МЕДИЦИНСКИ УНИВЕРСИТЕТ – ПЛЕВЕН

ФАКУЛТЕТ „ФАКУЛТЕТ ФАРМАЦИЯ“

ЦЕНТЪР ЗА ДИСТАНЦИОННО ОБУЧЕНИЕ

Лекция №03

Анализ на лекарства, действащи на сърдечно-съдовата система - АСЕ инхибитори, АТ1 антагонисти и вазодилататори, 1 част

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Анализ на ACE инхибитори, AT1 антагонисти и вазодилататори

КЛАСИФИКАЦИЯ:

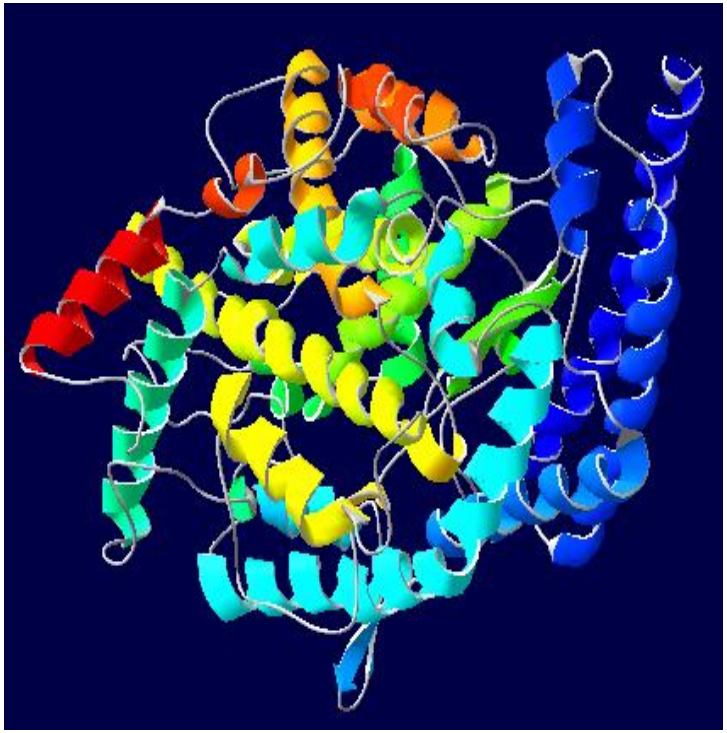
Sulfhydryl-containing agents:
Captopril (trade name Capoten)
Zofenopril

Dicarboxylate-containing agents:
Enalapril (Vasotec/Renitec)
Ramipril
(Altace/Tritace/Ramace/Ramiwin)
Quinapril (Accupril)
Perindopril (Coversyl/Aceon)
Lisinopril (Lisodur/Lopril/Novatec/
Prinivil/Zestril)
Benazepril (Lotensin)

Phosphonate-containing agents:
Fosinopril (Monopril)

Naturally occurring:
casein
tripeptides Val-Pro-Pro and Ile-Pro-Pro

Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1

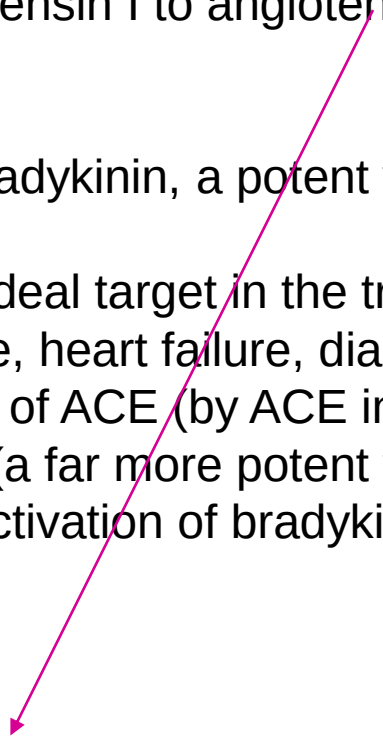


ФУНКЦИИ НА ACE :

1. It catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor.

2. It is involved in the inactivation of bradykinin, a potent vasodilator.

These two actions of ACE make it an ideal target in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy and type 2 diabetes mellitus. Inhibition of ACE (by ACE inhibitors) results in decreased formation of Angiotensin II (a far more potent vasoconstrictor than Angiotensin I) and decreased inactivation of bradykinin.

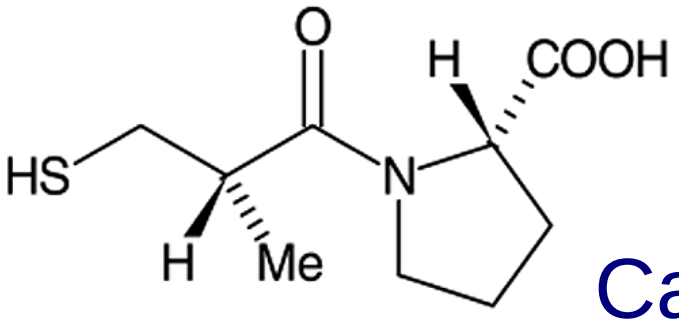


Angiotensin II:

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe | His-Leu

Анализ на ACE-инхибитори

Идентифициране



Captopril

(S)-1-(3-меркапто-α-метил-1-оксопропил)-L-пролин

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25.0 ml with the same solvent.

pH *(2.2.3)*

2.0 to 2.6 for solution S.

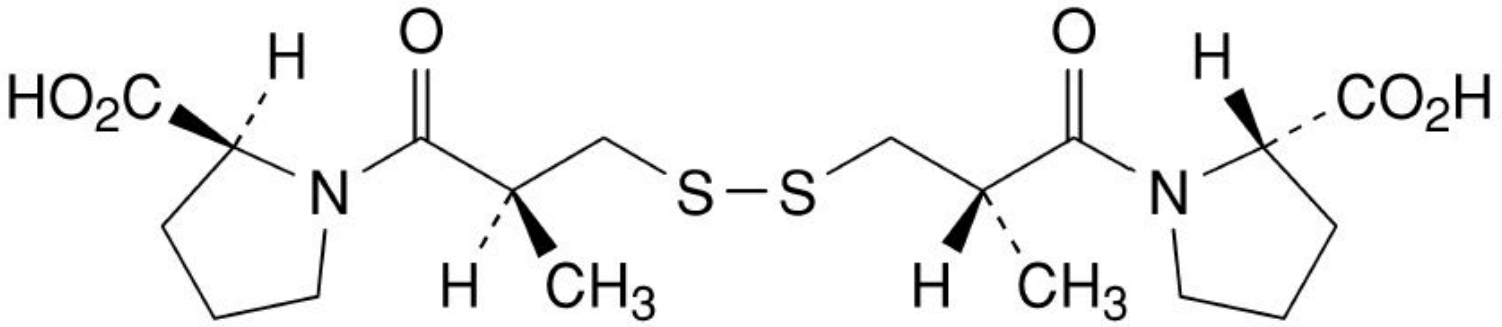
It dissolves in dilute solutions of alkali hydroxides.

ASSAY

Dissolve 0.150 g in 30 ml of *water R*. Titrate with *0.05 M iodine*, determining the end-point potentiometrically *(2.2.20)*. Use a combined platinum electrode.

1 ml of *0.05 M iodine* is equivalent to 21.73 mg of $C_9H_{15}NO_3S$.

