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Review Article

PHARMACOKINETIC SOLUBILITY AND DISSOLUTION PROFILE OF NON-STERIODAL ANTI-INFLAMATORY DRUGS

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Abstract

Pharmacokinetic data And Solubility Profile Of drugs are the basic requirement of any researcher, for selecting an appropriate drug for any kind of formulation development. To get such data of all drugs of any category at one place is very difficult task; we by our review article have tried to give all such data of NSAIDS drugs at one place.

Keywords: - : Solubility profile, pharmacokinetic parameters.Non-steriodal anti-inflamatory

Introduction

Classification:- [1]

A).Non –Selective cox inhibitor: -

Salicylates: - Aspirin.

Propionic acid derivative: - Ibuprofen, Naproxen, Ketoprofen, Flubiprofen.

Antranillic acid derivative: - Mephanimic acid.

Arylic-acetic acid dreivative: - Diclofenac, Acelofenac.

Oxicam derivative: - Piroxicam, Tenoxicam.

Pyrolle-pyrole derivative: - Ketorolac.

Indole derivative: - Indomethacin.

Pyrazolone-derivative:- Phenyl butazone, oxyphen butazone.

B).Preferential cox-2 inhibitors: - Nimesulide, Meloxicam, Nabumetone.

C).Selective Cox2 Inhibitors: - Celecoxib, Etoricoxib, Parecoxib.

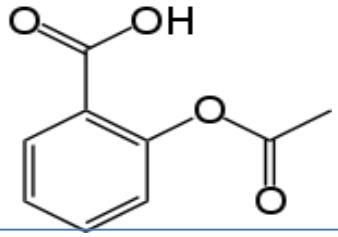
D).Analgesic-Antipyretic,with Anti-inflammatory action: -

Paraaminophenol derivative: - Paracetamol.

Pyrazolone derivative:- Metamizol, Propio phenazone.

Benzoxazocine derivative: - Nefopam.

Aspirin[2]



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Systematic (IUPAC) name: - 2-acetoxybenzoic acid.

Chemical data

Formula: - $C_9H_8O_4$

Mol. Mass: -180.157 g/mol

Physical data

Melt. Point: - 135 °C (275 °F)

Boiling point: -140 °C (284 °F) (decomposes)

Mechanism of action: -

There are at least two different types of cyclooxygenase: PTGS1 and PTGS2. Aspirin irreversibly inhibits PTGS1 and modifies the enzymatic activity of PTGS2. Normally, PTGS2 produces prostanoids, most of which are proinflammatory. Aspirin-modified PTGS2 produces lipoxins, most of which are anti-inflammatory. Newer NSAID drugs, COX 2 inhibitors, have been developed to inhibit only PTGS2, with the intent to reduce the incidence of gastrointestinal side effects.

However, several of the new COX 2 inhibitors, such as rofecoxib (Vioxx), have been withdrawn recently, after evidence emerged that PTGS2 inhibitors increase the risk of heart attack. Endothelial cells lining the microvasculature in the body are proposed to express PTGS2, and, by selectively inhibiting PTGS2, prostaglandin production (specifically PGI2; prostacyclin) is downregulated with respect to thromboxane levels, as PTGS1 in platelets is unaffected. Thus, the protective anticoagulative effect of PGI2 is removed, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new PTGS once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

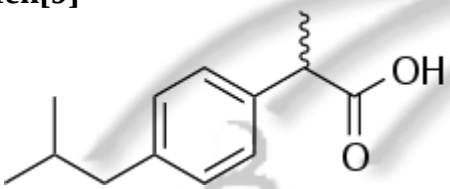
Description: - White cystals, commonly tubular or needle like or white crystalline powder. Is orderless or has a faint order. Is stable in dry air, in moist air it gradually hydrolyse to salicylic acid and acrtic acid.

Solubility Profile: - Slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether, sparingly soluble in absolute ether**.[USP][3]**

Solubility Profile: - Freely soluble in ethanol, soluble in chloroform and in ether, slightly soluble in water.**[IP][4]**

Pharmacokinetic data
Bioavailability: - Rapidly and completely absorbed
Protein binding: - 99.6%
Metabolism: - Hepatic
Half-life: -300–650 mg dose: 3.1–3.2 h,1 g dose: 5 h,2 g dose: 9 h
Excretion: -Renal
Nature: - Hydrophillic**.[5]**
Pka: - 4.5**.[6]**
Log p: - 1.19**.[7]**
Dissolution:- Aspirin Extended Release Tablet
Medium: - 0.1 N hydrochloric acid(2 in 100),1000ml
Apparatus: - 2[USP]
Rpm: - 60 rpm
Time: - 1 to 4 hours**.[8]**

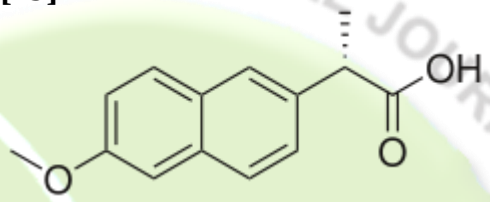
Ibuprofen[9]



Systematic (IUPAC) name: -(*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid.
Chemical data
Formula: - $C_{13}H_{18}O_2$
Mol. Mass: - 206.29 g/mol.
Physical Data
Boiling point: - 157 ºC (4 mmHg)**.[10]**
Melting Point: - 75 – 78**.[11]**
Mechanism of action: - The exact mechanism of action of ibuprofen is unknown. Ibuprofen is a non-selective inhibitor of cyclooxygenase, an enzyme invovled in prostaglandin synthesis via the arachidonic acid pathway. Its pharmacological effects are believed to be due to inhibition cylooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Inhibition of COX-1 is thought to cause some of the side effects of ibuprofen including GI ulceration. Ibuprofen is administered as a racemic mixture. The R-enantiomer undergoes extensive interconversion to the S-enantiomer *in vivo*. The S-enantiomer is believed to be the more pharmacologically active enantiomer**.[12]**
Description:- White to off white crystalline powder. Having a slight chacterstic odor**.[USP][13]**
Solubility profile: - Practically insoluble in water, very soluble in alcohol, in methanol, in acetone and in chloroform. Slightly soluble in ethylacetate**.[USP][13]**
Solubilty Profile: - Freely soluble in acetone, in chloroform, in ethanol(95 percent) and in ether. Practically insoluble in water.it dissolves in dilute solutions of alkali hydroxides and carbonates**.[IP][14]**

