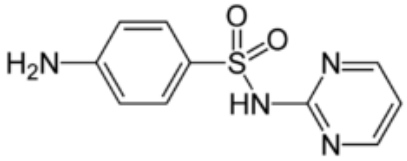
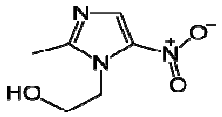
1. Sulfadiazine



Sulfadiazine is a sulfonamide antibiotic.
Uses It eliminates bacteria that cause infections by stopping the production of folic acid inside the bacterial cell, and is commonly used to treat urinary tract infections (UTIs). In combination, sulfadiazine and pyrimethamine, can be used to treat toxoplasmosis, a disease caused by *Toxoplasma gondii*.
What is it used for? Preventing recurrence of rheumatic fever, which is a complication that can develop after a streptococcal throat infection. Toxoplasmosis (unlicensed use).
Warning! You should make sure that you drink plenty of fluid while receiving treatment with this medicine. This is to reduce the risk of the medicine forming crystals in the urine. If in hospital, this fluid may be given via a drip.

- Broad-spectrum antibiotics can sometimes cause inflammation of the bowel (colitis). For this reason, if you get diarrhoea that becomes severe or persistent or contains blood or mucus, either during or after taking this medicine, you should consult your doctor immediately.
- This medicine may rarely cause jaundice. Consult your doctor immediately if you notice any yellowing of your skin or the whites of your eyes while taking this medicine.
- This medicine may rarely cause serious skin rashes, which may be life-threatening and require treatment in hospital. For this reason you should consult your doctor immediately if you develop a rash, skin blistering, peeling, itching, or other unexplained skin reaction while taking this medicine.
- This medicine may rarely cause a decrease in the normal amounts of blood cells in the blood. For this reason you should consult your doctor immediately if you experience any of the following symptoms: unexplained bruising or bleeding, purple spots, sore throat, mouth ulcers, high temperature (fever), feeling tired or general illness. Your doctor may want to take a blood test to check your blood cells.
- If you are taking this medicine for prolonged periods of time you should have regular monthly blood tests to monitor your blood cells.

2. Metronidazole



2-(2-methyl-5-nitro-1*H*-imidazol-1-yl) ethanol

and others) is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal. It is the drug of choice for first episodes of mild-to-moderate *Clostridium difficile* infection. It is marketed in the U.S.A. by Pfizer and globally by Sanofi under the trade name **Flagyl**, and is also sold under other brand names. Metronidazole was developed in 1960.

Metronidazole is used also as a gel preparation in the treatment of the dermatological conditions such as rosacea (**Rozex** and **MetroGel** by Galderma) and fungating tumours (**Anabact**, Cambridge Healthcare Supplies).

Uses Metronidazole is indicated for the treatment of:

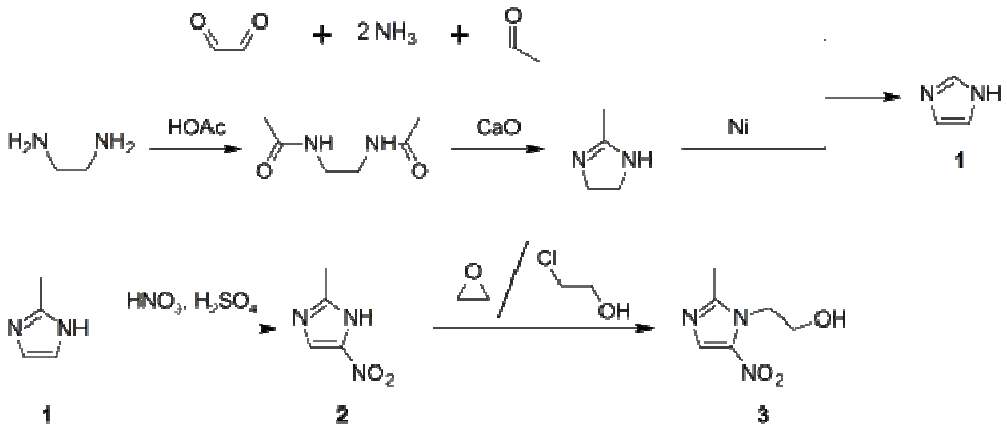
Bacterial Bacterial vaginosis, commonly associated with overgrowth of *Gardnerella* species and coinfective anaerobes (Mobiluncus, Bacteroides), in symptomatic patients
Pelvic inflammatory disease in conjunction with other antibiotics such as ofloxacin, levofloxacin, or ceftriaxone
Anaerobic infections such as *Bacteroides fragilis, spp*, *Fusobacterium spp*, *Clostridium spp*, *Peptostreptococcus spp*, *Prevotella spp*, or any other anaerobes in intra-abdominal abscess, peritonitis, diverticulitis, empyema, pneumonia, aspiration pneumonia, lung abscess, diabetic foot ulcer, meningitis and brain abscesses, bone and joint infections, septicemia, endometritis, or endocarditis
Pseudomembranous colitis due to *Clostridium difficile*
Helicobacter pylori eradication therapy, as part of a multi-drug regimen in peptic ulcer disease
Dental infection of bacterial origin, such as periapical abscess, periodontal abscess, acute pericoronitis of impacted or partially erupted teeth; often used in conjunction with Amoxicillin