ВЕТХ определяне на примеси



1,1-[disulphanediylbis[(2*S*)-2-methyl-1-oxopropane-3,1-diyl]-bis[pyrrolidine-2-carboxylic] acid (captopril-disulphide).

Стандартен р-р на онечистването – приготвя се *in situ* чрез обработване с окислител (йод)

Тест за пригодност на системата

Оценява се разделянето между три хроматографски пика, два от които съответстват на основното вещество и примеса

Оценка на хроматограмата

Граница на допустими примеси – сумарно 2%

Пренебрегват се всички пикове с време на задържане по-малко от 1,4 мин.

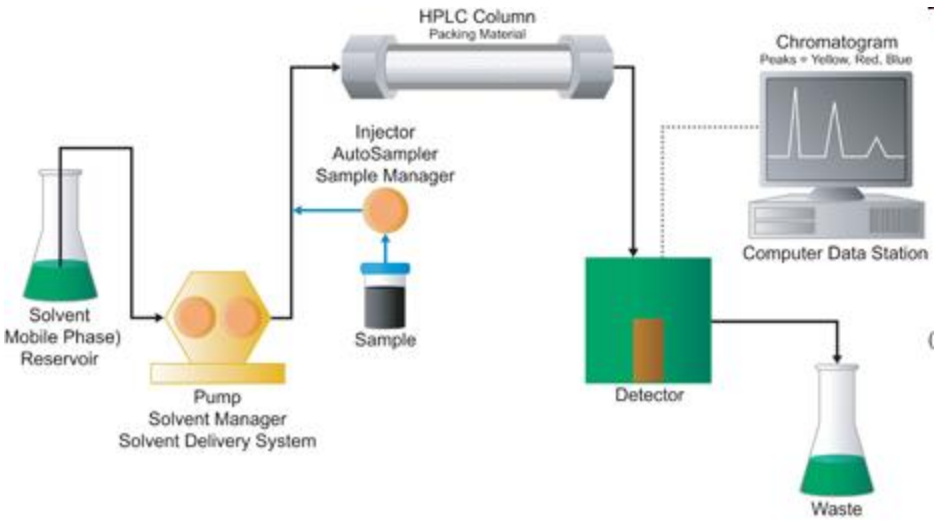
Количествено определяне

Субстанция

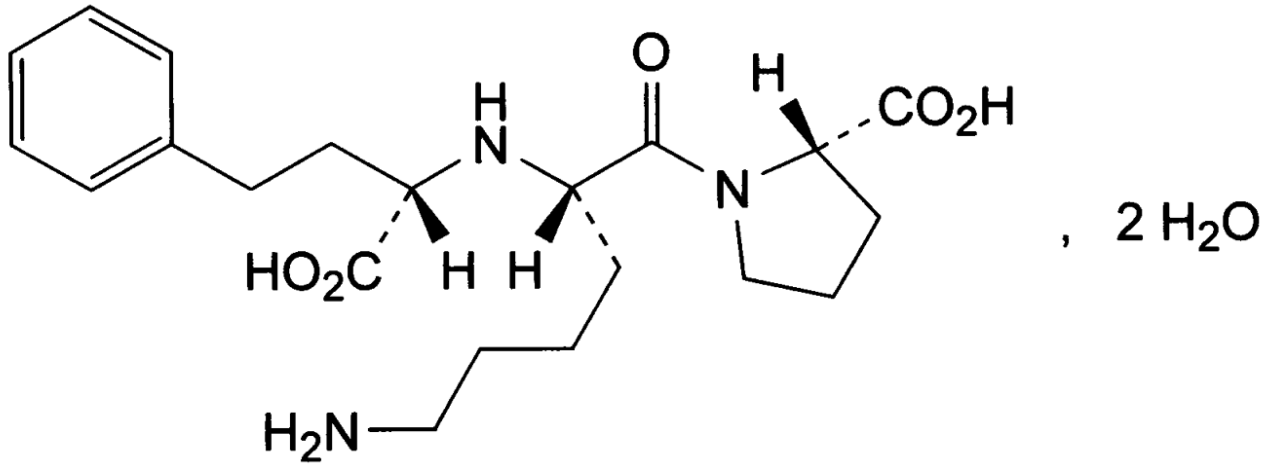
Йодометрично титруване, потенциометрично определяне на еквивалентния пункт

Таблетки

BETX



Lisinopril Dihydrate

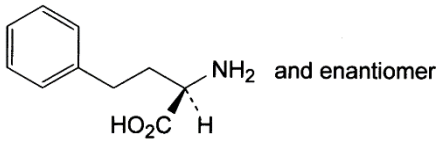


(2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrole-2-carboxylic acid

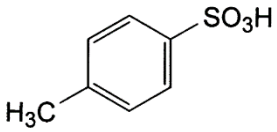
(S)-1-[N-(1-карбокси-3-фенилпропил)-L-лизил]-L-пролин дихидрат

Lisinopril Dihydrate

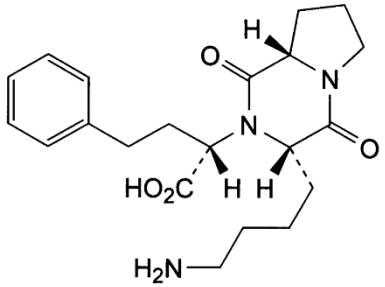
(2*RS*)-2-amino-4-phenylbutanoic acid,



4-methylbenzenesulphonic acid,



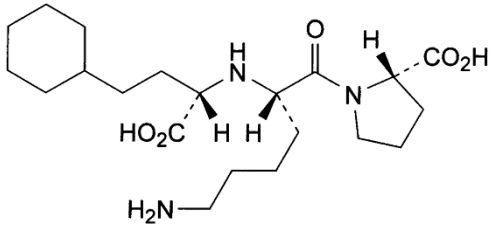
(2*S*)-2-[(3*S*,8a*S*)-3-(4-aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid (**S,S,S-diketopiperazine**),



S,S,S-diketopiperazine

(2*S*)-1-[(2*S*)-6-amino-2-[[(1*R*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrole-2-carboxylic acid (**lisinopril *R,S,S*-isomer**),

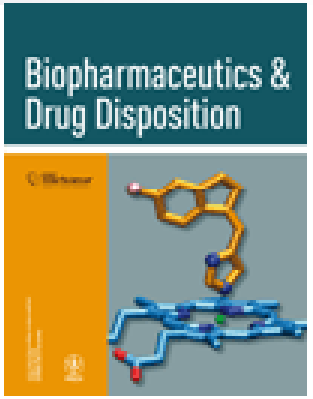
(2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-cyclohexylpropyl]amino]hexanoyl]pyrrole-2-carboxylic acid (**cyclohexyl analogue**).