Pharmacokinetic data
Bioavailability: -49–73%
Protein binding: -99%
Metabolism: - Hepatic (CYP2C9)
Half-life: -1.8–2 h
Excretion: -Renal
Nature: - Hydrophobic**.[15]**
Pka: - 5.2**.[16]**
Log p: - 5.63**.[17]**
Dissolution:- Ibuprofen Tablet
Medium: - Ph 7.2 phosphate buffer.900 ml.
Apparatus: - 2[USP]
Rpm: - 50 rpm
Time: - 60 minutes**.[18]**

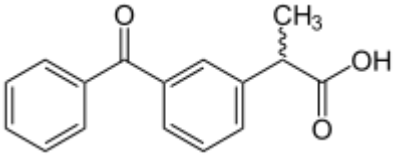
Naproxen[19]



Systematic (IUPAC) name: - (+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid.
Chemical data
Formula: - $C_{14}H_{14}O_3$
Mol. Mass: - 230.259 g/mol
Physical Data
Melting Point: - 157 - 158 C**.[20]**
Boiling Point:- 403.9°Cat760mmHg**.[21]**
Mechanism of action: - The mechanism of action of naproxen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity**.[22]**
Description: - White to off white, practically odorless, crystalline powder**.[USP][23]**
Solubility Profile: - Soluble in chloroform, in dehydrated alcohol and in alcohol.sparingly soluble in ether, practically insoluble in water**.[USP][23]**
Pharmacokinetic data
Bioavailability: -95% (oral)
Protein binding: - 99%
Metabolism: - Hepatic (to 6-desmethylnaproxen)
Half-life: -12–24 hours
Excretion: -Renal
Nature: - Hydrophillic**.[24]**
Log p: - 3.22**.[25]**
Pka: - 4.8**.[26]**
Dissolution:- Naproxen Tablet
Medium: - 0.1M Ph 7.2 phosphate buffer.900 ml.
Apparatus: - 2[USP]

Rpm: - 50 rpm
Time: - 45 minutes**.[27]**

Ketoprofen.[28]



Systematic (IUPAC) name: - (RS)-2-(3-benzoylphenyl)propanoic acid.

Chemical data: -
Formula: -$C_{16}H_{14}O_3$
Mol. Mass: - 254.281 g/mol.

Physical Data: -
Boiling Point: -431.3 °C at 760 mmHg.**[29]**
Melting Point: - 94 - 97 C**.[30]**

Mechanism of action: -The anti-inflammatory effects of ketoprofen are believed to be due to inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Ketoprofen is a non-specific cyclooxygenase inhibitor and inhibition of COX-1 is thought to confer some of its side effects, such as GI upset and ulceration. Ketoprofen is thought to have anti-bradykinin activity, as well as lysosomal membrane-stabilizing action. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation**.[31]**

Solubility Profile:- Freely soluble in ethanol, in chloroform and in ether, practically insoluble in water**.[IP][32]**

Pharmacokinetic data
Protein binding: -99%
Half-life: -2-2.5 hours

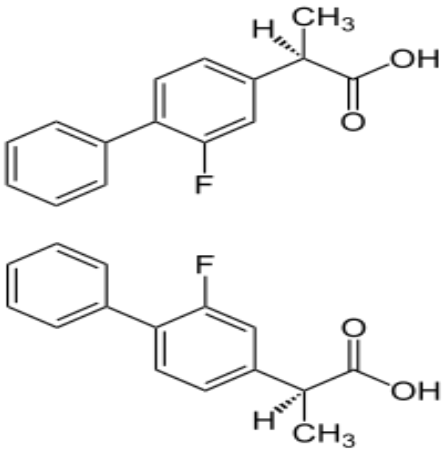
Metabolism: -Rapidly and extensively metabolized in the liver, primarily via conjugation to glucuronic acid. No active metabolites have been identified.

Route of elimination: -In a 24 hour period, approximately 80% of an administered dose of ketoprofen is excreted in the urine, primarily as the glucuronide metabolite.

Absorption: -Ketoprofen is rapidly and well-absorbed orally, with peak plasma levels occurring within 0.5 to 2 hours.

Nature: - Hydrophillic**.[33]**
pKa: -5.94**.[34]**
Log p: -0.97**.[35]**
Dissolution: - Not Available.

Flubiprofen.[36]



Systematic (IUPAC) name: -(*RS*)-2-(2-fluorobiphenyl-4-yl)propanoic acid.

Chemical data: -
Formula:- $C_{15}H_{13}FO_2$
Mol. mass: -244.261 g/mol.

