

Sulyma M.I.,

Ass. Prof., Danylo Halytsky

Lviv National Medical University

Ogurtsov V.V.,

PhD, Danylo Halytsky

Lviv National Medical University

CALCIUM CHANNEL BLOCKERS: SIMILARITIES AND DIFFERENCES IN PHARMACOLOGICAL PROFILE

Summary. Cardiovascular diseases (CVD) have to be considered a major public health challenge over the coming decades. Update research showed increase in number of annual incidences caused by heart and blood vessels diseases and they are supposed to be the leading cause of mortality worldwide [1, P. 38-42.]. In 2013, 50,744 cases of acute heart attack was registered according to the report of Ministry of Healthcare of Ukraine. Lowering of blood pressure can significantly reduce the incidence of complications. So, a large number of clinical trials have addressed this issue, but have failed to show that one or more drug-classes are superior to the others and the best choice for the first-line medication among the all available. In 2012, the Ministry of Healthcare of Ukraine recommended the calcium channel blockers(CCB) as the first-line drugs in CVD treatment [3, 108 p.].

Key words: amlodipine, nifedipine, nimodipinum, felodipinum, diltiazemi hydrochloridum, verapamili hydrochloridum.

Calcium channel blocking drugs are a chemically heterogenous group, so it might be expected that their effects on vascular smooth muscle, cardiac contractility, may differ. So, the effects of individual drugs vary by their degrees of selectivity at different tissue sites and by baroreceptor responses to vasodilation caused by the CCB. They inhibit the entry of excess calcium into cells and prevent the mobilization of calcium from intracellular stores, resulting in relaxation of blood vessel walls and cardiac muscle for blood to flow more freely. This causes lowering of blood pressure

thereby reducing oxygen demand in the heart and relieving anginal pain. In the chemical classification of calcium channel blockers, a list of drugs which significantly expands with new research consists of 4 main classes: dyfenilalkilamines , dyfenilpiperazines, benzodiazepines and dihydropyridine. The most dynamic and most promising is a group of dihydropyridine derivatives. It consists of a maximum number of drugs, some of which is included in the standard treatment protocols.

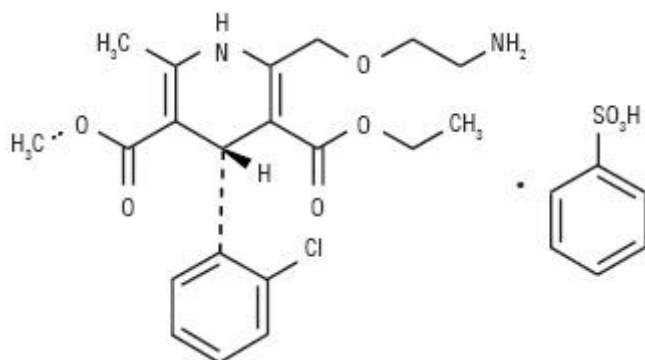
Several new dihydropyridine calcium antagonists (CA) have been introduced in recent years. The advantages of the newer compounds, such as amlodipine, felodipine, isradipine, lacidipine and lercanidipine, may include: vasoselectivity, hence little or no cardiodepressant activity; an improved kinetic profile, resulting in a slow onset and long duration of action, fewer side-effects such as reflex tachycardia and headache, owing to the slow onset of the antihypertensive action. For a few newer CA a predominant effect on specialized circulatory beds (renal, coronary and cerebral) has been claimed. The new CA, which are clearly lipophilic, deserve special attention. Owing to the lipophilic character of such compounds considerable concentration occurs in lipid-containing membrane depots. The CA thus concentrated are slowly released from these depots and, subsequently, reach their targets, the L-type calcium channels. This phenomenon explains both the slow onset and the long duration of action of these CA[8, P. 2105–2014.; 10, P.175-184.; 4, P. 50-52.].

According to the literature sources, a number of authors investigated antihypertensive drugs including pharmacokinetics, pharmacodynamics and efficacy (6, P.96-105.; 9, P.112-114.). The updated research trials showed that Ukrainian market of calcium channel blockers based mainly on 9 substances (nifedipine, nikardypine, amlodipine, nimodipine, felodipine, lacidipine, lercanidipine, verapamil, diltiazem) [2, 620 p.; 5, 3199p.; 7, 2416 p.]. The purpose of this study was to compare the different molecular properties of CCBs.