cyclohexyl analogue

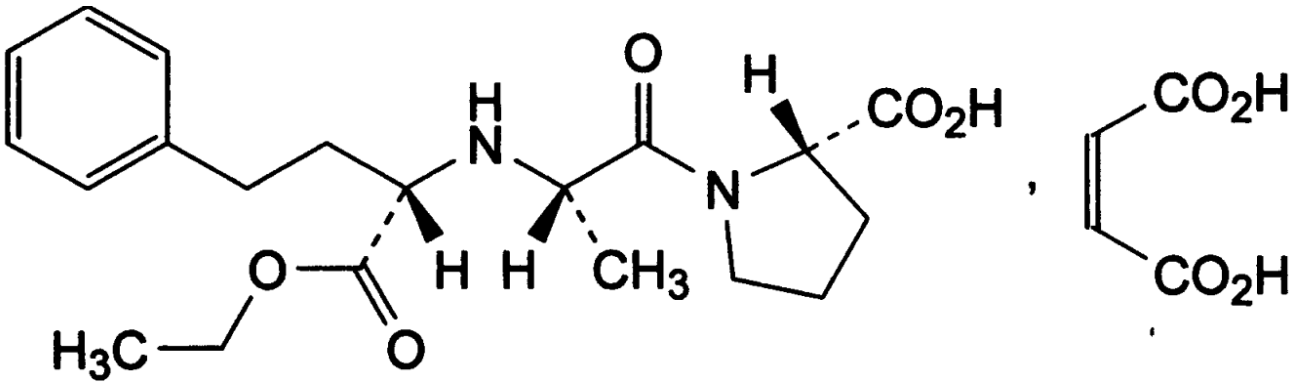
Bioequivalence evaluation of two brands of ***lisinopril tablets*** (Lisotec and Zestril) in healthy human volunteers

J. J. I. Tamimi [1], I. I. Salem [1], S. Mahmood Alam [2], Q. Zaman [2], Ruwayda Dham [2 *]



The bioequivalence of two brands of lisinopril 20 mg tablets was demonstrated in 28 healthy human volunteers after a single oral dose in a randomized cross-over study, conducted at ACDIMA Center for Bioequivalence and Pharmaceutical Studies, Amman, Jordan. Reference (Zestril, AstraZeneca, UK) and test (Lisotec, Julphar, UAE) products were administered to fasting volunteers on 2 treatment days separated by a 2-week washout period; blood samples were collected at specified time intervals, and the plasma was separated and analysed for lisinopril using a **validated LC-MS/MS** method at ACDIMA Laboratory. The pharmacokinetic parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}\alpha}$, C_{MAX}, T_{MAX}, $T_{1/2}$ and the elimination rate constant were determined from the plasma concentration-time profiles for both formulations and were compared statistically to evaluate bioequivalence between the two brands, using the statistical modules recommended by the FDA. The analysis of variance (ANOVA) did not show any significant difference between the two formulations and 90% confidence intervals fell within the acceptable range for bioequivalence. Based on these statistical inferences it was concluded that the two brands exhibited comparable pharmacokinetic profiles and that Julphar's Lisotec is bioequivalent to Zestril of AstraZeneca, UK.

Enalapril Maleate



(2*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl] amino]propanoyl]pyrrolidine-2-carboxylic acid (*Z*)-butenedioate

Идентифициране

Първа група – ИЧ-спектър

Втора група – определяне на точка на топене и две качествени цветни реакции:

-Взаимодействие с бромна вода/резорцин

-Хидроксамова проба – доказване на карбоксилна група

Контрол на чистотата – градиентна ВЕТХ

Онечиствания – от A до I

Примес C Enalaprilat

Примеси, които се оценяват – сумарно не повече от 1%

Част от онечистванията само се детектират

Количествено определяне

Неутрализационен титриметричен анализ

със стандартен р-р на натриев хидроксид

водна среда

потенциометрично установяване на края на титруването по втората инфлексна точка

ASSAY

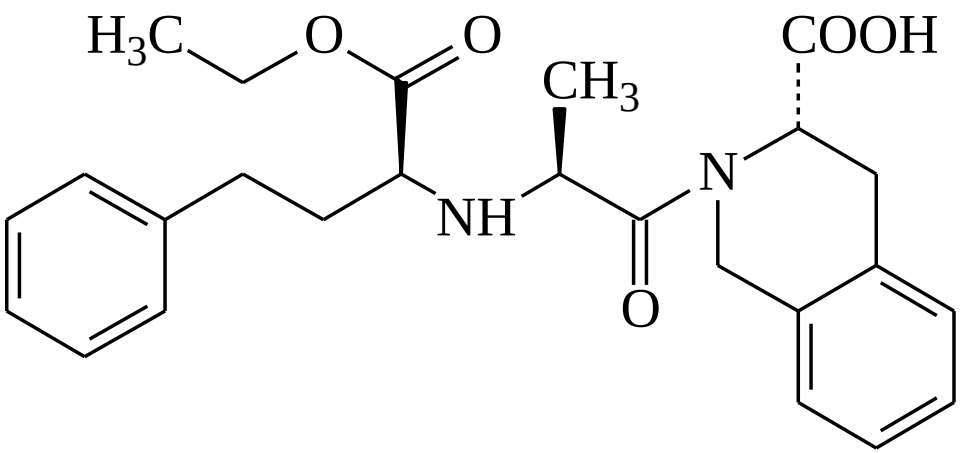
Dissolve 0.100 g in *carbon dioxide-free water R* and dilute to 30 ml with the same solvent. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically *(2.2.20)*. Titrate to the second point of inflexion.

1 ml of *0.1 M sodium hydroxide* is equivalent to 16.42 mg of $C_{24}H_{32}N_2O_9$.

pH *(2.2.3)*

The pH of solution S is 2.4 to 2.9.

Quinapril



Quinapril

Quinapril is a **prodrug**. It is converted to its active metabolite, quinaprilat, in the liver.

Indications

Quinapril is indicated for the treatment of high blood pressure (hypertension) and as adjunctive therapy in the management of heart failure. It may be used for the treatment of hypertension by itself or in combination with thiazide diuretics, and with diuretics and digoxin for heart failure.

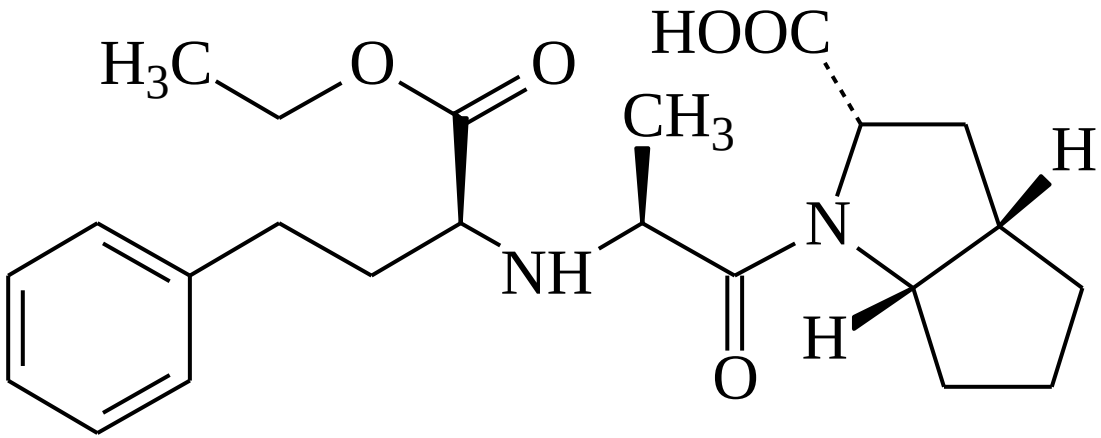
Contraindications

Pregnancy
Impaired renal and liver function
Patients with a history of angioedema related to previous treatment with an ACE inhibitor.
Hypersensitive to Quinapril

Side effects

Side effects of quinapril include dizziness, cough, vomiting, upset stomach, angioedema and fatigue.