Protozoal Amoebiasis: Infections caused by *Entamoeba histolytica*.
Giardiasis: infection of the small intestine caused by the ingestion of infective cysts of protozoan *Giardia lamblia*.
Trichomoniasis: infection caused by *Trichomonas vaginalis*, which is a common cause of vaginitis and is the most frequently presenting new infection of the common sexually transmitted diseases.
Nonspecific Prophylaxis for those undergoing potentially contaminated colorectal surgery or appendectomies and may be combined with neomycin

Crohn's disease with colonic or perianal involvement (non-FDA approved) – believed to be more effective in combination with ciprofloxacin.Topical metronidazole is indicated for the treatment of rosacea, and in the treatment of malodorous fungating wounds.

Preterm births Metronidazole has also been used in women to prevent preterm birth associated with bacterial vaginosis, amongst other risk factors including the presence of cervicovaginal fetal fibronectin (fFN). A randomised controlled trial demonstrated that metronidazole was ineffective in preventing preterm delivery in high-risk pregnant women and, conversely, the incidence of preterm delivery was actually higher in women treated with metronidazole. In a study it has been found that metronidazole is not the right antibiotic to administer in these circumstances and that it was often administered too late to be of use. Clindamycin administered early in the second trimester to women who test positive for bacterial vaginosis seemed to be more effective.

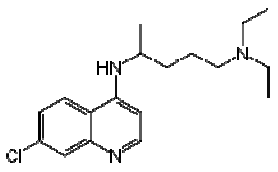
Synthesis 2-Methylimidazole (**1**) may be prepared via the Debus-Radziszewski imidazole synthesis, or from ethylenediamine and acetic acid, followed by treatment with lime, then Raney nickel. 2-Methylimidazole nitrated to give 2-methyl-4(5)-nitroimidazole (**2**), which is in turn alkylated with ethylene oxide or 2-chloroethanol to give metronidazole (**3**):



What Is Metronidazole Used For? Various types of bacterial and parasitic infections, including bacterial vaginosis, rosacea, and trichomoniasis are often treated with metronidazole. The oral form is approved to treat amebic infections in children (although it is not approved for other uses in children). Healthcare providers may occasionally recommend off-label metronidazole uses, such as treating Crohn's disease or infections caused by bacteria that are susceptible to this antibiotic.

3. Chloroquine

Chloroquine /□kl□rəkw□n/ is a 4-aminoquinoline drug used in the treatment or prevention of malaria.



Uses

- It has long been used in the treatment or prevention of malaria. After the malaria parasite *Plasmodium falciparum* started to develop widespread resistance to chloroquine, new potential uses of this cheap and widely available drug have been investigated. Chloroquine has been extensively used in mass drug administrations, which may have contributed to the emergence and spread of resistance.
- As it mildly suppresses the immune system, it is used in some autoimmune disorders, such as rheumatoid arthritis and lupus erythematosus.
- Chloroquine is in clinical trials as an investigational antiretroviral in humans with HIV-1/AIDS and as a potential antiviral agent against chikungunya fever.
- The radiosensitizing and chemosensitizing properties of chloroquine are beginning to be exploited in anticancer strategies in humans.
- In biomedicinal science, chloroquine is used in in vitro experiements to inhibit lysosomal degradation of protein products.