Amlodipine

The active pharmaceutical ingredient of synthetic origin. White or almost white powder, soluble in water, soluble in methanol, moderately in ethanol, and slightly

soluble in propanol. Store in a sealed container well shielded from light. Identified by the infrared absorption spectrum of substance ; by TLC. UV spectrum of substances in solution 0.01 M hydrochloric acid in methanol has $\lambda_{\max}=360$ nm ($A_{1\text{cm}}^{1\%}=113-121$). Quantitatively determined by liquid chromatography.



Chemical Names: Amlodipine; 88150-42-9; Norvasc; Amlodis; Amlocard; Coroval;

Molecular Formula: C₂₀H₂₅ClN₂O₅

Molecular Weight: 408.8759 g/mol

IUPAC Name 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

Melting Point 178-179 °C

Solubility

In water, 75.3 mg/L at 25 deg C (est)

Water Solubility

75.3 mg/L

Vapor Pressure

1.19X10⁻⁹ mm Hg at 25 deg C (est)

LogP

log Kow = 3.00

Dissociation Constants

pKa = 8.79 (amine) (est)

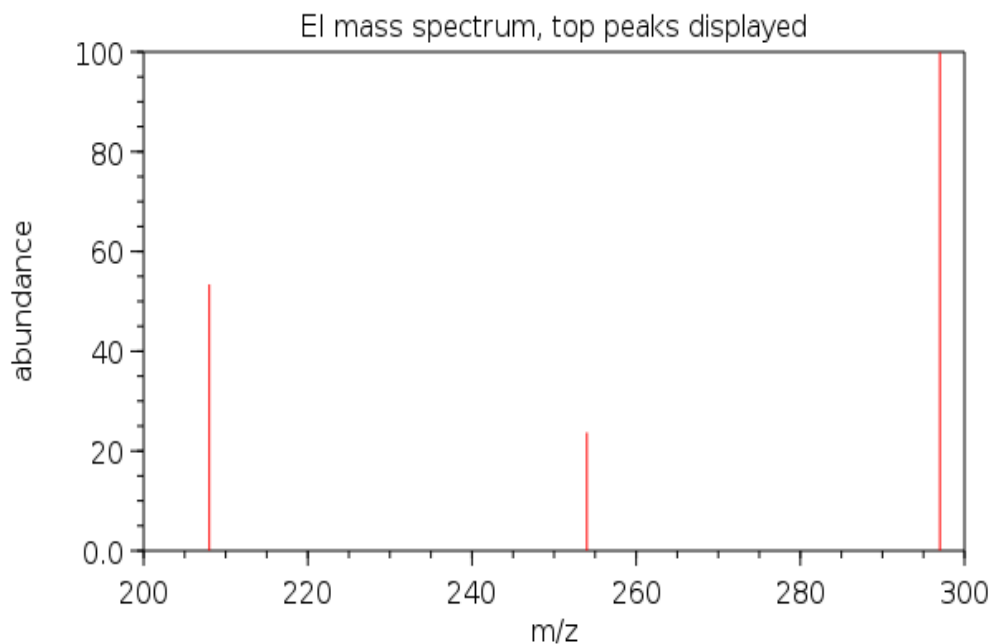
Spectral Properties

Total Peaks 263

m/z Top Peak 297

m/z 2nd Highest 208

m/z 3rd Highest 254



Amlodipine is a long-acting 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, amlodipine prevents calcium-dependent myocyte contraction and vasoconstriction. A second proposed mechanism for the drug's vasodilatory effects involves pH-dependent inhibition of calcium influx via inhibition of smooth muscle carbonic anhydrase. Some studies have shown that amlodipine also exerts inhibitory effects on voltage-gated N-type calcium channels. N-type calcium channels located in the central nervous system may be involved in nociceptive signaling and pain sensation. Amlodipine is used to treat hypertension and chronic stable angina.

Identification

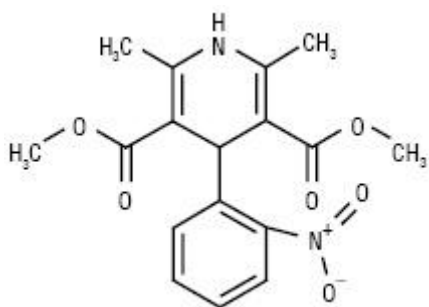
1. Analytic Laboratory Methods

A gas chromatography assay with electron capture has a limit of detection 0.2 ug/L. A gas chromatography-mass spectrometry method has also been described to assay amlodipine and its major metabolites.