Ramipril



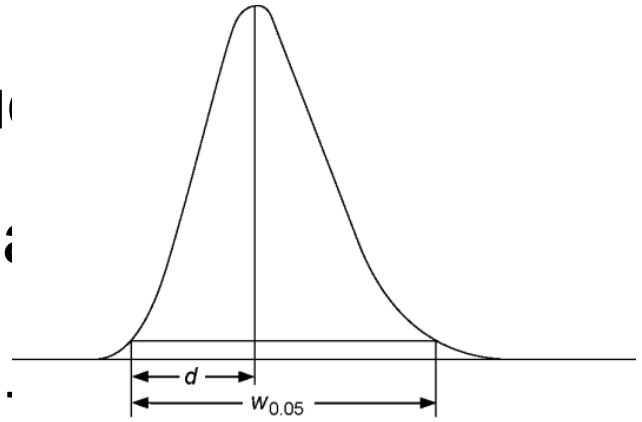
Идентичност и количествено определяне –

аналогично с Enalapril maleate

Количествено определяне на сродни вещества

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)	Comment
0 - 6	90	10	isocratic
6 - 7	90 → 75	10 → 25	linear gradient
7 - 20	75 → 65	25 → 35	linear gradient
20 - 30	65 → 25	35 → 75	linear gradient
30 - 40	25	75	isocratique
40 - 45	25 → 90	75 → 10	linear gradient
45 - 55	90	10	re-equilibration

Време за установяване на равн
модифициране на подвижна
неподходяща за анализ базова

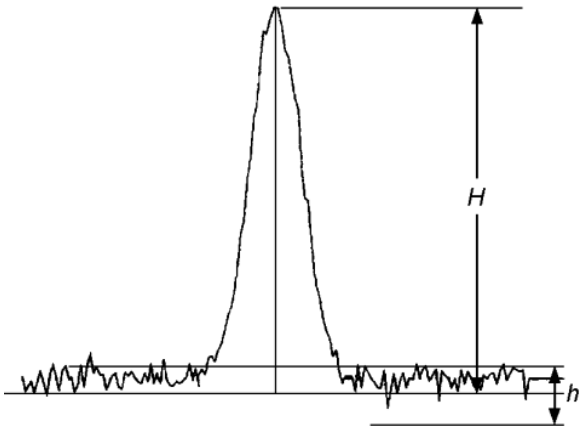


Условия за валидност на резултатите от хроматографския анализ

Степен на разделяне – основно вещество и примес А

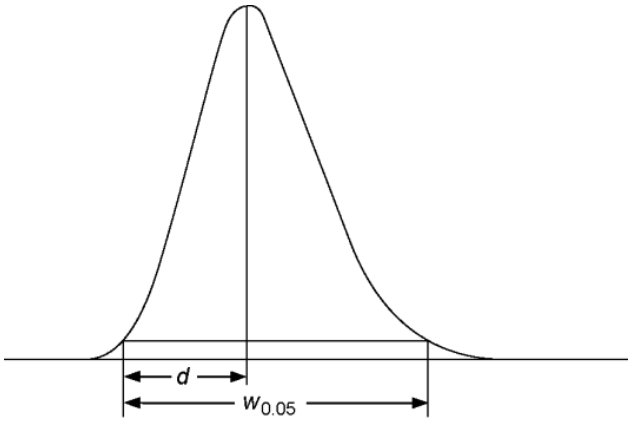
Отношение сигнал/шум

$$S/N = \frac{2H}{h}$$

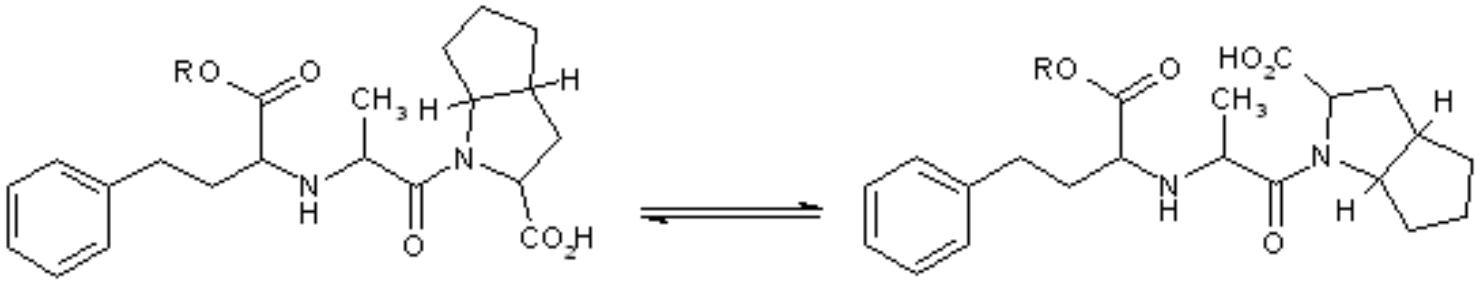


Фактор на симетрия

$$A_s = \frac{w_{0.05}}{2d}$$



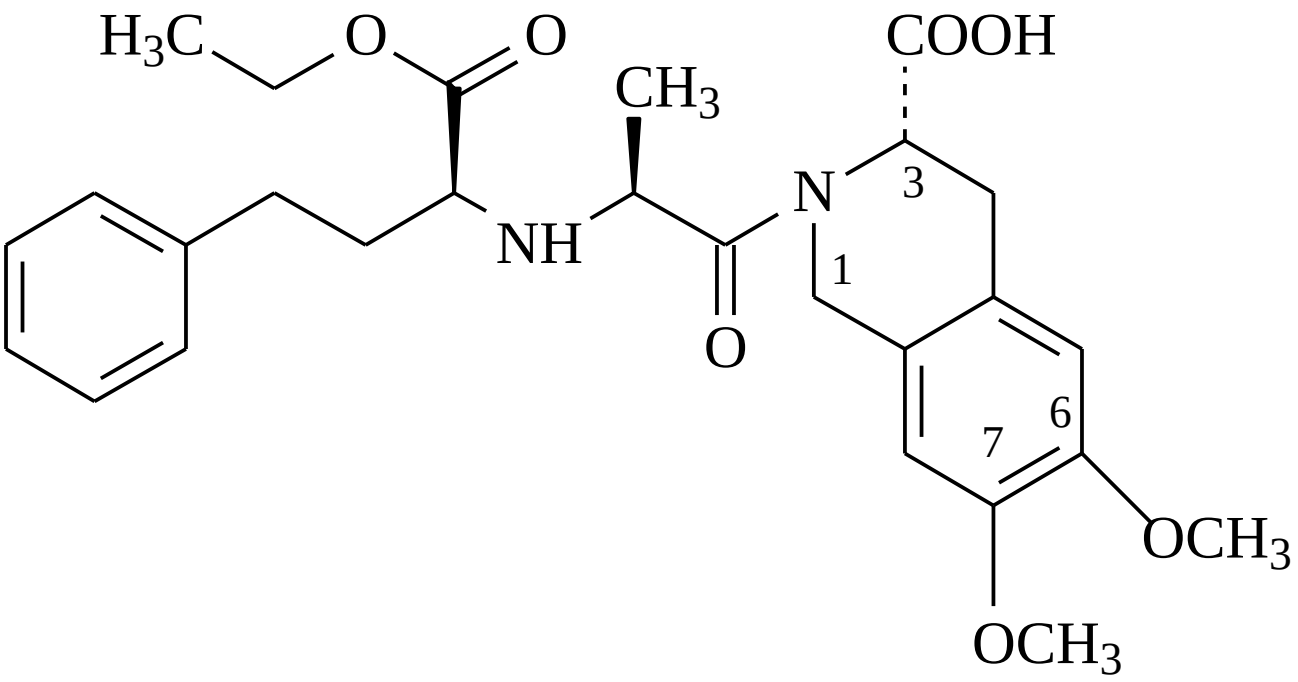
It is well known from **NMR** studies that both, priles and prilates, as a substituted amides, can exist in solution as *cis* and *trans* rotamers and may interconvert around the amide bond (see for example, rotamers of ramipril and ramiprilat).

