Латвийский Институт Органического синтеза

1915-1975

- Основан в 1957 году для комплексной разработки новых медицинских препаратов
- В настоящее время в Институте работает ≈ 300 сотрудников в том числе 110 докторов наук
- Институт располагает 5000 м^2 научно-исследовательских лабораторных помещений. Денежный оборот в 2016 году превысил 15 миллионов евро
- За 60 лет в Институте открыто и внедрено 18 оригинальных и более 70 ресинтезированных препаратов.

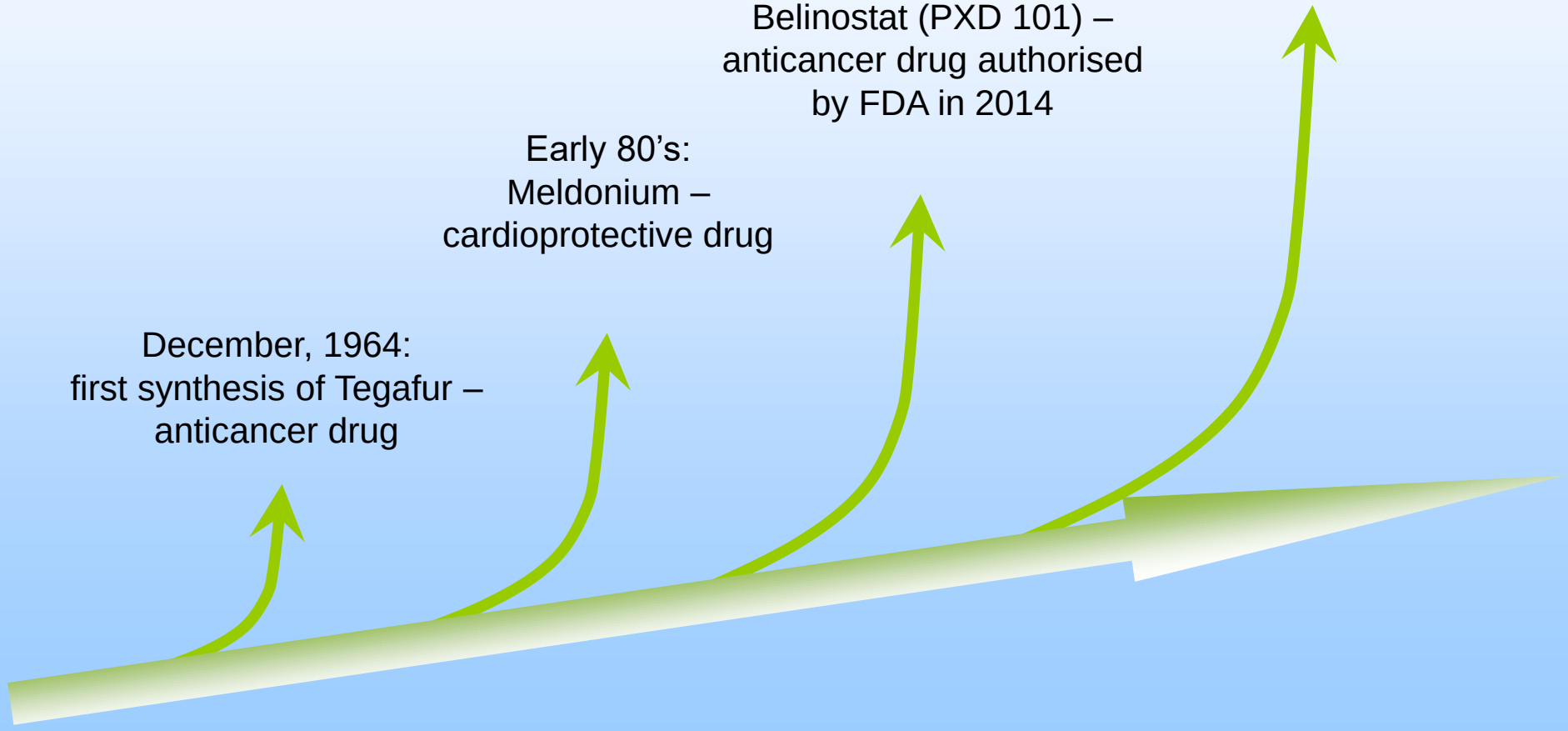
Главные достижения в создании оригинальных прераратов

December, 1964:
first synthesis of Tegafur –
anticancer drug

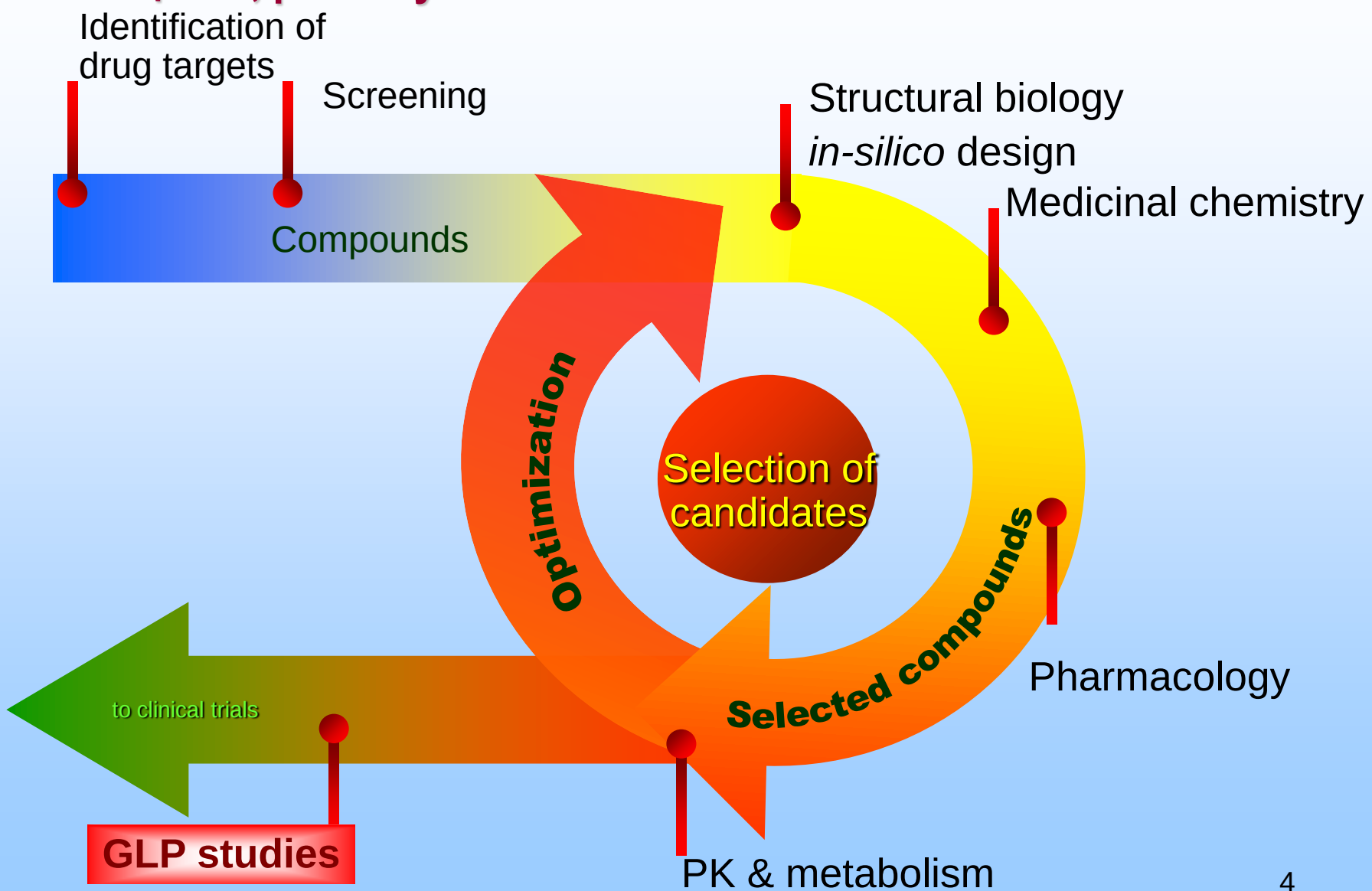
Early 80's:
Meldonium –
cardioprotective drug

Early 2000's:
Belinostat (PXD 101) –
anticancer drug authorised
by FDA in 2014

2014:
GX-EG –
cardioprotective drug
candidate



Принципиальная схема разработки новых лекарственных веществ, реализуемая в ИОС

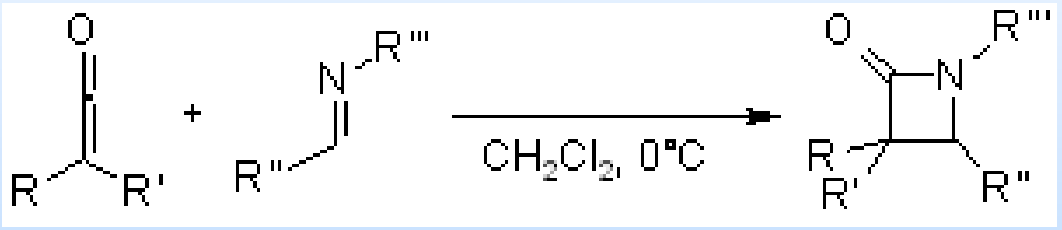


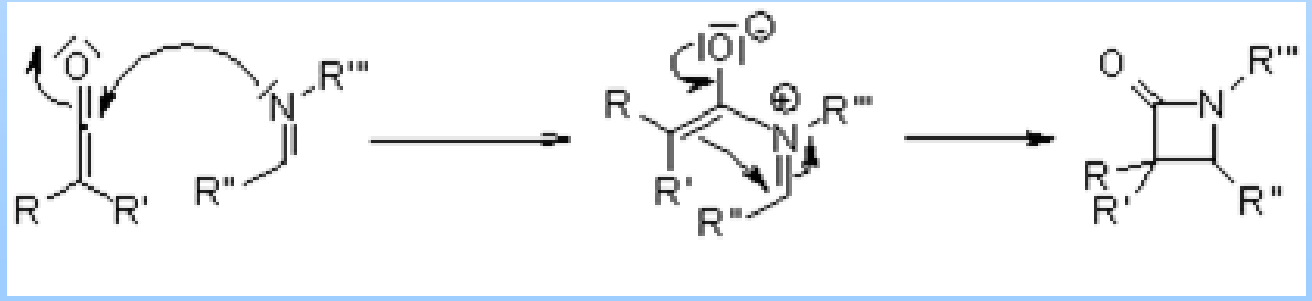
1991

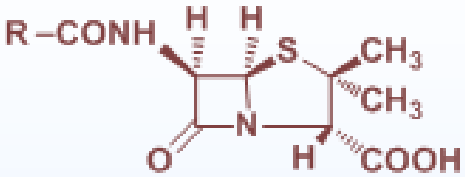
1. Распад СССР.
2. Восстановление государственной независимости Латвийской Республики.
3. Фундаментальные перемены в экономике, образовании и науке.

Синтез и биологические свойства производных β-лактамов

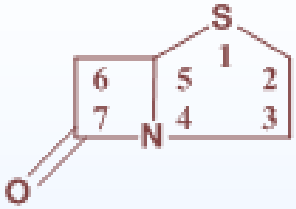
Реакция Штаудингера (1919. g.)





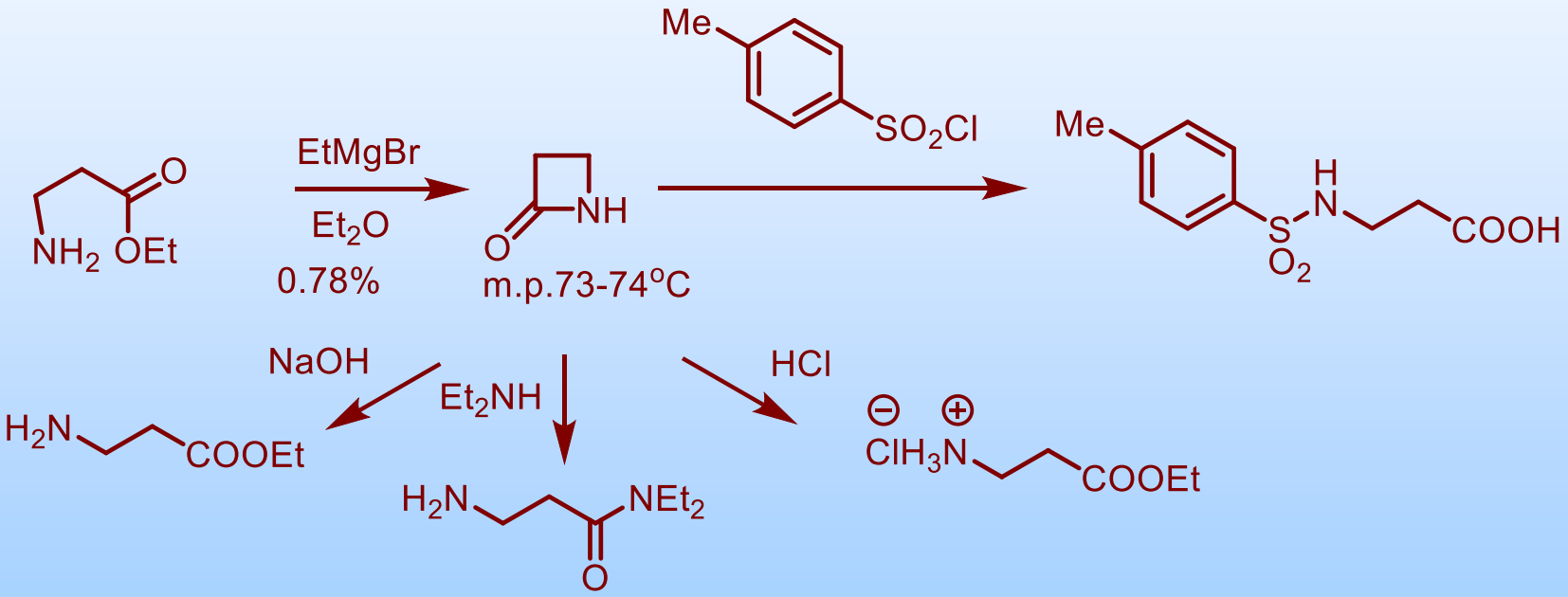


Penicilīns

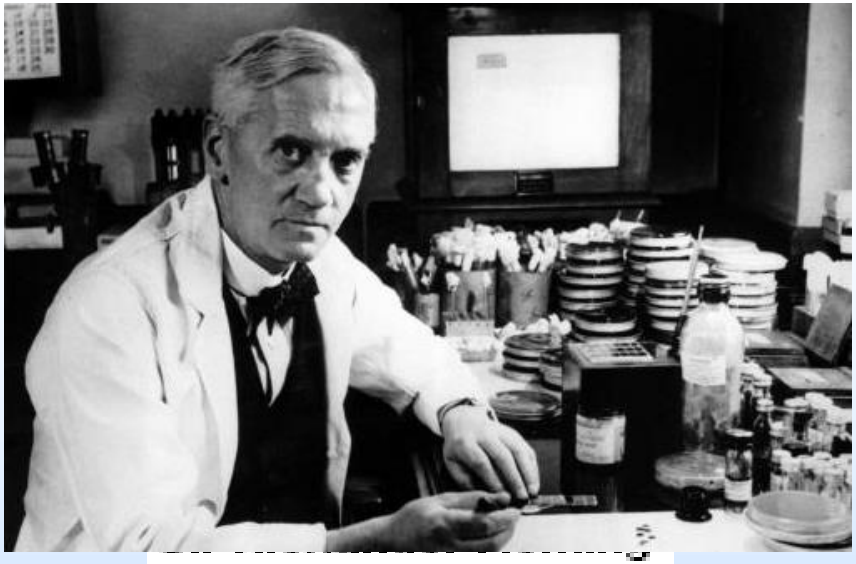


Penāms

2-Azetidinons



J. Am. Chem. Soc., 1949, 71, 2129-2131



Sir Ernst Boris Chain

Howard Walter Florey, Baron Florey

Photograph courtesy of Merck Archives, ©Merck & Co. Inc.

