REVIEW

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Compounds Isolated at the Institute of Microbiology in 1989–2001 and Future Trends

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ABSTRACT. A total of 307 new compounds, natural, semisynthetic or synthetic, were isolated at the *Institute of Microbiology* during the last twelve years. Due to the development of separation (chromatographic) methods and of analytical methods used to determine the chemical structure of these compounds, *i.e.* NMR, MS and X-ray diffraction, many new metabolites could be described.

CONTENT

1 INTRODUCTION

The compounds are listed according to their chemical relatedness and organized in several groups such as derivatives of ergot alkaloids, cyclic oligopeptides, glycosylated compounds *etc*.

Biologically active secondary metabolites produced by microorganisms, plants and other biological producers and their semisynthetic derivatives belong to the most commonly used therapeutics in both human and veterinary medicine. The discovery of antibiotics contributed substantially to the successful control of many infectious diseases and the use of antibiotics often resulted in eradication of some of them. New applications of natural biologically active compounds in medicine, *e.g.*, as immunosuppresives or antisclerotic compounds, but also in agriculture as growth stimulators in plants and animals or as pesticides, make the search for new biologically active compounds produced by microorganisms, plants and other living organisms a permanent process (Vining and Stuttard 1995*a*,*b*).

Natural compounds usually represent a 5–8 % yearly increase in the world market of pharmaceuticals. Some natural compounds have been used in their original form or as their semisynthetic derivatives. Numerous examples of such semisynthetic drugs are available. β-Lactam antibiotics such as penicillins, cephalosporins, clavulanates and carbapenems have long dominated the antiinfectious therapy. Other antibiotics such as aminoglycosides, tetracyclines and macrolides were discovered later. The permanently increasing occurrence of resistant microorganisms, particularly of nosocomial and opportunistic pathogens (very dangerous especially in patients with AIDS and tumors, in which natural immunity is suppressed) calls for the search of new derivatives of known drugs and for discovery of new compounds (Gräfe 1992; Lancini and Lorenzetti 1993; Hutchinson 1994). Some natural compounds are not only active as antibiotics but are also important anticancer drugs, *e.g.*, doxorubicin, bleomycin and mitomycin C (Fox 1991), others are efficient immunosuppressives, *e.g.*, cyclosporins, yet others are valuable immunostimulators. Some examples of natural compounds with different biological activities were listed by Strohl (1997).

The present paper represents an addition to the first review by Podojil *et al.* (1984) and its first supplement by Podojil and Cudlín (1989). During the last ten years the chemistry and biochemistry of natural compounds developed extremely rapidly, and, together with the relatively recently introduced grant funding, it led to the discovery of a great number of compounds that had not yet been described. Thanks to this, a total of 307 new compounds were described, considerably exceeding the number of 267 new compounds identified over the 35-year period of 1954–1988.

Some of this pool of compounds may hopefully find their use in modern currently developed application strategies briefly described at the end of this review.

2 ERGOT ALKALOIDS

Submerged fermentation of *Claviceps paspali* strain MG-6 was studied with regard to the fate of individual alkaloids in the course of fermentation (Bumbová-Linhartová *et al.*, 1991). Isolation of *trans*-10-hydroxypaspalamide (**1**) from post-production phase (days 15–30) signifies the existence of an alternative biosynthetic pathway for production of simple lysergic acid derivatives; *see* Table I for derivatives of ergot alkaloids. Both diastereoisomers, *viz. trans*-10-hydroxypaspalamide (**1**) and *cis*-10-hydroxypaspalamide (**2**) were described by Flieger *et al.* (1993). They were found as metabolites of the post-production phase of submerged fermentation of *C. paspali*.

Natural glycosides of ergot alkaloids, namely fructosides, were also identified. Submerged culture of *C. fusiformis* supplemented with chanoclavine produced chanoclavine O-β-D-fructofuranoside (**3a**) and chanoclavine O-β-D-fructofuranosyl-(2→1)-O-β-D-fructofuranoside (**3b**) (Flieger *et al.* 1990).

The structure of a new elymoclavine O-β-D-fructofuranosyl-(2→1)-O-β-D-fructofuranoside (**4a**) produced in saprophytic cultures of strains *Claviceps* sp. SD 58 and *C. purpurea* 88 EP in a sucrose medium was described by Flieger *et al.* (1989).

