; while the remainder is excreted in the faeces.

However, the exact mechanism by which this **'drug'** exhibits its therapeutic effect in rheumatoid arthritis is still not properly understood, although there are ample evidences whereby the *'drug'* does affect a plethora of cellular processes directly linked with inflammation. Importantly, in contrast to the parenteral gold preparations, it is not recognized as a potent inhibitor of sulphydryl moiety reactivity.

2.5.1.2. Aurothioglucose

It is, in fact, well known that once the **'adrenal steroids'** mostly displaced for the *'gold compounds'* from the therapeutic armamentarium for the treatment of active and progressive rheumatoid arthritis and disseminated *lupus erythematosus.* *However, bearing in mind the recognition of the numerous hazardous dangers of **steroid therapy** and the potential curative properties has virtually restored the usage of gold

*A chronic autoimmune inflammatory disease involving multiple organ systems and marked by periods of exacerbation and remission.

compounds. It has been duly demonstrated that no other *'antirheumatic drug'* is as capable of arresting the progression of the disease, as gold compounds can do in certain instances.

The best therapy normally takes place when the **'drug'** is employed almost in the early active stages of the disease, and also it is solely based on the daily excretion rate of gold in an individual patient.

It has been observed that the **'drug'** invariably comprises of 50% gold, time to peak effect is 4-6 hours, almost 95-99% gets bound to plasma protein, plasma half-life after a single dose varies from 3 to 27 days ; and finally about 70% is excreted in the urine and 30% in the faeces.

2.5.1.3. Aurothioglycanide

It is one of the sulphur containing gold compounds with a heterocyclic moiety in which the gold (Au) is imbeded strategically. The **'drug'** gets absorbed *in vivo* rather slowly by virtue of its poor solubility in water.

2.5.1.4. Sodium Aurothiomalate

The **'drug'** gets absorbed rapidly after the intramuscular injection and 85 to 95% becomes bound to plasma proteins. It is widely distributed to body tissues and fluids, including synovial fluid, and hence accumulates in the body. The serum half-life of gold is nearly 5/6 days ; however, it increases after successive doses and after a complete course of treatment, gold may be seen in the urine even upto 1 year or more due to its presence in deep body compartments. It is mainly excreted in the urine, with similar quantum in the faeces.

2.6. Miscellaneous Anti Inflammatory Drugs

There are a number of compounds which incidentally do not fall into any of the categories mentioned so far but they possess anti-inflammatory actions. A few such compounds are described here.

2.6.1. Antimalarial Agents

Chloroquine and **hydroxychloroquine** belonging to the class of **4-amino-quinoline anthmalarials** are being used in clinical practice in the cure and treatment of rheumatoid arthritis since 1957. However, the two important disadvantageous factors, namely : slow onset of therapeutic effect and significant ocular toxicity seemed to have shadowed the clinical supremacy of these drugs.