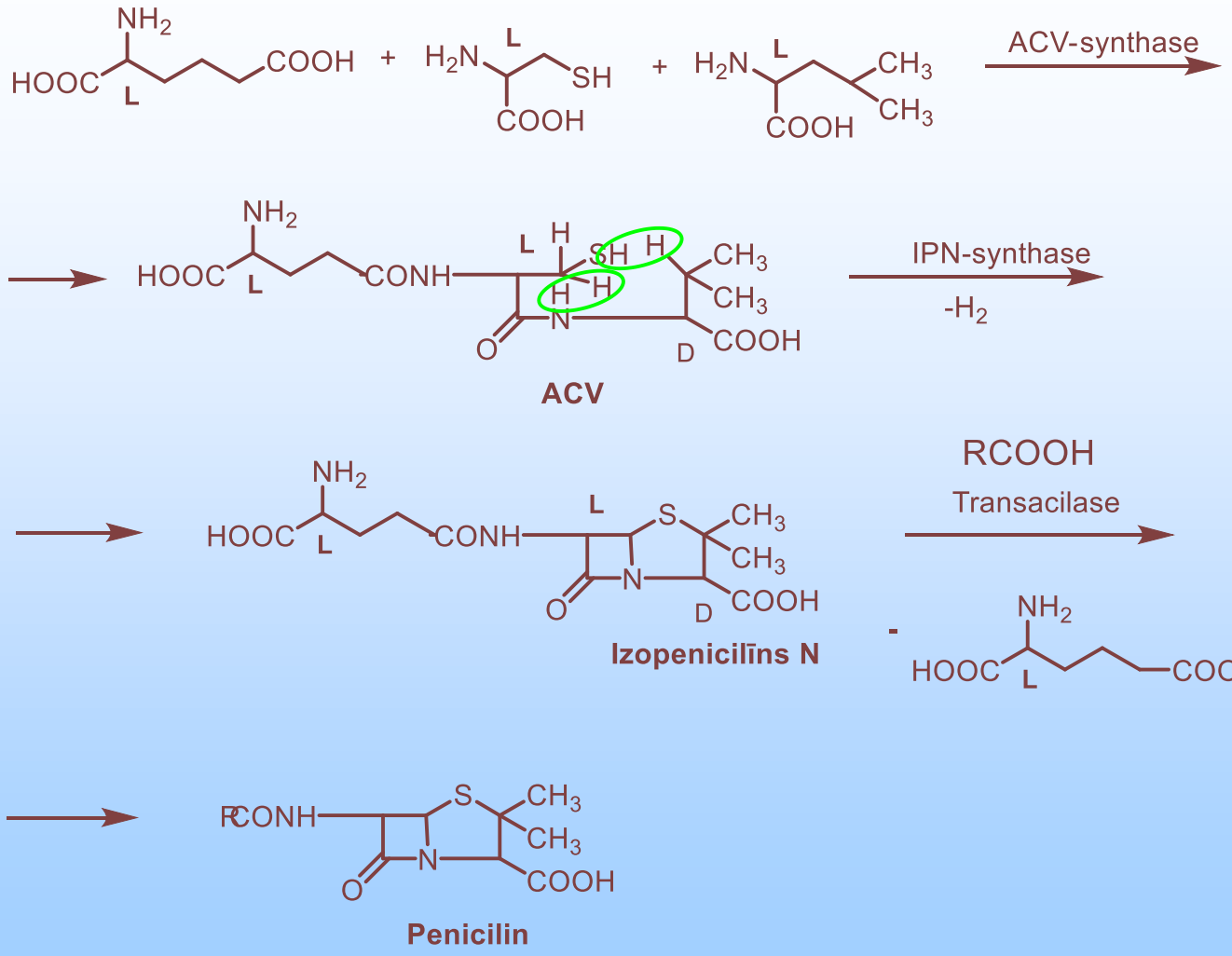
Refrigeration equipment for large fermentation unit at Cherokee Plant, Danville, PA.

Photograph courtesy of Merck Archives, ©Merck & Co. Inc.

Fermentation unit used in purifying penicillin in 1945.

Photograph courtesy of Merck Archives, ©Merck & Co. Inc.

Upper part of fermentors (tanks) used to produce penicillin and vitamin B12.



R= $C_6H_5CH_2$ Benzylpenicillin (Penicillin G)

Lend-Lease (Public Law 77-11) was the name of the program under which the U.S. supplied the UK, USSR, China, France and other Allied nations with vast amounts of war material between 1941 and 1945.

A total of $50.1 billion (equivalent to $759 billion at 2008 prices) worth of supplies were shipped:

$31.4 billion to Britain,

$11.3 billion to the Soviet Union

$3.2 billion to France

$1.6 billion to China.

There was no debt; the U.S. did not charge for aid supplied under this legislation.

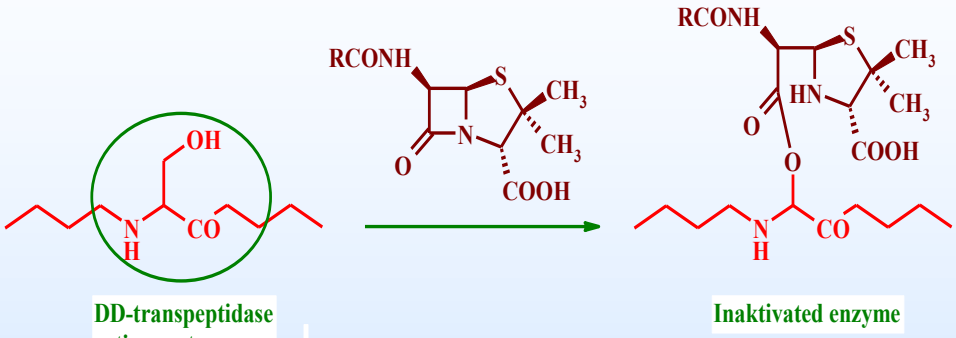
Lend-Lease program included the transfer of Penicillin technology and technological equipment in following USSR towns: Moscow, Riga, Saransk, Penza, Kurgan.

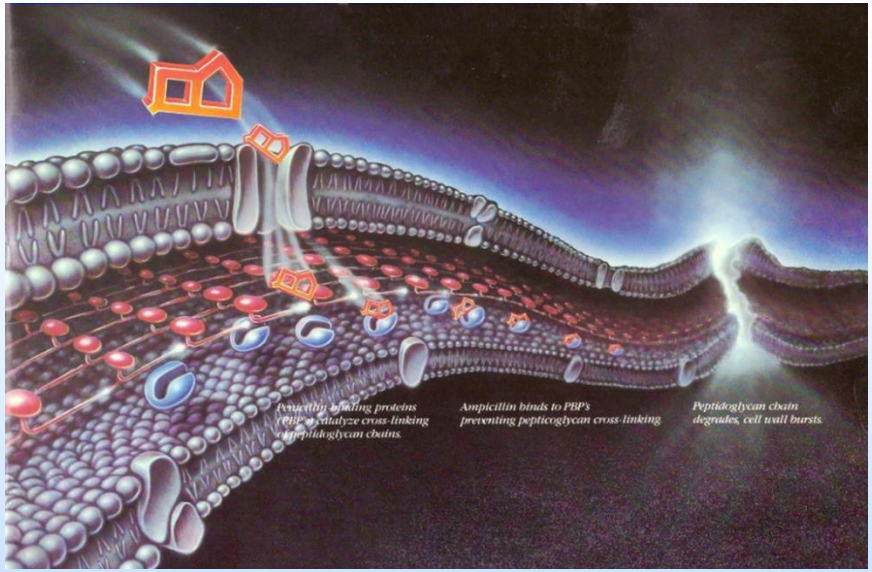
Riga Peniclillin factory started production of antibiotic in 1945.

Динамика смертностиот инфекционных заболеваний до и после внедрения антибиотикв в медицину

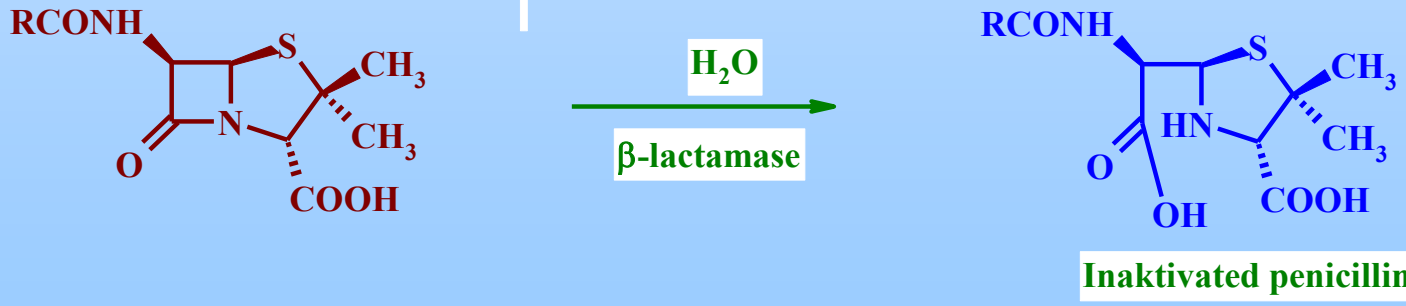
Заболевание	Сметность на 100000 жителей				
	1920. g	1930. g	1940. g	1950. g	1960. g
Все формы туберкулеза	113	71	46	22	6
Дизентерия	4	28	2	0.6	0.2
Дефтерия	15	5	1	0.3	Нет данных
Коклюш	12	5	2	0.7	0.1
Менингококковые инфекции	11.6	3.6	0.5	0.6	0.3
Пневмония	207	102	70	31	36
Ангина	9	3	0.5	0.3	0.2

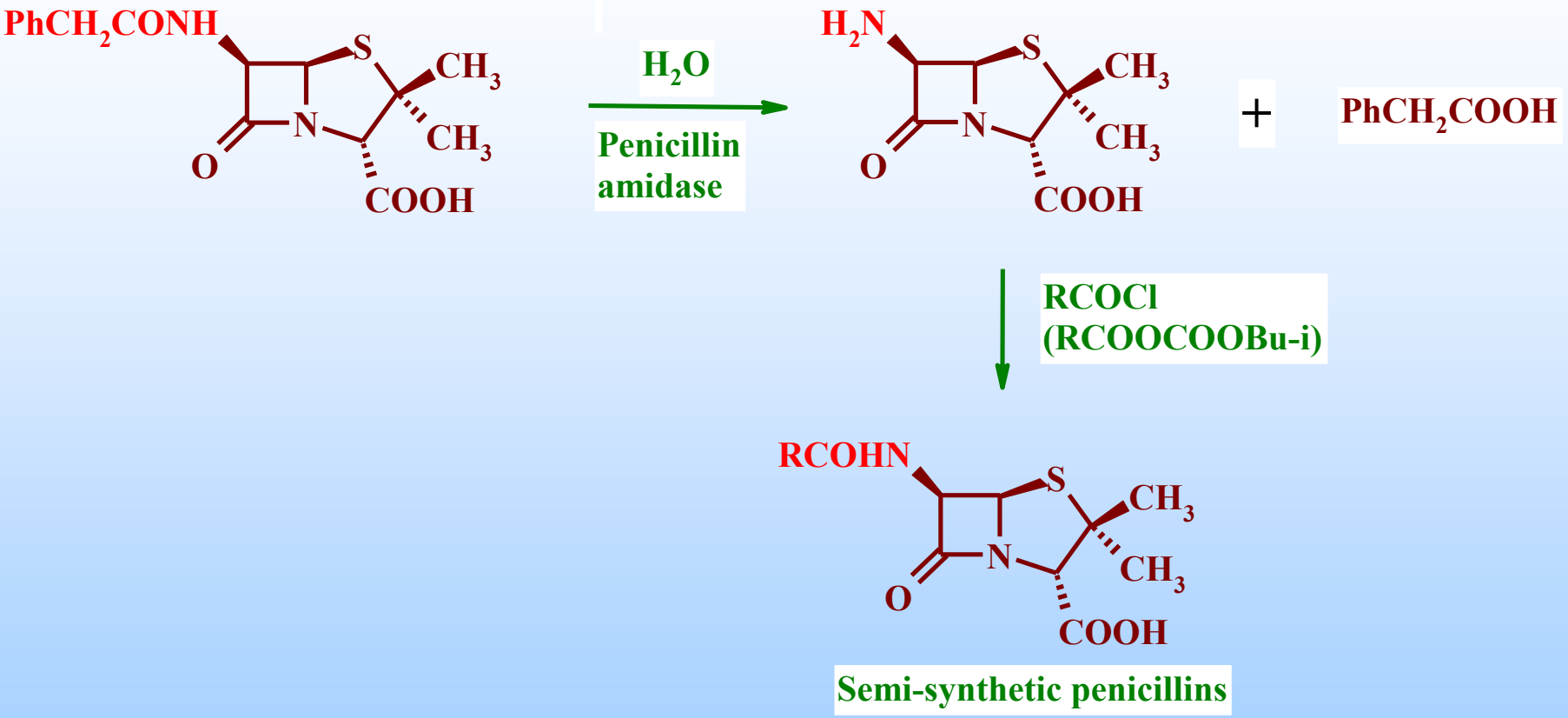
The mechanism of penicillin action on molecular level



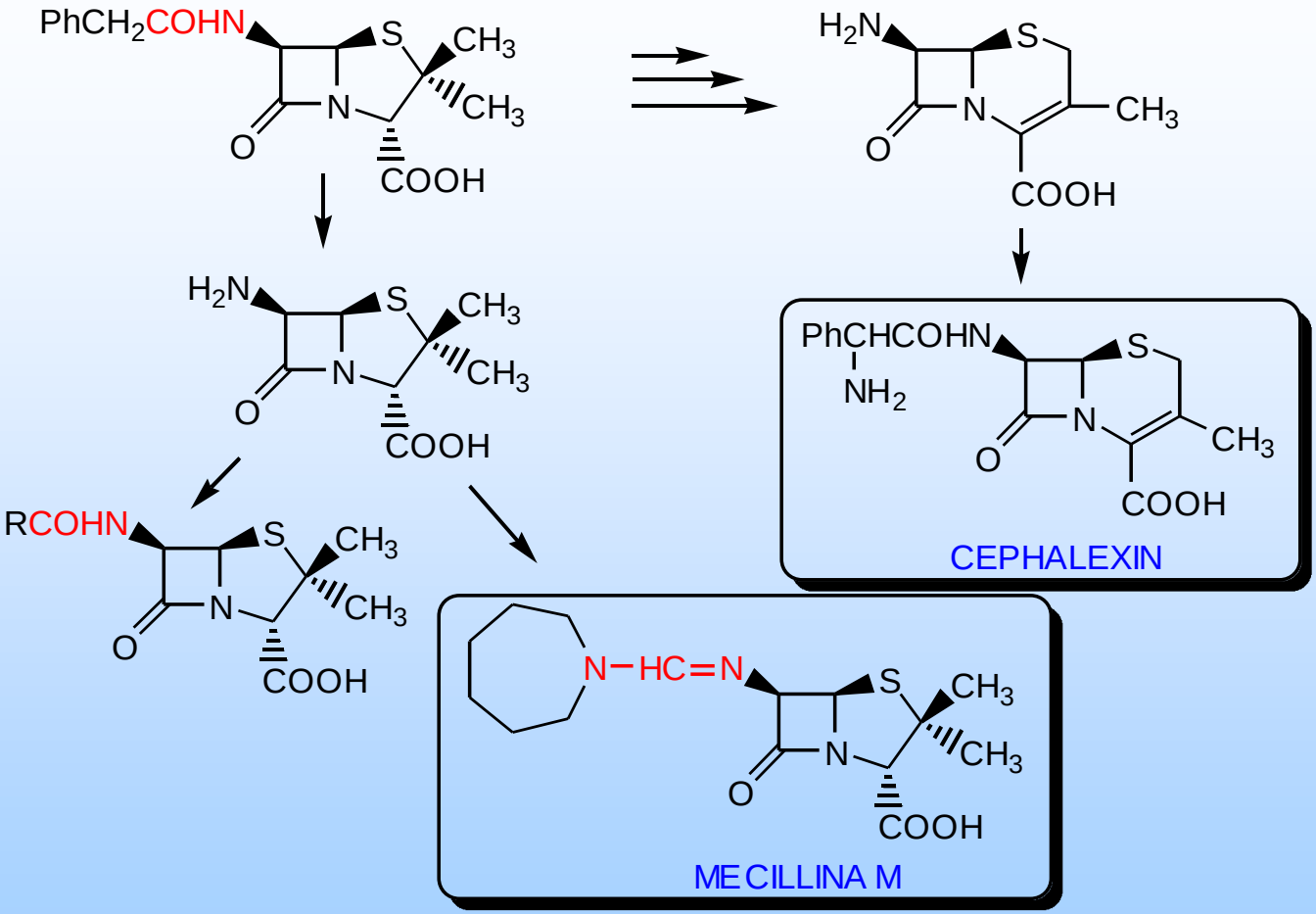


The mechanism of penicillin inactivation by bacterial β-lactamase

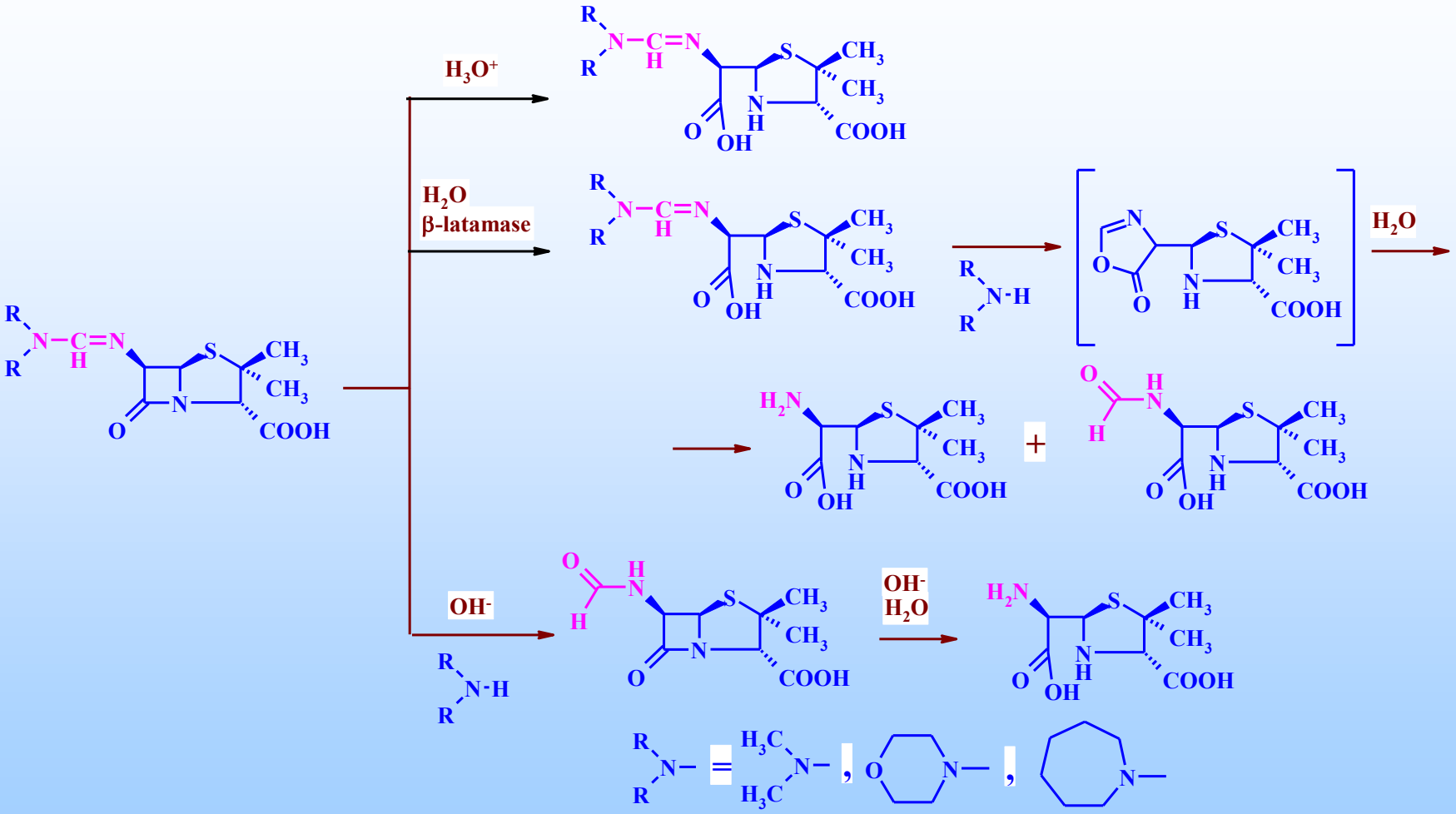



PhCH2CONH
S
CH3
CH3
N
O
COOH
H2O
Penicillin amidase
H2N
S
CH3
CH3
N
O
COOH
+
PhCH2COOH
RCOCl
(RCOOCOOBu-i)
RCOHN
S
CH3
CH3
N
O
COOH
Semi-synthetic penicillins