A series of naturally occurring elymoclavine oligoglycosides containing tri- (**4b**) and tetrafructoside (**4c**) units was investigated by fragmentation of the fast atom bombardment mass spectra (FAB-MS) (Havlíček *et al.* 1994).

Cultures of *C. purpurea* alkaloid-blocked by 5-fluorotryptophan were used to prepare further fructosides of lysergol (**5**) and 9,10-dihydrolysergol (**6**) (Křen *et al.* 1993). Two new metabolites of *C. purpurea* strain 129/35, *i.e.* derivatives of quinoline (**7a,b**), were isolated from the culture broth. These metabolites are assumed to be the products of ergot alkaloid turnover (degradation) (Flieger *et al.* 1991).

Many new metabolites were isolated from genus *Claviceps*, *e.g.*, a new peptide ergot alkaloid containing L-homoisoleucine (**8**) (Cvak *et al.* 1994*a*), hydroxylated at C-8 of the lysergic acid moiety (**9a**) (Cvak *et al.* 1997) or ergoladinine, containing methionine (**9b**) (Cvak *et al.* 1996). They were isolated from ergot sclerotia of the field-growing parasitic fungus *C. purpurea*.

Collision-induced dissociation (CID) mass spectra of natural ergopeptines have been studied and a new ergot alkaloid, ergosedmine (**9c**), a congener of ergocristine produced by *C. purpurea* was discovered (Halada *et al.* 1998). CID spectra complete the information on the alkyl side chain size of the amino acid obtained to characterize the alkyl branching pattern of the ergot alkaloid.

Seven-membered heterocyclic oxepinoderivates were prepared using an unusual reaction catalyzed by halogen peroxidase. The structures of oxepino[5,4,3-*cd*]indole derivatives (**10**, **11**) and 3,4-disubstituted indoles (**12a,b**) resulting from biotransformation of chanoclavine by *Euphorbia calyptrata* cell culture were elucidated by Křen *et al.* (1996*d*).

Agroclavine was oxidized (Křen *et al.* 1997*b*) by haloperoxidase from *Streptomyces aureofaciens* to yield acetoxy derivative (**13a**). Incorporation of propionate into the product was observed in a propionate buffer, yielding ergolenone (**13b**) as a by-product. In this buffer, the biotransformation proceeded rapidly affording also the higher oxidation product oxobenzo[*f*]quinoline (**14**).

New derivatives of clavin alkaloids were prepared using cell cultures from higher plants exhibiting peroxidase activity such as *Ajuga reptans*, *Armoracia rusticana*, *Atropa belladonna*, *Duboisia myoporoides*, *Euphorbia calyptrata*, *Papaver somniferum* and *Solanum aviculare*. Agroclavine and elymoclavine were modified using plant cell cultures; setoclavine (**15a**) and isosetoclavine (**15b**) were isolated from the media after transformation of agroclavine on a semipreparative scale. 10-Hydroxyelymoclavine (**16**) resulted from a similar treatment of elymoclavine (Ščigelová *et al.* 1995).

Exchange of function groups was frequently observed in ergot alkaloids during chemical synthesis. 2,3-Dihydro-2-oxo-α-ergocryptine (**17**) and 2,3-dihydro-2-oxo-3-hydroxy-α-ergokryptine (**18**) were found as side reaction products in the bromination of α-ergokryptine (Cvak *et al.* 1992). A general procedure for the preparation of 2-oxo derivatives of 8- (**20**, **21a,b**) or 9-ergolene (**22a–e**) was also reported (Cvak *et al.* 1994*b*). N^1-Trimethylsilyl derivatives of five different suitably protected parent ergot (clavine) alkaloids, *i.e.* agroclavine (**23a**), elymoclavine (**23b**), lysergol (**24**), lysergene (**25**), and 9,10-dihydrolysergol (**26**) were prepared by Křen and Sedmera (1996*d*). Six 6′-deoxoergopeptines (**27a,b**, **28**, **29a–c**) were identified after a selective reduction of parent alkaloids (Cvak *et al.* 2000).

Many different glycosides were prepared using enzymes of submerged producer *Claviceps* cultures or enzymes from other microorganisms and even higher plants. β-D-Galactosides of elymoclavine (**30a**), cha-

noclavine (**31**), lysergol (**32**), 9,10-dihydrolysergol (**33**) and ergometrine (**34**) were prepared by using β-galactosidase from *Aspergillus oryzae* (Křen *et al.* 1992).