Physical Data: -
Boiling Point: -424.3 °C at 760 mmHg**.[37]**
Melting Point: - 114 - 117 C**.[38]**

Mechanism of action: - Similar to other NSAIAs, the anti-inflammatory effect of flurbiprofen occurs via reversible inhibition of cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin synthesis pathway. This effectively decreases the concentration of prostaglandins involved in inflammation, pain, swelling and fever. Flurbiprofen is a non-selective COX inhibitor and inhibits the activity of both COX-1 and -2. It is also one of the most potent NSAIAs in terms of prostaglandin inhibitory activity**.[39]**

Description: - White crstalline powder**.[40][USP]**

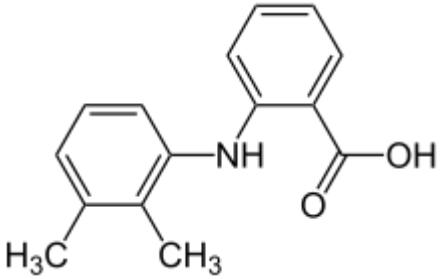
Solubility profile: - Freely soluble in acetone, in dehydrated alcohol, in ether and in methanol, soluble in acetonitrile, practically insoluble in water, optically inactive 50 solution in dehydrated alcohol**.[USP]**

Solubility profile: - Freely soluble in ethanol, in chloroform and in ether, practically insoluble in water. It dissolves in aqueous solution of alkali hydroxides and carbonates**.[IP][41]**

Pharmacokinetic data
Protein binding: - > 99%
Metabolism: -Hepatic (CYP2C9)
Half-life: -4.7-5.7 hours
Excretion: -Renal
Nature: - Hydrophillic**.[42]**
pKa: - 4.2**.[43]**
Log p: - 4.16**.[44]**

Dissolution:- Fluribiprofen Tablet.
Medium: - Ph 7.2 phosphate buffer.900 ml.
Apparatus: - 2[USP]
Rpm: - 50 rpm
Time: - 45 minutes**.[45]**

Mephanimic acid.[46]



Systematic (IUPAC) name: - 2-(2,3-dimethylphenyl)aminobenzoic acid.

Chemical data

Formula: - $C_{15}H_{15}NO_2$

Mol. mass: - 241.285 g/mol

Physical Data

Melting point: - 230°-231°C**.[47]**

Boiling Point: -398.8 °C at 760 mmHg**.[48]**

Mechanism of action:- Mefenamic acid binds the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. As these receptors have a role as a major mediator of inflammation and/or a role for prostanoid signaling in activity-dependent plasticity, the symptoms of pain are temporarily reduced**.[49]**

Description: - White to off white crystalline powder. Melt at about 230 degree with decomposition**.[USP][50]**

Solubility Profile: - Soluble in solution of alkali hydroxides, sparingly soluble in chloroform, slightly soluble in alcohol and in methanol, practically insoluble in water**.[USP][50]**

Pharmacokinetic data

Bioavailability: -90%

Protein binding: - 90%

Metabolism : - Hepatic: - (CYP2C9)

Half-life: - 2 hours

Excretion: - Renal and fecal

Nature: - Hydrophillic**.[51]**

pKa: - 4.2**.[52]**

log P: - 3.31**.[53]**

Dissolution:- Mefanimic acid capsule.[54]

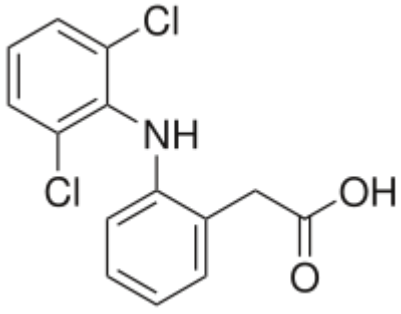
Medium: - 0.05 M Tris Buffer..900 ml.

Apparatus: - 1[USP]

Rpm: - 100 rpm

Time: - 45 minutes**.**

Diclofenac.[55]



Systematic (IUPAC) name: - 2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid

Chemical data: -

Formula: -$C_{14}H_{11}Cl_2NO_2$

Mol. mass: -296.148 g/mol.

Physical Data: -

Boiling Point: -412 °C at 760 mmHg**.[56]**

Melting Point: -284°C (543.2°F)**.[57]**

Mechanism of action: -The antiinflammatory effects of diclofenac are believed to be due to inhibition of both leukocyte migration and the enzyme cylooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis is responsible for the analgesic effects of diclofenac. Antipyretic effects may be due to action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat dissipation**.[58]**

Description: - White to off white, hygroscopic, crystalline powder, melt at about 284 degree**.[USP][59]**

Solubility Profile: - Freely soluble in methanol, soluble in ethanol, sparingly soluble in water, practically insoluble in chloroform and in ether**.[USP]**

Solubility Profile: - Freely soluble in methanol, soluble in methanol, sparingly soluble in water and in glacial acetic acid, practically insoluble in ether, in chloroform and in toluene**.[IP][60]**

Pharmacokinetic data

Protein binding: - more than 99%

Metabolism: - hepatic, no active metabolites exist

Half-life: - 1.2-2 hr (35% of the drug enters enterohepatic recirculation)

Excretion: - biliary, only 1% in urine

Nature: - Hydrophobic**.[61]**

Pka:- 4**.[62]**

Log p: - 4.75**.[63]**

Dissolution:- Diclofenac Sodium extended release Tablet.[64]

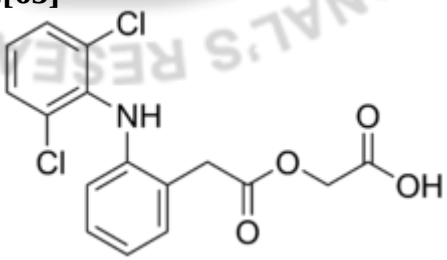
Medium: - 0.05 M Phosphate buffer,900 ml.

Apparatus: - 1[USP]

Rpm: - 100 rpm

Time: - 45 minutes**.**

Acelofenac.[65]



Systematic (IUPAC) name: - 2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid

Chemical data

Formula: - $C_{16}H_{13}Cl_2NO_4$

Mol. mass: - 354.18472 g/mol.