1970-1991


PhCH2COHN
S
CH3
CH3
N
O
COOH
H2N
S
CH3
CH3
N
O
COOH
H2N
S
CH3
CH3
N
O
COOH
PhCHCOHN
NH2
S
CH3
N
O
COOH
CEPHALEXIN
RCOHN
S
CH3
CH3
N
O
COOH
N−HC=N
S
CH3
CH3
N
O
COOH
MECILLINA M

Products of the hydrolytic degradation of amidine analog penicillins

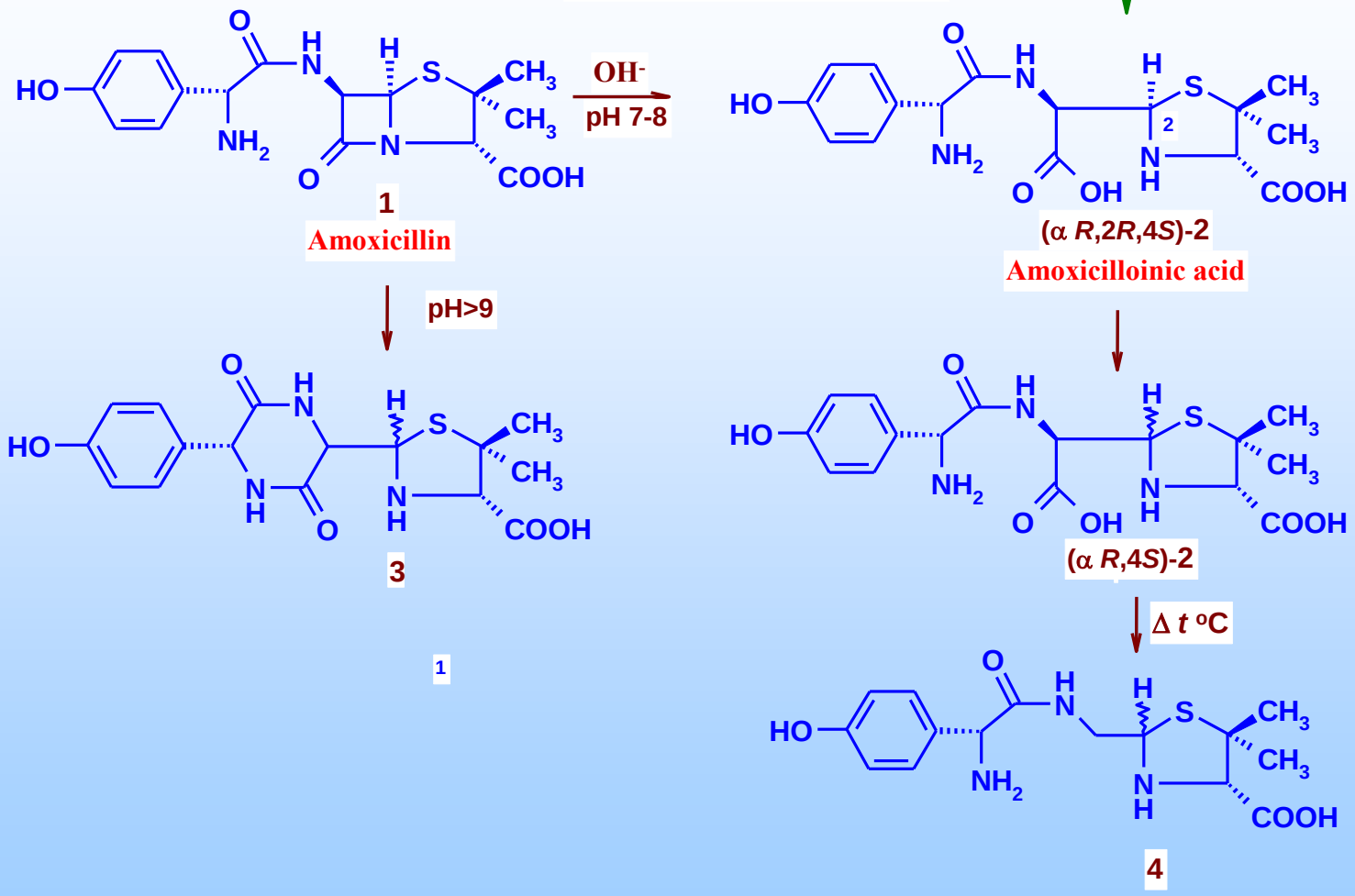


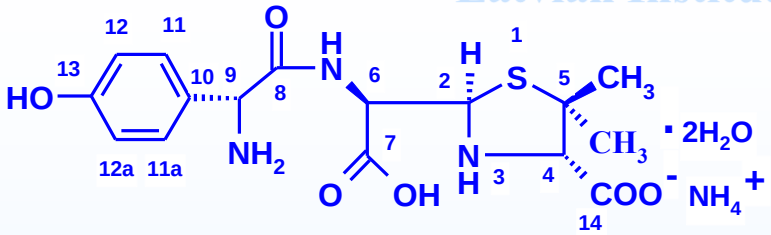
G. Veinberg, Y. Belevich, *Antibiotics*, 1978, №7, 593-598 (Rus).

Preparation of amoxicilloinic acid

H_2O, pH 7.5, 30°C

β-Lactamase (Bacillus cereus)





(4S,2R)-2-[[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid ammonium salt dihydrate

(amoxicilloic acid)

Molecular formula: $C_{16}H_{28}N_4O_8S$
Molecular weight: 436,50

Elemental analysis:

Found: C 44.65; H 6.30; N 12.92
Calculated: C 44.03; H 6.47; N 12.84

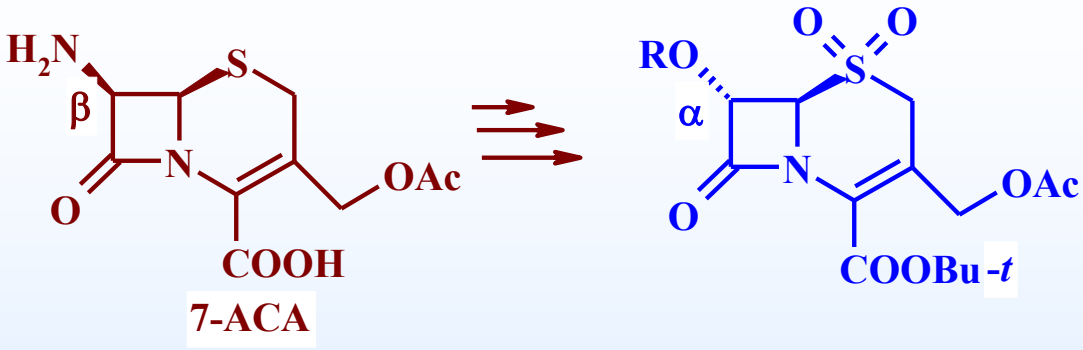
Identity:

^{1}H NMR spectrum: (Varian 400 MHz) (D_2O, TMS) δ: 0.96 (3H, s, 5-CH_3); 1.01 (3H, s, 5-CH_3); 2.93 (1H, s, 4-H); 4.10 (1H, d, 6-H); 4.90 (1H, d, 2-H); 4.97 (1H, s, 9-H); 6.80 (2H, d, 12-H, 14-H); 7.26 (2H, d, 11-H, 15-H).

^{13}C NMR spectrum: (Varian 400 MHz) (D_2O, TMS) δ: 23.54 (5-$\underline{C}H_3$); 23.96 (5-$\underline{C}H_3$); 54. 2 (9-C); 56. 4 (5-C); 57. 5 (6-C); 63.5 (2-C); 73.2 (4-C); 114.4 (12-C); 122.0 (10-C); 127.9 (11-C); 155.0 (13-C); 166.8 (8-C); 173.13 (7-C); 173.54 (7-C).

ESI-MS (MeCN) for amoxicilloic acid ($C_{16}H_{21}N_3O_6S$, M.w. 383.43)***: 384 [MH^+].***
Single Mass analysis (elemental composition report): 384.1296

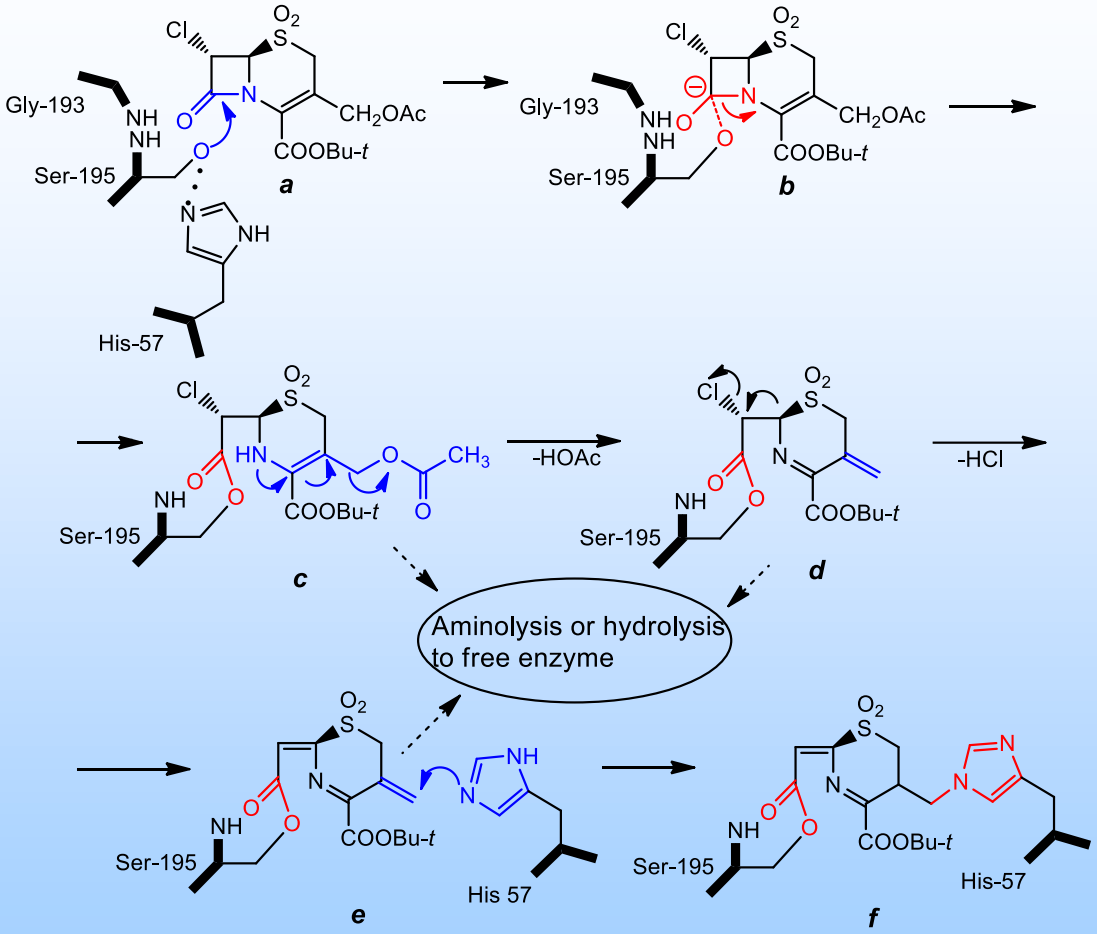
M. Vorona, G. Veinberg, E. Liepinsh, H. Kazoka, G. Andreeva, E. Lukevic, ***Chemistry of Heterocyclic Compounds*****, 2009, 936-938.**



R	IC50, μM						
	HLE	PPE	α-Chy-motryp-sin	Cathep-sin G	Trypsin	Plasmin	Thrombin
Me	0.5	<0.1	7-8	>50	>50	>> 20	6
Et	1.5	0.5	10	>> 20	>> 20	>> 20	>> 20
Ph	0.8	5	5	>> 20	>> 20	20	1

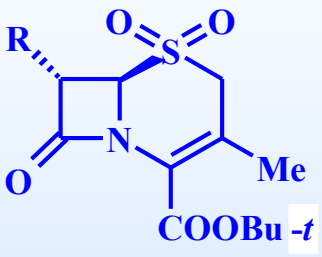
Doherty, J.B., Ashe, B.M., Argenbright, L.W., Barker, P.L., Bonney, R.J., Chandler, G.O., Dahlgren, M.E., Dorn, Jr C.P., Finke, P.E., Firestone, R.A., Fletcher, D., Hagmann, W.K., Mumford, R., O'Grady, L., Maycock, A.L., Pisano, J.M., Shah, S.K., Thompson, K.R., Zimmerman, M. ***Nature***, **1986**, *322*, 192-194.

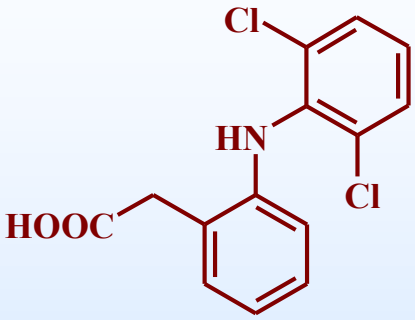
The mechanism of Porcine Pancreatic Eelastase inhibition by *tert*-butyl 7α-chlorocephalosporanate sulfone *



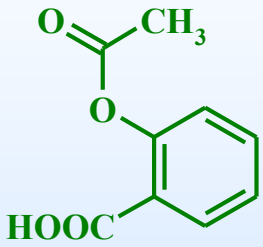
* Shah, S.K., Brause, K.A., Chandler, G.O., Finke, P.E., Ashe, B.M., Weston, H., Knight, W.B., Maycock, A.L., Doherty, J.B. *J. Med. Chem*. 1990, *33*, 2529-2535.

Latvian Taiho Fond Project: *Dual Action Anti-inflammatory Cephalosporis* (1994 - 1996).