2-Acetamido-2-deoxy-O-β-D-galactopyranosides and 2-acetamido-2-deoxy-O-β-D-glucopyranosides of the ergot alkaloids elymoclavine (**35a,b**), chanoclavine (**36a,b**), ergometrine (**37a,b**) and ergometrinine (**38**) were prepared *via* transglycosylation catalyzed by β-N-acetylhexosaminidase from *A. oryzae* (Křen *et al.* 1994).

Agroclavine was converted into its 1-hydroxymethyl derivative (**39**) by condensation with formaldehyde, and enzymically glycosylated using β-galactosidase from *A. oryzae* (Křen *et al.* 1999).

β-D-Glucosides of elymoclavine and dihydrolysergol were obtained either by chemical synthesis or by enzymic transglycosylation (glycosidase from *A. oryzae*), lactosides (**40a**, **41**) were prepared by using β-1,4-galactosyltransferase and α-neuraminylelymoclavine (**40b**) was prepared using α-2,6-sialyltransferase. The immunomodulatory activity of glycosylated derivatives on natural killer cell-mediated cytotoxicity of human resting and activated human peripheral blood mononuclear cells was investigated by Křen *et al.* (1996*a*).

Enzymic synthesis of lysergol β-D-glucuronide (**42**) using ovine microsomal uridine-5′-diphosphoglucuronyl transferase and uridine 5′-diphosphoglucuronic acid was described by Stevenson *et al.* (2000).

N-Deoxyribosides of agroclavine (**43**, **44**), lysergol (**45**, **46**), and 9,10-dihydrolysergol (**47**, **48**) were prepared by N-glycosylation of 1-chloro-3,5-di-O-toluoyl-2-deoxy-D-ribofuranose (Křen *et al.* 1997d).

Enzymic reactions catalyzed by α-glycosidases (α-galactosidase, α-glucosidase, α-mannosidase, α-fucosidase, *etc*.) yielded α-glycosides of chanoclavine (**49a–d**), elymoclavine (**50a–c**), lysergol (**51a,b**) and 9,10-dihydrolysergol (**52a–c**) (Ščigelová *et al.* 1998). α-D-Glycosides were prepared with regard to their further uses as potential immunomodulatory and antiviral agents. Elymoclavine, ergometrine (**53**) and chanoclavine were mannosylated with α-mannosidase as catalyst (Ščigelová *et al.* 1994).

Chemical synthesis was used to produce glycosides with a configuration that could not be obtained by using biosynthetic means (Křen *et al.* 1997*e*). N-β-D-ribosides of agroclavine (**54a**), elymoclavine (**54b**), lysergene (**55b**), lysergol (**55a**) and 9,10-dihydrolysergol (**56**) were prepared by ribosylation with a derivative of β-D-ribofuranose.

Compounds have recently been prepared in which two or more ergot skeletons were combined, *e.g.*, a new spiro-oxa dimer (**57**) of lysergene was isolated as a product of the biotransformation of lysergene by *E. calyptrata* suspension cell culture (Křen *et al.* 1996*c*). 1,1-Linked dimers of semisynthetic ergoline alkaloids with antiparkinsonic activity were prepared from the pergolide and/or terguride by action of α,ω-dihalogenalkanes (**58a–c**, **61**). N^1-ω-halogenalkyl pergolide and terguride precursors were used for the synthesis of non-symmetric dimers (**59**, **60**) (Křen *et al.* 2001).

Dimers linked *via* an aromatic spacer showed a high toxicity against lymphoma cells while dimers (**62**–**65c**) with an aromatic spacer exhibited an immunosuppressive effect and terguride trimer (**66**), tetramer (**67**) and hexamer (**68**) with aliphatic spacer had NK-cell stimulatory effect (Křen *et al.* 2002).