Malaria prevention

Chloroquine can be used for preventing malaria from *Plasmodium vivax*, *P. ovale* and *P. malariae*. Popular drugs based on chloroquine phosphate (also called nivaquine) are Chloroquine FNA, Resochin and Dawaquin. Many areas of the world have widespread strains of chloroquine-resistant *P. falciparum*, so other antimalarials, such as mefloquine or atovaquone, may be advisable instead. Combining chloroquine with proguanil may be more effective against chloroquine-resistant *P. falciparum* than treatment with chloroquine alone, but is no longer recommended by the CDC due to the availability of more effective combinations.[13] For children 14 years of age or below, the dose of chloroquine is 600 mg per week.

Resistance in malaria

Since the first documentation of *P. falciparum* chloroquine resistance in the 1950s, resistant strains have appeared throughout East and West Africa, Southeast Asia, and South America. The effectiveness of chloroquine against *P. falciparum* has declined as resistant strains of the parasite evolved. They effectively neutralize the drug via a mechanism that drains chloroquine away from the digestive vacuole. Chloroquine-resistant cells efflux chloroquine at 40 times the rate of chloroquine-sensitive cells; the related mutations trace back to transmembrane proteins of the digestive vacuole, including sets of critical mutations in the *PfCRT* gene (*Plasmodium falciparum* chloroquine resistance transporter). The mutated protein, but not the wild-type transporter, transports chloroquine when expressed in *Xenopus* oocytes and is thought to mediate chloroquine leak from its site of action in the digestive vacuole.[20] Resistant parasites also frequently have mutated products of the ABC transporter *PfMDR1* gene (*Plasmodium falciparum* multidrug resistance gene) although these mutations are thought to be of secondary importance compared to *Pfcrt*. Verapamil, a Ca^{2+} channel blocker, has been found to restore both the chloroquine concentration ability and sensitivity to this drug. Recently, an altered chloroquine-transporter protein CG2 of the parasite has been related to chloroquine resistance, but other mechanisms of resistance also appear to be involved.

Other agents that have been shown to reverse chloroquine resistance in malaria are chlorpheniramine, gefitinib, imatinib, tariquidar and zosuquidar.[22]

Research on the mechanism of chloroquine and how the parasite has acquired chloroquine resistance is still ongoing, other mechanisms of resistance are likely.

Uses other than for malaria

Disease-modifying antirheumatic drugs

Against rheumatoid arthritis, it operates by inhibiting lymphocyte proliferation, phospholipase A2, antigen presentation in dendritic cells, release of enzymes from lysosomes, release of reactive oxygen species from macrophages, and production of IL-1.

Antiviral

As an antiviral agent, it impedes the completion of the viral life cycle by inhibiting some processes occurring within intracellular organelles and requiring a low pH. As for HIV-1, chloroquine inhibits the glycosylation of the viral envelope glycoprotein gp120, which occurs within the Golgi apparatus.

Other studies suggest quite the opposite, with chloroquine being a potent inhibitor of interferons and enhancer of viral replication.

Antitumor

The mechanisms behind the effects of chloroquine on cancer are currently being investigated. The best-known effects (investigated in clinical and preclinical studies) include radiosensitizing effects through lysosome permeabilization, and chemosensitizing effects through inhibition of drug efflux pumps (ATP-binding cassette transporters) or other mechanisms (reviewed in the second-to-last reference below).

Chloroquine shows anti lung cancer effects in vitro through blocking lysosome function or inducing apoptosis or necrosis. At lower concentrations (from 0.25 to 32 μM), chloroquine inhibited the growth of A549 cells and, at the same time, it induced vacuolation with increased volume of acidic compartments (VAC). On the other hand, at higher concentrations (64-128 microM), chloroquine induced apoptosis at 24 h. The lactate dehydrogenase (LDH) assay showed that at an even higher concentration and longer treatment, chloroquine induced necrosis of A549 cells.