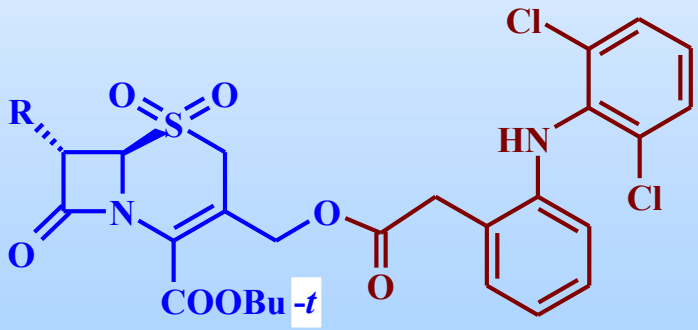




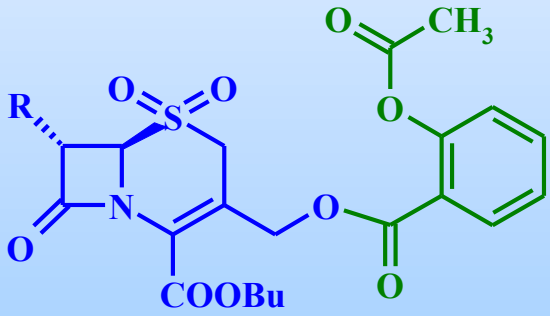
Diclofenac



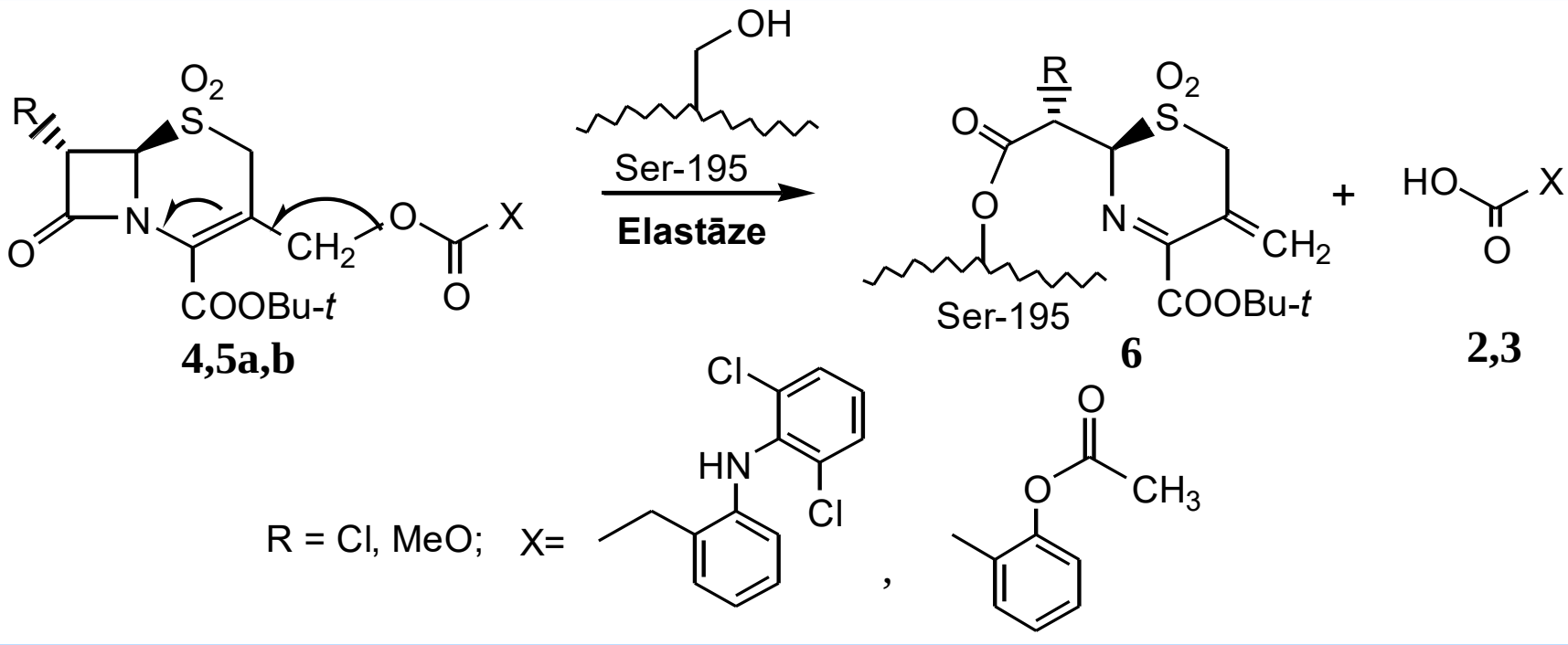
Aspirin

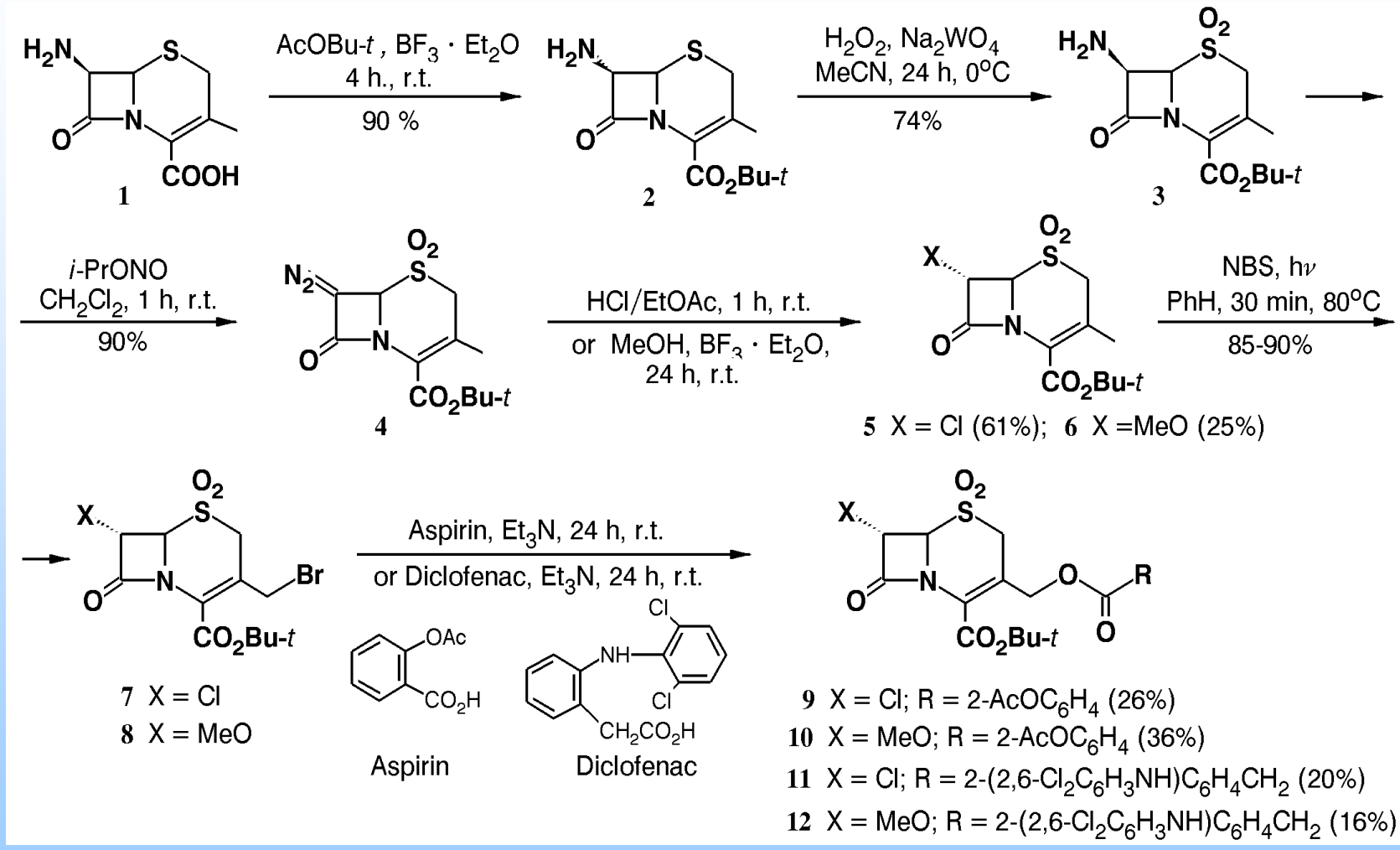


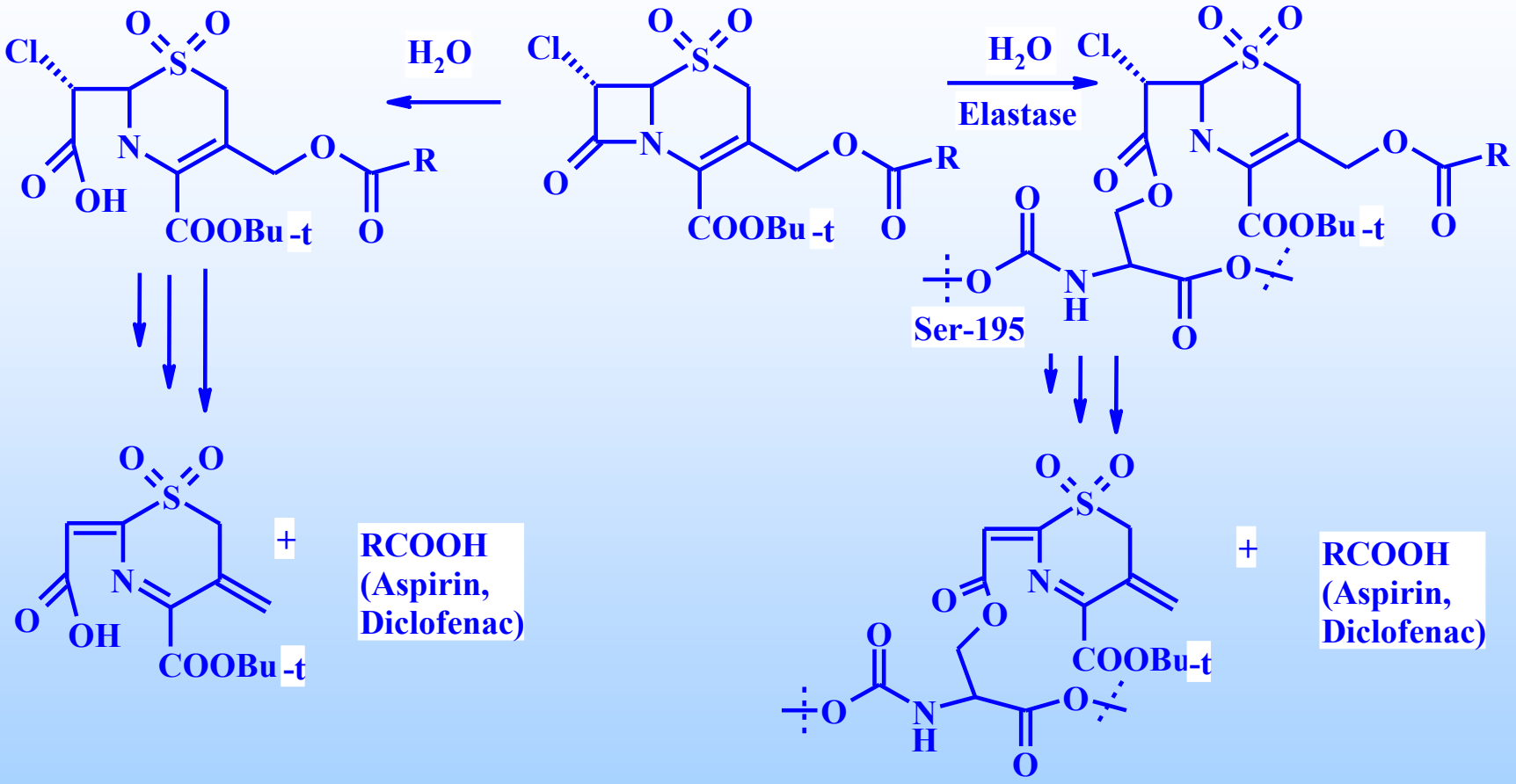
R=Cl, MeO



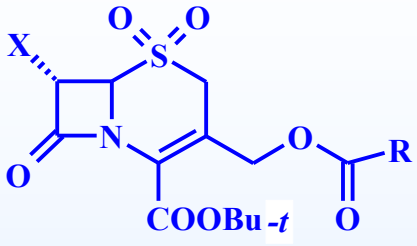
R=Cl, MeO


R
O2
S
N
O
CH2
O
X
O
COOBu-t
4,5a,b
OH
Ser-195
Elastāze
R
O2
S
O
O
N
CH2
Ser-195
COOBu-t
6
+
HO
X
O
2,3
R = Cl, MeO;
X=
Cl
HN
Cl
,
O
O
CH3

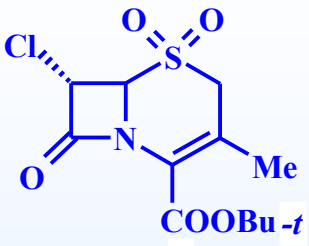

AcOBu-t , BF3 · Et2O
4 h., r.t.
90 %
H2O2, Na2WO4
MeCN, 24 h, 0°C
74%
i-PrONO
CH2Cl2, 1 h, r.t.
90%
HCl/EtOAc, 1 h, r.t.
or MeOH, BF3 · Et2O,
24 h, r.t.
NBS, hν
PhH, 30 min, 80°C
85-90%
Aspirin, Et3N, 24 h, r.t.
or Diclofenac, Et3N, 24 h, r.t.
1
2
3
4
5 X = Cl (61%); 6 X =MeO (25%)
7 X = Cl
8 X = MeO
Aspirin
Diclofenac
9 X = Cl; R = 2-AcOC6H4 (26%)
10 X = MeO; R = 2-AcOC6H4 (36%)
11 X = Cl; R = 2-(2,6-Cl2C6H3NH)C6H4CH2 (20%)
12 X = MeO; R = 2-(2,6-Cl2C6H3NH)C6H4CH2 (16%)

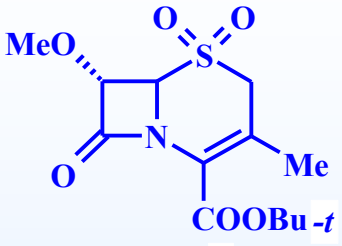

Cl
O
S
N
OH
COOBu -t
R
H_2O
Elastase
Ser-195
NH
RCOOH
(Aspirin,
Diclofenac)

Hydrolytic stability and PPE inhibitory properties of cephalosporanate sulfones



1





2

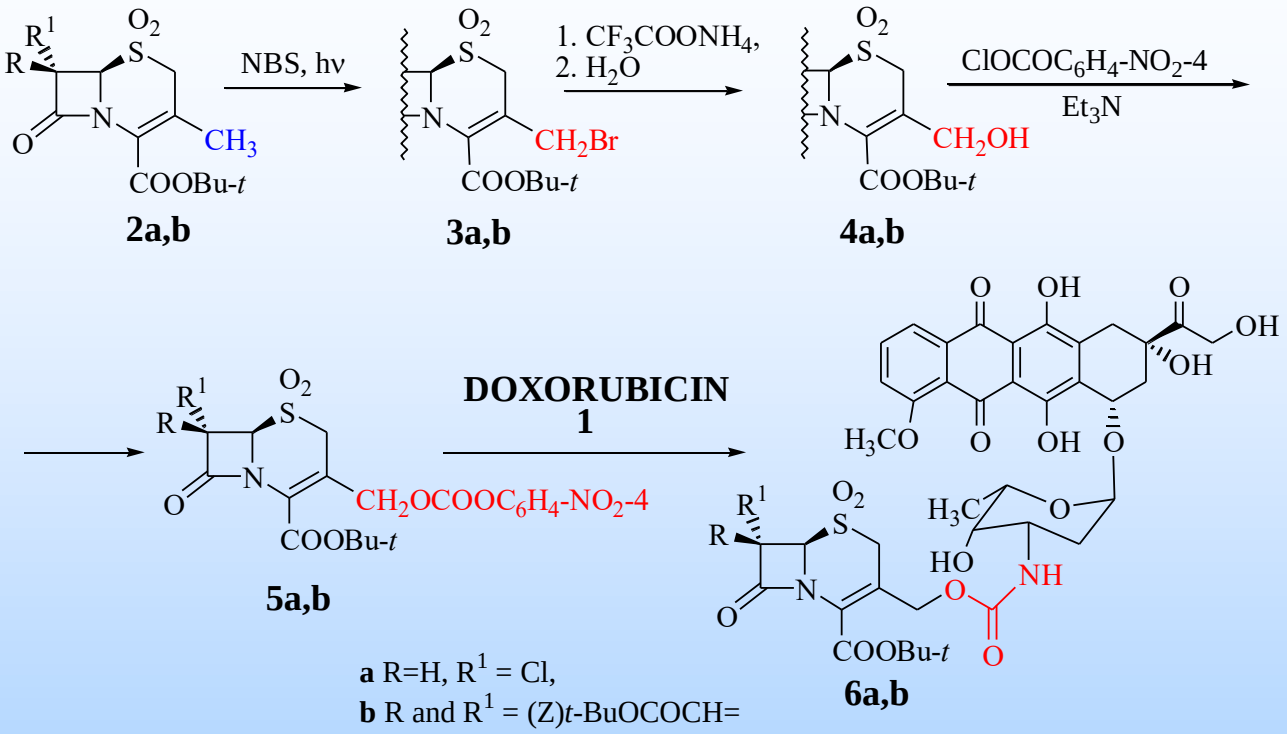
X	R	Hydrolysis at pH 7.3 and 37°C, $t_{1/2}$ (hours)	IC_{50}, μM*
Cl	2-$AcOC_6H_4$ (Aspirin)	2.3	0.20±0.03
Cl	2-(2,6-$Cl_2C_6H_3NH$)$C_6H_4CH_2$ (Diclofenac)	73	0.21±0.02
OMe	2-$AcOC_6H_4$	19	0.10±0.02
OMe	2-(2,6-$Cl_2C_6H_3NH$)C_6H_4	60	0.10±0.04
Cl	Ac	-	0.18±0.03**
1			35±1.1
2			73±1.5

oncentration causing 50% reduction of Porcine pancreatic elastase

**Reference substance

G. Veinberg, et al., *Synthesis and Evaluation of Dual Action Cephalosporins as Elastase Inhibitors.* Bioorganic & Medicinal Chemistry Letters, 1997, vol.7, No 7, 843-846.