Table I. Derivatives of ergot alkaloids

Compound	Formula	Origin[a]	Note	Reference
trans-10-Hydroxypaspalamide	**1**	*Claviceps paspali*	new metabolite	Bumbová-Linhartová *et al.* 1991
cis-10-Hydroxypaspalamide	**2**	*ditto*	*ditto*	Flieger *et al.* 1993
Chanoclavine O-β-D-fructofuranoside	**3a**	*C. fusiformis*	biosynthesis	Flieger *et al.* 1990
Chanoclavine O-β-D-fructofuranosyl-(2→1)-O-β-D-fructofuranoside	**3b**	*ditto*	*ditto*	*ditto*
Elymoclavine O-β-D-fructofuranosyl-(2→1)-O-β-D-fructofuranoside	**4a**	*C. purpurea*	*ditto*	Flieger *et al.* 1989
Elymoclavine trifructofuranoside	**4b**	*ditto*	–	Havlíček *et al.* 1994
Elymoclavine tetrafructofuranoside	**4c**	*ditto*	–	*ditto*
Lysergol O-β-D-fructofuranoside	**5**	*ditto*	inhibited with 5-F-Trp	Křen *et al.* 1993
9,10-Dihydrolysergol O-β-D-fructofuranoside	**6**	*ditto*	*ditto*	*ditto*
(4*aS*),(10*bS*)-7-Amino-3,4,4*a*,5,6,10b-hexahydro-2,4-dimethyl-6-oxobenzo[*f*]quinoline	**7a**	*ditto*	new metabolite	Flieger *et al.* 1991
(4*aS*),(10*bS*)-7-Amino-3,4,4*a*,5,6,10b-hexahydro-2-hydroxymethyl-6-oxobenzo[*f*]quinoline	**7b**	*ditto*	*ditto*	*ditto*

continued

Table I – *continued*

Ergogaline	**8**	*ditto*	*ditto*	Cvak *et al.* 1994
8α-Hydroxy-α-ergokryptine	**9a**	*ditto*	–	Cvak *et al.* 1997
Ergoladinine	**9b**	*ditto*	–	Cvak *et al.* 1996
Ergosedmine	**9c**	*ditto*	*ditto*	Halada *et al.* 1998
2-Methyl-3-(1,3,4,6-tetrahydroox-epino[5,4,3-*cd*]indol-6-yl)-oxiranemethanol	**10**	BT by *Euphorbia calyptrata*	–	Křen *et al.* 1996*d*
1-(1,3,4,6-Tetrahydrooxepino[5,4,3-*cd*]indol-6-yl)-2-methyl-1,2,3-propanetriol	**11**	*ditto*	–	*ditto*
4-[3-(2-Hydroxyethyl)-1*H*-indol-4-yl]-2-methyl-3-butene-1,2-diol	**12a**	*ditto*	–	*ditto*
4-(3,4-Dihydroxy-3-methyl-1-butenyl)-1*H*-indole-3-carboxaldehyde	**12b**	*ditto*	–	*ditto*
2,3-Dihydro-6,8-dimethyl-3β-acetoxy-8-ergolen-2-one	**13a**	by haloperoxidase from *Streptomyces aureofaciens*	–	Křen *et al.* 1997*b*
2,3-Dihydro-6,8-dimethyl-3β-hydroxy-8-ergolen-2-one	**13b**	*ditto*	–	*ditto*
(4*aS*),(10*bS*)-7-Amino-3,4,4*a*,5,6,10b-hexahydro-2,4-dimethyl-6-oxobenzo[*f*]quinoline	**14**	*ditto*	–	*ditto*
Setoclavine	**15a**	BT by plant-cell cultures	by peroxidase	Ščigelová *et al.* 1995
Isosetoclavine	**15b**	*ditto*	*ditto*	*ditto*
Penniclavine	**15c**	*ditto*	*ditto*	*ditto*
Isopenniclavine	**15d**	*ditto*	*ditto*	*ditto*
10-Hydroxyelymoclavine	**16**	*ditto*	*ditto*	*ditto*
2,3-Dihydro-2-oxo-α-ergokryptine	**17**	SC	–	Cvak *et al.* 1992
2,3-Dihydro-2-oxo-3-hydroxy-α-ergokryptine	**18**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxo-3-ethoxy-α-ergokryptine	**19**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxoagroclavine	**20**	*ditto*	–	Cvak *et al.* 1994*b*
2,3-Dihydro-2-oxolisuride	**21a**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxo-methylergometrine	**21b**	*ditto*	–	*ditto*
1-Methyl-2,3-dihydro-2-oxo-methylergometrine	**22a**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxo-ergotamine	**22b**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxo-ergocristine	**22c**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxo-α-ergokryptine	**22d**	*ditto*	–	*ditto*
2,3-Dihydro-2-oxo-3-hydroxylisuride	**22e**	*ditto*	–	*ditto*
N^1-Trimethylsilylagroclavine	**23a**	*ditto*	–	Křen and Sedmera 1997*f*
O-Acetyl-N^1-trimethylsilylelymoclavine	**23b**	*ditto*	–	*ditto*
O-Acetyl-N^1-trimethylsilyllysergol	**24**	*ditto*	–	*ditto*
N^1-Trimethylsilyllysergene	**25**	*ditto*	–	*ditto*
O-Acetyl-N^1-trimethylsilyl-9,10-dihydrolysergol	**26**	*ditto*	–	*ditto*
6′-Deoxy-α-ergokryptine	**27a**	*ditto*	–	Cvak *et al.* 2000
6′-Deoxy-α-ergocristine	**27b**	*ditto*	–	*ditto*
6′-Deoxy-α-ergocristinine	**28**	*ditto*	–	*ditto*
6′-Deoxy-9,10-dihydro-α-ergokryptine	**29a**	*ditto*	–	*ditto*
6′-Deoxy-9,10-dihydroergocristine	**29b**	*ditto*	–	*ditto*
6′-Deoxy-9,10-dihydroergotamine	**29c**	*ditto*	–	*ditto*
Elymoclavine β-D-galactopyranoside	**30a**	BT by β-galactosidase from *Aspergillus oryzae*	–	Křen *et al.* 1992
Elymoclavine β-D-galactopyranosyl-(1→6)-β-D-galactopyranoside	**30b**	*ditto*	–	*ditto*
Chanoclavine β-D-galactopyranoside	**31**	*ditto*	–	*ditto*
Lysergol β-D-galactopyranoside	**32**	*ditto*	–	*ditto*