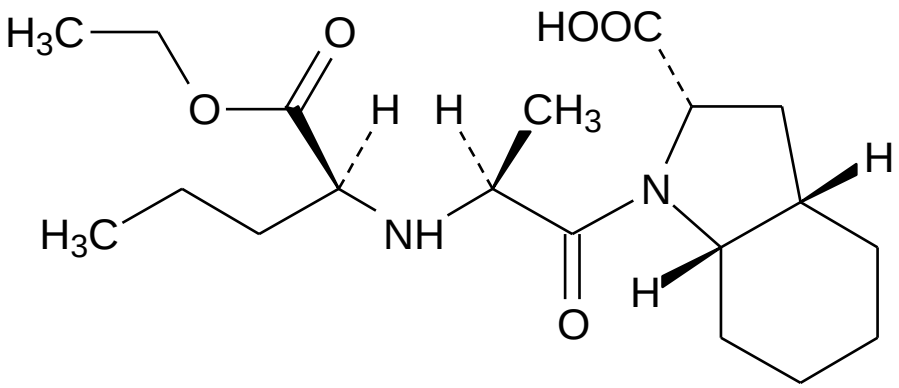


Ramipril R = Et
Ramiprilat R = H

The *cis-trans* isomerization process observed under HPLC condition can lead to misinterpretation of the identity of a peak, because peak broadening or even splitting can be easily attributed to an impurity. This should be taken into account when describing ACE inhibitors and their metabolism products in Pharmacopoeia.

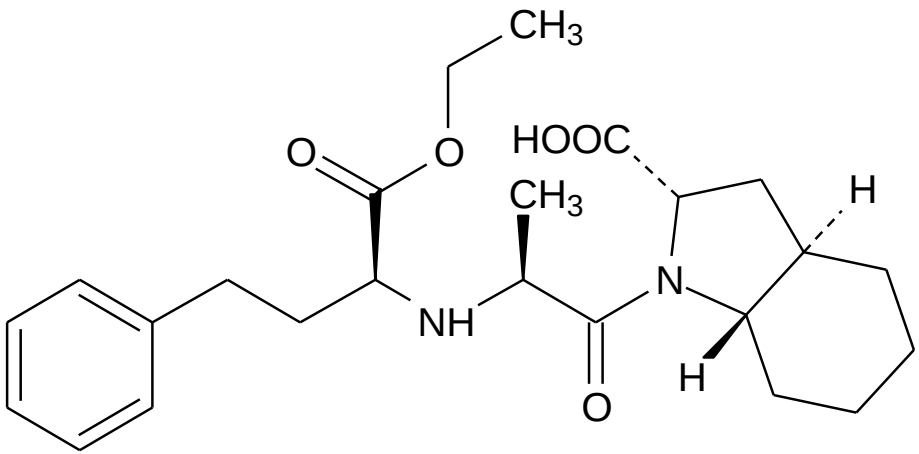
Moexipril



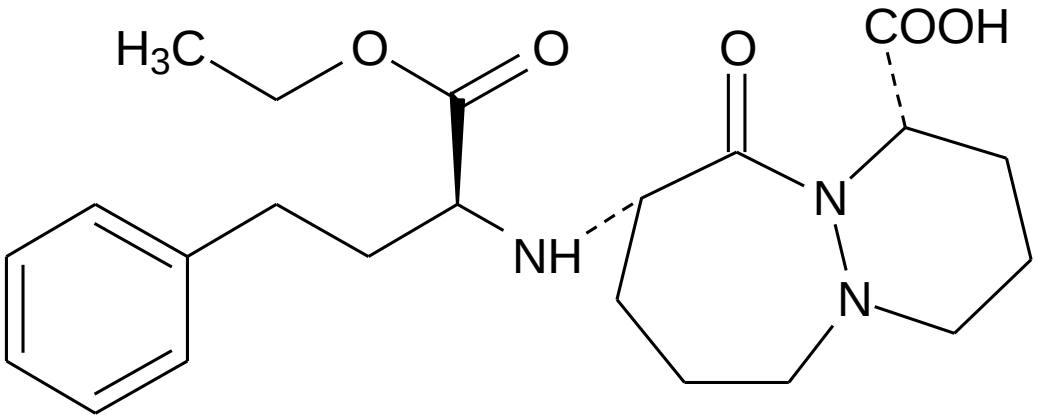


Perindopril

Trandolapril

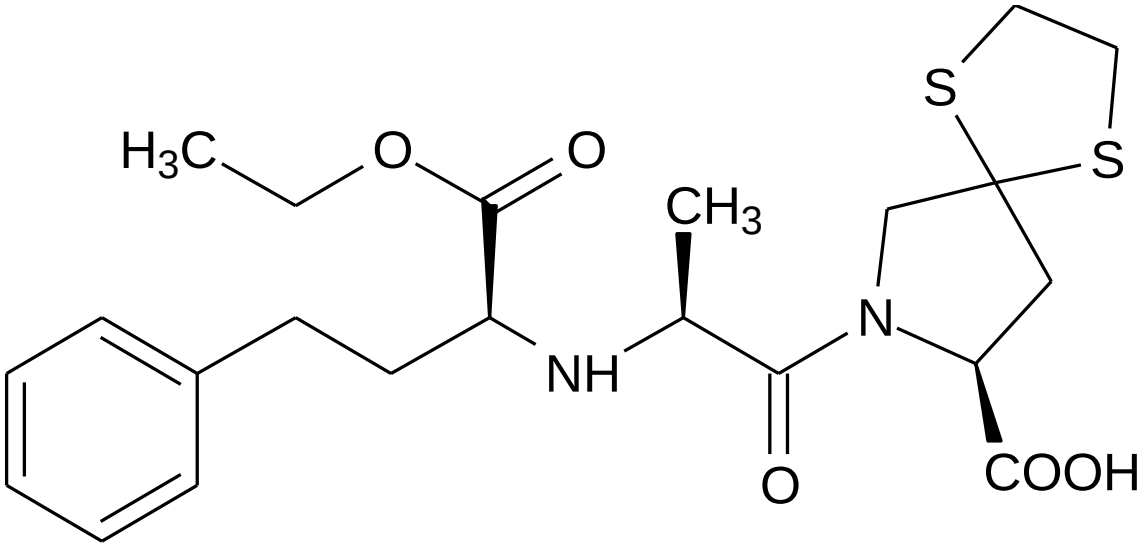


Cilazapril



(1*S*,9*S*)-9-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-*a*] [1,2]diazepine-1-carboxylic acid