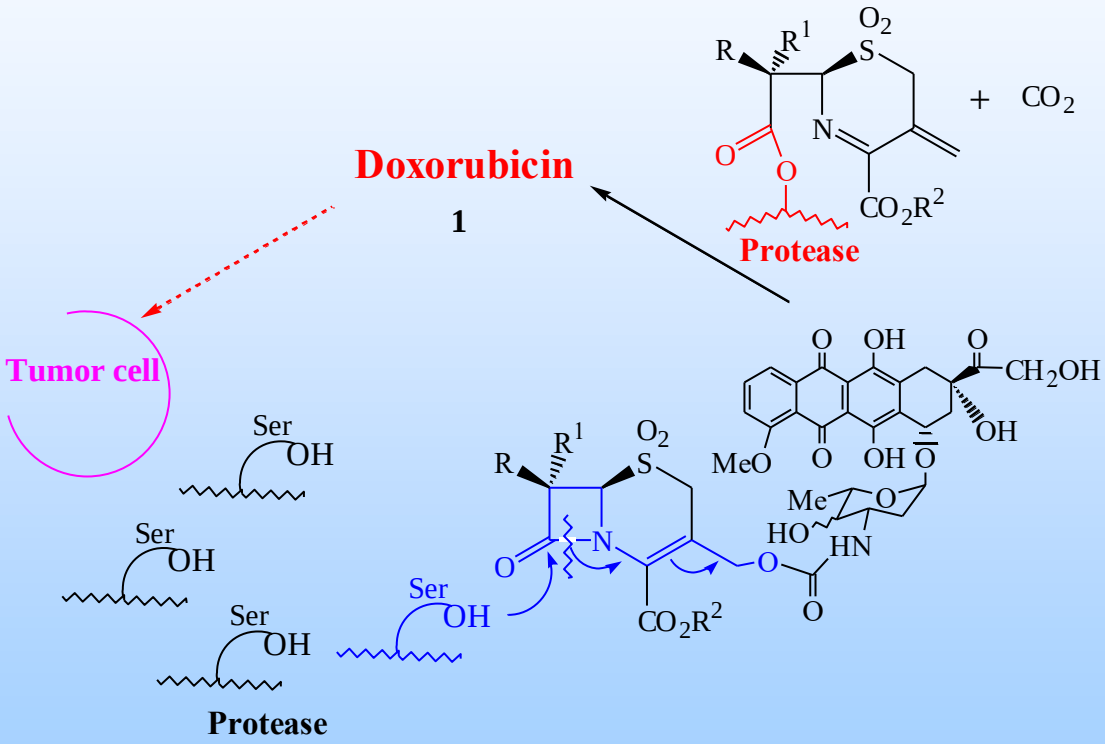
The synthesis of doxorubicin-cephalosporin prodrugs



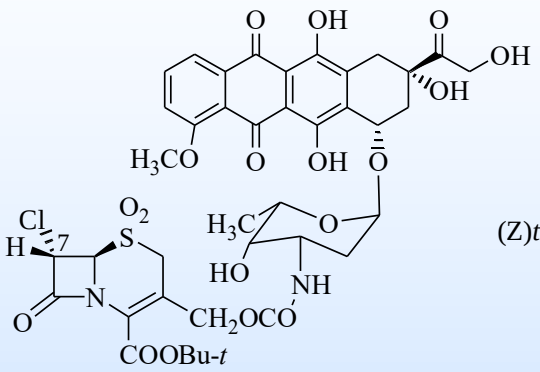
G. Veinberg, I. Shestakova, M. Vorona, I. Kanepe, I. Domrachova, E. Lukevics, *Doxorubicin Prodrug on the Base of tert-Butyl Cephalosporanate Sulfones* , Bioorg. Med. Chem. Letters, 2004, vol. 14, No 1, 147-150.

Latvian Taiho Fond Project: *Dual Antitumor β-Lactams* (1998 -1999).

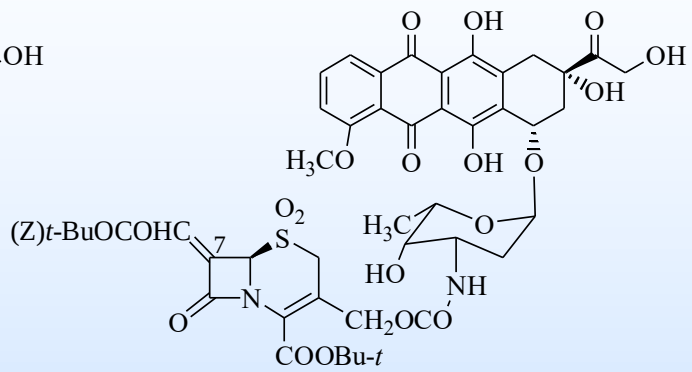
The concept of elastase mediated splitting of doxorubicin-cephalosporin prodrug



Antitumor effect of doxorubicin and prodrugs *in vivo* against Sarcoma S-180



6a



6b

Com-pound*	Dosage, mg/kg/day	Administration schedule, days	Tumor growth inhibition GI% on fixed date (%)		
			5	7	9
Doxorubicin	5.0	1, 2, 3, 4, 7	50	35	37
6a	5.0	1, 2, 3, 4, 5	-8	72	30
6b	5.0	1, 2, 3, 4,.7	-20	-10	22

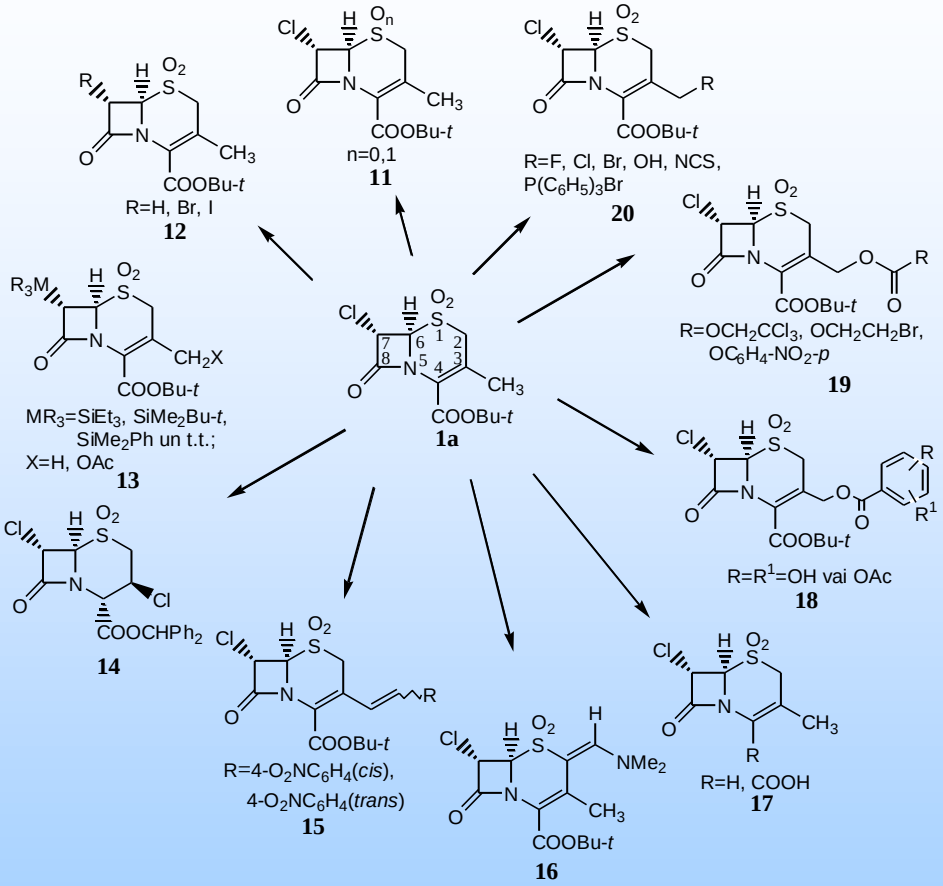
Physiologic changes in cardiomyocytes after the treatment of male JRC mice with doxorubicin and prodrugs

Compound	Dosage* mg/kg/day	Physiologic changes in cardiomyocytes *	
		Healthy mice**	Mice with transplanted Sarcoma 180**
		MTT	MTT
Doxorubicin	1.5	40±1	114±10
6a (R=Cl)	1.5	85±6	225±12
6b (R=*t*-BuOCOCH=)	1.5	54±6	270±12
Doxorubicin	5.0	39±4	130±10
6a (R=Cl)	5.0	87±4	230±21
6b (R=*t*-BuOCOCH=)	5.0	102±7	360±12

*Administration schedule: 1, 2, 3, 4, 7 days

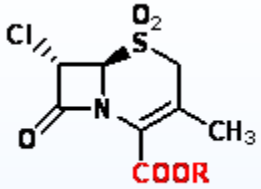
**Cells isolated on the 9th day of experiment

The usage of an effective HLE inhibitor *tert*-butyl 7α-chloro-3-methyl-1,1-dioxo-ceph-3-em-4-carboxylate as a template for the preparation of new antitumor cephalosporin derivatives.

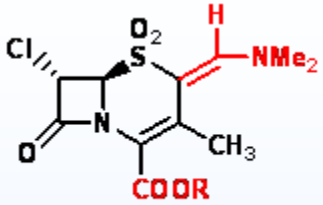


Chem. Heterocycl. Comp. 1998, Vol. 34, Nr. 11, 1276. Chem. Heterocycl. Comp, 2000, vol. 36, Nr. 6, 744.
Chem. Heterocycl. Comp, 2000, vol. 36, Nr.10, 1424. Chem. Heterocycl. Comp, 2003, vol. 39, Nr. 5, 680.
Chem. Heterocycl. Comp, 2004, vol. 40, Nr. 6, 949. Chem. Heterocycl. Comp, 2005, vol. 42, Nr. 5, 673.
Chem. Heterocycl. Comp, 2007, vol. 44, Nr. 2, 259. Chem. Heterocycl. Comp, 2007, vol. 44, Nr. 5, 769.
Chem. Heterocycl. Comp, 2007, vol. 44, Nr. 12, 1849.

Cytotoxic properties and LD_{50} values for 7α-chlorocephalosporanate sulfone esters



1



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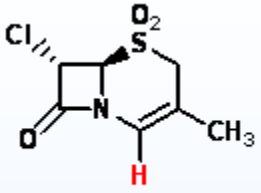


3

R	Cytotoxic activity in vitro, TD_{50} against tumor and normal cells, μg/ml									LD_{50}, mg/kg
	HT-1080		MG-22A		B16		Neuro2A		NIH3T3	
	CV	MTT	CV	MTT	CV	MTT	CV	MTT	NR	
1										
t-Bu	6	2	6	6	3	2	2	2	226	1162
Me	23	1	1	0,2	19	1	2	8	15	236
Et	3	19	4	4	13	27	11	16	35	490
i-Pr	11	12	4	3	8	20	20	22	52	600
	2	3	3	0.2	3	4	11	21	58	626
	15	27	5	1	13	27	22	14	31	495
	53	>100	0.3	2	1.5	1.1	7	0.8	55	659
2										
t-Bu	18	32	18	21	22	19	2	1.1	96	878
	4	5	0.4	0.3	12	26	32	21	n.t.	n.t.
3	2	2	1	2	2	2	2	2	11	252

n. t. – not tested

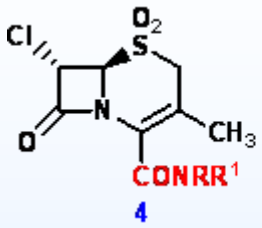
TD_{50} CV - Concentrations (μg/ml) providing 50% of Tumor Death effect using CV coloration.

TD_{50} MTT- Concentrations (μg/ml) providing 50% of Tumor Death effect effect using MTT coloration.

TD_{50} NR- Concentrations (μg/ml) providing 50% of Tumor Death effect effect using NR coloration.

$$\log LD_{50}(mg\ kg^{-1}) = 0.435 \cdot \log LC_{50}\ (mmol\ L^{-1}) + 0.625$$

Cytotoxic properties and LD_{50} values for 7α-chlorocephalosporanate sulfone amides



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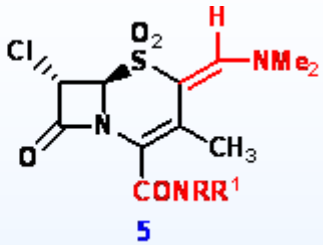
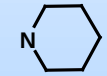
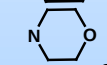
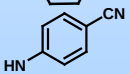
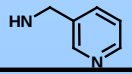
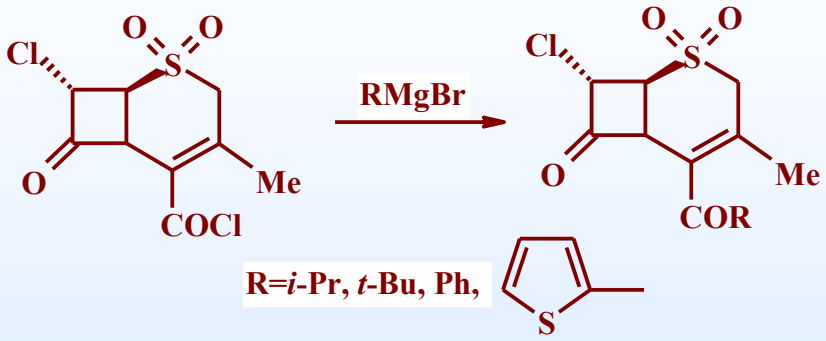
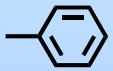
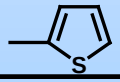


5

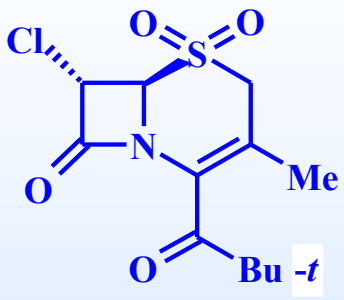
NRR¹	Cytotoxic activity in vitro, TD_{50} against tumor and normal cells, μg/ml									LD_{50},
	HT-1080		MG-22A		B16		Neuro2A		NIH3T3	
	CV	MTT	CV	MTT	CV	MTT	CV	MTT	NR	mg/kg
4										
$NHC(CH_3)_3$	1	2	2	3	2	2	2	3	49	597
$N(CH_3)_2$	2	2	11	7	6	1.4	>10	>10	105	790
$N(C_2H_5)_2$	6	12	2	2	n.t.	n.t.	n.t.	n.t.	30	481
	3	3	0.4	0.2	35	11	4	7	40	559
	28	9	0.4	0.6	20	30	>100	>100	316	1376
	8	3	1	0.2	10	25	45	100	63	718
$NHCH(C_6H_5)_2$	0.36	0.64	2	2	19	7	1	2	21	487
5										
$NHC(CH_3)_3$	6	6	3	7	26	18	5	5	179	1146
$NHCH(C_6H_5)_2$	3	2	3	2	23	17	2	3	14	438
	17	18	9	19	110	124	13	1.1	157	1138

Cytotoxic properties and LD_{50} values for 7α-chloro-1,1-dioxo-3-methylcephem-4-ketones

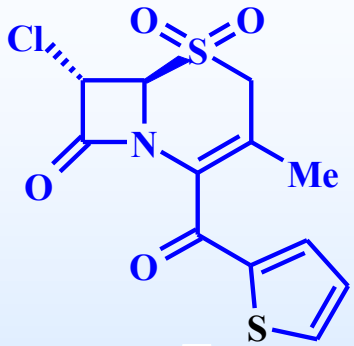


R	Cytotoxic activity in vitro, TD_{50} against tumor and normal cells, μg/ml											LD_{50}, mg/kg
	HT-1080		MG-22A		B16		Neuro2A		BHK-21		NIH3T3	
	CV	MTT	CV	MTT	CV	MTT	CV	MTT	CV	MTT	NR	
$CH(CH_3)_2$	2	3	3	3	39	26	0.8	2	3	4	72	671
$C(CH_3)_3$	3	5	3	3	19	6	1	9	34	28	277	1235
	14	35	4	9	18	12	13	35	n.t.	n.t.	65	854
	6	10	4	4	25	29	2	10	37	47	287	1313