Preparation and characterization of chloroquine loaded microspheres for prophylactic use.

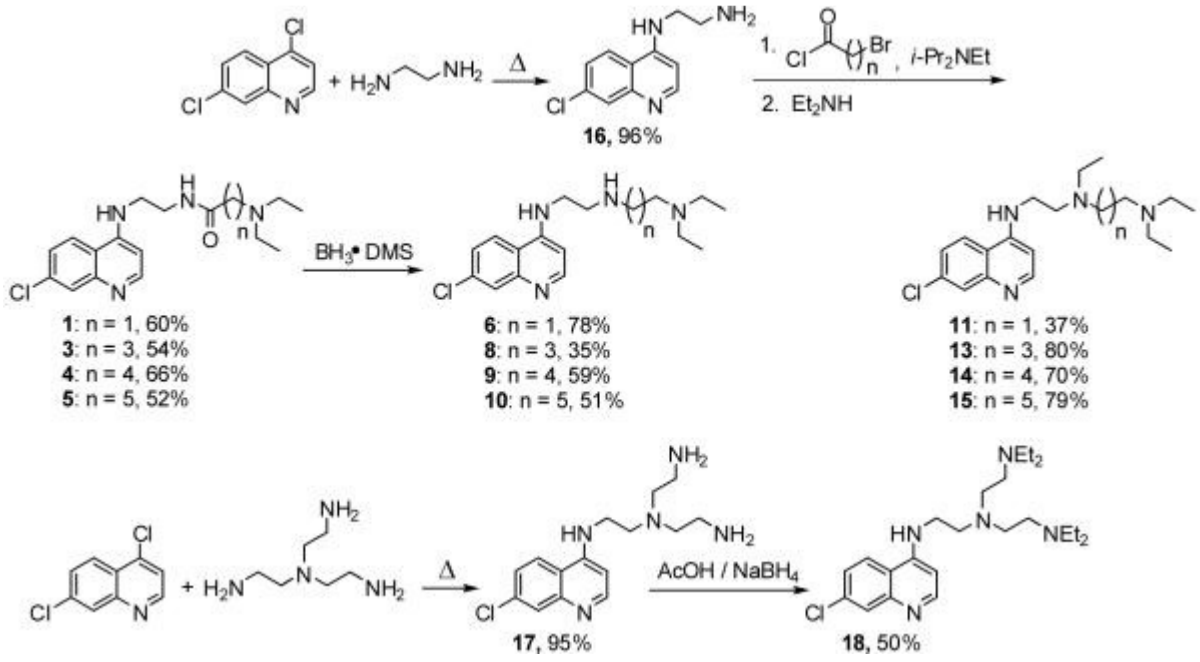
Malaria is one of the major public health problems in the developing countries. Numbers of drugs are available for the treatment of malaria but chloroquine diphosphate still remains a drug of choice. The aim of this study is to develop and characterize a suitable drug delivery system of antimalarial drug for prophylactic use. A depot system for controlled release of antimalarial drug was prepared. Drug loaded heat cross-linked gelatin microspheres were prepared by single emulsion thermal gelation technique. These were characterized by optical microscopy, scanning electron microscopy (SEM), percentage yield (63.20% to 86.13%), drug content (22.95% to 28.02%), encapsulation efficiency (41.46% to 68.26%), differential scanning calorimetry (DSC) and in vitro studies. Sizes of the microspheres as observed by optical microscopy were in the range of 44.06 ± 6.98 μm to 54.70 ± 8.19 μm, DSC pattern showed the absence of drug and polymer interaction. The gelatin microspheres were below 60 μm and spherical in shape as evidenced by the SEM photographs. Encapsulated chloroquine diphosphate was released slowly for 24 ± 1 hrs. The study indicated optimum drug release behavior (84.5% ± 0.96) in 25 hrs.