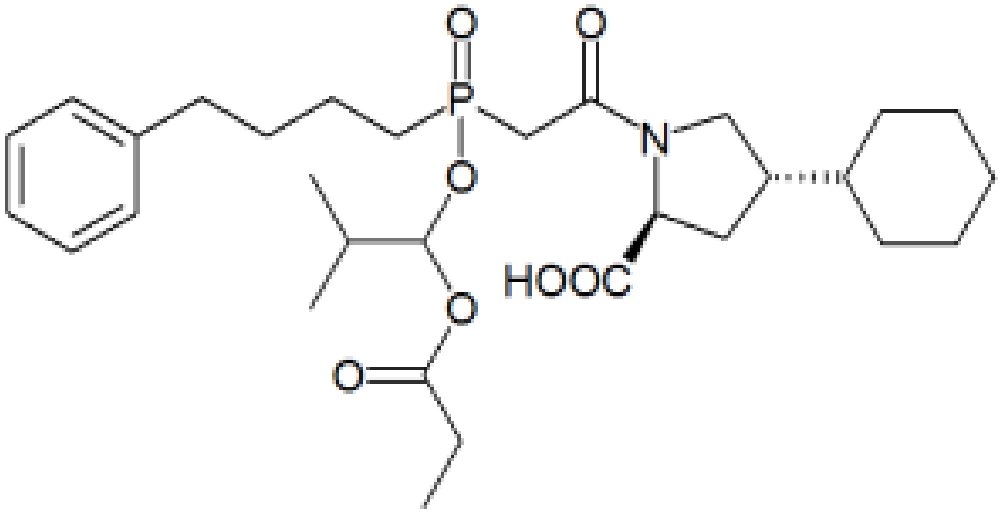
Spirapril



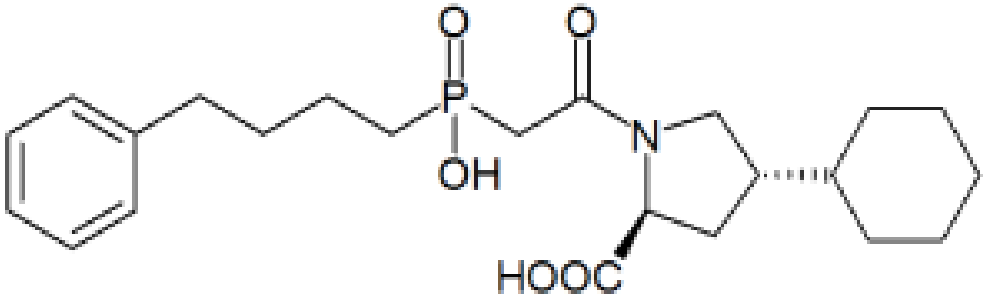
(8*S*)-7-[(2*S*)-2-[[(1*S*)-1-ethoxycarbonyl-3-phenyl-propyl] amino]propanoyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid

Spirapril

Pharmacokinetic data	
Bioavailability	50%
Metabolism	converted to spiraprilat
Half life	30 to 35 hours
Excretion	Hepatic and renal
Therapeutic considerations	
Pregnancy cat.	D
Legal status	℞ Prescription only
Routes	Oral