The inhibiting effect *in vivo* towards Sarcoma tumor transplanted in mice



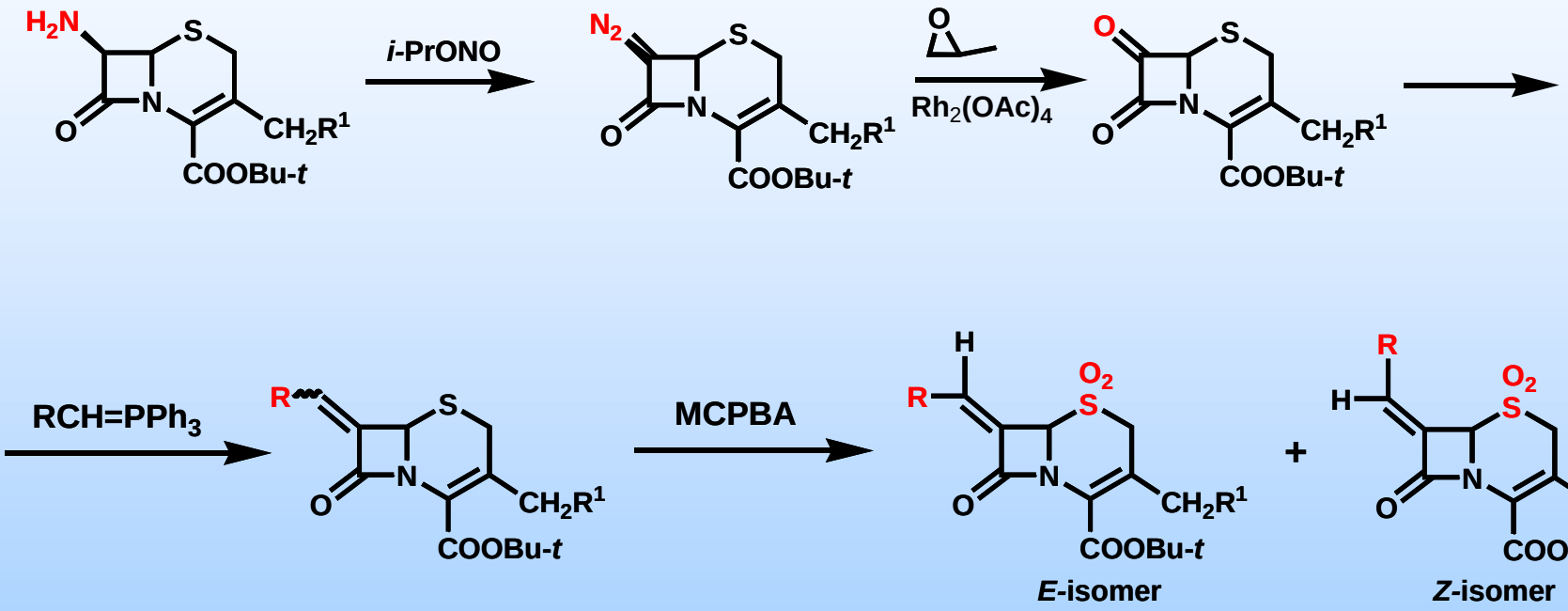
1



6

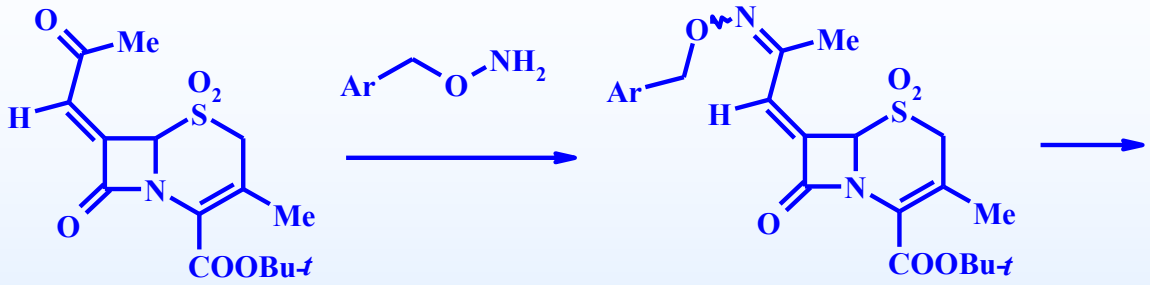
Com-pound	Tumor type	Administration schedule (days)	Dosage, mg/kg/day	Total dosage mg/kg	Tumor growth inhibition, % (in 9 days)
1	Sarcoma (S-180)	1, 2, 3, 4 ... 7, 8, 9	1	7	50 (p=0.329)
6	Sarcoma (S-180)	1,2,3,4…7,8	10	60	76 (p=0.393)

Preparation of 7-alkylidenechlorophalosporanate sulfone esters

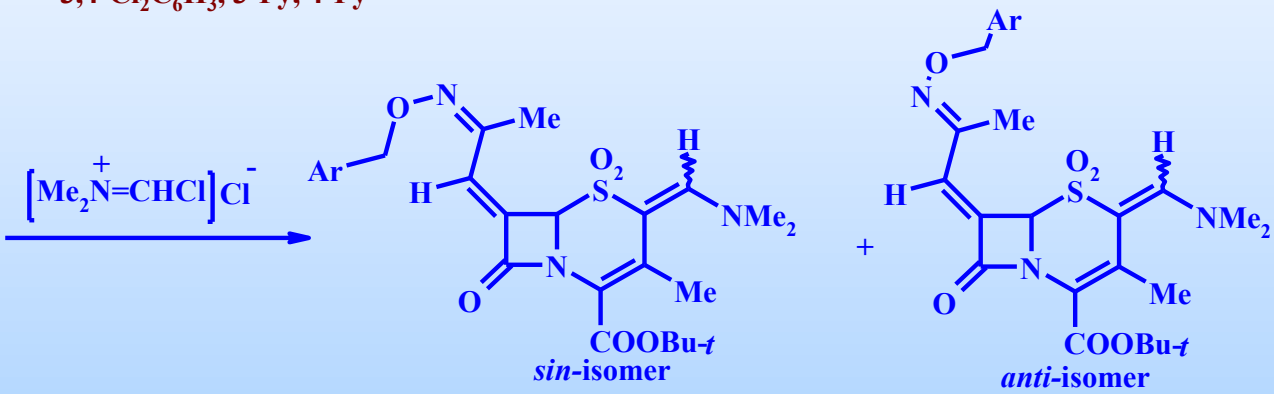


R = *t*-BuOCO, MeOCO, MeCO, Ph, 4-0_2N-C_6H_4, 4-Pyridyl, 2-Furyl

R^1= H, $OCOCH_3$



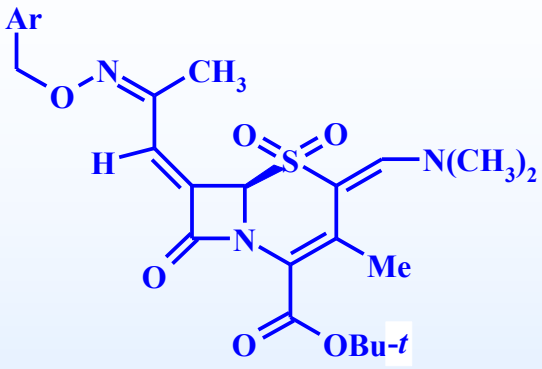
Ar=Ph, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 2-FC_6H_4, 2-$CF_3C_6H_4$, 2,6-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 3-Py, 4-Py



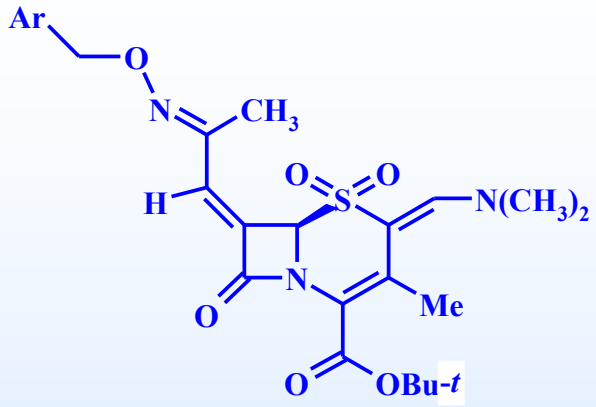
Ar=Ph, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4,2-FC_6H_4

1. Bioorg. Med. Chem., 2000, Vol. 8, Nr 5, 1033-1040.
2. Chem. Heterocycl. Comp., 2008, vol. 44, Nr. 4, 618.
3. Chem. Heterocycl. Comp., 2008, vol. 44, Nr. 6, 918.
3. Chem. Heterocycl. Comp., 2009, vol. 45, Nr. 2, 284.

Cytotoxic properties *in vitro* of *tert*-butyl 1,1-dioxo-7-alkylidenedeacetoxycephalosporanates



sin-isomer

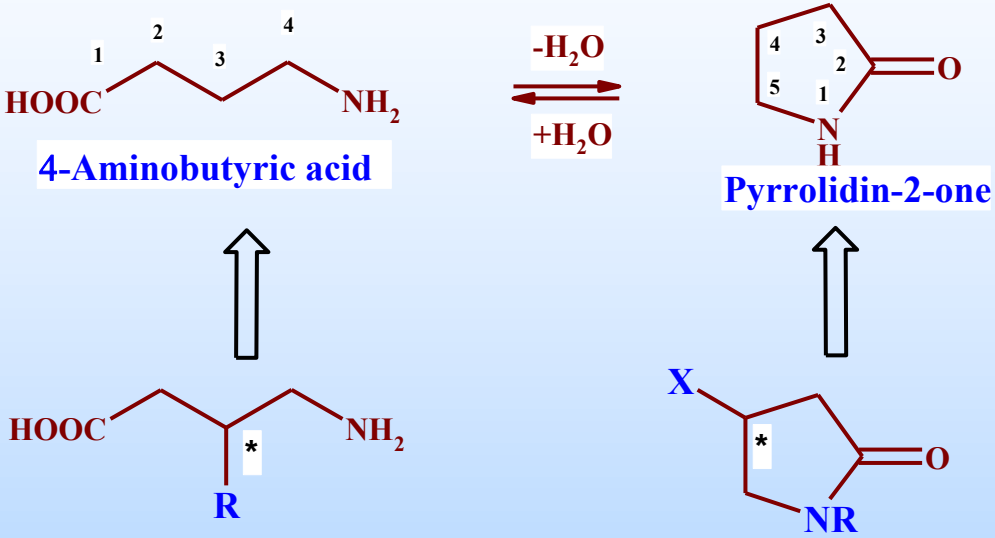


anti-isomer

Compound	Cytotoxic activity in vitro, TD_{50}, μg/ml					
	Tumor cells				Normal cells	
Ar	HT-1080		MG-22A		NIH3T3	LD_{50} mg/kg
	CV	MTT	CV	MTT	NR	
syn $C_6H_5CH_2$	3	3	3	2	12	417
anti $C_6H_5CH_2$	3	3	2	2	87	1003
syn 4-Br-$C_6H_4CH_2$	3	3	2	2	151	1335
anti 4-Br-$C_6H_4CH_2$	3	3	1	2	30	639
syn 3-Br-$C_6H_4CH_2$	10	11	2	2	920	2961
anti 3-Br-$C_6H_4CH_2$	10	10	3	3	100	1161
anti 2-Br-$C_6H_4CH_2$	90	37	3	3	534	2380

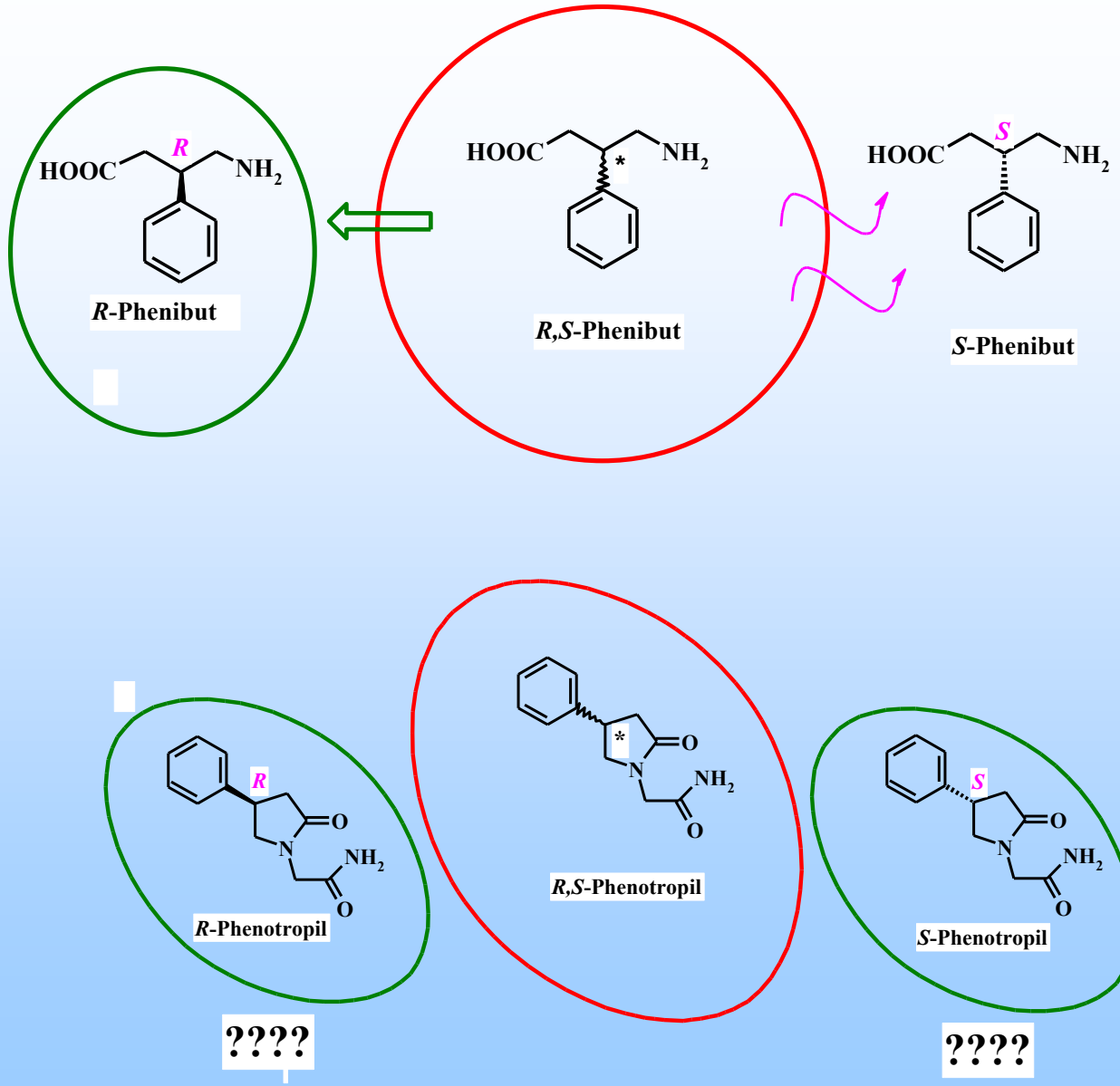
Синтез и биологические свойства производных γ-лактамов

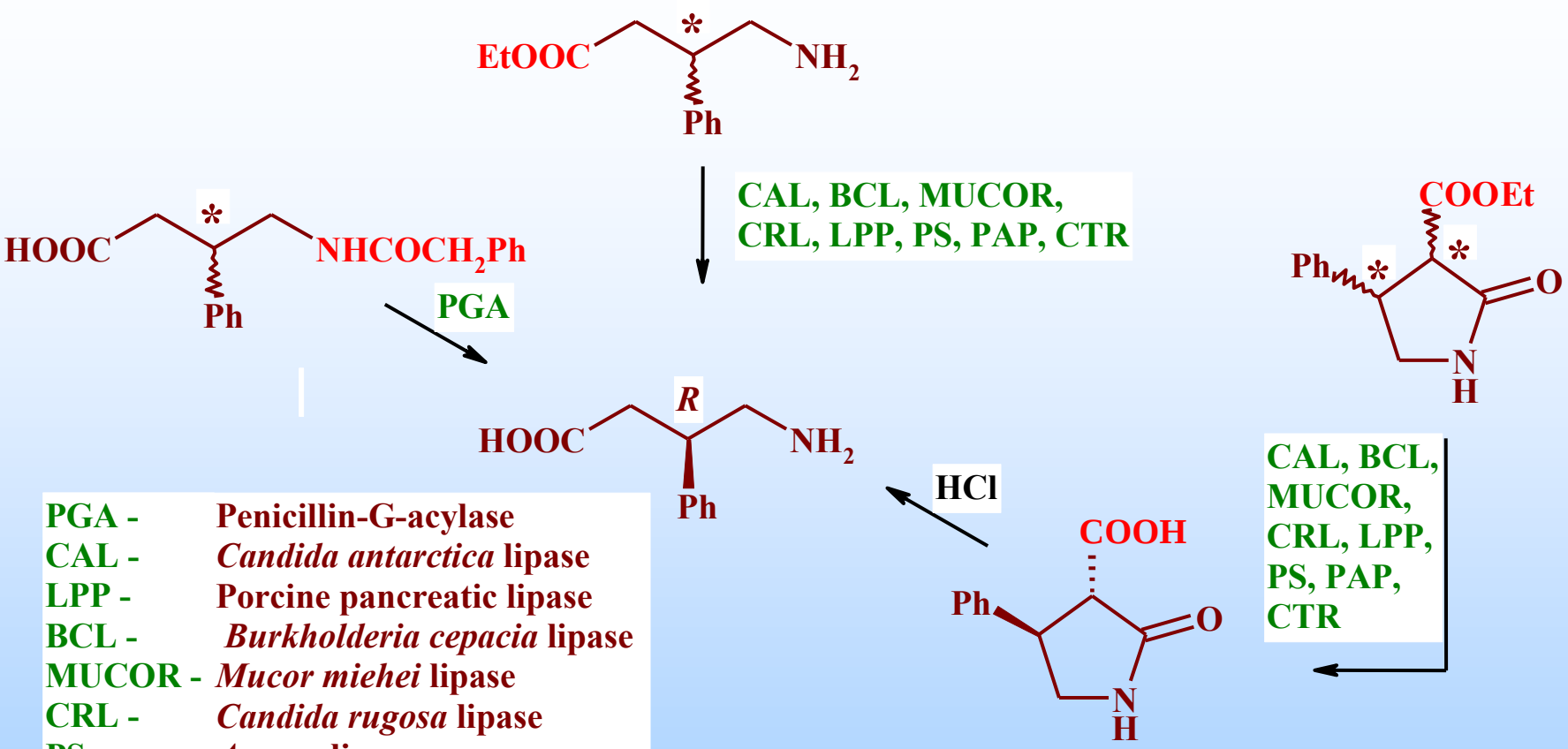
GABA molecule in linear and cyclic form serves as pharmacophore in following nootropic and psychotropic drugs



