Chemistry of Heterocyclic Compounds, Vol. 31, No. 6, 1995

PYRIDINE DERIVATIVES IN THE DRUG ARSENAL (150 YEARS OF PYRIDINE CHEMISTRY)

É. Lukevits

Almost 150 years ago, T. Anderson reported isolation of picoline from coal tar at a meeting of the Edinburgh Royal Society (April, 1846). Several years later, he isolated lutidine and pyridine from a bone oil fraction. Not inconsiderable efforts were still required to prove its structure (Kerner, 1869; Dewar, 1871), to synthesize it (Ramsay, 1877), and to formulate the idea of pyridine as an azabenzene (Ladenburg, 1888). But the first step had been taken. Three reports by T. Anderson laid out the beginning of the chemistry of pyridine, whose derivatives proved to be also widely distributed in living matter and in most cases exhibited high biological activity (for example, the coenzyme nicotinamide adenine dinucleotide; the alkaloids nicotine, anabasine, ricinine, atropine, and cocaine).

A number of rather simple pyridine derivatives also exhibit high biological activity, nicotinic acid and its amide are contained in the organs of animals and are prosthetic groups of the enzymes codehydrogenase I and codehydrogenase II, which are hydrogen transfer agents and accomplish oxidation–reduction processes.

The daily requirement for nicotinic acid (niacin) for a human adult is about 20 mg; pellagra develops when a deficiency is present. Nicotinic acid (and its amide) is a specific pellagra preventative, but it also exhibits vasodilating action and hypocholesterinemic activity. Considering this, for more than 75 years new biologically active substances have been sought among the derivatives of nicotinic acid and other pyridine derivatives, which has led to the discovery of a number of important classes of drugs.

Back in the 1920's, the analeptic cordiamin (diethylnicotinamide) was introduced into medical practice and used for acute and chronic circulatory disorders, reduction of vascular tone, and respiratory insufficiency. At the end of the 1940's, antituberculars based on isonicotinic acid hydrazide appeared (isoniazid, gluconiazide, pasiniazide, streptoniazide, and later phthivazid). In the 1950's, pyridinaldoxime salts acquired special importance as cholinesterase reactivators: antidotes in poisoning by organophosphorus compounds (dipiroxime, obidoxime). In the 1960's, tetrahydropyridine- and piperidine-containing neuroleptics of the butyrophenone series occupied their own place in the drug arsenal (droperidol, benperidol, bromperidol), in addition to the antiemetic domperidone, anti-inflammatory drugs based on aminopyridine (piroxicam), the aminopyridone-based cardiotonic amrinone, the antiatherosclerotic drug Parmidine (2,6-bishydroxymethylpyridine carbamate), spasmolytics and antihistaminics based on piperidine (the highest sales at the end of the 1980's were for terfenadine), the antiasthmatic drug ketotifen.

At the beginning of the 1990's, of the 1500 most familiar drugs, 91 are piperidine derivatives and 73 are pyridine derivatives. A special place belongs to 1,4-dihydropyridines. A new class of calcium antagonists has been created based on them. The principal representative of these drugs (whose annual sales exceed two billion US dollars) is nifedipine (Adalat from the Bayer company, Procardia from the Pfizer company), used to reduce blood pressure and for stenocardia.

At the present time, already dozens of drugs of the 1,4-dihydropyridine series have been created which have more specific or prolonged action. Some of them inhibit aggregation of thrombocytes and potentiate the action of antineoplastics.

A number of drugs based on pyridine derivatives are presented in the following list of drugs, and the entire issue of this journal is devoted to pyridine chemistry, which celebrates its 150 years with new ideas and results.

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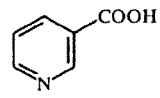
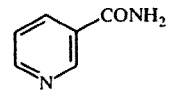
0009-3122/95/3106-0639$12.50

PYRIDINE DERIVATIVES

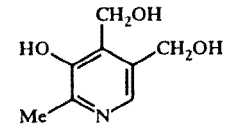
Vitamins



B_3

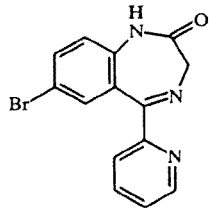


P. P. factor (niacinamide)



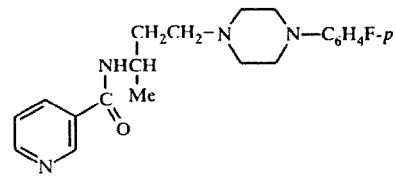
B_6 (pyridoxine)