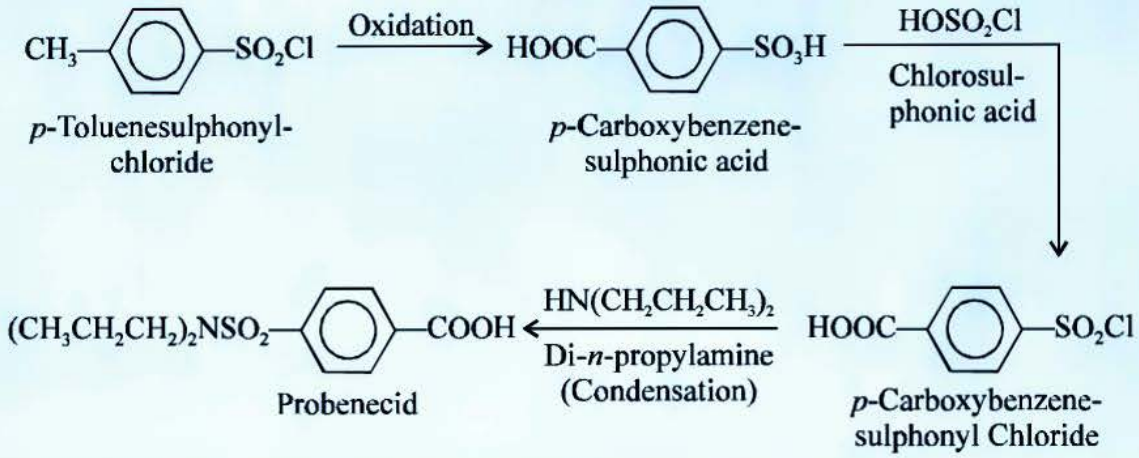
2.6.2. Uricosuric Agents

Such drugs that help in the enhanced excretion of excess uric acid through urination and thus reduce the urea concentration in the plasma are known as **uricosuric agents.** There are two important agents which are frequently used in hyperuricemia *viz.*, **sulfinpurazone** and **probenecid** both of which enhance the level of penicillin in plasma by inhibiting its secretion. The former agent has already been dealt under antipyretic analgesics in pyrazolones and pyrazolodiones ; the latter will be discussed here.

A. Probenecid INN, BAN, USAN,

p-(Dipropyl-sulfamoyl) benzoic acid ; Benzoic acid, 4-[(dipropylamino) sulfonyl]-; BP ; USP ; Int. P., Benemid$^{(R)}$ (MSD) ; SK-Probenecid$^{(R)}$ (SKF).

Synthesis

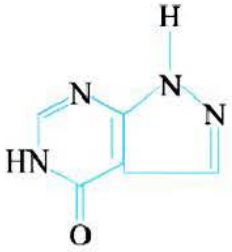


p-Carboxybenzenesulphonic acid is obtained by the oxidation of the methyl group present in *p*-toluenesulphonyl chloride which on further treatment with chlorosulphonic acid yields the corresponding *p*-carboxybenzene sulphonyl chloride. Condensation with di-*n*-propylamine gives rise to the official compound.

Probenecid inhibits renal tubular reabsorption of water and by this mechanism enhances the urinary excretion of uric acid. This lowers the level of urate in the serum. It thus serves as a potent uricosuric agent in the treatment of gout. Probenecid also blocks the renal tubular secretion of penicillins and cephalosporins. It is, therefore, used as *an adjuvant therapy with penicillin V or G, ampicillin, cloxacillin, oxacillin, methicillin and naficillin to increase and prolong their plasma levels.* Besides it also *enhances the plasma levels of anti-inflammatory agents like naproxen and indomethacin,* and a host of medicinal compounds such as sulphonamides, sulphonylureas, dapsone, etc.

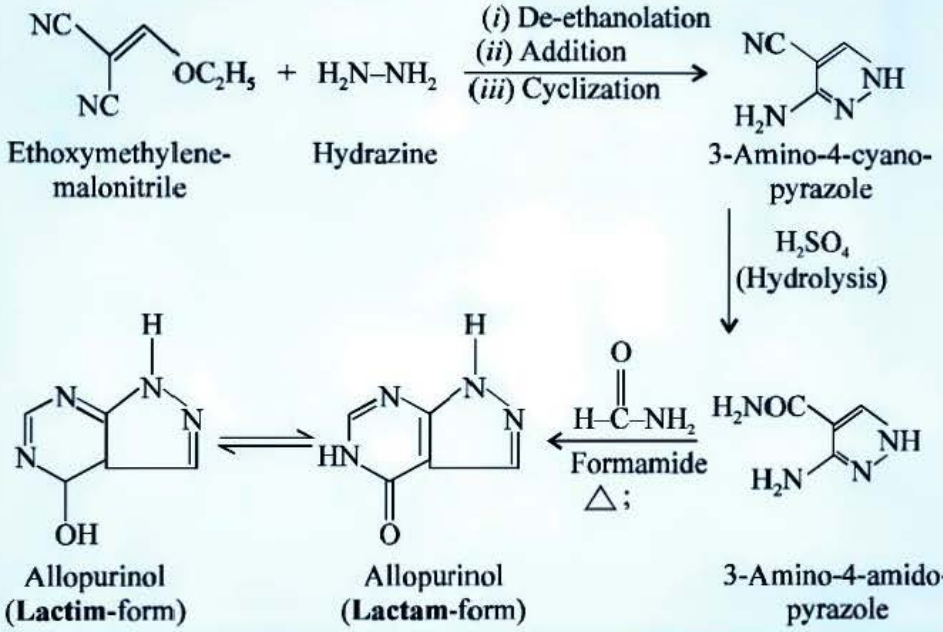
Dose : *Adult, oral, 500 mg to 2 g per day ; usual, 250 mg 2 times daily for one week, then 500 mg twice a day thereafter.*