Chloroquine

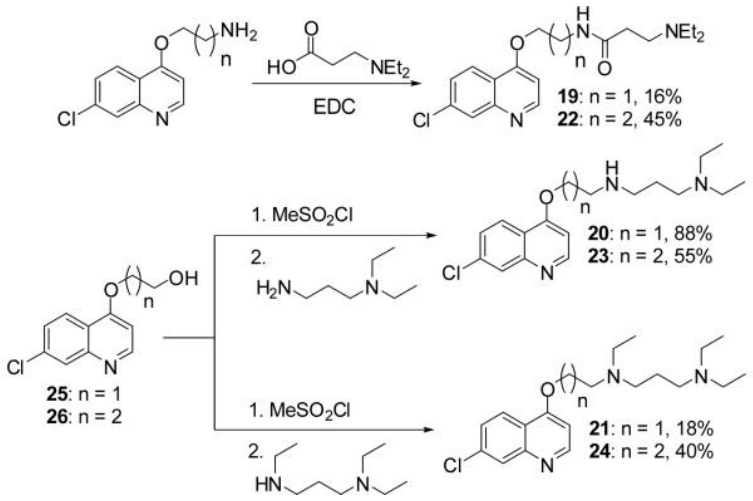
IUPAC Name:-N'-(7-Chloro-4-quinolinyl)-N,N-diethyl-1,4-pentanediamine M. P.:- 86-87 °C MW: 319.24

Drug information:- Chloroquine have been catagorized an Anti-microbial drug further classified as anti-parasitic drug more particularly anti-protozoal agent. This quinoline compound is used in treatment of malaria.

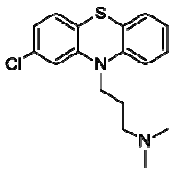
Scheme 1



Synthesis of CQ-derived antimalarials carrying a linear side chain and of branched 4-aminoquinoline **18**.



4. Chlorpromazine



Chlorpromazine (as chlorpromazine hydrochloride, abbreviated **CPZ**; marketed in the United States as **Thorazine** and elsewhere as **Largactil** or **Megaphen**) is a dopamine antagonist of the typical antipsychotic class of medications possessing additional antiadrenergic, antiserotonergic, anticholinergic and antihistaminergic properties used to treat schizophrenia.[1][2] First synthesized on December 11, 1950, chlorpromazine was the first drug developed with specific antipsychotic action, and would serve as the prototype for the phenothiazine class of drugs, which later grew to comprise several other agents. The introduction of chlorpromazine into clinical use has been described as the single greatest advance in psychiatric care, dramatically improving the prognosis of patients in psychiatric hospitals worldwide.[3] The availability of antipsychotic drugs curtailed indiscriminate use of electroconvulsive therapy and psychosurgery[*citation needed*], and was one of the driving forces behind the deinstitutionalization movement.

Chlorpromazine works on a variety of receptors in the central nervous system, producing anticholinergic, antidopaminergic, antihistaminic, and weak antiadrenergic effects. Both the clinical indications and side effect profile of CPZ are determined by this broad action: its anticholinergic properties cause constipation, sedation, and hypotension, and help relieve nausea. It also has anxiolytic (anxiety-relieving) properties. Its antidopaminergic properties can cause extrapyramidal symptoms such as akathisia (restlessness, aka the 'Thorazine shuffle' where the patient walks almost constantly, despite having nowhere to go due to mandatory confinement, and takes small, shuffling steps) and dystonia. It is known to cause tardive dyskinesia, which can be irreversible.[4] In recent years, chlorpromazine has been largely superseded by the newer atypical antipsychotics, which are usually better tolerated, and its use is now restricted to fewer indications. In acute settings, it is often administered as a syrup, which has a faster onset of action than tablets, and can also be given by intramuscular injection. IV administration is very irritating and is not advised; its use is limited to severe hiccups, surgery, and tetanus.[5]