Tranquilizer



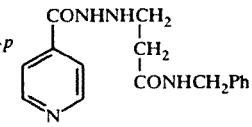
Bromazepam

Sedative



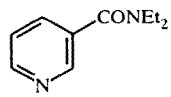
Niaprazine

Antidepressant

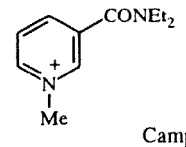


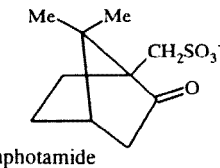
Nialamide

Analeptics



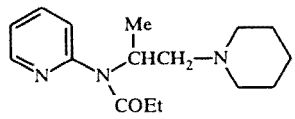
Nicethamide
(Cordiamin)



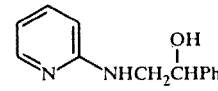


Camphotamide

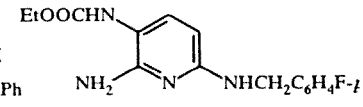
Analgesics



Propiram

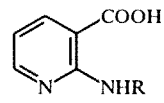


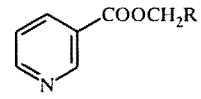
Phenyramidol

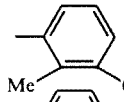


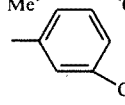
Flupirtine

Anti-inflammatory drugs

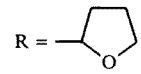


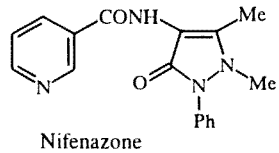


R =  Clonixin

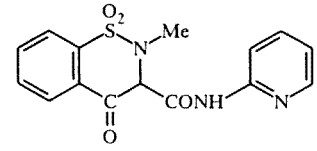
R =  Nifluril

R = CH_2OBu Nicoboxil

R =  Nicotafuryl

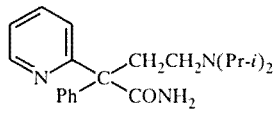


Nifenazone

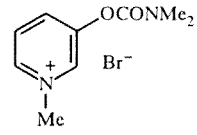


Piroxicam

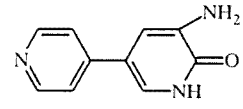
Antiarrhythmic | Anticholinesterase | Cardiotonic



Disopyramide

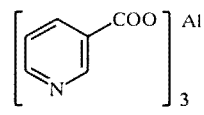


Pyridostigmine bromide

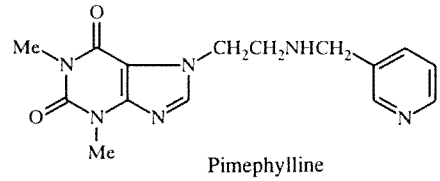


Amrinone

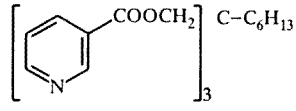
Spasmolytics and Vasodilators



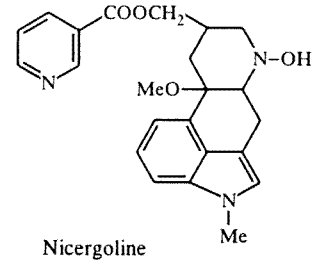
Aluminum nicotinate



Pimephylline

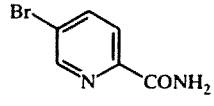


Hepronicate

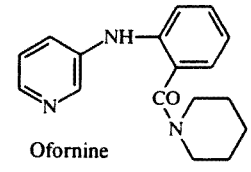


Nicergoline

Antihypertensives

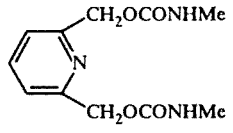


Bupicomide

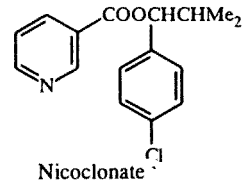


Ofornine

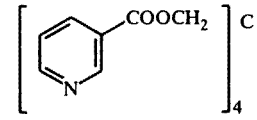
Antiatherosclerotics



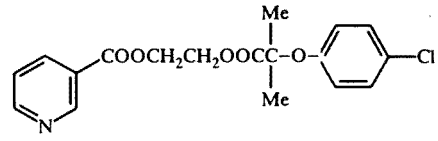
Pyridinol carbamate (Parmidine)