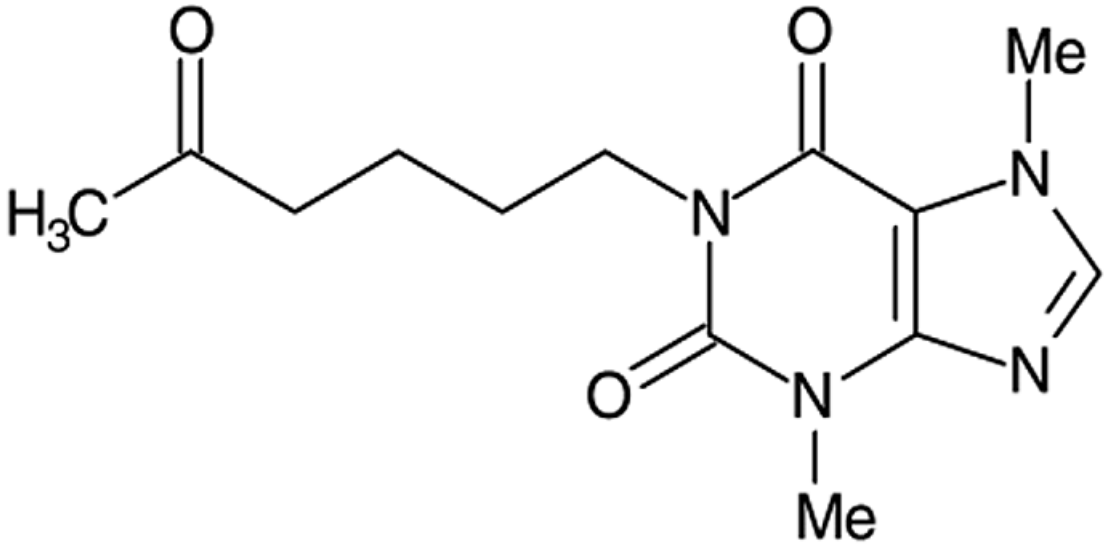
Fosinopril



Fosinoprilat

Анализ на вазодилататори

Pentoxifylline

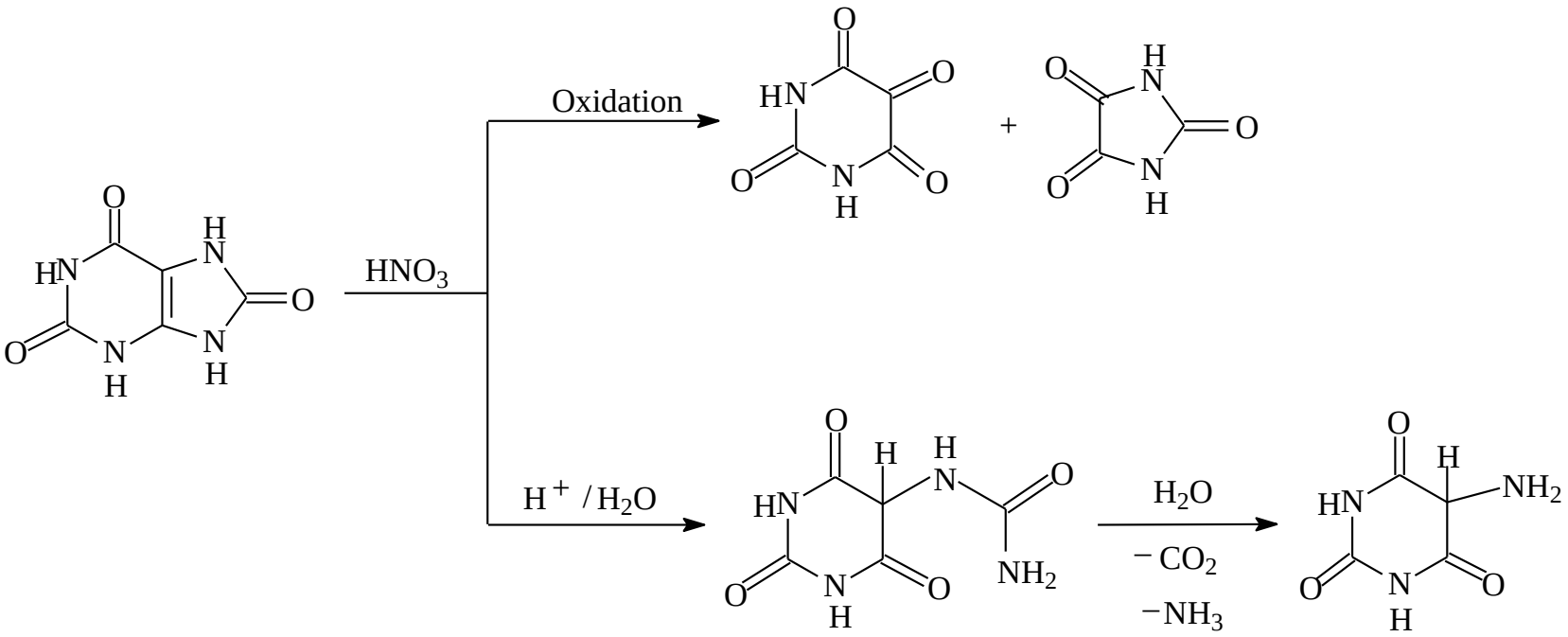


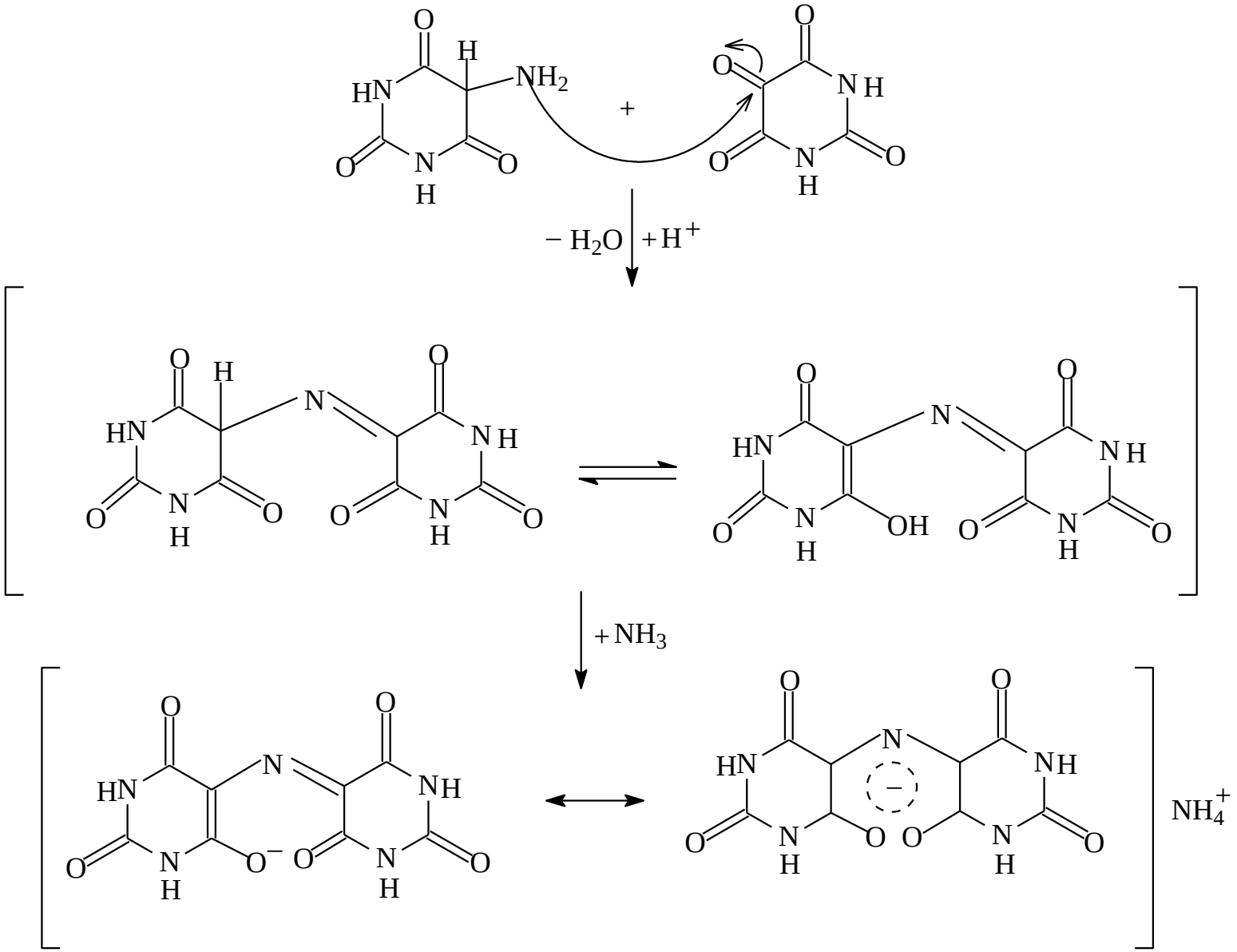
Подходи при идентифициране

Първа група – определяне на точка на топене и ИЧ-спектър

Втора група – т.т., ТСХ и качествена реакция за доказване на ксантини

Мурексидна проба




+
− H2O
+ H+
+ NH3
NH4+

Количествено определяне

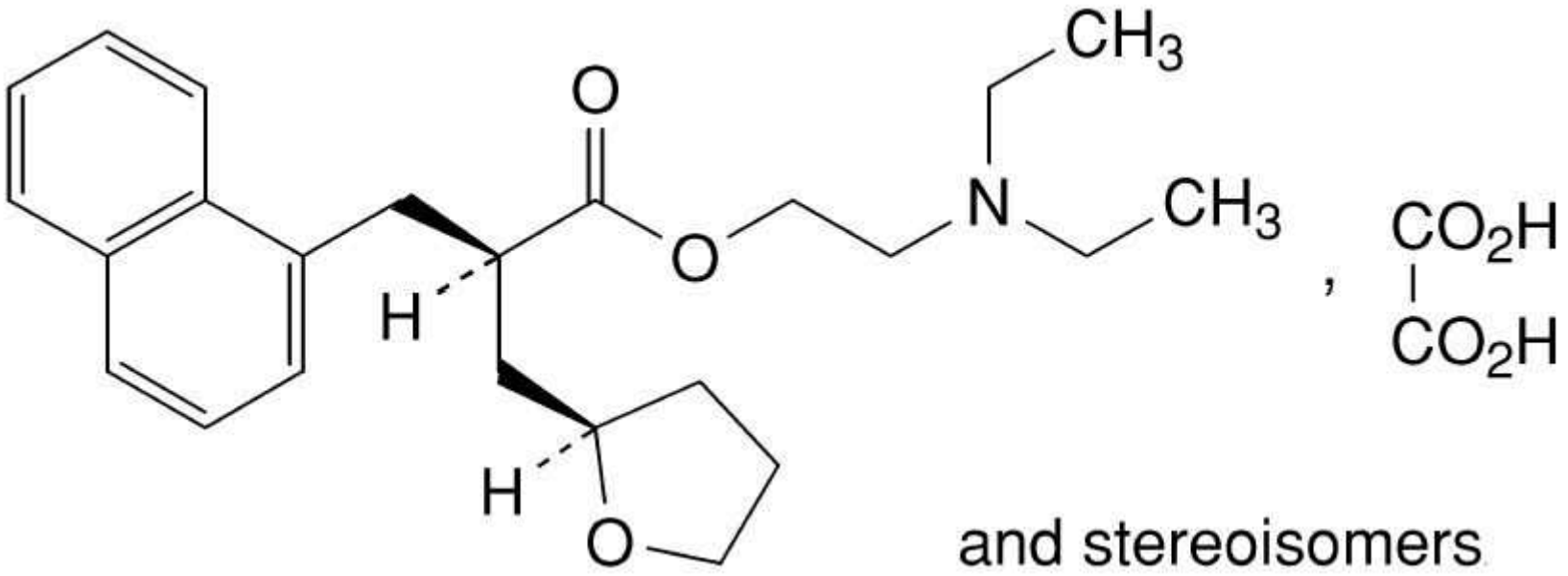
потенциометрично титруване

с перхлорна киселина

в среда от ледена оцетна киселина

N.B. Субстанцията е разтворима във вода

Naftidrofuryl Oxalate



Подходи при идентифициране

Първа група – ИЧ-спектър

Втора група – т.т., УВ-спектър и качествена реакция за доказване на оксалати

Определяне на примеси – BETX

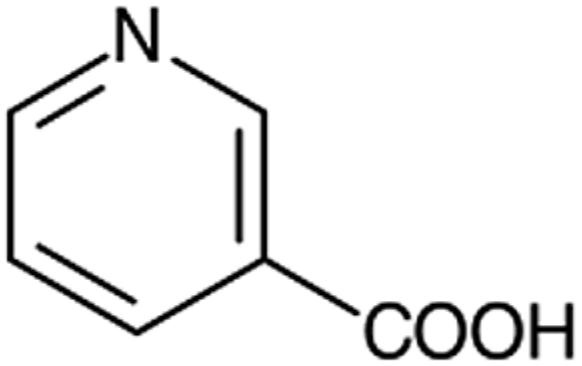
Количествено определяне –

потенциометрично титруване с перхлорна киселина в среда от ледена оцетна к-на

Идентичност

Т.т. и ИЧ-спектър

Nicotinic acid



Тест за чистота

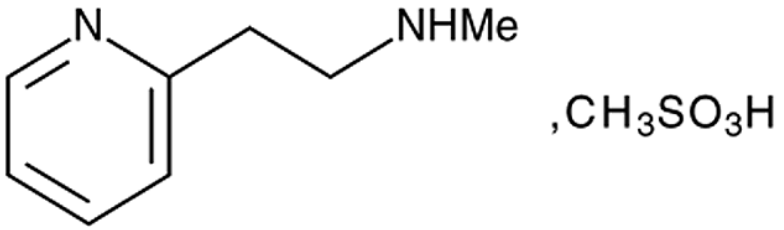
ТСХ, граница – 0.5%

Количествено определяне

Индикаторно титруване с NaOH във водна среда

