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Review Article

PHARMACOKINETIC DATA AND SOLUBILITY PROFILE OF ANTIFUGAL 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 Antifungal drugs at one place.

Keywords: - : Solubility profile, pharmacokinetic parameters, Antifungal drugs.

Introduction

Classification[1]

1. Amphotericin B
2. Butoconazole
3. Ciclopirox
4. Clotrimazole
5. Econazole
6. Fluconazole
7. Flucytosine
8. Griesofulvin
9. Ketoconazole
10. Miconazole
11. Nystatin
12. Sulconazole nitrate
13. Terbinifine Hydrochloride
14. Tolnaflate
15. Undecylenic
16. Capsofugin
17. Itraconazole
18. Nafitifine Hydrochloride
19. Oxiconazole Nitrate
20. Terconazole
21. Ticonazole
22. Voriconazole

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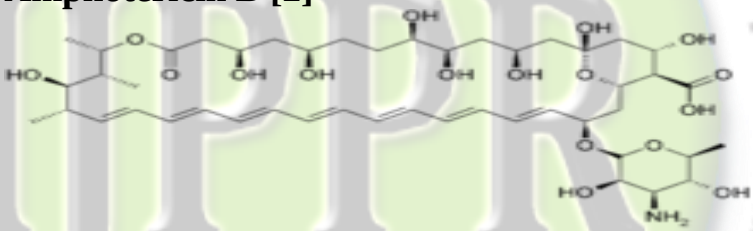
Amphotericin B [2]



Systematic (IUPAC) name (1R,3S,5R,6R,9R, 11R,15S,16R,17R,18S,19E,21E, 23E,25E,27E,29E,31E,33R,35S,36R,37S)- 33-[(3-amino-3,6-dideoxy- β-D-mannopyranosyl)oxy]- 1,3,5,6,9,11,17,37-octahydroxy- 15,16,18-trimethyl- 13-oxo- 14,39-dioxabicyclo [33.3.1] nonatriaconta- 19,21,23,25,27,29,31-heptaene- 36-carboxylic acid

Chemical data

Formula: - C47H73NO17

Mol. mass: - 924.084

Melting Point: - 170.0 oC. **[3]**

Description: - Yellow to Orange Powder. Odorless. **[USP]**

Solubility Profile: - Or Practically insoluble in water, In Anhydrous alcohol, In Ether, In Benzene And IN Toluene, Soluble in Dimethyl Formamide, In Dimethyl Sulfoxide And In Propylene Glycol, Slightly Soluble In Methanol.**[USP][4]**

Solubility Profile: - Soluble In Dimethyl Sulfoxide, Slightly Soluble In Dimethyl Formamide. In Soluble in Benzene, In Ethanol, in ether And in Water. **[IP][5]**

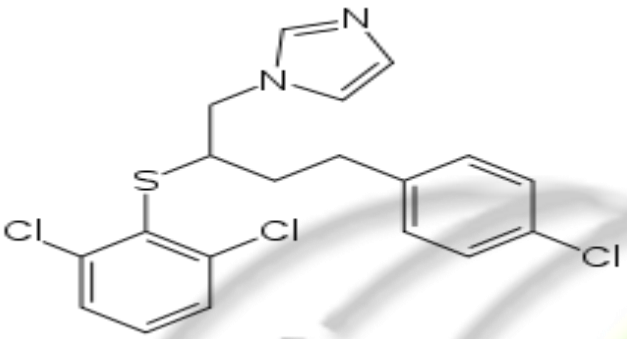
Pharmacokinetic data

Bioavailability: -100% (IV)

Metabolism: - renal

Half-life: - initial phase: 24 hours,
Second phase: approx. 15 days
Excretion: - 40% found in urine after single cumulated over several days
Biliar excretion also important

Butoconazole [6]



Systematic (IUPAC) name1-[4-(4-chlorophenyl)-2-(2,6-dichlorophenyl)sulfanylbutyl]imidazole

Chemical data

Formula: -C19H17Cl3N2S

Mol. mass: -411.776 g/mol

Melting Point: - Melts at about 159 Â°C with decomposition (nitrate salt) **[7]**

Description: - White To Off White, Crystalline Powder. **[USP]**

Solubility Profile: - Melt At About 160 Degree. Practically Insoluble In Water, Very Slightly Soluble IN Ethyl Acetate, Slightly Soluble In Acetonitrile, In Acetone, In Dichloromethane And In Tetrahydrofuran, Sparingly soluble in methanol. **[USP][8]**