Nicoclonate

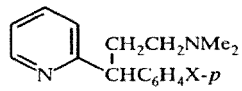


Niceritrol



Ethofibrate

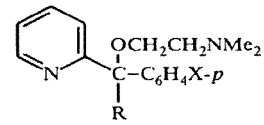
Antihistaminics



Pheniramine X = H

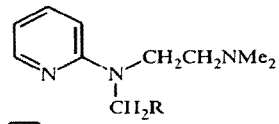
Brompheniramine X = Br

Chlorpheniramine X = Cl

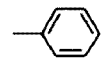


Carbinoxamine R = H, X = Cl

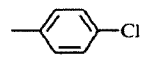
Doxylamine R = Me, X = H



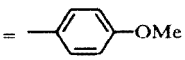
Tripelennamine R =



Chloropyramine R =



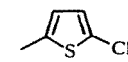
Mepiramine R =

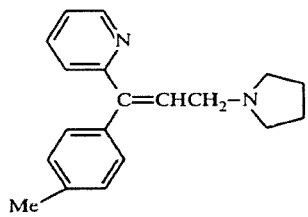


Methyapyrilene R =

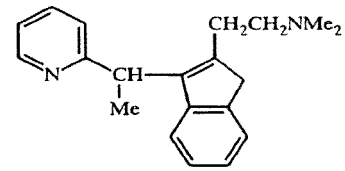
Thenyldiamine R =

Chloropicilene R =



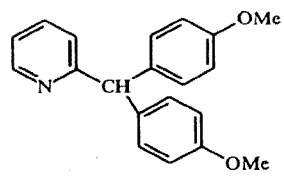


Triprolidine

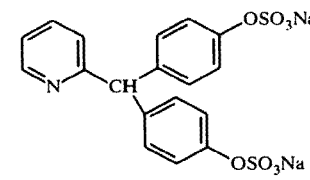


Dimethindene

Laxatives

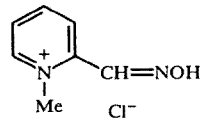


Bisacodyl

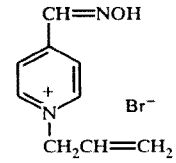


Picosulfol

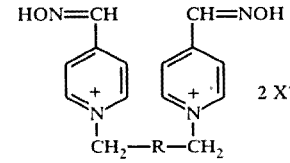
Cholinesterase reactors



Pralidoxime

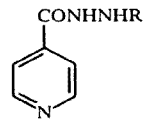


Alloxime

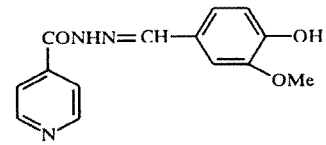


R = CH_2, X = Br Dipiroxime
R = O, X = Cl Obidoxime

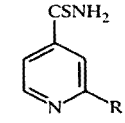
Antituberculars



R = H Isoniazid
R = *i*-Pr Iproniazid

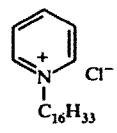


Phthivazid

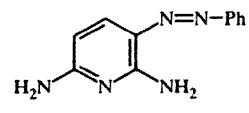


R = Et Ethionamide
R = Pr Protionamide

Antiseptics

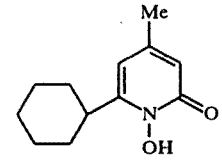


Cetylpyridinium chloride



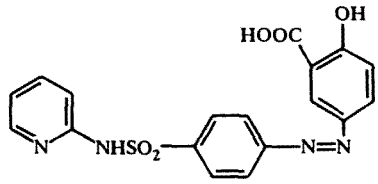
Phenazopyridine

Fungicide

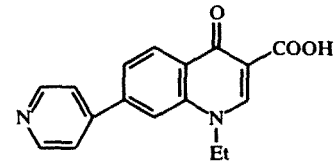


Ciclopirox

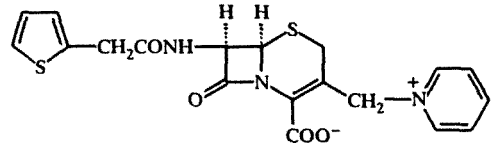
Antibacterials