B. Allopurinol INN, BAN, USAN,



1H-Pyrazolo [3, 4-*d*] purimidin-4-ol ; 1, 5-Dihydro-4H-pyrazolo [3, 4-*d*] pyrimidin-4-one ; BP ; USP ; Zyloprim(R) (Burroughs Wellcome).

Synthesis



Condensation of ethoxymethylenemalonitrile with hydrazine *via* deethylation, addition and cyclization gives rise to 3-amino-4-cyanopyrazole which upon hydrolysis in the presence of sulphuric acid yields 3-amino-4-amino pyrazole. This on heating with formamide inserts the last carbon atom to afford allopurinol which exhibits tautomerism.

It is a structural analogue of hypoxanthine and is classified as xanthine oxidase inhibitor. It is administered for an indefinite duration in the *treatment of chronic gout.* It helps to decrease the concentration of uric acid in plasma by blocking the conversion of hypoxanthine and xanthine to uric acid and by reducing purine synthesis. Thus it *causes gradual resolution of tophi and minimises the risk of the formation of uric acid calculi.*

Dose : *Usual, adult, oral, antigout, 100 to 200mg 2 or 3 times a day.*

C. Piroxicam INN, BAN, USAN,

4-Hydroxy-2-methyl-N-2-pyridyl-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide ; 2H-1, 2-benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1, 1-dioxide ;

Feldene(R) (Pfizer)

It is employed for acute and long-term therapy for the *relief of symptoms of osteoarthritis and rheumatoid arthritis.* It also possesses uricosuric actions and has been used in the *treatment of acute gout.*

Dose : *Usual, adult, oral, 20 mg daily.*

2.6.2.1. Mechanism of Action

The mechanism of action of some of the typical compounds described under. Section 16.2.6.2. are treated in the sections that follows :

2.6.2.1.1. Probenecid

The **'drug'** is found to inhibit its tubular reabsorption of urate at the proximal convoluted tubule, thereby enhancing the urinary excretion of uric acid and mimising serum uric acid levels. Interestingly, with respect to the **'outward renal transport phenomenon'** the *'drug'* blocks the secretion of weak organic acids at the proximal as well as distal tubules. Therefore, it is overwhelmingly effective and useful as an **'adjuvant therapy'** with such drugs as : pencillin G, O, or V, or with ampicillin, methicillin, oxacillin, cloxacillin, or naficillin for the distinctive elevation as well as prolongation of penicillin plasma levels by whatever route the antibiotic is actually administered.

The **'drug'** get absorbed rather rapidly and completely after an oral administration. It has been observed that plasma levels of 100 to 200 mcg. mL^{-1} are almost necessary for an adequate and sufficient uricosuric effect ; whereas, an equivalent plasma levels of 40-60 mcg. mL^{-1} produce maximal inhibition of the pencillin excretion. The plasma half-life varies from 4 to 17 hour. However, at a plasma concentration of 14 mcg. mL^{-1}, about 17% of the drug invariably gets bound to the plasma protein.

SAR of Probenecid. In this **'drug'** the presence of its electron withdrawing carboxy and sulphonamido-moieties, has not been reported to undergo any aromatic hydroxylation, which explains its fast absorption after an oral administration.

2.6.2.1.2. Allopurinol

It has been observed that the **'drug'** is not uricosuric, but it does inhibit the production of uric acid by way of blocking categorically the biochemical reactions that are essentially involved immediately preceding uric acid formation. Hence, it also inhibits **xanthine oxidase** (enzyme), which is exclusively responsible for the conversion of hypoxanthine to xanthine and of xanthine ultimately to uric acid.