Clinical Laboratory Methods

Gas chromatography determination in plasma.

Nifedipine



Chemical Names: Nifedipine; 21829-25-4; Adalat; Procardia; Procardia XL; Adalat CC;

Molecular Formula: C₁₇H₁₈N₂O₆

Molecular Weight: 346.33462 g/mol

IUPAC Name - dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Physical Description

PHYSICAL DESCRIPTION: Odorless yellow crystals or powder. Tasteless. (NTP, 1992)

Color Yellow crystals

Melting Point 172-174 °C

Solubility at 20 °C (g/L): acetone 250, methylene chloride 160, chloroform 140, ethyl acetate 50, methanol 26, ethanol 17

Water Solubility Insoluble

Vapor Pressure 2.6X10⁻⁸ mm Hg at 25 °C

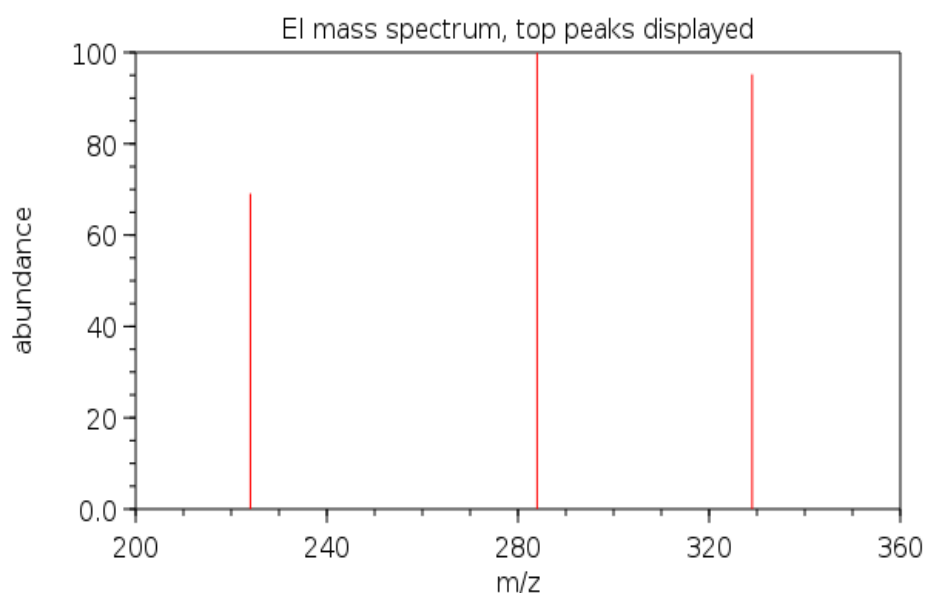
LogP log Kow = 2.20

Decomposition

When heated to decomposition, it emits toxic fumes of /nitrogen oxides/.

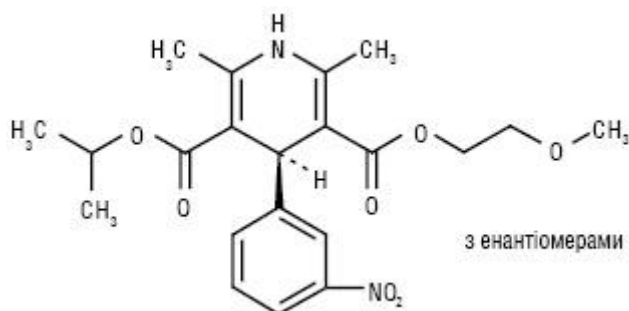
Spectral Properties

UV max (methanol): 340, 235 nm (E 5010, 21590); (0.1N HCl): 338, 238 nm (E 5740, 20600); (0.1N NaOH): 340, 238 (E 5740, 20510)



Nifedipine is a dihydropyridine calcium channel blocking agent. Nifedipine inhibits the transmembrane influx of extracellular calcium ions into myocardial and vascular smooth muscle cells, causing dilatation of the main coronary and systemic arteries and decreasing myocardial contractility. This agent also inhibits the drug efflux pump P-glycoprotein which is overexpressed in some multi-drug resistant tumors and may improve the efficacy of some antineoplastic agents. (NCI04)

Nimodipinum



Chemical Names: Nimodipine; Nimotop; 66085-59-4; Periplus; Nimodipino; Nimodipinum.