Pharmacokinetic data

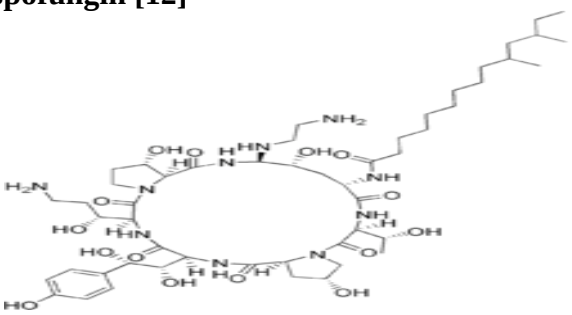
Absorption: - Following vaginal administration of butoconazole nitrate vaginal cream, 2% to 3 women, 1.7% (range 1.3-2.2%) of the dose was absorbed on average. **[9]**

Toxicity: - Oral, rat: LD_{50} = >1720 mg/kg. **[9]**

Plasma half-life: - 21 to 24 hours **[10]**

Excreted: - urine and faeces **[11]**

Caspofungin [12]



Systematic (IUPAC) nameN-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S)-3-[(1R)-3-amino-1-hydroxypropyl]-21-[(2-aminoethyl)amino]-6-[(1S,2S)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl]-11,20,25-trihydroxy-15-[(1R)-1-hydroxyethyl]-2,5,8,14,17,23-hexaoxo-1,4,7,13,16,22-hexaazatricyclo[22.3.0.$0^{9,13}$] heptacosan-18-yl]-10,12-dimethyltetradecanamide

Chemical data

Formula: - C52H88N10O15

Mol. mass: - 1093.31 g/mol

Description: -Caspofungin acetate is a hygroscopic, white to off-white powder.**[13]**

Solubility Profile- Freely soluble in water and methanol, slightly soluble in ethanol {01} pH approximately 6.6{01}.**[14]**

Pharmacokinetic data

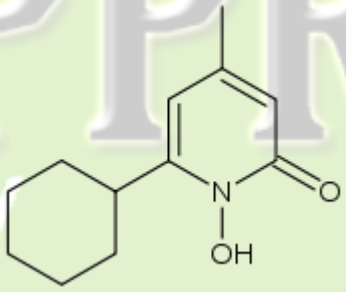
Bioavailability: - 100% (i.v.-use only)

Protein binding: - 97%

Half-life: - 9-11 hours

Excreted: - unchanged in urine (~1.4% of dose).**[15]**

Ciclopirox [16]



Systematic (IUPAC) name6-cyclohexyl-1-hydroxy-4-methylpyridin-2(1H)-one

Chemical data

Formula: - C12H17NO2

Mol. mass: - 207.269 g/mol

Melting Point: - 144 oC**[17]**

Description: - White To Slightly Yellowish White, Crystalline Powder**[USP]**

Solubility Profile: -, Slightly Soluble In Water, Freely Soluble In Ethanol And In Methylene Chloride, Soluble In Ether. **[USP][18]**

Pharmacokinetic data

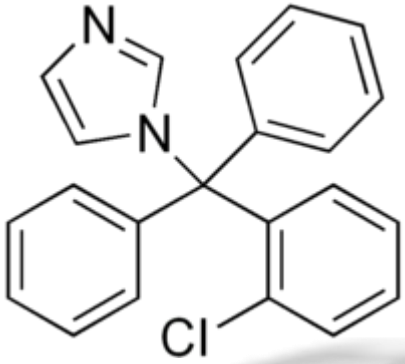
Bioavailability: - <5% with prolonged use

Protein binding: - 94 to 97%

Half-life : - 1.7 hours

Excretion: - urinary **[19]**

Clotrimazole [20]



Systematic (IUPAC) name 1-[(2-chlorophenyl)(diphenyl)methyl]-1H-imidazole

Chemical data

Formula: - C22H17ClN2

Mol. mass: - 344.837 g/mol

Melting Point: - 142-145 °[21]

Description: - White To Pale Yellow, Crystalline Powder**[USP]**

Solubility Profile:. Melt At About 142 Degree With Decomposition. Practically Insoluble In Water, Freely Soluble In Methanol, In Acetone, In Chloroform, In Alcohol. **[USP][22]**