Table I – *continued*

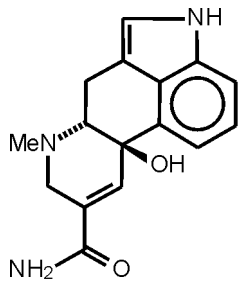
9,10-Dihydrolysergol β-D-galactopyranoside	**33**	*ditto*	–	*ditto*
Ergometrine O-β-D-galactopyranoside	**34**	*ditto*	–	*ditto*
Elymoclavine 2-acetamido-2-deoxy-O-β-D-galactopyranoside	**35a**	BT by β-N-acetyl-hexosaminidase from *A. oryzae*	–	Křen *et al.* 1994
Elymoclavine 2-acetamido-2-deoxy-O-β-D-glucopyranoside	**35b**	*ditto*	–	*ditto*
Chanoclavine 2-acetamido-2-deoxy-O-β-D-galactopyranoside	**36a**	*ditto*	–	*ditto*
Chanoclavine 2-acetamido-2-deoxy-O-β-D-glucopyranoside	**36b**	*ditto*	–	*ditto*
Ergometrine 2-acetamido-2-deoxy-O-β-D-galactopyranoside	**37a**	*ditto*	–	*ditto*
Ergometrine 2-acetamido-2-deoxy-O-β-D-glucopyranoside	**37b**	*ditto*	–	*ditto*
Ergometrinine 2-acetamido-2-deoxy-O-β-D-galactopyranoside	**38**	*ditto*	–	*ditto*
Agroclavine 1-N-[methyl (β-D-galactopyranoside)]	**39**	*ditto*	–	Křen *et al.* 1999
Elymoclavine O-[β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside]	**40a**	ES	–	Křen *et al.* 1996*a*
Elymoclavine O-[α-5-N-acetylneuraminyl-(2→6)-β-D-galactopyranosyl-(1→4)-2-acetamido-2-deoxy-β-D-glucopyranoside]	**40b**	*ditto*	–	*ditto*
9,10-Dihydrolysergol O-[β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside]	**41**	*ditto*	–	*ditto*
Lysergol O-β-D-glucuronide	**42**	*ditto*	–	Stevenson *et al.* 2000
Agroclavine 1-N-(β-D-2′-deoxyribofuranoside)	**43**	SC	–	Křen *et al.* 1997*e*
Agroclavine 1-N-(α-D-2′-deoxyribofuranoside)	**44**	*ditto*	–	*ditto*
Lysergol 1-N-(β-D-2′-deoxyribofuranoside)	**45**	*ditto*	–	*ditto*
Lysergol 1-N-(α-D-2′-deoxyribofuranoside)	**46**	*ditto*	–	*ditto*
9,10-Dihydrolysergol 1-N-(β-D-2′-deoxy-ribofuranoside)	**47**	*ditto*	–	*ditto*
9,10-Dihydrolysergol 1-N-(α-D-2′-deoxyribofuranoside)	**48**	*ditto*	–	*ditto*
Chanoclavine α-D-galactopyranoside	**49a**	BT by α-glycosidases	–	Ščigelová *et al.* 1998
Chanoclavine α-D-glucopyranoside	**49b**	*ditto*	–	*ditto*
Chanoclavine α-D-mannopyranoside	**49c**	*ditto*	–	*ditto*
Chanoclavine α-L-fucopyranoside	**49d**	*ditto*	–	*ditto*
Elymoclavine α-D-galactopyranoside	**50a**	*ditto*	–	*ditto*
Elymoclavine α-D-galactosyl-(1→3)- α-D-galactopyranoside	**50b**	*ditto*	–	*ditto*
Elymoclavine α-D-mannopyranoside	**50c**	*ditto*	–	*ditto*
Lysergol α-D-galactopyranoside	**51a**	*ditto*	–	*ditto*
Lysergol α-D-mannopyranoside	**51b**	*ditto*	–	*ditto*
9,10-Dihydrolysergol α-D-galactopyranoside	**52a**	*ditto*	–	*ditto*
9,10-Dihydrolysergol α-D-glucopyranoside	**52b**	*ditto*	–	*ditto*
9,10-Dihydrolysergol α-D-mannopyranoside	**52c**	*ditto*	–	*ditto*
Ergometrine α-D-mannopyranoside	**53**	BT by α-mannosidase	–	Ščigelová *et al.* 1994
Agroclavine 1-N-(β-D-ribofuranoside)	**54a**	SC	–	Křen *et al.* 1997*b*
Elymoclavine 1-N-(β-D-ribofuranoside)	**54b**	*ditto*	–	*ditto*
Lysergol 1-N-(β-D-ribofuranoside)	**55a**	*ditto*	–	*ditto*
Lysergene 1-N-(β-D-ribofuranoside)	**55b**	*ditto*	–	*ditto*
9,10-Dihydrolysergol 1-N-(β-D-ribofuranoside)	**56**	*ditto*	–	*ditto*