Molecular Formula: $C_{21}H_{26}N_2O_7$

Molecular Weight: 418.44034 g/mol

IUPAC Name 3-O-(2-methoxyethyl) 5-O-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Melting Point 125 °C

LogP 3.05

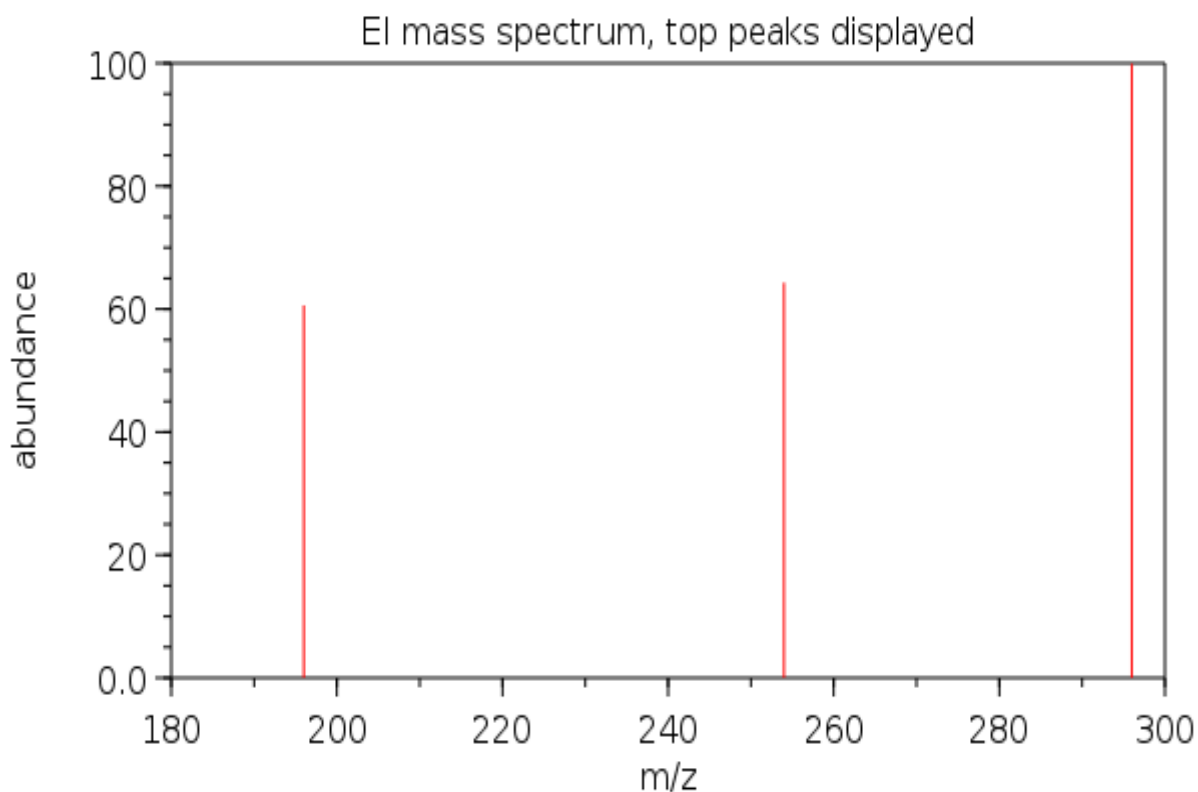
Spectral Properties

Total Peaks 201

m/z Top Peak 296

m/z 2nd Highest 254

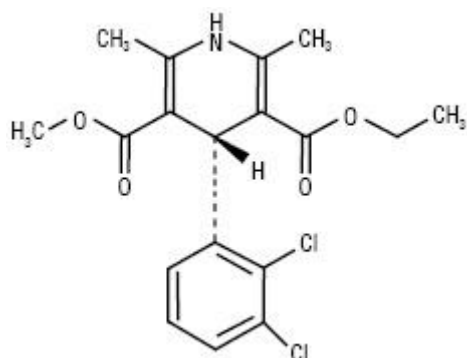
m/z 3rd Highest 196



Nimodipine is a 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, nimodipine prevents calcium-dependent smooth muscle contraction and subsequent vasoconstriction. Compared to other calcium channel blocking agents,

nimodipine exhibits greater effects on cerebral circulation than on peripheral circulation. Nimodipine is used to as an adjunct to improve the neurologic outcome following subarachnoid hemorrhage from ruptured intracranial aneurysm.