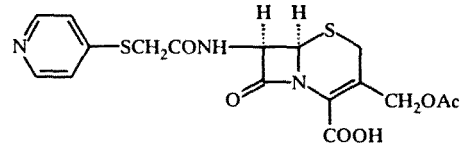
Salazosulfapyridine



Rosoxacin

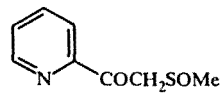


Cephaloridine

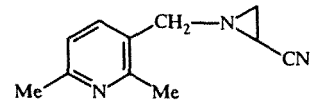


Cephapirin

Antineoplastics



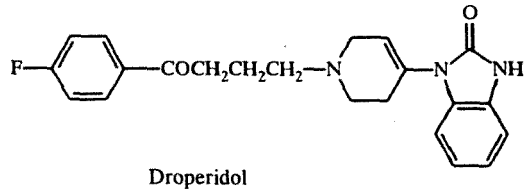
Oxisuran



Ciamexon (immunomodulator)

TETRAHYDROPYRIDINE DERIVATIVES

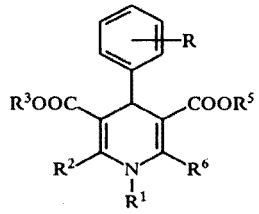
Neuroleptic

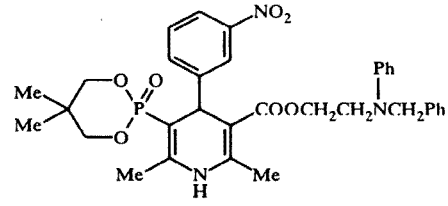


Droperidol

DIHYDROPYRIDINE DERIVATIVES

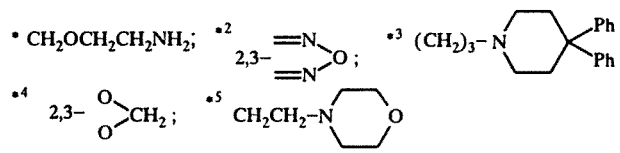
Antihypertensives and Vasodilators of the 1,4-dihydropyridine





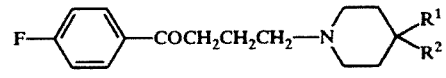
Efonidipine

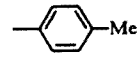
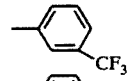
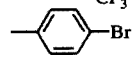
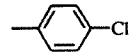
Name	R^1	R^2	R^6	R^3	R^5	R
Amlodipine	H	Me	*	Me	Et	2-Cl
Darodipine	H	Me	Me	Et	Et	*2
Isradipine	H	Me	Me	Me	Pr-*i*	*2
Nicardipine	H	Me	Me	Me	$(CH_2)_2NMeCH_2Ph$	3-NO_2
Niguldipine	H	Me	Me	Me	*3	3-NO_2
Nilvadipine	H	Me	CN	Pr-*i*	Me	3-NO_2
Niludipine	H	Me	Me	CH_2CH_2OPr	CH_2CH_2OPr	3-NO_2
Nimodipine	H	Me	Me	Pr-*i*	CH_2CH_2OMe	3-NO_2
Nisoldipine	H	Me	Me	Me	CH_2CHMe_2	2-NO_2
Nitrendipine	H	Me	Me	Me	Et	3-NO_2
Nifedipine	H	Me	Me	Me	Me	2-NO_2
Oxodipine	H	Me	Me	Me	Me	*4
Riodipine	H	Me	Me	Me	Me	2-$OCHF_2$
Felodipine	H	Me	Me	Me	Et	2,3-di-Cl
Flordipine	*5	Me	Me	Et	Et	2-CF_3

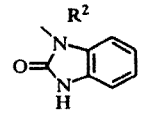
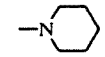
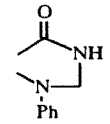


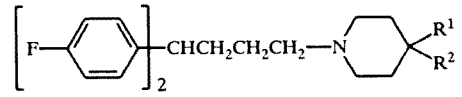
PIPERIDINE DERIVATIVES

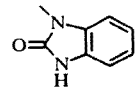
Neuroleptics

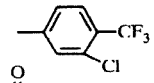
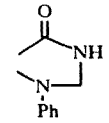