Physical Data: -

Boiling Point(℃):- 486°C at 760**.[66]**

Melting point: - 149-153 ºC.**[67]**

Mode of action: - Aceclofenac is a potent inhibitor of cyclooxygenase. Inhibition of COX leads to suppression of pro inflammatory **prostaglandins** & **cytokines**. Thus, it acts as **analgesic** & **antipyretic** by central as well peripheral action.**[68]**

Solubility Profile: - Practically insoluble in water, freely soluble in acetone, soluble in ethanol.**[IP][69]**

Pharamacokinetic Data: -

half-life: - 2–4 h.**[70]**

protein bindi*ng*: - 40%.**[71]**

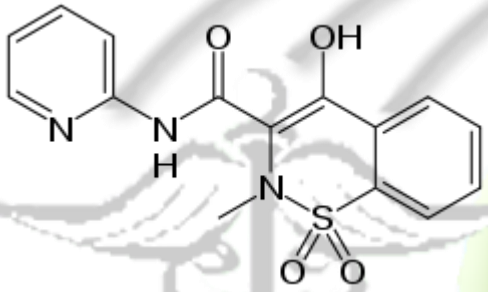
Nature: - Hydrophobic.**[72]**

pKa = 4.7.**[73]**

log P: - 0.22.**[74]**

Dissolution:- Not available.

Piroxicam.[75]



Systematic (IUPAC) name: - (8*E*)-8-[hydroxy-(pyridin-2-ylamino)methylidene]-9-methyl-10,10-dioxo-10λ^6-thia-9-azabicyclo[4.4.0]deca-1,3,5-trien-7-one.

Chemical data

Formula: -$C_{15}H_{13}N_3O_4S$

Mol. Mass: -331.348 g/mol.

Physical Data

Boiling Point: - 512.9 °C at 760 mmHg.**[76]**

Melting Point: - 240 - 245 C.**[77]**

Mechanism of action: - The antiinflammatory effect of Piroxicam may result from the reversible inhibition of cyclooxygenase, causing the peripheral inhibition of prostaglandin synthesis. The prostaglandins are produced by an enzyme called Cox-1. Piroxicam blocks the Cox-1 enzyme, resulting into the disruption of production of prostaglandins. Piroxicam also inhibits the migration of leukocytes into sites of inflammation and prevents the formation of thromboxane A2, an aggregating agent, by the platelets.**[78]**

Descriotion: - off white to light tan or light yellow, odorless powder. Forms a monohydrate that is yellow.**[USP][79]**

Solubility: - very slightly soluble in water, in diliute acids, and in most organic solvents. Slightly soluble in alcohol and in aqueous alkaline solutions.**[USP][79]**

Solubility: - Slightly soluble in ethanol and in aqueous alkaline solutions. Very slightly soluble in aqueous alkaline solutions. Very slightly soluble in water, in dilute acids and in mostly organic solvents.**[IP][80]**

Pharmacokinetic data

Metabolism: - 4 to 10% renal

Half-life: - 30 to 86 hours

Excretion: - 4 to 10% renal

Nature: - Hydrophobic.**[81]**

Log P: - 1.8.**[82]**

pKa1: - 1.86.**[83]**

Dissolution:- Piroxicam capsule.[84]

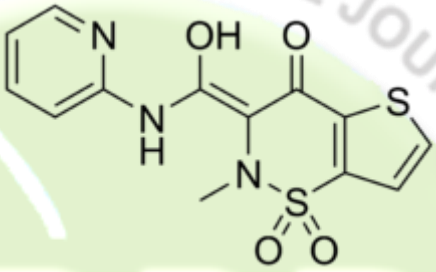
Medium: -Simulated gastric fluid, prepared with pepsin.900ml.

Apparatus: - 1[USP]

Rpm: - 50 rpm

Time: - 45 minutes.

Tenoxicam.[85]



Systematic (IUPAC) name: - (3*E*)-3-[hydroxy(pyridin-2-ylamino)methylene] -2-methyl-2,3-dihydro-4*H*-thieno[2,3-*e*] [1,2]thiazin-4-one 1,1-dioxide.

Chemical data

Formula: - $C_{13}H_{11}N_3O_4S_2$

Mol. mass: - 337.376 g/mol

Physical Data: -

Boiling Point:-524.1 °C at 760 mmHg.**[86]**

Melting Point: - 209-2130 °C.**[87]**

Mechanism of action: - The antiinflammatory effects of tenoxicam may result from the inhibition of the enzyme cycooxygenase and the subsequent peripheral inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, their inhibition accounts for the peripheral analgesic effects of tenoxicam. Antipyresis may occur by central action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat loss.**[88]**

Description: - Pale yellow crystalline powder.**[89]**

Solubility Profile: - very slightly soluble in *water* (0.01 g/. 100 ml).**[90]**

Pharmacokinetic data

Protein binding: - High

Half-life: - 30–140hours

Eliminated: - liver metabolism.**[91]**

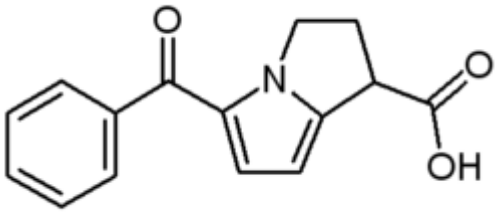
Nature: - Hydrophobic.**[92]**

logP: - 1.82.**[88]**

***pKa*: -** 5.3.**[93]**

Disollution Profile: - Not available.

Ketorolac.[94]



Systematic (IUPAC) name: - (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid,2-amino-2-(hydroxymethyl)-1,3-propanediol.

Chemical data

Formula: - $C_{15}H_{13}NO_3$

Mol. Mass: - 255.27 g/mol.