Solubility Profile: - Freely Soluble In Acetone, In chloroform, In Ethanol And In Methanol, Practically Insoluble In Water**. [IP][23]**

Pharmacokinetic data

Bioavailability: - Poorly and erratically absorbed orally

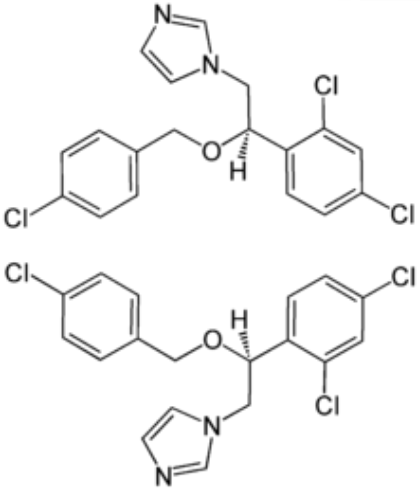
Protein binding: - 90%

Metabolism: -hepatic

Half-life: - 2 hours

Econazole [24]

1 : 1 mixture (racemate)



Systematic (IUPAC) name (RS)-1-{2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole

Chemical data

Formula: - C18H15Cl3N2O

Mol. mass: - 381.683 g/mol

Melting Point: - 162 ºC **[25]**

Description: - White To Practically White, Crystalline Powder. Having Not More Than a Slight Odor.Very Slightly Soluble In Water and In Ether.**[USP]**

Solubility Profile: - Slightly Soluble In Alcohol, Sparingly Soluble In Chloroform, Soluble In Methanol. **[USP][26]**

Solubility Profile: - Soluble in Methanol, Sparingly Soluble In Dichloromethane, Slightly Soluble In Ethanol, Very Slightly Soluble In Water, Practically Insoluble In Diethyl ether**. [IP][27]**

Pharmacokinetic data

Bioavailability: - Percutaneous absorption of econazole nitrate appears to be rapid but minimal following topical application of the drug to intact skin. **[28]**

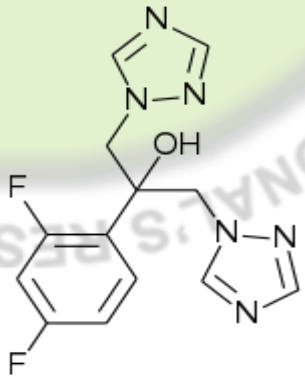
Protein binding: - strong protein binding. **[30]**

Metabolism: - into human milk following topical application **[28]**

Half-life: - approximately 35 min **[29]**

Elimination: - less than 1% of the applied doses are excreted in urine and feces; most of the systemically absorbed fraction of the dose appears to be excreted in urine within 24 hours. **[28]**

Fluconazole [31]



Systematic (IUPAC) name 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol

Chemical data

Formula: - C13H12F2N6O

Mol. mass: - 306.271 g/mol

Melting Point: - 138.4 °C**[32]**

Description: - White to Almost White, Crystalline Powder **[USP]**

Solubility Profile: - Freely Soluble In Methanol. Soluble In Alcohol and In Acetone.Sparingly Soluble In Isopropanol and In Chloroform.Slightly Soluble in Water, Very Slightly Soluble In toluene. **[USP][33]**

Pharmacokinetic data

Bioavailability: - >90%

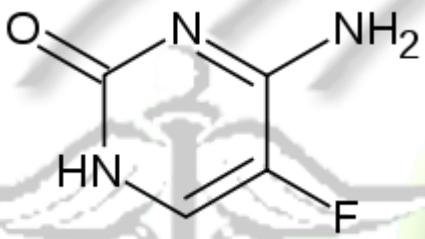
Protein binding: - 11–12%

Metabolism: - Hepatic 11%

Half-life: - 30 hours (range 20-50 hours)

Excretion: -Renal 61–88%

Flucytosine [34]



Systematic (IUPAC) name 4-amino-5-fluoro-1, 2-dihydropyrimidin-2-one

Chemical data

Formula: - C4H4FN3O

Mol. mass: - 129.093 g/mol

Melting Point: - 295-297°C**[35]**

Description: - White To Off White, Crystalline Powder. [USP]

Solubility Profile: - Is Odorless or Has a Slight odor. Sparingly Soluble In Water, Slightly Soluble In Alcohol, Practically Insoluble In Chloroform And In Ether. **[USP][36]**