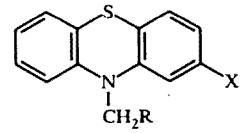
	R^1	R^2
Melperone	H	Me
Moperone	OH	
Trifluperidol	OH	
Bromperidol	OH	
Haloperidol	OH	

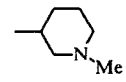
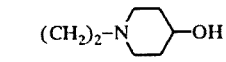
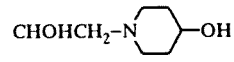
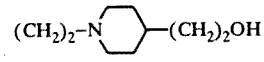
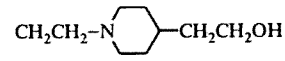
	R^1	R^2
Benperidol	H	
Pipamperone	$CONH_2$	
Spiperone		



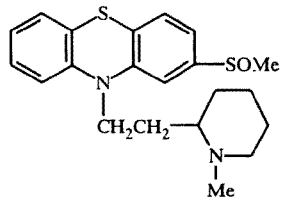
	R^1	R^2
Pimozide	H	

	R^1	R^2
Penfluridol	OH	
Fluspirilene		



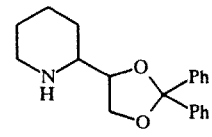
	R	X
Pecazine		H
Pericyazine		CN
Perimethazine		OMe
Piperacetazine		COMe
Pipotiazine		SO_2NMe_2

Sedative



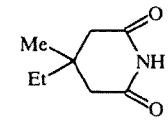
Mesoridazine

Antidepressant



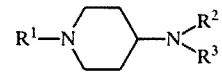
Dioxadrol

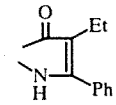
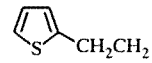
Analeptic

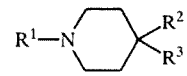


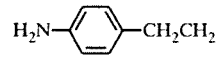
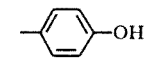
Bemegride

Analgesics

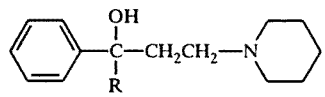


	R^1	R^2	R^3
Piperylone	Me		
Sufentanil		COEt	CH_2OMe
Fentanyl	$PhCH_2CH_2$	COEt	Ph



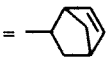
	R^1	R^2	R^3
Anileridine		COOEt	Ph
Ketobemidone	Me	COEt	
Piritramide	$Ph_2C(CN)CH_2CH_2$	$CONH_2$	
Phenoperidine	$PhCH(OH)CH_2CH_2$	COOEt	Ph

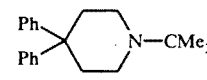
Antiparkinsonians



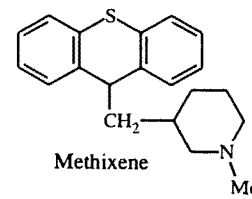
Cycrimine R = 

Trihexyphenidyl R = 

Biperiden R = 

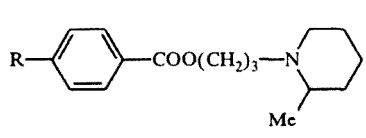


Budipine

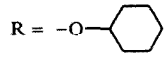


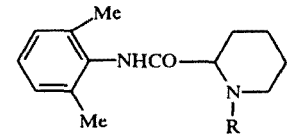
Methixene

Local Anesthetics



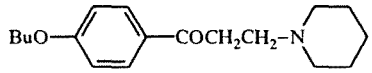
Piperocaine R = H

Cyclomethycaine R = 

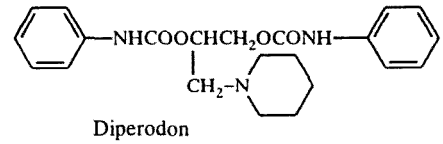


Mepivacaine R = Me

Bupivacaine R = Bu

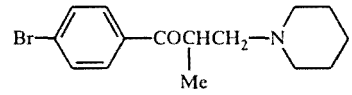


Dyclonine



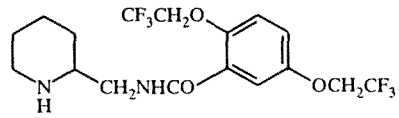
Diperodon

Muscle relaxant



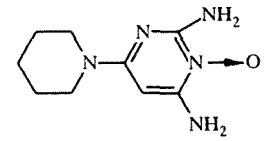
Eperisone

Antiarrhythmic



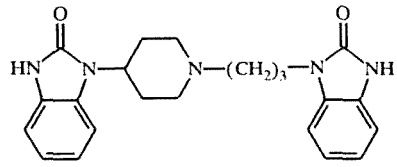
Flecainide

Antihypertensive

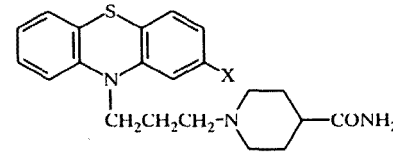


Minoxidil (stimulates hair growth)