Physical Data

Boiling Point: - 223.7 °C at 760 mmHg**.[95]**

Melting Point: - 162°C**.[96]**

Mechanism of action: - Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) chemically related to indomethacin and tolmetin. Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity. Its antiinflammatory effects are believed to be due to inhibition of both cylooxygenase-1 (COX-1) and cylooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis leading to decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid. The resultant reduction in prostaglandin synthesis and activity may be at least partially responsible for many of the adverse, as well as the therapeutic, effects of these medications. Analgesia is probably produced via a peripheral action in which blockade of pain impulse generation results from decreased prostaglandin activity. However, inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation may also contribute to the analgesic effect. In terms of the ophthalmic applications of ketorolac - ocular administration of ketorolac reduces prostaglandin E2 levels in aqueous humor, secondary to inhibition of prostaglandin biosynthesis**.[97]**

Description: - white to off white crystalline powder, melt between 165 to 170 degree with decomposition**.[USP][98]**

Solubility: - Freely soluble in water and in methanol, slightly soluble in alcohol, in dehydrated alcohol and in tetrahydrofuran, practically insoluble in acetone, in dichloromethane, in toluene, in ethyl acetate , in dioxane, in hexane ,in butyl alcohol and in acetonitrile**.[USP][98]**

Pharmacokinetic data

Bioavailability: - 100% (All routes)

Metabolism: - Hepatic

Half-life: - 3.5-9.2 hrs, young adults: - 4.7-8.6 hrs, elderly (mean age 72)

Excretion: - Renal:91.4% (mean)Biliary:6.1% (mean)

Nature: - hydrophilic**.[99]**

logP: - 0.9**.[100]**

Dissolution:- Ketorolac Tromethamine tablet.[101]

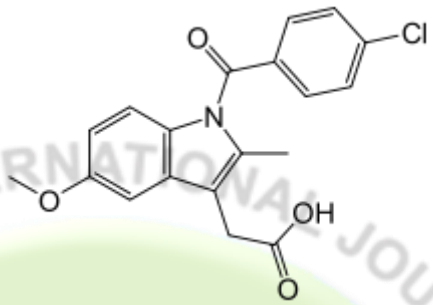
Medium: -water, 600ml.

Apparatus: - 2[USP]

Rpm: - 50 rpm

Time: - 45 minutes.

Indometacin.[102]



Systematic (IUPAC) name: - 2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

Chemical data

Formula: - $C_{19}H_{16}ClNO_4$

Mol. mass: - 357.787 g.mol.

Physical Data

Boiling point: - 189 °C**.[103]**

Melting point: - 155 - 161 C**.[104]**

Mechanism of action: - Indomethacin is a prostaglandin G/H synthase (also known as cyclooxygenase or COX) inhibitor that acts on both prostaglandin G/H synthase 1 and 2 (COX-1 and -2). Prostaglandin G/H synthase catalyzes the conversion of arachidonic acid to a number of prostaglandins involved in fever, pain, swelling, inflammation, and platelet aggregation. Indomethacin antagonizes COX by binding to the upper portion of the active site, preventing its substrate, arachidonic acid, from entering the active site. Indomethacin, unlike other NSAIDs, also inhibits phospholipase A2, the enzyme responsible for releasing arachidonic acid from phospholipids. Indomethacin is more selective for COX-1 than COX-2, which accounts for its increased adverse gastric effects relative to other NSAIDs. COX-1 is required for maintaining the protective gastric mucosal layer. The analgesic, antipyretic and anti-inflammatory effects of indomethacin occur as a result of decreased prostaglandin synthesis. Its antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation**.[105]**

Description: - pale yellow to yellow tan, crystalline powder, having not more than a slight odor, is sensitive to light. Melt at about 162 degree**.[USP][106]**

Solubility: - Practically insoluble in water, sparingly soluble in alcohol, in chloroform, in ether**.[USP][106]**

Solubility: - Soluble in chloroform, sparingly soluble in ethanol and in ether, practically insoluble in water**.[IP][107]**

Pharmacokinetic data

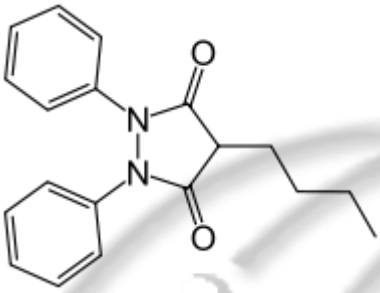
Bioavailability: - 100% (oral), 80–90% (rectal)

Protein binding: - 99%

Metabolism: - Hepatic

Half-life: - 4.5 hours
Excretion: - Renal 60%, faecal 33%.
Nature: - Hydrophobic**.[108]**
Log P: - 3.8. **[109]**
pKa*:* - 4.5**.[110]**
Dissolution:- Indometacin capsile.[111]
Medium: -valume of 2 ph 7.2 phosphate buffer, 750ml.
Apparatus: - 1[USP]
Rpm: - 100 rpm
Time: - 20 minutes.

Phenylbutazone.[112]



Systematic (IUPAC) name: - 4-butyl-1,2-diphenyl-pyrazolidine-3,5-dione.

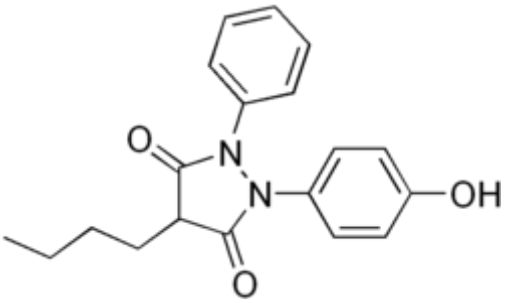
Chemical data

Formula: - $C_{19}H_{20}N_2O_2$
Mol. mass: - 308.374 g/mol.