Pharmacokinetic data

Bioavailability: - 75 to 90% (oral)

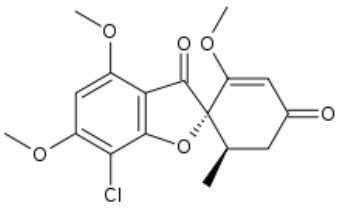
Protein binding: - 2.9 to 4%

Metabolism: - Minimal, in the GI tract

Half-life: - 2.4 to 4.8 hours

Excretion: - Renal (90%)

Griseofulvin [37]



Systematic (IUPAC) name(2S,6'R)- 7-chloro- 2',4,6-trimethoxy- 6'-methyl- 3H,4'H-spiro [1-benzofuran- 2,1'-cyclohex[2]ene]- 3,4'-dione

Chemical data

Formula: - $C_{17}H_{17}ClO_6$

Mol. mass: - 352.766 g/mol

Melting Point: - 218 – 222**[38]**

Description: - White To Off White, Crystalline Powder. **[USP]**

Solubility Profile: - Is Odorless or Has a Slight odor. Sparingly Soluble In Water, Slightly Soluble In Alcohol, Practically Insoluble In Chloroform And In Ether. **[USP][39]**

Solubility Profile: - Freely Soluble In Dimethylformamide, Soluble In Acetone and In Chloroform. Slightly Soluble In Ethanol and IN Methanol.Practically Insoluble in Water. **[IP][40]**

Pharmacokinetic data

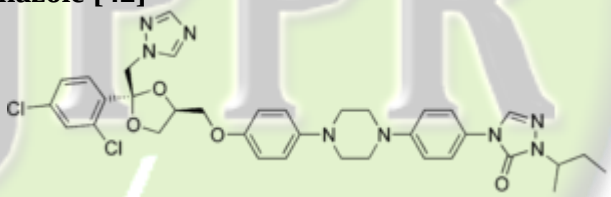
Bioavailability: - Highly variable (25 to 70%)

Metabolism: -Hepatic demethylation and glucuronidation

Half-life: - 9-21 hours

Protein binding: - 84% (0.2 to 2 l.tg/ml)**[41]**

Itraconazole [42]



Systematic (IUPAC) name(2R,4S)-rel-1-(butan-2-yl)-4-{4-[4-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]phenyl}-4,5-dihydro-1H-1,2,4-triazol-5-one

Chemical data

Formula: - C35H38Cl2N8O4

Mol. mass: - 705.64

Description: - showing light yellow color **[44]**

Melting Point: - 169.2˚C **[43]**

Solubility Profile: - insoluble in water (solubility of less than 1 µg/m&litre**)[44]**

Pharmacokinetic data

Bioavailability: - 55%, maximal if taken with full meal

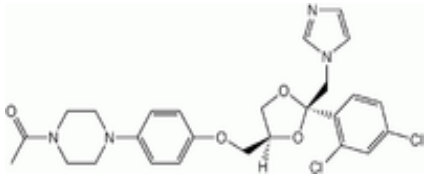
Protein binding: - 99.8%

Metabolism: - hepatic (CYP3A4)

Half-life: - 21 hours

Excretion: - Biliary **[45]**

Ketoconazole [46]



Systematic (IUPAC) name 1-[4-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]ethan-1-one

Chemical data

Formula: - C26H28Cl2N4O4

Mol. mass: - 531.431 g/mol

Description: - light yellow color**[47]**

Melting Point: - 169.2˚C**[48]**

Solubility Profile: - Freely Soluble In Dichloromeyhane, Soluble In Chloroform and In Methanol. Sparingly Soluble In Ethanol, Practically Insoluble In Water And In Ether. **[IP][49]**

Pharmacokinetic data

Bioavailability: - Variable

Protein binding: - 84 to 99%

Metabolism: - Hepatic

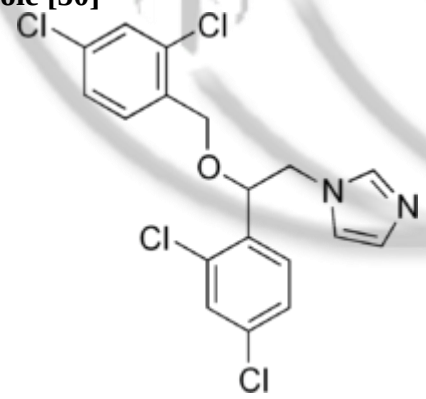
Half-life: - Biphasic:

Initial phase: 2 hours

Terminal phase: 8 hours

Excretion: - Biliary and renal

Miconazole [50]



Systematic (IUPAC) name: - (RS)-1-(2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole

Chemical data

Formula: - C18H14Cl4N2O

Mol. mass: - 416.127 g/mol

Melting Point: - 170.5 °C**[51]**

Description: -- White To Pale Cream powder**[USP]**

Solubility Profile: - Melts In The Range Of 78 to 88 Degree. May Exhibit Polymorphism. Insoluble in Water, Soluble In Ether, Freely Soluble In Alcohol, In Methanol, In Isopropyl Alcohol, In Acetone, In Propylene Alcohol, In Chloroform And InDimethylformamide. **[USP][52]**

Solubility Profile: - Freely Soluble In Methanol, Slightly Soluble In Ethanol And In Chloroform. Very Slightly Soluble In Water and IN Ether**. [IP][53]**

Pharmacokinetic data

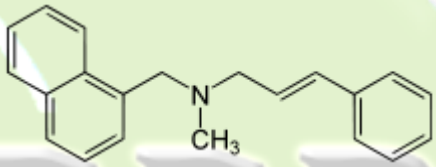
Bioavailability: - low (25-30%) **[54]**

Protein binding: - 91% to 93% **[55]**

Metabolism: - liver **[56]**

Half-life: - 24.1 to 25.4 hours **[57]**

Naftifine [58]



Systematic (IUPAC) name: - (2E)-N-methyl-N-(1-naphthylme

Chemical data

Formula: - C21H21N

Mol. mass: - 287.398 g/mol

Melting Point: -170.5 °C **[59]**

Description: -- White Or White Crystal or Crystalline Powder; Odorless or Almost Odorless. **[60]**

Solubility Profile: - Slightly soluble in water freely soluble in anhydrous ethanol and methanol **[61]**

Pharmacokinetic data

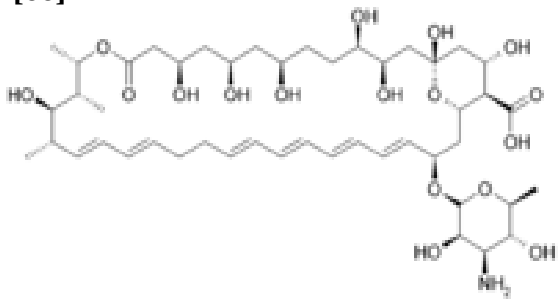
Bioavailability: - decreased with antacids, H2 blockers, proton pump inhibitors &food**[62]**

Protein binding: - (%) 91-95 4 91-93 99 >99**[63]**

Metabolism: - liver **[64]**

Half-life: - 2 to 3 days **[65]**

Nystatin [66]



Systematic (IUPAC) name: - (1S,3R,4R,7R,9R,11R,15S,16R,17R,18S,19E,21E,25E,27E,29E,31E,33R,35S,36R,37S)-33-[(3-amino-3,6-

dideoxy-β-L-mannopyranosyl)oxy]-1, 3,4,7,9,11,17,37-octahydroxy-15, 16,18-trimethyl-13-oxo-14, 39-dioxabicyclo[33.3.1]nonatriaconta-19, 21,25,27,29,31-hexaene-36-carboxylic acid

Chemical data

Formula: - C47H75NO17

Mol. mass: - 926.09

Melting Point: -160 °C without melting by 250 °C**.[67]**

Description: - Yellow To Light Tan Powder, Having an Odor Suggestive Of Cerals, Is Hygroscopic And Is Affected By Long, Exposure To light, Heat And Air. **[USP]**

Solubility Profile: - Soluble In Dimethylformamide And In dimrthysulfoxide, Sparingly Soluble in Methanol And In N-Propylalcohol And In N-Butyl alcohol, Practically Insoluble In Alcohol And In Alcohol, Insoluble In Chloroform And IN Ether. **[USP] [68]**

Solubility Profile: - Freely Soluble In Dimethylformamide, Slightly Soluble In methanol, Very Slightly Soluble In Water, Insoluble In Chloroform, In Ether And In Ethanol**[IP][69]**