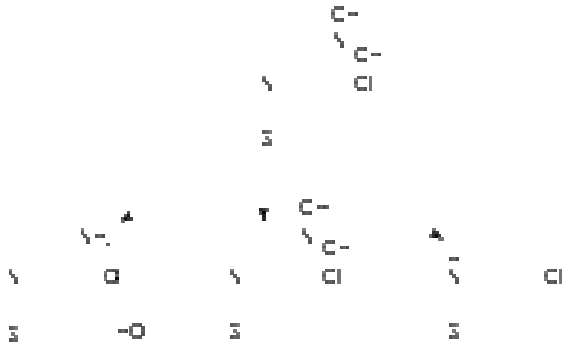
Medical uses

Chlorpromazine is classified as a low-potency typical antipsychotic and in the past was used in the treatment of both acute and chronic psychoses, including schizophrenia and the manic phase of bipolar disorder as well as amphetamine-induced psychoses. Low-potency antipsychotics have more anticholinergic side effects such as dry mouth, sedation and constipation, and lower rates of extrapyramidal side effects, while high-potency antipsychotics (such as haloperidol) have the reverse profile[*citation needed*].

The use of chlorpromazine and other typical antipsychotics has been largely replaced by newer generation of atypical antipsychotics which are generally better tolerated[*citation needed*]. Recent global review of data supports its effectiveness as an antipsychotic.[6][7]

Chlorpromazine has also been used in porphyria and as part of tetanus treatment. It still is recommended for short term management of severe anxiety and aggressive episodes. Resistant and severe hiccups, severe nausea/emesis and preanesthetic conditioning are other uses.[7][8] Symptoms of delirium in medically hospitalized AIDS patients have been effectively treated with low doses of chlorpromazine.[9]

Bioavailability: Only about 32% of the administered dose is available to the systemic circulation in the active form. Over time and multiple administrations, bioavailability may drop to 20%. Peak concentrations are achieved in 1 to 4 hours[34] (range 1.5–8 hours), after an oral dose.[35]



Three Common Metabolites of Chlorpromazine

Chlorpromazine is derived from phenothiazine, has an aliphatic side chain, typical for low to middle potency antipsychotics. Chlorpromazine is slowly absorbed from the intramuscular injection site with the peak plasma concentration occurring 6–24 hours after administration of the drug. The oral bioavailability is estimated to be 30–50% that of intramuscular doses and about 10% that of intravenous doses due to extensive first pass metabolism in the liver. Its elimination half-life is 16–30 hours (8–35 hours, although it is as short as 2 hours or as long as 60 hours in some individuals),[35] due to high lipophilicity, high membrane-binding, and high protein-binding. It has many active metabolites (more than 100 metabolites being theoretically possible) with greatly varying halflives and pharmacological profiles.A number of the metabolites may contribute to the pharmacological effects of chlorpromazine including 7-hydroxychlorpromazine, chlorpromazine-N-oxide, 3-hydroxychlorpromazine and desmethylchlorpromazine.)[35] Although the metabolite chlorpromazine-N-oxide does not possess activity in vitro, it can exert an indirect pharmacological effect in vivo by reverting to chlorpromazine. The major routes of metabolism include hydroxylation, N-oxidation, sulphoxidation, demethylation, deamination and conjugation. There is little evidence supporting the development of metabolic tolerance or an increase in the metabolism of chlorpromazine due to microsomal liver enzymes following multiple doses of the drug.[36] The mechanism of action of chlorpromazine is that the drug can act as an uncoupling agent of oxidative phosphorylation and also as an inhibitor of ATP-ase and cytochrome oxidase. However, the relationship that may exist between these mechanisms are not entirely understood.

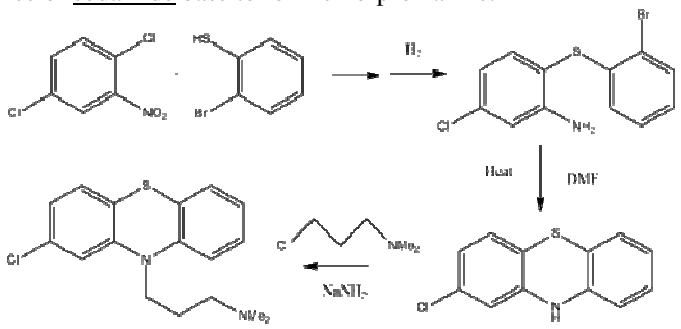
The cytochrome P450 isoenzymes 1A2 and 2D6 are needed for metabolism of chlorpromazine. CYP 2D6 is the main enzyme catalyzing 7-hydroxylation of chlorpromazine, the reaction being partially catalyzed by CYP 1A2.[27]