Physical Data

Boiling point: - 401.7°C at 760 mmHg**.[113]**
Melting Point: - 105°C (221°F)**.[114]**
Mechanism of action: - Phenylbutazone binds to and inactivates prostaglandin H synthase and prostacyclin synthase through peroxide (H2O2) mediated deactivation. The reduced production of prostaglandin leads to reduced inflammation of the surrounding tissues**.[115]**
Description: - White to off white, odorless, crystalline powder**.[USP][116]**
Solubility: - Very slightly soluble in water, freely soluble in acetone and in ether, soluble in alcohol**.[USP]**
Solubility:- Freely soluble in chloroform and in acetone. Soluble in ether, sparingly soluble in ethanol. Practically insoluble in water.it dissolves in solutions of alkali hydroxides**.[IP][117]**
Pharmacokinetic Parameters: -
Half life: - 1.5 to 6 days**.[118]**
Protein binding: - 0-26 mM in order**.[119]**
Elimination: - Liver**.[120]**
Metabolism: - 5% in male rats free feeded**.[121]**
Nature: - Hydrophobic**.[122]**
Pka: - 4.43**.[123]**
LogP: - 3.63**.[124]**
Dissolution:- Indometacin capsile.[125]
Medium: -ph 7.5 simulated intestinal fluidt.TS 900ml.
Apparatus: - 1[USP]
Rpm: - 100 rpm
Time: - 30minutes.

Oxyphenbutazone.[126]



Systematic (IUPAC) name: - (*RS*)-4-butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione

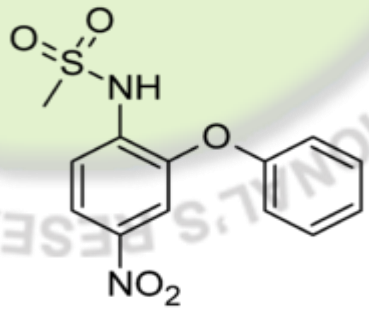
Chemical data

Formula: -$C_{19}H_{20}N_2O_3$
Mol. Mass: - 324.379 g/mol

Physical Data

Boiling point: - 485.6 °C at 760 mmHg**.[127]**
Melting point: - mp 96**.[128]**
Description: - A white crystalline powder**.[129]**
Solubility Profile:- Freely soluble in ethanol, soluble in acetone, in chloroform and in ether, practically insoluble in water. It dissolve in dilute solution of alkali hydroxides**.[130]**
Mechanism of action: - The proposed mechanism of action is by the inhibition of cyclooxygenase, thereby reducing prostaglandin synthesis**.[131]**
Pharamacokinetic Data: -
Half life: - 23.9 +/- 2.09 hours**.[132]**
Protein Binding: - About 99%**.[133]**
Metabolism: - liver**.[134]**
Nature: - Less hydrophobic**.[135]**
pKa: - 9.29**.[136]**
Log P: - 2.5**.[136]**
Dissolution Profile: - Not available.

Nimesulide.[137]



Systematic (IUPAC) name: - *N*-(4-Nitro-2-phenoxyphenyl)methanesulfonamide.

Chemical data

Formula: - $C_{13}H_{12}N_2O_5S$
Mol. Mass: - 308.311 g/mol.

Physical Data

Boiling Point: - 442 °C at 760 mmHg**.[138]**
Melting Point: - 143 – 144**.[139]**
Mechanism of Action: - Nimesulide is a sulfonanilide non-steroidal anti-inflammatory drug whose anti-inflammatory analgesic and antipyretic activities have been demonstrated in

several widely used animal experimental models2. At the recommended dose of 200 mg per day, it is as effective as an analgesic and anti-inflammatory agent as classical NSAIDs, and a well-tolerated drug with fewer side effects as evidenced by a number of controlled and un-controlled comparative trials3. Nimesulide is a unique NSAID, not only due to its chemical structure but also because of its specific affinity to inhibit Cyclooxygenase_2, thus exerting milder effects on the gastrointestinal mucosa. Nimesulide is the only NSAID able to affect all the mediators of pain and inflammation. Nimesulide inhibits COX-1 to some extent, leading to better treatment of inflammatory pain. Nimesulide also reduces pain at central level through a spinalsupraspinal mechanism. Moreover, Nimesulide also has a potent and long lasting anti-pyretic affect**.[140]**

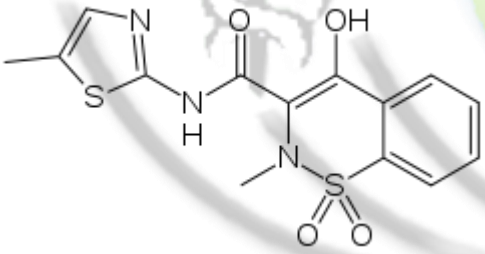
Description: - Nimesulide is a yellowish crystalline powder**.[140]**

Solubility Profile: - It is practically insoluble in water, freely soluble in acetone and slightly soluble in ethanol**.[140]**

Pharmacokinetic data

Protein binding : - >97.5%
Metabolism: - Hepatic
Half-life: - 1.8–4.7h
Excretion: - Renal (50%), fecal (29%)
Nature: - Hydrophobic**.[141]**
pKa: - 6.5**.[142]**
logP: - 2.56**.[143]**
Dissolution Profile: - Not Available.

Meloxicam.[144]



Systematic (IUPAC) name: - 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.

Chemical data

Formula: - $C_{14}H_{13}N_3O_4S_2$
Mol. Mass: - 351.403 g/mol.

Physical Data

Boiling Point: - 1253.5°Cat760mmHg**.[145]**
Melting Point: - 242 - 250 C**.[146]**

Mechanism of action: - Anti-inflammatory effects of meloxicam are believed to be due to inhibition of prostaglandin synthetase (cylooxygenase), leading to the inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis may be associated with the analgesic and antipyretic effects of meloxicam**.[147]**

Description: - It is a pastel yellow powder**.[148]**

Solubility profile: - Practically insoluble in *water*, with higher *solubility* observed in strong acids and bases**.[149]**

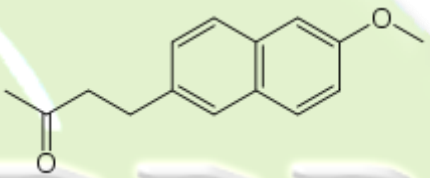
Pharmacokinetic data

Bioavailability: - 89%
Protein binding: - 99.4%
Metabolism: - Hepatic (CYP2C9 and 3A4-mediated)
Half-life: - 15 to 20 hours
Excretion: - Urine and faeces equally
Nature: - Hdrophobic**.[150]**
pKa: - 1.1 and 4.2**.[151]**
(*log P*)app: -0.1 in n-octanol/buffer pH 7.4**.[152]**

Dissolution:- Meloxicam Tablet.[153]

Medium: -phosphate Buffer 7.5,900ml
Apparatus: - 2
Rpm: - 25 rpm
Time: - 30minutes.