Felodipinum



Chemical Names: Felodipine; Plendil; 72509-76-3; Splendil; Flodil; Munobal;

Molecular Formula: C₁₈H₁₉Cl₂NO₄

Molecular Weight: 384.25376 g/mol

IUPAC Name 5-O-ethyl 3-O-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Melting Point 145 °C

Solubility. Water Solubility 19.7 mg/L

LogP 3.86

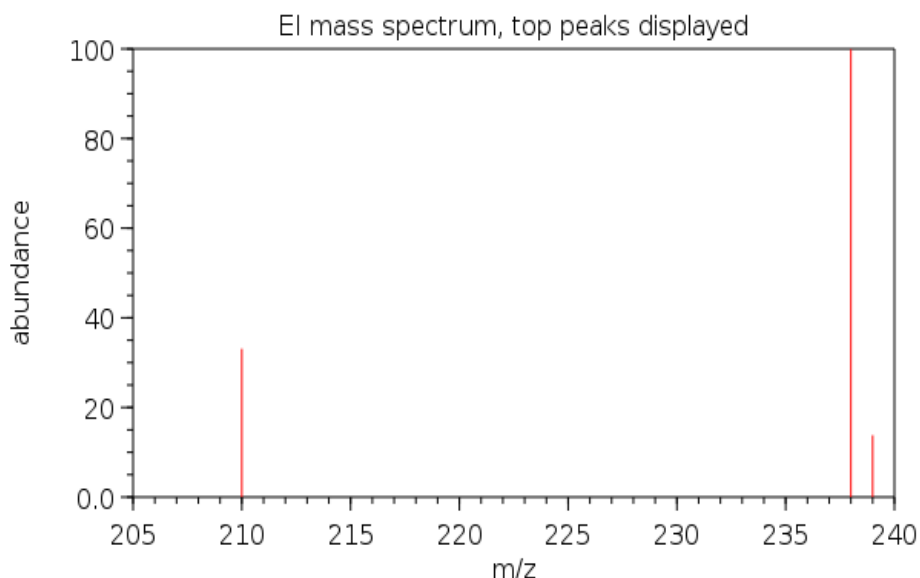
Spectral Properties

Total Peaks 317

m/z Top Peak 238

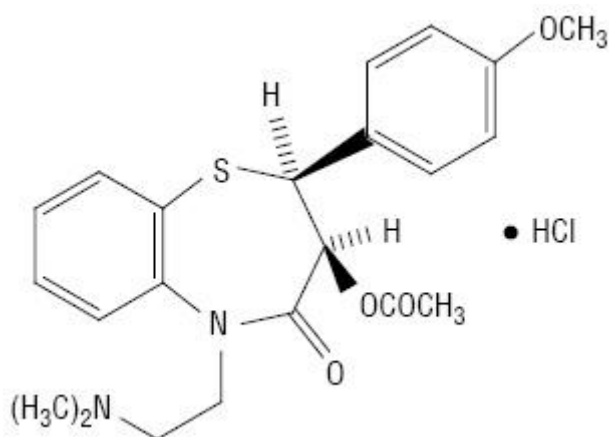
m/z 2nd Highest 210

m/z 3rd Highest 239



Felodipine is a long-acting 1,4-dihydropyridine calcium channel blocker (CCB). It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, felodipine prevents calcium-dependent myocyte contraction and vasoconstriction. Felodipine is the most potent CCB in use and is unique in that it exhibits fluorescent activity. In addition to binding to L-type calcium channels, felodipine binds to a number of calcium-binding proteins, exhibits competitive antagonism of the mineralocorticoid receptor, inhibits the activity of calmodulin-dependent cyclic nucleotide phosphodiesterase, and blocks calcium influx through voltage-gated T-type calcium channels. Felodipine is used to treat mild to moderate essential hypertension.

Diltiazem hydrochloridum



Chemical Names: Diltiazem hydrochloride; Diltiazem HCl; 33286-22-5; Tiazac; Dilzene; Herbesser.