Besides, **allopurinol**, inhibits *de novo* purine synthesis *via* a feedback mechanism, that specifically provides another benefit to the subject. It is found to get metabolized by xananthine oxidase to *oxypurinol,* that also invariably inhibits xanthine oxidase. However, **oxypurinol** possesses a much longer half-clearance time from plasma than allopurinol.

2.6.2.1.3. Piroxicam

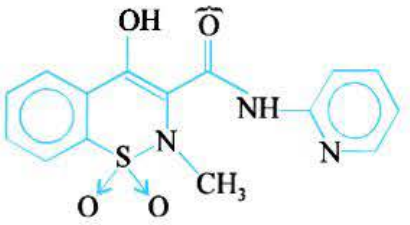
The **'drug'** represents a class of *acidic inhibitors* of **prostaglandin (PG) synthesis**, although it fails to antagonize PGE_2 directly.* It is found to be exerting a rather long duration of action having a plasma half-life of 38 hour, which remarkably pegs a dosage of only 20 to 30mg once daily. Besides, its overall pharmacologic activity has been determined to be almost equivalent to either 400mg of *ibuprofen* or 25mg of **indomethacin** 3-times daily.**

Like other **NSAIDs**, the *'drug'* inhibits **prostaglandin (PG) synthesis** chemotaxis and the release of liposomal enzymes (from liver). It has been observed duly that a chronic administration with 20mg per day causes steady state plasma levels of 3-5 mcg. mL^{-1} within a span of 7 to 12 days. The volume of

*Wiseman EH : *R Soc Med Int Congr Ser,* **1,** 11, 1978.

Balogh Z *et al. Curr Med Res Opin,* **6, 148, 1979.

distribution is found to be 0.12–0.14 $L.kg^{-1}$; mean half life is ~ 50 hour (range, 30-86 hour). It gets metabolized mostly *via* hydroxylation and excreted in the urine ultimately.



Piroxicam
(*keto*-form)

Piroxicam
(*enol*-form) **(Acidic)**

2.7 Salicylic Acid Analogues

A good number of **salicylic acid analogues** have also been found to possess anti-inflammatory actions, *e.g.*, **aspirin**, **salol**, **salsalate**, **sodium salicylate**, **salicylamide**, **benorilate**, **choline salicylate**, **flufenisal** etc., in addition to their antipyretic analgesic property. These compounds have been individually treated in Chapter 9.

2.8 Pyrazolones and Pyrazolodiones

Drugs like **phenazone**, **aminophenazone (aminopyrine)**, **dipyrone**, **phenylbutazone**, **oxyphenbutazone**, **sulfinpyrazone**, etc., belonging to this category, besides their antipyretic-analgesic action, have also been reported to exhibit anti-inflammatory properties. These compounds have been dealt separately in the chapter on '**antipyretic-analgesics**'.

Probable Questions for B. Pharm. Examinations

1. What are the advantages of NSAID(s) over the steroidal drugs used as anti-inflammatory drugs ? Support your answer with the suitable examples.
2. Classify NSAID based on their chemical structures. Give examples of **one** potent drug from each category.
3. Indomethacin and Tolmetin Sodium are two typical examples of heteroarylacetin acid analogue of NSAID. Give the synthesis of one of them while differentiating their chemical structures.
4. Give the structure, chemical name and uses of **three** important members of arylacetic acid analogues employed as NSAID. Discuss the synthesis of any **one** drug selected by you.
5. 'The arylpropionic acid analogue also exhibits potent anti-inflammatory properties besides analogesic and antipyretic activities'. Justify the statement with suitable examples of NSAID.
6. Naproxen derived from **naphthalene acetic acid analogue** proved to be the leading compound of an extensive series of promising clinical agents. Describe its synthesis from 6-methoxy naphthalene.
7. Discuss the monovalent gold compounds as NSAID. Give the synthesis of **auranotin** and **aurothioglucose** along with their usage.
8. Give the structure, chemical name and uses of the following uricosuric agents :

   (*a*) Allopurinol (*b*) Probenecid (*c*) Piroxicam

   Describe the synthesis of any **one** drug.