Nabumetone.[154]



Systematic (IUPAC) name: - 4-(6-methoxy-2-naphthyl)-2-butanone.

Chemical data

Formula: - $C_{15}H_{16}O_2$
Mol. mass: - 228.29 g/mol.

Physical Data

Boiling point: - 371.1 °C at 760 mmHg**.[155]**
Melting Point: -185-195 ° (hydrochloride salt)**.[156]**

Mechanism of action: - The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), that is a potent inhibitor of prostaglandin synthesis, most likely through binding to the COX-2 and COX-1 receptors**.[157]**

Description: - A white or almost white, crystalline powder**.[158][USP]**

Solubility Profile: - Soluble in acetone, sparingly soluble in alcohol and in methanol. Practically insoluble in water**.[USP]**

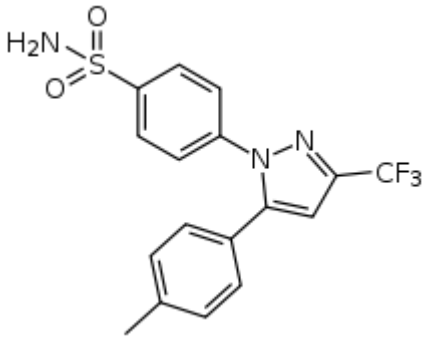
Pharmacokinetic data

Protein binding: - > 99% (active metabolite)
Metabolism: - Hepatic, to active metabolite 6-methoxy-2-naphthylacetic acid; 6-MNA
Half-life: - 23 hours (active metabolite)
Excretion: - Renal
Nature: - hydrophobic**.[159]**
pKa: - lies 3.5-5.5**.[160]**
LogP: - 2.817**.[161]**

Dissolution:- Nabumetone tablet.[162]

Medium: -Sodium lauryl phosphate(2 in 100 ml),900ml
Apparatus: - 2
Rpm: - 50 rpm
Time: - 45 minutes.

Celecoxib.[163]



Systematic (IUPAC) name: - 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide.

Chemical data

Formula: - $C_{17}H_{14}F_3N_3O_2S$

Mol. mass: - 381.373 g/mol

Physical data

Boiling Point: - 529 °C at 760 mmHg**.[164]**

Melting point: - 161.3 °C - 162.2**.[165]**

Mechanism of action: - The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme. It binds with its polar sulfonamide side chain to a hydrophilic side pocket region close to the active COX-2 binding site. Both COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin (PG) H2, the precursor of PGs and thromboxane**.[166]**

Description: - It is a white powder**.[167]**

Solubility Profile: - It has very low *water solubility*. It forms a complex with β-cyclodextrin (βCD) both in aqueous and in solid state**.[168]**

Pharmacokinetic data

Bioavailability: - 40%

Protein binding: - 97% (mainly to serum albumin)

Metabolism: - Hepatic (mainly CYP2C9)

Half-life: - ~11 h

Excretion: - Renal 27%, faecal 57%

Nature: - hydrophilic**.[169]**

pKa: - 11.1**.[170]**

log P: - 3.82**.[171]**

Dissolution:- Celecoxib capsule.[172]

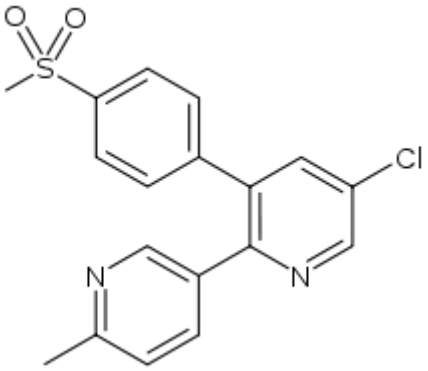
Medium: - Tier 1 Medium: 0.04 M tribasic sodium phosphate (pH 12) with 1% SLS. Tier 2 Initial Medium: 750 mL of simulated gastric fluid, USP (includes pepsin); At 20 minutes, while stirring, add 180 mL of appropriate concentrations of SLS solution (for a final concentration of 1% SLS). Add about 70 mL of 1.2 N NaOH to adjust the pH to 12. Tier 1: 1000 mL Tier 2: 750 mL (initial) 1000 mL (final)

Apparatus: - 2

Rpm: - 70 rpm

Time: - 10,20,30,40,60 minutes.

Etoricoxib.[173]



Systematic (IUPAC) name: - 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

Chemical data

Formula: - $C_{18}H_{15}ClN_2O_2S$

Mol. mass: - 358.842 g/mol.

Physical Data

Boiling Point: - 510 °C at 760 mmHg**.[174]**

Melting Point: - 134-135**.[175]**

Mechanism of action: - Like any other COX-2 selective inhibitor Etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces prostaglandins (PGs) generation from arachidonic acid**.[176]**

Description: - Off white to pale yellow powder**.[177]**

Solubility Profile: - It is poorly water soluble drug**.[178]**

Pharmacokinetic data

Bioavailability: - 100%

Protein binding: - 92%

Metabolism: - Hepatic, CYP extensively involved (mainly CYP3A4)

Half-life: - 22 hours

Excretion: - Renal (70%) and fecal (20%)

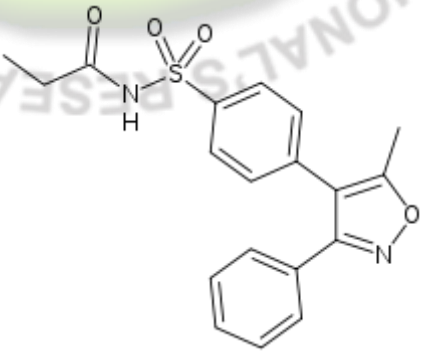
Nature: - Hydrophillic**.[179]**

pKa: - 4.6**.[180]**

logP: - 3.70**.[176]**

Dissolution Profile: - Not Available.