Chlorpromazine is typically degraded by the liver by the action of cytochrome-P450 family enzymes, usually CYP2D6. Less than 1% of the unchanged drug is excreted via the kidneys in the urine. In which 20-70% is excreted as conjugated or unconjugated metabolites, whereas 5-6% is excreted in feces.[35] There are on the order of 10 or more major metabolites generated by the hepatic pathway in appreciable concentrations. The three most common appear in the accompanying image. The first is the doubly N-demethylated species, followed by the 7-hydroxylated form, and finally chlorophenothiazine, in which the entire R1 side chain is missing.[37]

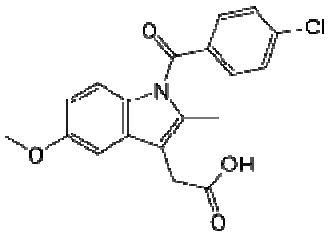
Often, due to their high lipophilic character, these and other metabolites may be detected in the urine up to 18 months.[35] after discontinuation of use. Most metabolites lack any sort of antipsychotic activity, but a few are biologically active. These include 7-hydroxychlorpromazine, mesoridazine, and a few *N*-demethylated metabolites.[34]

Synthesis

The synthesis of chlorpromazine begins with the reaction of 1,4-dichloro-2-nitrobenzene with 2-bromobenzenethiol.[43][44][45] Hydrogen chloride is evolved as a by-product of this step and a thioether is formed as the product. Although not verified, it appears that the *ortho* chlorine is eliminated preferentially. In the second step the nitro group is reduced with hydrogen gas. Upon heating in Dimethylformamide (DMF) solvent, ring cyclization occurs. The 2-chloro-10H-phenothiazine thus produced is combined with 3-chloro-N,N-dimethylpropan-1-amine in the presence of sodamide base to form chlorpromazine.



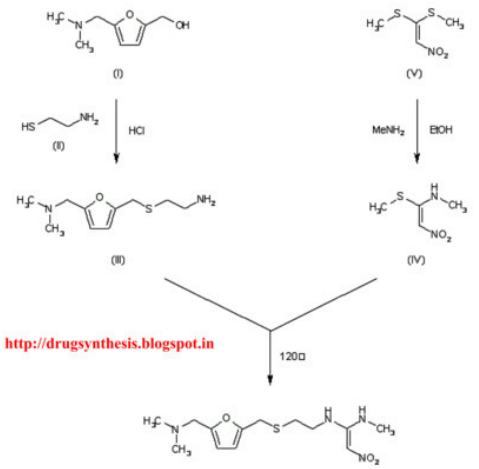
5. **Indometacin**



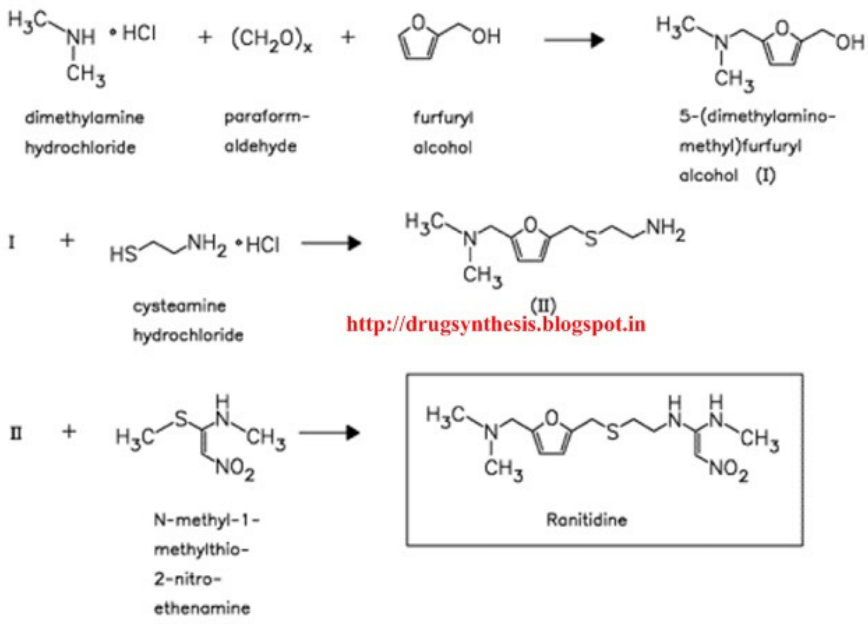
2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid
Indometacin (INN) or **indomethacin** (USAN and former BAN) is a non-steroidal anti-inflammatory drug (NSAID) commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. It is marketed under more than seventy different trade names.[1]
Indomethacin has also been used clinically to delay premature labor, reduce amniotic fluid in polyhydramnios, and to close patent ductus arteriosus.
Indomethacin is a potent drug with many serious side effects a00000000000000000000000000nd should not be considered an analgesic for minor aches and pains or fever. The medication is better described as an anti-inflammatory, rather than an analgesic. Indomethacin can also affect warfarin and subsequently raise INR.