continued

Table I – *continued*

Spiro-oxalysergene	**57**	*Euphorbia calyptrata*	–	Křen *et al.* 1996*c*
1,6-Bis(6′-propyl-8β′-methylthiomethyl-ergolin-1′-yl)-hexane	**58a**	SS	antiparkinsonic activity	Křen *et al.* 2001
1,4-Bis(6′-propyl-8β′-methylthiomethyl-ergolin-1′-yl-methyl)-benzene	**58b**	*ditto*	*ditto*	*ditto*
1,6-Bis(8β′-methylthiomethylergolin-6′-yl-)-hexane	**58c**	*ditto*	*ditto*	*ditto*
1-(6′′-Propyl-8β′-methylthiomethylergolin-1′-yl-)-6-(8β′-methylthiomethylergolin-6′′-yl)-hexane	**59**	*ditto*	*ditto*	*ditto*
1-(6′-Propyl-8β′-methylthiomethylergolin-1′-yl-)-6-(6′′-methyl-8α′′-(diethylcarbamoylamino)-ergolin-1′′-yl)hexane	**60**	*ditto*	*ditto*	*ditto*
1,6-Bis(8β-methylthiomethylergolin-1-yl-)-hexane	**61**	*ditto*	*ditto*	*ditto*
Bis(8,9-didehydro-6,8-dimethylergolin-1-yl)-methane	**62**	SC	immunosup-pressive activity	Křen *et al.* 2002
1,4-Bis(8,9-didehydro-6,8-dimethylergolin-1-yl-methyl)benzene	**63**	*ditto*	*ditto*	*ditto*
Bis(6-methyl-8-(diethylcarbamoylamino)ergo-lin-1-yl)methane	**64a**	*ditto*	*ditto*	*ditto*
1,6-Bis(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl)hexane	**64b**	*ditto*	*ditto*	*ditto*
1,4-Bis(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl) benzene	**64c**	*ditto*	*ditto*	*ditto*
1,2-Bis(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl)benzene	**64d**	*ditto*	*ditto*	*ditto*
1,3-Bis(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl)benzene	**64e**	*ditto*	*ditto*	*ditto*
1,3-Dibromo-2-bromomethyl-2-(6-methyl-8-(diethylcarbamoylamino)ergolin-1-yl-methyl)-propane	**65a**	*ditto*	*ditto*	*ditto*
1,3-Dibromo-2,2-bis(6-methyl-8-(diethylcarb-amoylamino)ergolin-1-yl-methyl)propane	**65b**	*ditto*	*ditto*	*ditto*
1-Bromo-2,2-di(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl)-3-(6-methy-8-(diethyl-carbamoylamino)ergolin-1-yl)propane	**65c**	*ditto*	*ditto*	*ditto*
1,3,5-Tris(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl)-2,4,6-trimethyl-benzene	**66**	*ditto*	*ditto*	*ditto*
1,2,4,5-Tetrakis(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl)benzene	**67**	*ditto*	*ditto*	*ditto*
1,2,3,4,5,6-Hexa(6-methyl-8-(diethylcarbamoyl-amino)ergolin-1-yl-methyl)benzene	**68**	*ditto*	*ditto*	*ditto*