Parecoxib.[181]



Systematic (IUPAC) name: - *N*-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}propanamide.

Chemical data

Formula: - $C_{19}H_{18}N_2O_4S$

Mol. Mass:- 370.422 g/mol

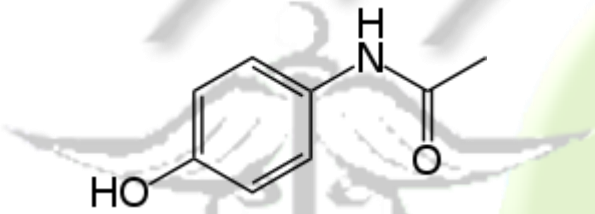
Physical Data

Boiling Point: - 538°Cat760mmHg.**[182]**
Melting point: - mp 148.9-151°.**[183]**
Mechanism of action: - It is believe to inhibit the prostagladin sysnthesis by acting on cyclogenase-2 enzyme.(COX-2)**.[184]**
Description: - It is a white to off-white solid**.[185]**
Solubility Profile: - High water solubility.**[186]**

Pharmacokinetic data

Bioavailability: - 100%
Protein binding: - 98%
Metabolism: - Hepatic to valdecoxib and propionic acid CYP extensively involved (mainly CYP3A4 and 2C9)
Half-life:- 22 minutes (parecoxib).8 hours (valdecoxib)
Excretion: - Renal (70%, metabolites)
Nature:- Hydrophillic**.[187]**
pKa: - 4.9**.[188]**
logP:- 3.51**.[189]**
Dissolution Profile: - Not available.

Paracetamol.[190]



Systematic (IUPAC) name: - *N*-(4-hydroxyphenyl)ethanamide*N*-(4-hydroxyphenyl)acetamide.

Chemical data

Formula: - $C_8H_9NO_2$
Mol. mass: - 151.17 g/mol.

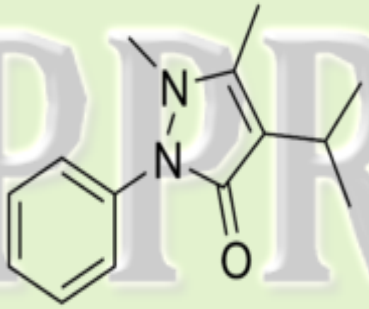
Physical Data

Boiling point: - >500°C**.[191]**
Melting Point: - 169 - 172 C**.[192]**
Mechanism of action: - Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory affects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that acetaminophen indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why acetaminophen is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that acetaminophen selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works. The antipyretic properties of acetaminophen are likely due to direct effects on the heat-regulating centres of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation**.[193]**
Description:- white crystalline powder**.[194]**
Solubility Profile: - Freely soluble in ethanol and in acetone, sparingly soluble in water, very slightly soluble in dichlorormethane and in ether**.[195]**

Pharmacokinetic data

Bioavailability: - ~100%
Metabolism:- 90 to 95% Hepatic
Half-life: - 1–4 h
Excretion: - Renal
Nature: - Hydrophillic**.[196]**
Pka: - 9.5**.[197]**
log P: - 0.51**.[198]**
Dissolution Profile: -
Dissolution:- Paracetamol Tablet.[199]
Medium: - Phosphate buffer ph 5.8
Apparatus: - 1
Rpm: - 50 rpm
Time: - 30 minutes.

Propyphenazone.[200]



Systematic (IUPAC) name: - 1,5-dimethyl- 2-phenyl- 4-propan- 2-ylpyrazol- 3-one.

Chemical data

Formula: - $C_{14}H_{18}N_2O$
Mol. mass: -230.306 g/mol.

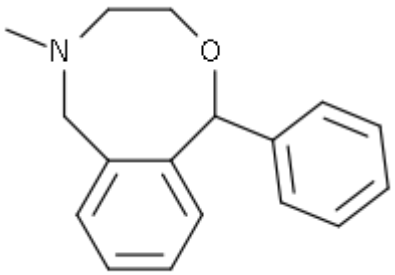
Physical Data

Boiling Point: - 319 °C at 760 mmHg**.[201]**
Melting point: - 102 °C to 106 °C**.[202]**
Mechanism of Action: - Propyphenazone is an NSAID derived from pyrazolone and is related to phenazone. It has antipyretic and analgesic properties**.[203]**
Description: - white and yellowish crystal powder**.[204]**
Water Solubility: - soluble in *water*, practically insoluble in alcohol**.[205]**

Pharmacokinetic Data: -

half-life: - 2.79+0.53 h**.[206]**
Protein Binding: - Not available.
Nature: - Hydrophillic**.[207]**
pKa: - 7.9**.[208]**
Log P: - Not available.
Dissolution Profile: - Not available.

Nefopam.[209]



Systematic (IUPAC) name: - 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine.

Chemical data

Formula: - $C_{17}H_{19}NO$

Mol. mass: - 253.34 g/mol.

Physical Data

Boiling Point*:* - 369.5 °C at 760 mmHg**.[210]**

Melting point: - 248 ~ 253 ℃**.[211]**

Mechanism of action: - Not cleraly defined.

Description: - white crystalline powder**.[212]**

Solubility Profile: - sparingly soluble in water**.[213]**

Pharmacokinetic Parameters: -

Half life: - 5.1+/-1.3 hr**.[214]**

Protein-binding: - 73%**.[215]**

Nature: - Not available.

pKa: - 9.2**.[216]**

log P: - 3.519**.[217]**

Dissolution Profile: - Not available.

Reference: -

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