Betahisine Mesilate

Разтворим във вода



Първа група – ИЧ-спектър

Втора група – т.т., ТСХ и качествена реакция за доказване на сулфати

Тест за остатъчен 2-пропанол-газова хроматография. Граница – 0.5 %

Контрол на чистотата – BETX с йонни двойки
Стандартен р-р „а“– смес от основно вещество и примес А (винилпиридин)-тест за пригодност на с-мата

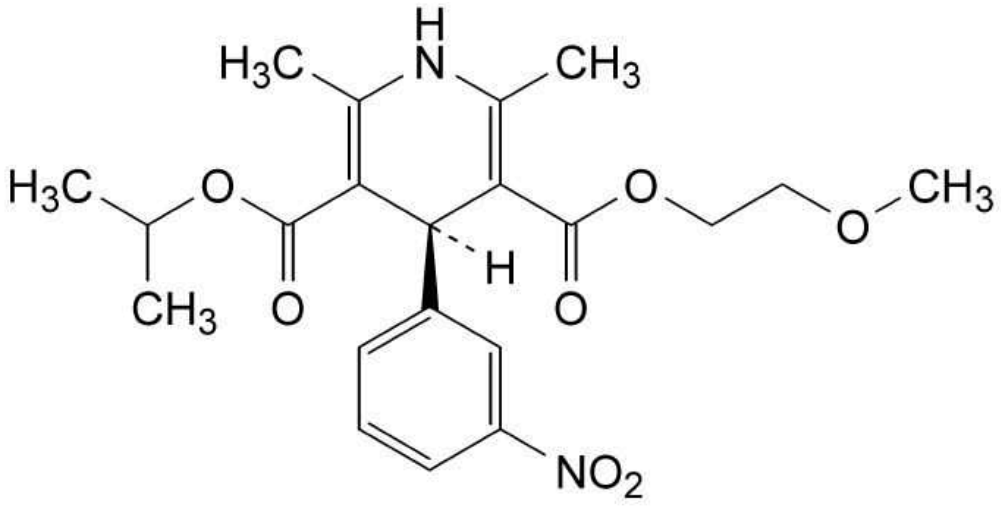
Стандартен р-р „в“ – приготвя се чрез разреждане на изследвания р-р

Граница на допустими примеси – 0.2 % поотделно, 0.5 % сумарно

Количествено определяне

Потенциометрично титруване с $HClO_4$ в среда от оцетен анхидрид

Nimodipine

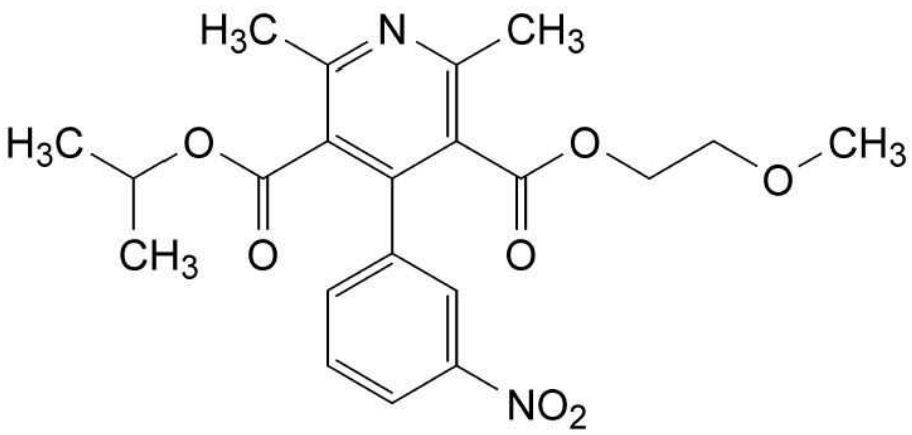


and enantiomer

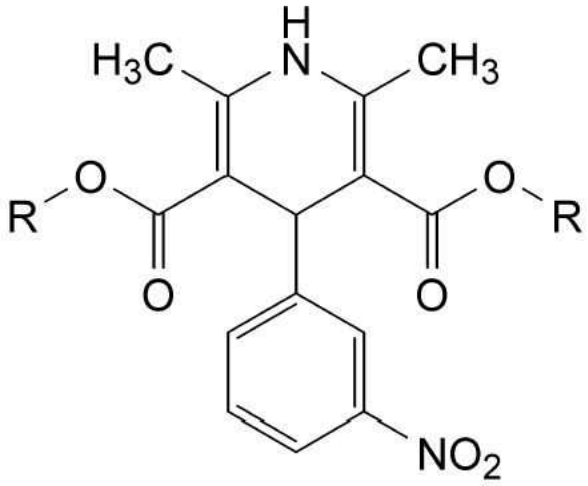
Жълто кристално в-во, неразтворимо във вода

При провеждане на тестовете, разтворите се приготвят непосредствено преди употреба – получава се нитрофенилпиридиново производно (примес А) под влияние на светлина

ВЕТХ контрол на чистотата



Примес А



Примес В. R = $CH(CH_3)_2$

Примес С. R = CH_2-CH_2-OCH_3

Количествено съдържание – цериметрично титруване