Antiemetics



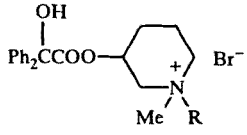
Domperidone



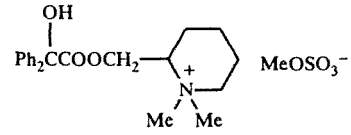
Metopimazine X = SO_2Me

Pipamazine X = Cl

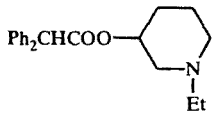
Spasmolytics, Vasodilators



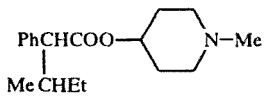
Mepenzolate bromide R = Me
Pipenzolate bromide R = Et



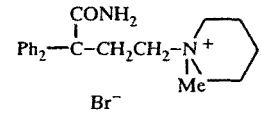
Bevonium



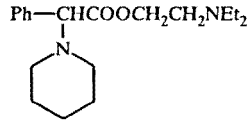
Piperidolate



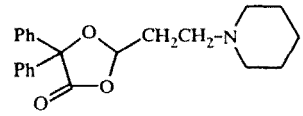
Pentapiperide



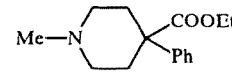
Fenpiverinium bromide



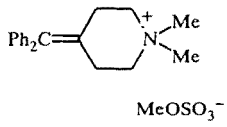
Bietamiverine



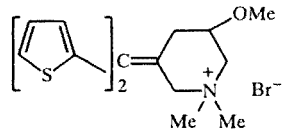
Pipoxolan



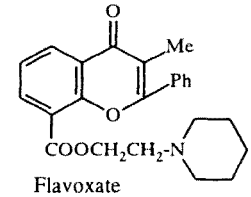
Pethidine



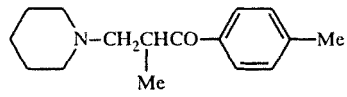
Diphemanil



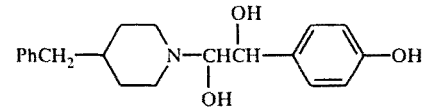
Timepidium bromide



Flavoxate

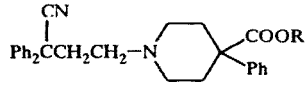


Tolperisone

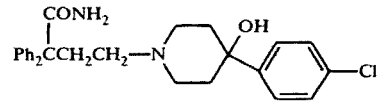


Fenprodil

Antidiarrheals

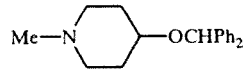


Difenoxin R = H
Diphenoxylate R = Et
Butoxylate R = Bu

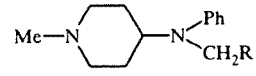


Loperamide

Antihistaminics

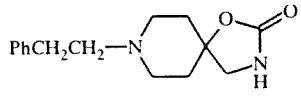


Diphenylpyraline

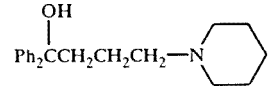


Bamipine R = Ph

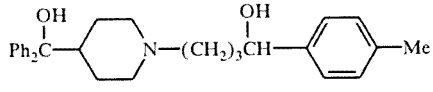
Thenalidine R = 



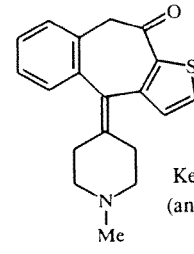
Fenspiride



Diphenidol

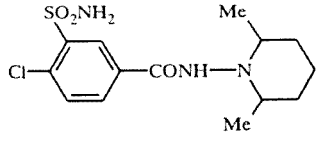


Terfenadine

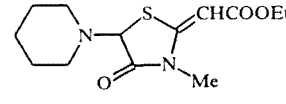


Ketotifen (antiasthmatic)

Diuretics



Clopamide



Etozolin