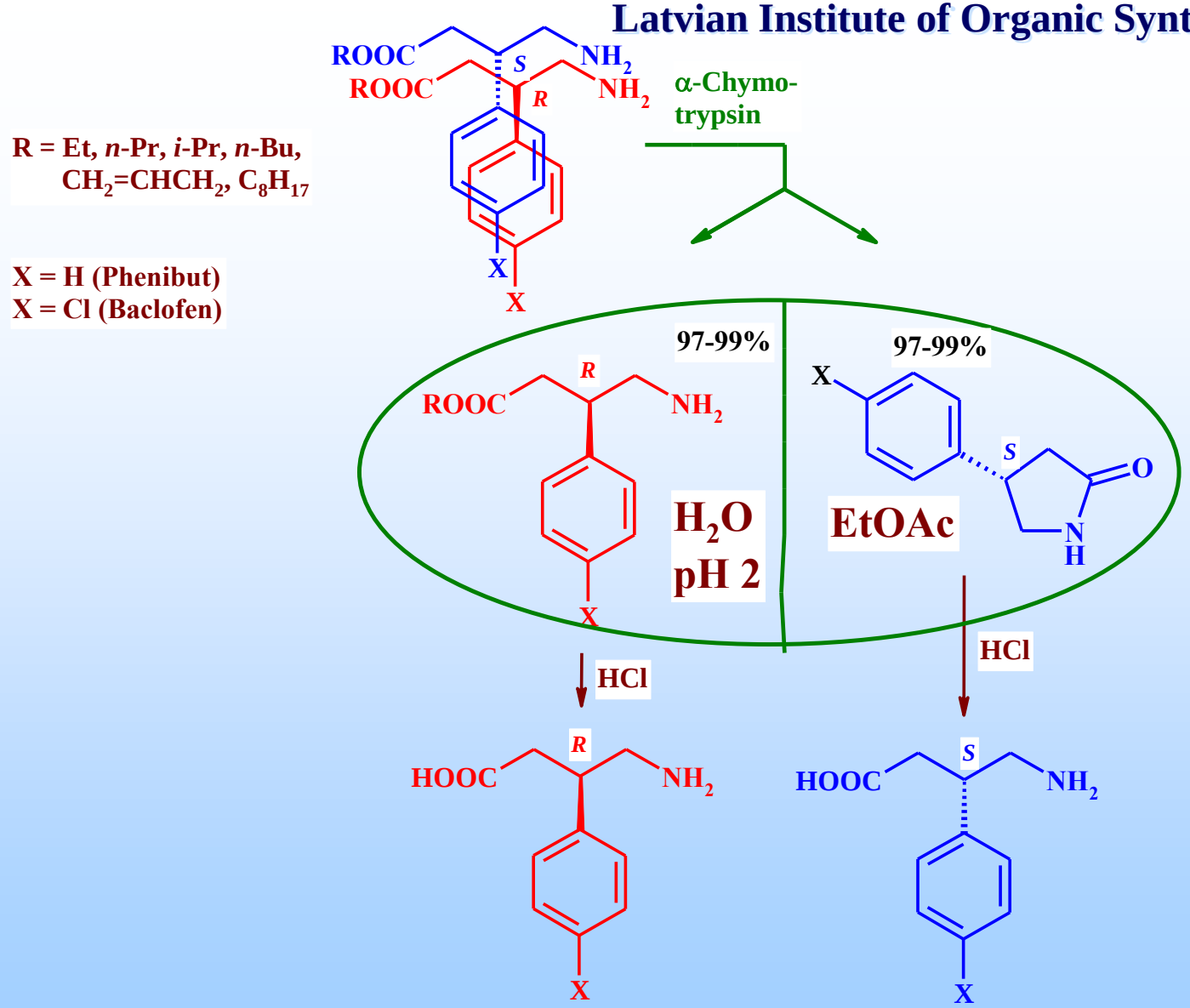
R = C_6H_5	Phenibut
R = 4-ClC_6H_5	Baclofen
R = *i*-Bu	Pregabalin
R = -$(CH_2)_5$-	Gabapentin

R = CH_2CONH_2; X = H	Piracetam
R = $CH(Et)CONH_2$; X = H	Levetiracetam
R = CH_2CONH_2; X = OH	Oksiracetam
R = CH_2CONH_2; X = C_6H_5	Phenotropil


HOOC
R
NH2
R-Phenibut
HOOC
*
NH2
R,S-Phenibut
HOOC
S
NH2
S-Phenibut
R
O
N
NH2
O
R-Phenotropil
????
*
O
N
NH2
O
R,S-Phenotropil
S
O
N
NH2
O
S-Phenotropil
????



PGA -	Penicillin-G-acylase
CAL -	*Candida antarctica* lipase
LPP -	Porcine pancreatic lipase
BCL -	*Burkholderia cepacia* lipase
MUCOR -	*Mucor miehei* lipase
CRL -	*Candida rugosa* lipase
PS -	*Amano* lipase
PAP -	Papain proteinase
CTR -	α-Chymotrypsine proteinase



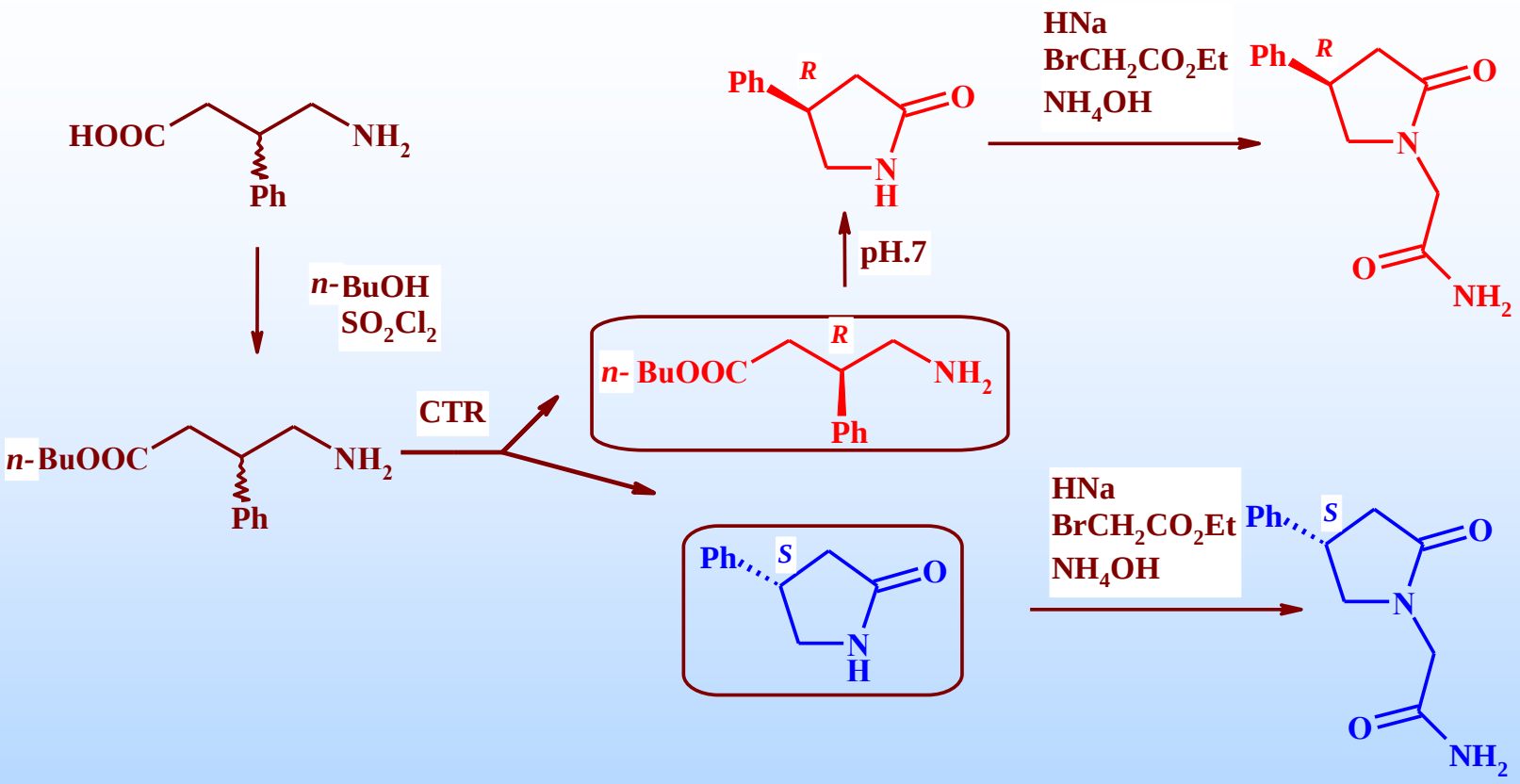
G. Veinberg, M. Vorona, A. Lebedevs, A. Chernobrovijs, I. Kalvinsh, *Enzymatic resolution of racemic 3-aryl-4-aminobutyric acids*, LR Pat. 13635, (2006). WO2007096314 - 2007-08-30

Effective dosages (mg/kg) providing similar activity of racemic phenibut and its *R*- un *S*-enantiomers

Test	Phenibut	*R*- Phenibut	*S*- Phenibut
	ED_{50}*	ED_{50}	ED_{50}
Rectal temperature	312 ± 99	117 ± 24	>500
Analgesic effect	59 ± 32	47 ±10	>500
Cylinder test	338 ± 160	157 ± 69	>500
Traction	312 ± 62	129 ± 16	>500
Rotarod test	536 ± 139	123 ± 12	>500

* Effective dosage, mg/kg

The preparation of *R*- and *S*-phenotropil



G. Veinberg, M. Vorona, M. Dambrova, L. Karina, L. Zvejniece, A. Chernobrovijs, I. Kalvinsh, *Method of preparation and use of pharmacologically active N-carbamoylmethyl-4(R)-phenyl-2-pyrrolidinone*, LR Pat. 13630 (2006). WO2007104780 - 2007-09-20

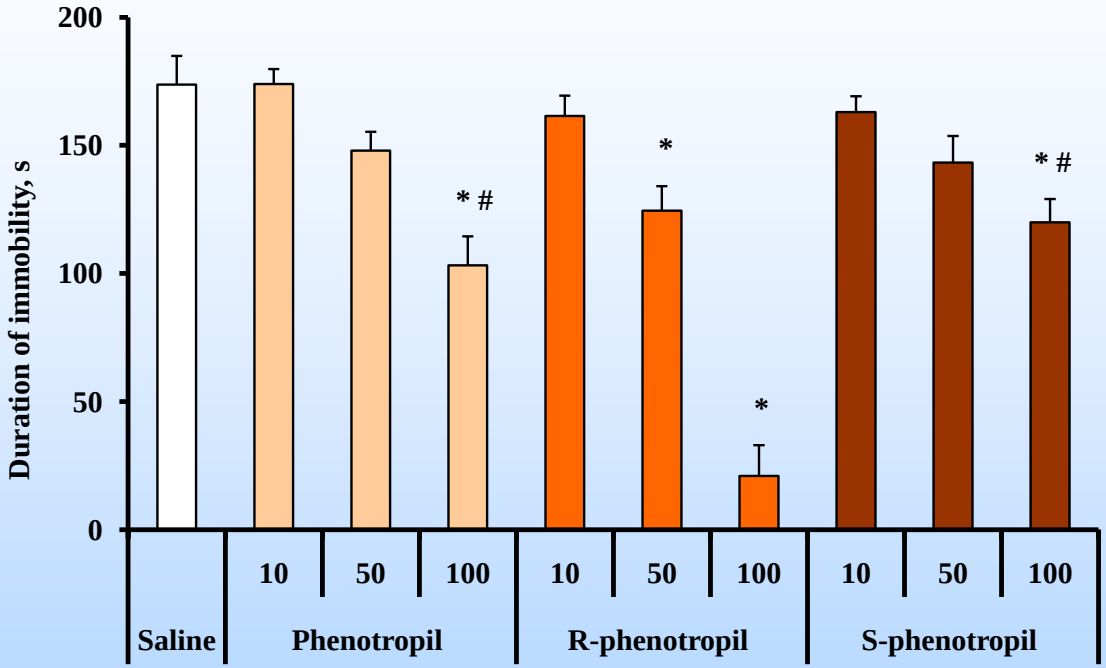
G. Veinberg, M. Vorona, A. Lebedev, A. Chernobrovijs, I. Kalvinsh, *Manufacturing method of N-carbamoylmethyl-4(R)-phenyl-2-pyrrolidinone*, LR Pat. 13631 (2006). WO2007104781 - 2007-09-20

Activity of *R*- and *S*-phenotropil in cylinder, traction and rota-rod tests (Dunham et.al., 1957)

Tested substance	ED_{50} (mg/kg) *		
	Muscle relaxant activity		
	Cylinder	Traction	Rota-rod
R-Phenotropil	199±38	456±122	193±26
S-Phenotropil	286±78	548±75	459±87

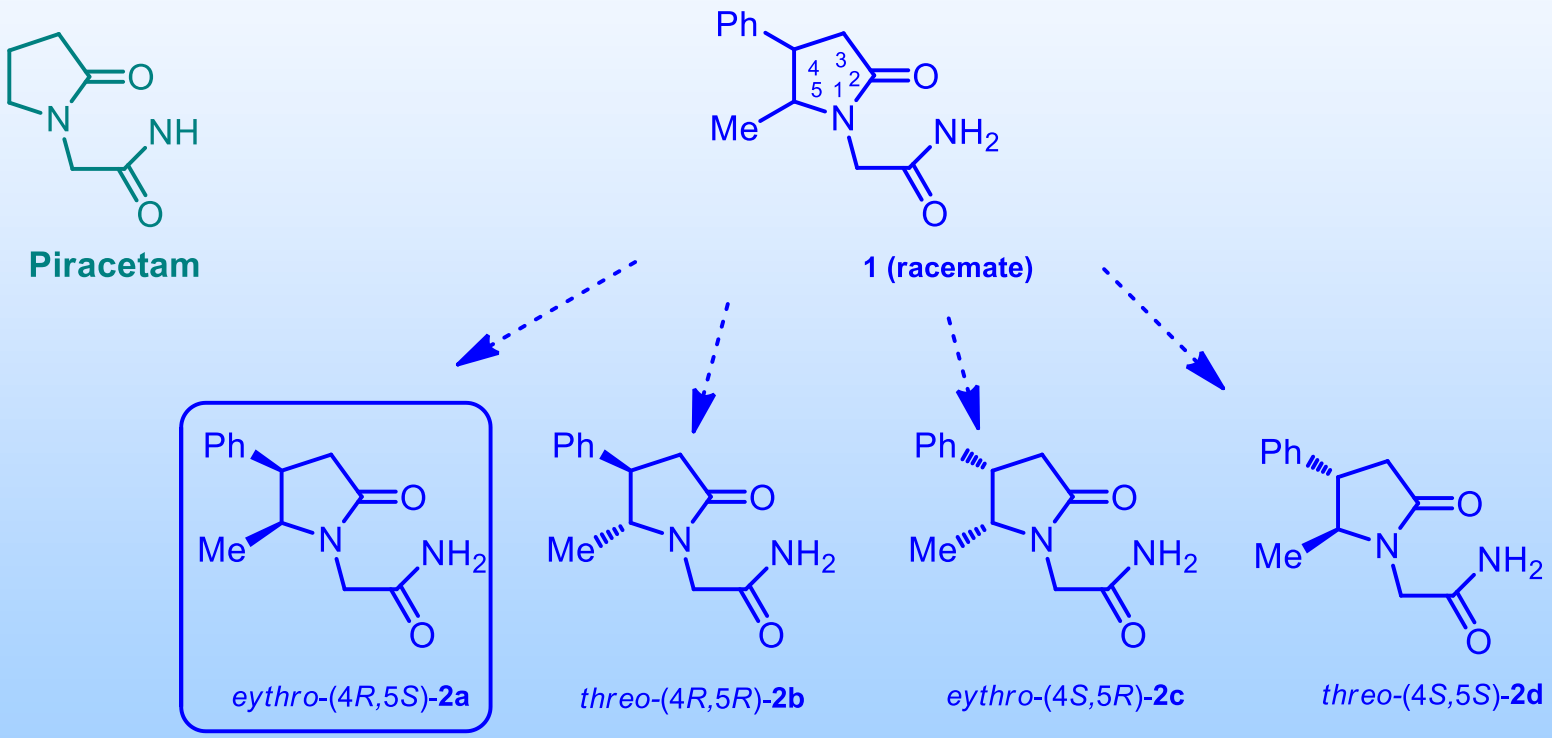
* Compounds were administered i.p. at doses of 50, 100, 250 and 500 mg/kg. The effects were observed 30, 60, 120 and 180 min after drug administration.