Pharmacokinetic data

Bioavailability: - 0%

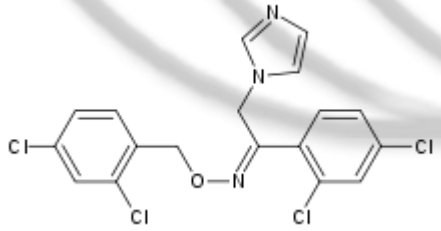
Metabolism: - on oral ingestion

on oral ingestion

Half-life: - 0.96 to 1.51 h**[70]**

Excretion: - unchanged in the faeces**[71]**

Oxiconazole [72]



Systematic (IUPAC) name: - (E)-[1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethylidene][(2,4-dichlorophenyl)methoxy]amine

Chemical data

Formula: - C18H13Cl4N3O

Mol. mass: - 429.126 g/mol

Description: -Oxiconazole nitrate is a nearly white crystalline powder**[73]**

Solubility Profile: soluble in methanol; sparingly soluble in ethanol, chloroform, and acetone; and very slightly soluble in water.

Pharmacokinetic data

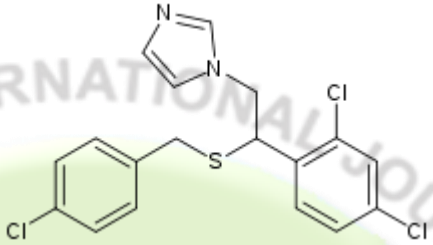
Metabolism: - enzyme cytochrome P450-3A4 **[74]**

Half-life: - serum 3 to 5 hours **[75]**

Excretion: - liver **[75]**

Protein binding: - 11–12%. **[75]**

Sulconazole[76]



Systematic (IUPAC) name: -1-(2-{[(4-chlorophenyl)methyl]sulfanyl}-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole

Chemical data

Formula: -$C_{18}H_{15}Cl_3N_2S$

Mol. mass: - 397.749 g/mol

Melting Point: -130°C**[77]**

Description: - White to off white , Crystalline powder**[USP]**

Solubility Profile: -. Melt at about 130 degree with decomposition. Very slightly soluble in water, in toluene, and in dioxane, slightly soluble in alcohol, in chloroform, in acetone and in methylene chloride, Sparingly soluble in mrthanol, Freely soluble in pyridine. **[USP][78]**

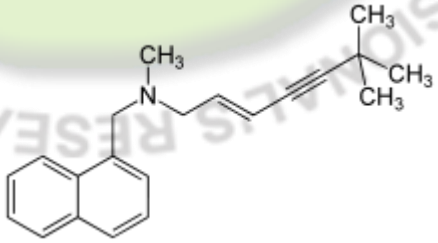
Pharmacokinetic data

Bioavailability: - 0.4 to 0.47**[79]**

Half-life: - 2 hr **[80]**

Excretion: - 85% is excreted unchanged via the kidneys **[81]**

Terbinafine [82]



Systematic (IUPAC) name: - [(2E)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl)amine

Chemical data

Formula: -$C_{21}H_{25}N$

Mol. mass: - 291.43 g/mol

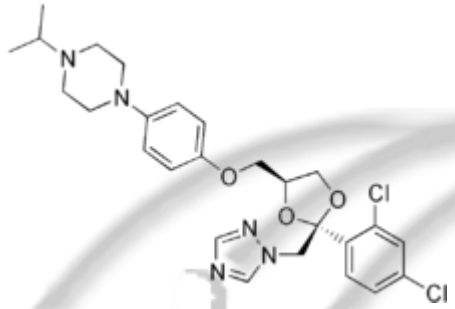
Melting Point: -145-151 C **[83]**

Description: White to off white powder **[USP]**

Solubility Profile: -. Freely soluble in dehydrated alcohol and in methanol.Slightly soluble in acetone.Very slightly and

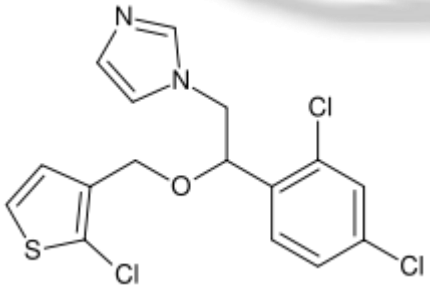
slightly soluble in water. **[USP][84]**
Pharmacokinetic data
Bioavailability: - Readily absorbed: 70 - 90%
Protein binding: ->99%
Metabolism: - Hepatic
Half-life: - Highly variable