6. Ranitidine

N-(2-[(5-[(dimethylamino)methyl]furan-2-yl)methylthio]ethyl)-*N′*-methyl-2-nitroethene-1,1-diamine
Ranitidine (/rə□n□t□di□n/; trade name **Zantac**) is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Ranitidine is also used alongside fexofenadine and other antihistamines for the treatment of skin conditions such as hives. Ranitidine is also known to give false positives for methamphetamine on drug tests.[1]
Medical use
Certain preparations of ranitidine are available over the counter (OTC) in various countries. In the United States, 75-mg and 150-mg tablets are available OTC. Zantac OTC is manufactured by Boehringer Ingelheim. In Australia, packs containing seven or 14 doses of the 150-mg tablet are available in supermarkets, small packs of 150-mg and 300-mg tablets are schedule 2 pharmacy medicines. Larger doses and pack sizes still require a prescription.
Outside the United States and Canada, ranitidine is combined with bismuth (which acts as a mild antibiotic) as a citrate salt (ranitidine bismuth citrate, Tritec), to treat *Helicobacter pylori* infections. This combination is usually given with clarithromycin, an antibiotic.
Ranitidine can also be coadministered with NSAIDs to reduce the risk of ulceration. Proton-pump inhibitors (PPIs) are more effective for the prevention of NSAID-induced ulcers.[2]
Ranitidine can be administered preoperatively to reduce the risk of aspiration pneumonia. The drug not only increases gastric pH, but also reduces the total output of gastric juice. Ranitidine may have an antiemetic effect when administered preoperatively.
It can be administered intravenously in intensive care units to critically ill patients (particularly geriatric ones) to reduce the risk of gastric bleeding.
The usual dose of ranitidine is either 150 mg twice a day or 300 mg once every 24 hours, usually at night. For ulcer treatment, a 300-mg night-time dose is especially important - as the increase in gastric/duodenal pH promotes healing overnight when the stomach and duodenum are empty. Conversely, for treating reflux, smaller and more frequent doses are more effective.
Ranitidine used to be administered long term for reflux treatment, sometimes indefinitely. However, PPIs have taken over this role.
In some patients with severe reflux, up to 600 mg of ranitidine can be administered daily, usually in four lots of 150 mg. Such a high dose was not unusual in the past, but nowadays a once-a-day PPI is used instead - both for convenience and because they are more effective in raising gastric pH. Patients with Zollinger-Ellison syndrome have been given doses of 6000 mg per day without any harm.



Laboratory Synthesis Of Ranitidine



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Ranitidine Synthetic procedure/method of synthesis

The reaction of 5-dimethylaminomethyl-2-furanylmethanol (I) with 2-mercaptoethylamine (II) by means of aqueous HCl gives 2-[[(5-dimethylamino-methyl-2-furanyl)methylthio]ethaneamine (III), which is then condensed with N-methyl-1-methylthio-2-nitrotheneamine (IV) by heating at 120 C. Compound (IV) is obtained by reaction of 1,1-bis(methylthio)-2-nitroethene (V) with methylamine in refluxing ethanol