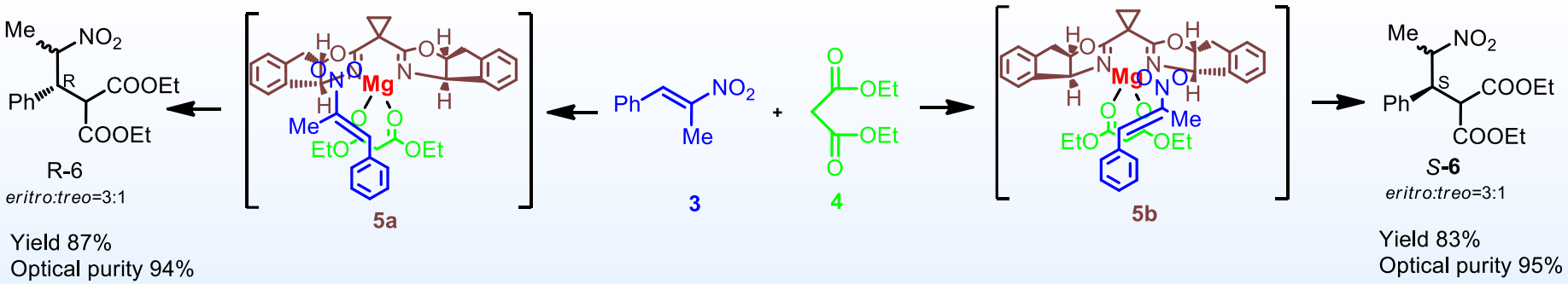
Antidepressant properties tested in Porsolt (Porsolt et.al., 1977) forced swim test

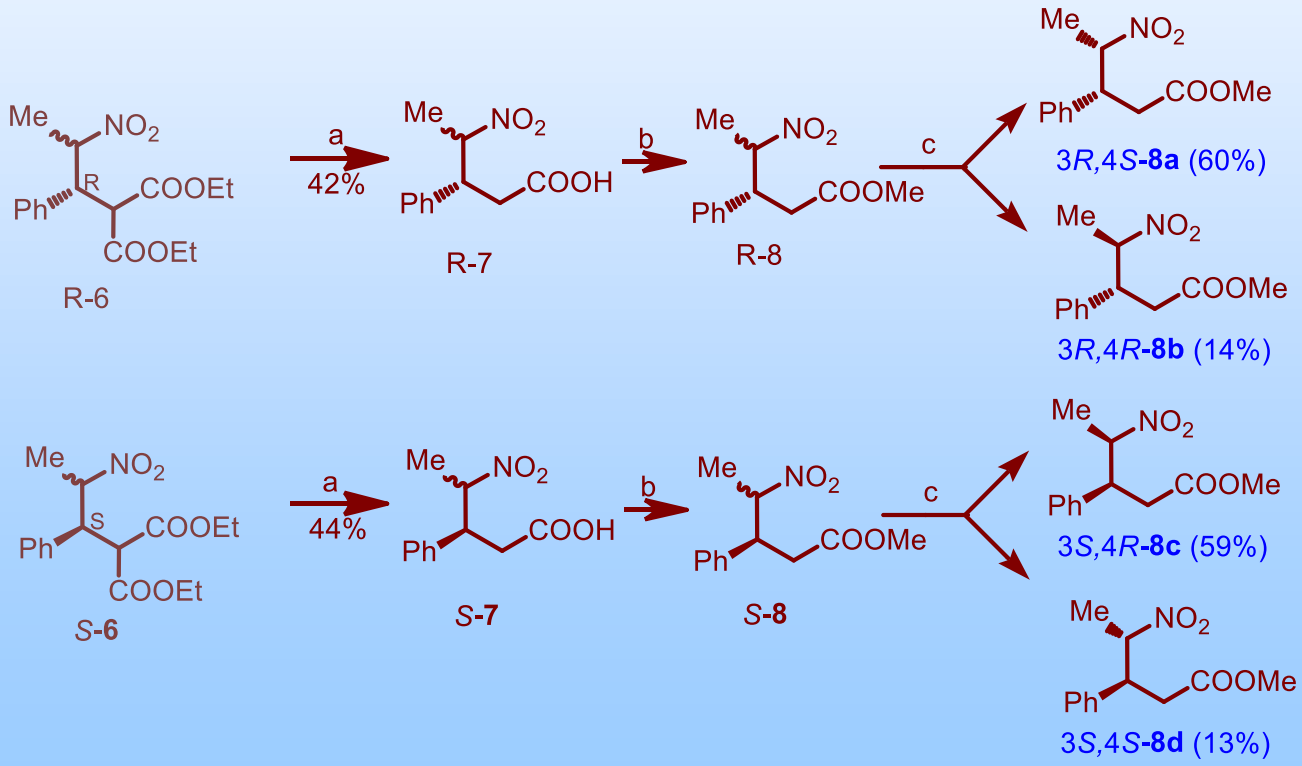


Effects of racemic, R- and S- phenotropil in the forced swim test. The compounds were administered i.p. 30 min prior to the experiment at doses of 5, 10, 50 and 100 mg/kg. Each column represents the mean ± S.E.M. of 10 animals. *p > 0.05 vs. saline-treated group, #p > 0.05 vs. the respective dose of R-phenotropil.

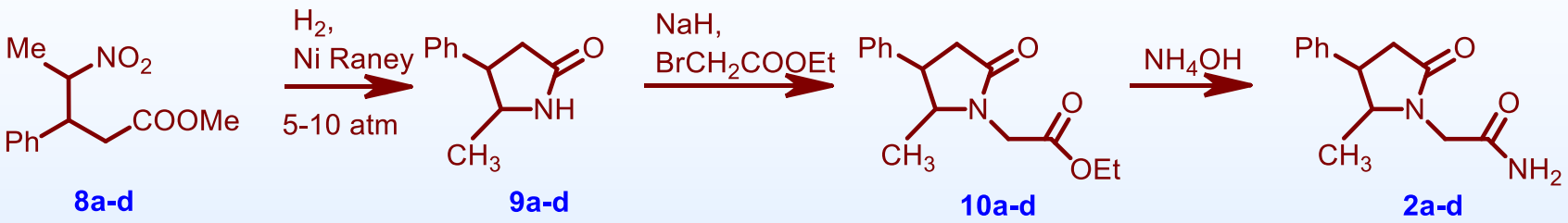
Berestovitskaya et al., International Conference on the Synthesis of Nitrogen Heterocycles, Moscov, Oct. 9-12, 2001, *1*, 229







Reagents and conditions: (a) 36% HCl and CH_3COOH mixture (1:3), reflux, 18 hours; (b) MeOH, $SOCl_2$ (cat) 20 hours, reflux; (c) chromatographic separation on silica gel.

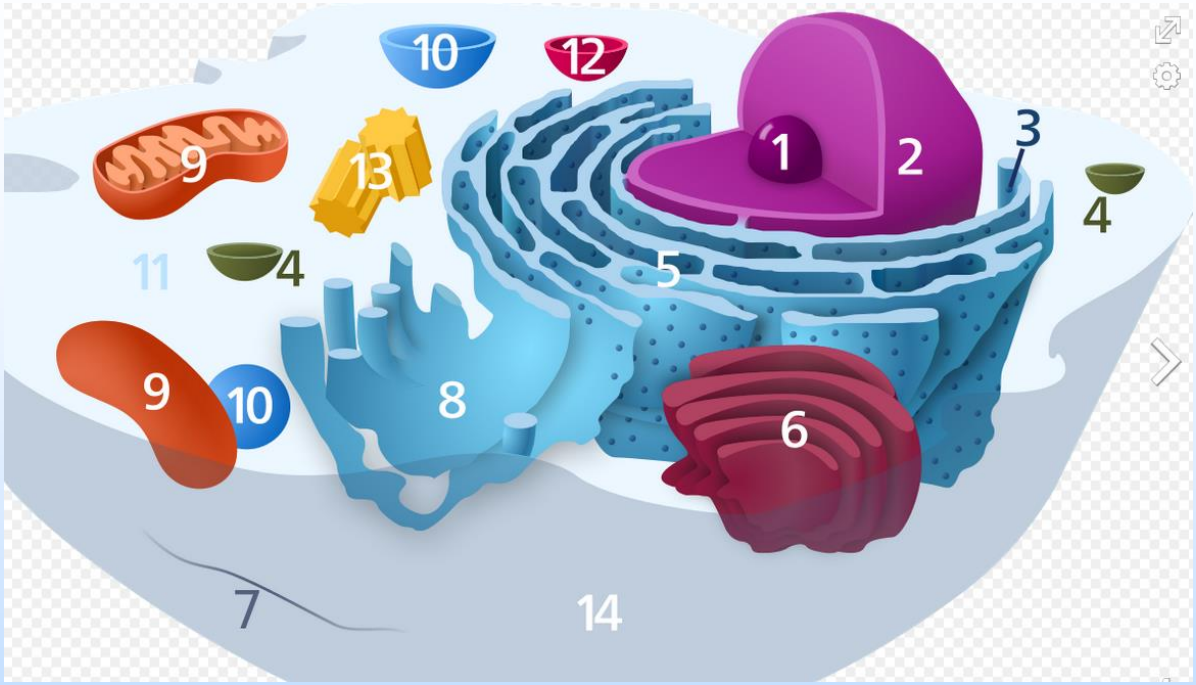


2, 8, 9, 10 a = *erythro*-4*R*,5*S*; b= *threo*-4*R*,5*R*; c= *erythro*-4*S*,5*R*;d = *threo*-4*S*,5*S*

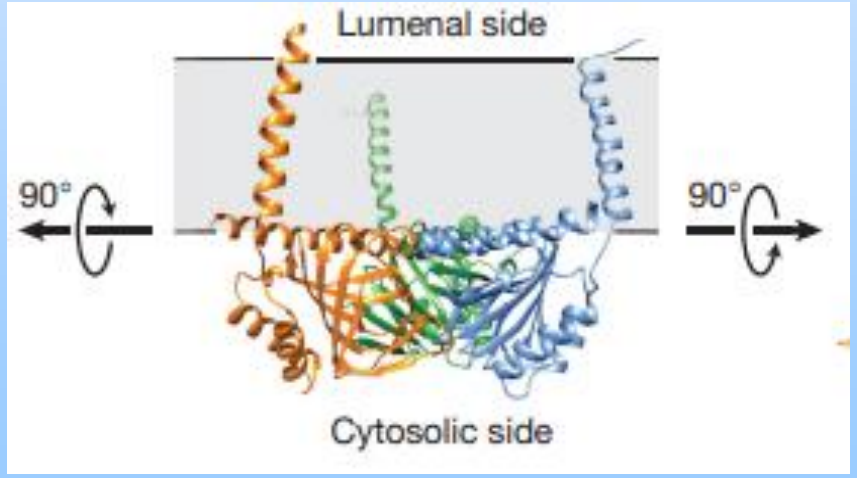
Table 1. Angles of optical rotation for 2-(5-methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide (2) stereoisomers

Compound	$[\alpha]_D^{20}$	Solvent, concentration
4*R*,5*S*-2a	-96.7°	c = 0.05, MeOH
4*R*,5*R*-2b	+22.9°	c = 0.05, MeOH
4*S*,5*R*-2c	+94.1°	c = 0.05, MeOH
4*S*,5*S*-2d	-26.0°	c = 0.05, MeOH

Veinberg, G.; Vorona, M.; Zvejniece, L.; Vilskersts, R.; Vavers, E.; Liepinsh, E.; Kazoka, H.; Belyakov, S.; Mishnev, A.; Kuznecovs, J.; Vikainis, S.; Orlova, N.; Lebedev, A.; Ponomaryov Yu.; Dambrova, M. *Bioorg. Med. Chem*. 2013, 21, 2764.

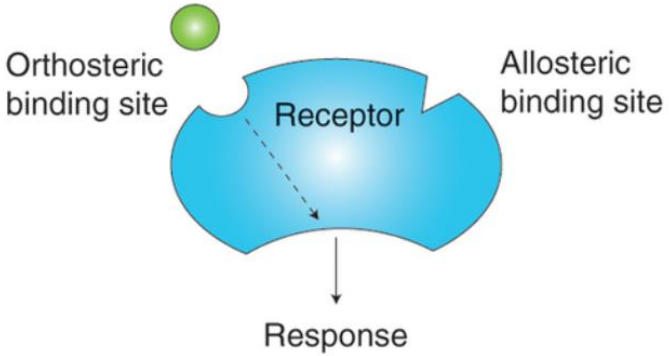


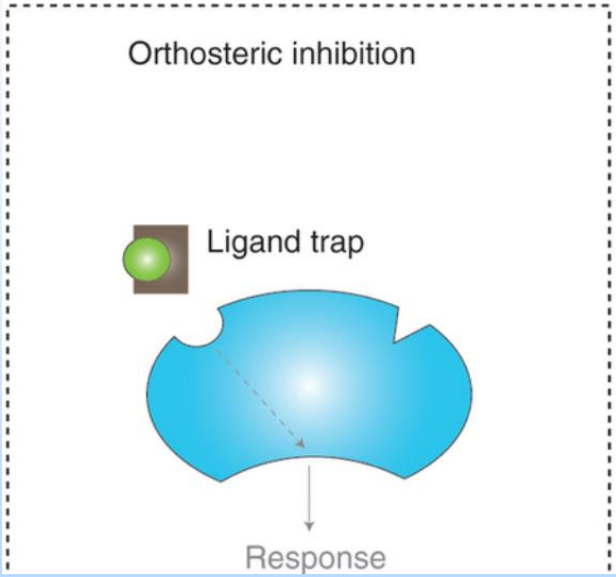
Nr 5/ Эндоплазматический рутикулум

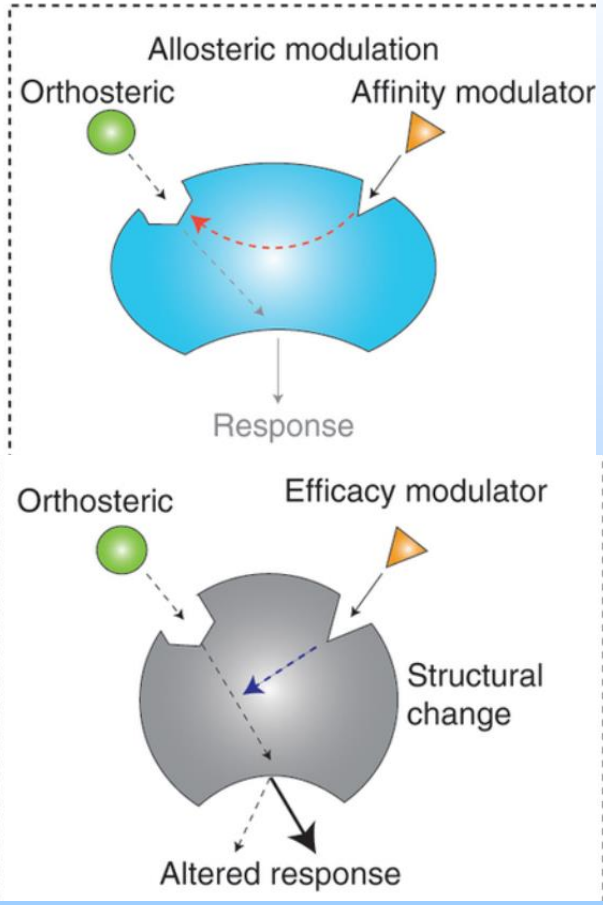


Кристаллическая структура Сигма-1 рецептора

Nature, 2016 letter research





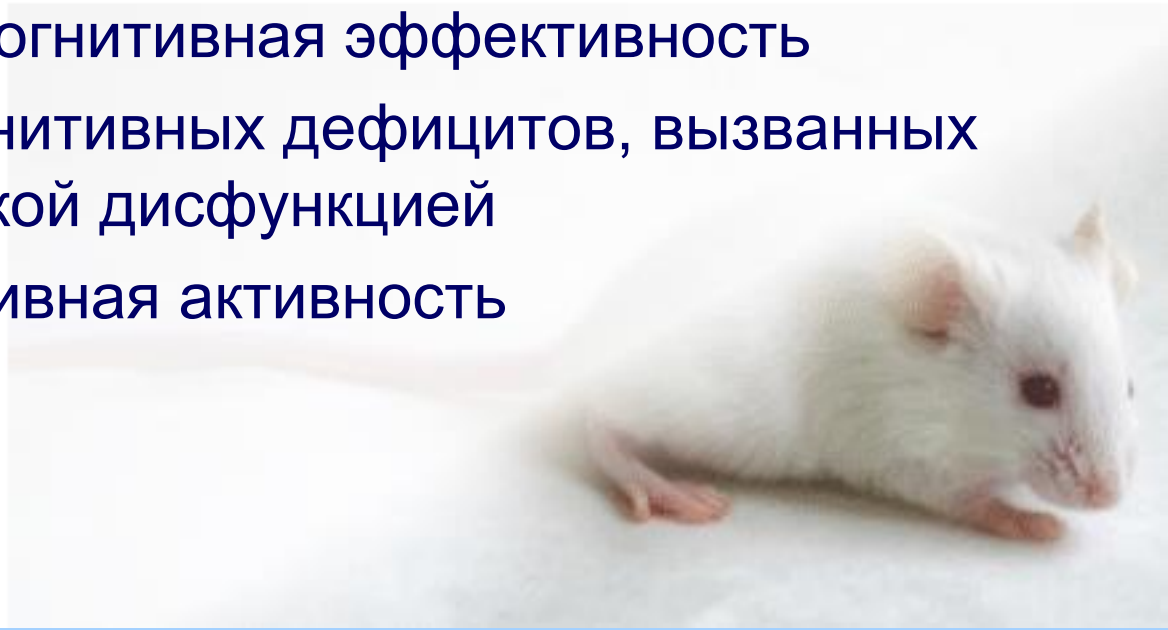


Механизм аллостерического модулирования лиганда

Результаты доклинических испытаний

Фармакологическая эффективность E1R:

- Улучшенная когнитивная эффективность
- Снижение когнитивных дефицитов, вызванных холинергической дисфункцией
- Антиконвульсивная активность



Благодарю за внимание!