Molecular Formula: $C_{22}H_{26}N_2O_4S$

Molecular Weight: 450.97878 g/mol

IUPAC Name [(2S,3S)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl] acetate; hydrochloride

The active pharmaceutical ingredient of synthetic origin. The white crystalline powder, soluble in water, methanol, methylene chloridi, slightly soluble in ethanol.

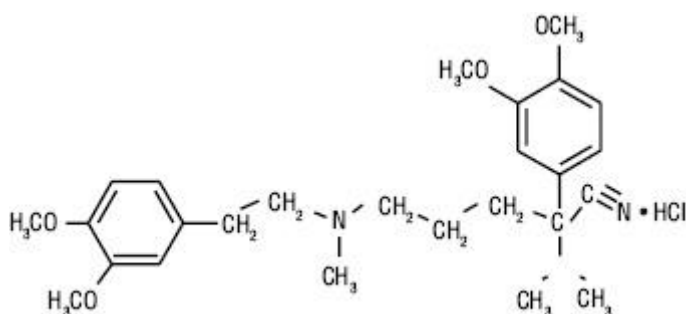
Melting point close 213 °C with decomposition.

UV spectrum: $\lambda_{\max}=239$ nm ($A_{1\text{ cm}}^{1\%}=537$) in methanol, $\lambda_{\max}=236$ nm ($A_{1\text{ cm}}^{1\%}=522$) in water, $\lambda_{\max}=236$ nm ($A_{1\text{ cm}}^{1\%}=533$) in 0,1 M hydrochloric acid solution, $\lambda_{\max}=237$ nm ($A_{1\text{ cm}}^{1\%}=285$) in 0,1 M sodium hydroxide. $[\alpha]_D^{20}$ = from +115° to +120° (1% water solution). Stored in a sealed container well, which prevents light. Identified by the infrared absorption spectrum of substance; by TLC; by reaction with a solution of ammonium reineckates - formed pink precipitate; It gives the typical reaction of chlorides.

Quantitatively determined by Acidimetry in non-aqueous media (formic acid and anhydrous acetic anhydride) potentiometrically.

Diltiazem hydrochloride is a benzothiazepine calcium channel blocking agent. Diltiazem hydrochloride inhibits the transmembrane influx of extracellular calcium ions into select myocardial and vascular smooth muscle cells, causing dilatation of coronary and systemic arteries and decreasing myocardial contractility. Because of its vasodilatory activity, this agent has been shown to improve the microcirculation in some tumors, thereby potentially improving the delivery of antineoplastic agents to tumor cells. (NCI04)

Verapamili hydrochloridum



Chemical Names: Verapamil hydrochloride; Verapamil HCl; 152-11-4; Manidon; Calcan hydrochloride; Cardibeltin;

Molecular Formula: $C_{27}H_{39}ClN_2O_4$

Molecular Weight: 491.06256 g/mol

IUPAC Name 2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethylmethylamino]-2-propan-2-ylpentanenitrile;hydrochloride

Color. Crystals,dec 138.5-140.5 °C

Melting Point 131-133 °C

Solubility. Solubility (mg/mL): water 83, ethanol (200 proof) 26, propylene glycol 93, ethanol (190 proof) >100, methanol >100, 2-propanol 4.6, ethyl acetate 1.0, DMF >100, methylene chloride >100, hexane 0.001.

LogP log Kow = 3.79

Stability Verapamil HCl should be stored at room temperature and protected from light. Infusion stability studies indicate that verapamil HCl does not adsorb to glass, PVC, or polyolefin containers. It is physically compatible in soln over a pH range of 3-6 but may precipitate in solns having a pH >6 or 7.

Decomposition

When heated to decomposition it emits toxic fumes of /nitrogen oxides and cyanide/.

pH: pH of 0.1% aq soln: 5.25; pKa 8.6.

Dissociation Constants: $pK_a = 8.92$

Spectral Properties: Intense mass spectral peaks: 59 m/z, 260 m/z, 303 m/z, 438 m/z, 454 m/z UV max 232, 278 nm.

Conclusion. The clinical efficacy of drugs mostly depends on their absorption, distribution, metabolism or elimination pathway (Di and Kernsy, 2003), which is extremely determined by lipophilic features of pharmacological agent. Nevertheless, a great number of the other molecular properties, such as molecular weight (M_w), molecular volume (Vol), polar surface area (PSA) and solubility data ($\log S$), also play an important role in drug absorption, penetration into tissues, degree of distribution, degree of plasma protein binding and route of elimination.

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