Terconazole[85]



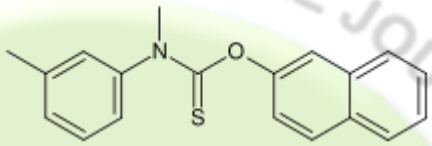
Systematic (IUPAC) name 1-[4-[[(2S,4S)-2-(2,4-Dichlorophenyl)-2- (1,2,4-triazol-1-ylmethyl)- 1,3-dioxolan-4-yl]methoxy]phenyl]- 4-propan-2-yl-piperazine
Chemical data
Formula: -$C_{26}H_{31}Cl_2N_5O_3$
Mol. mass: - 532.462 g/mol
Melting Point: -126.3°C**[86]**
Description: white to almost-white powder**[87]**
Solubility Profile: - Insoluble in water; sparingly soluble in ethanol and soluble in butanol**[87]**
Pharmacokinetic data
Protein binding: - 94.9%
Bioavailability: - 25% (fasting) **[88]**
Half-life: - 6.9 hours (range 4.0-11.3) **[89]**
Excretion: - urine **[90]**

Tioconazole [91]



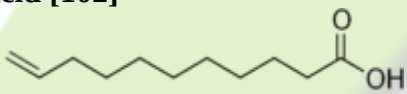
Systematic (IUPAC) name(RS)-1-[2-[(2-Chloro-3-thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole
Chemical data
Formula$C_{16}H_{13}Cl_3N_2OS$
Mol. mass 387.711 g/mol
Melting Point: -126.3°C**[92]**
Description: white to almost-white powder**[93]**
Solubility Profile: - Insoluble in water, Soluble in ethanol and soluble in butanol.
Pharmacokinetic data
Half-life:- (6 to 12 hours) **[94]**
Protein binding:-25% **[95]**
Metabolism: - In the liver **[95]**

Tolnaftate[96]



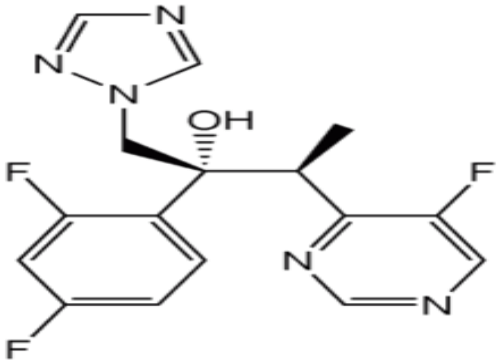
Systematic (IUPAC) name: -O-2-naphthyl methyl(3-methylphenyl)thiocarbamate
Chemical data
Formula: -$C_{19}H_{17}NOS$
Mol. mass: - 307.41 g/mol
Melting Point: -111 oC**[97]**
Solubility Profile: - practically insoluble in water **[98]**
Pharmacokinetic data
Half-life:- 1.7 hours **[99]**
Protein binding: -99% **[100]**
Bioavailability: - 80%**[101]**

UndecylenicAcid [102]



Systematic (IUPAC) name:-undec-10-enoic acid
Chemical data
Formula:-$C_{11}H_{20}O_2$
Mol. mass:-184.28 g/mol
Melting Point:-22 - 25 C**[103]**
Description:- Clear, Colorless to pale yellow liquid having a characterstic odor. **[USP][104]**
Solubility Profile: -. Practically insoluble in water, Miscible with alcohol, with chloroform, With ether, With benjene and with fixed and volatile oil. **[USP] [104]**
Pharmacokinetic data
Half-life:- 15 to 20 minutes**[105]**
Protein binding : -not available
Bioavailability: -20%**[106]**

Voriconazole[107]



Systematic (IUPAC) name:-(2R,3S)- 2-(2,4-difluorophenyl)- 3-(5-fluoropyrimidin-4-yl)- 1-(1H-1,2,4-triazol-1-yl) butan- 2-ol

Chemical data

Formula: - C16H14F3N5O

Mol. mass: - 349.311 g/mol

Melting Point:-127 C**[108]**

Description:-white to off white crystalline powder**[108]**

Solubility Profile: - Poor water solubility in water.**[109]**

Pharmacokinetic data

Bioavailability: - 96%

Protein binding: - 58%

Metabolism: -Hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, CYP3A4

Half-life: - Dose-dependent

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