[a]BT – biotransformation, ES – enzymic synthesis, SC – synthetic compound, SS – semisynthetic compound.



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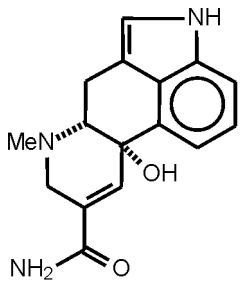

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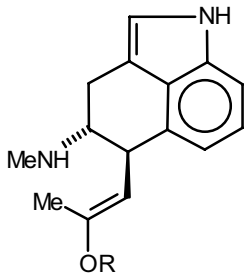
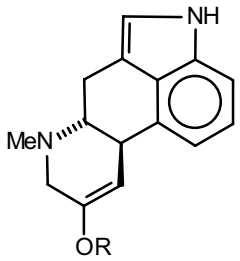


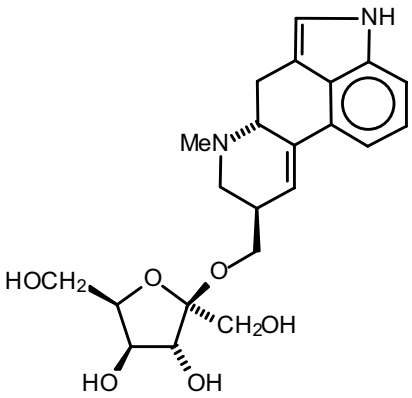
3a,b



4a–c

	R
3a	β-D-Fru
3b	β-D-Fru-(2→1)-β-D-Fru

	R
4a	β-D-Fru-(2→1)-β-D-Fru
4b	β-D-Fru-(2→1)-β-D-Fru-(2→1)-β-D-Fru
4c	β-D-Fru-(2→1)-β-D-Fru-(2→1)-β-D-Fru-(2→1)-β-D-Fru



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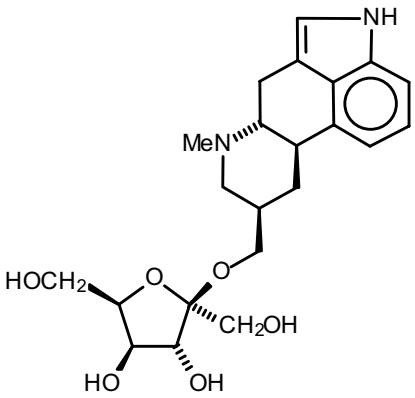

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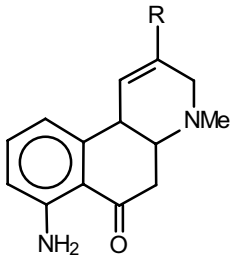
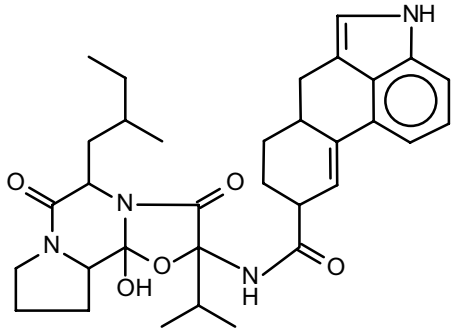


7a,b

	R
7a	Me
7b	CH_2OH



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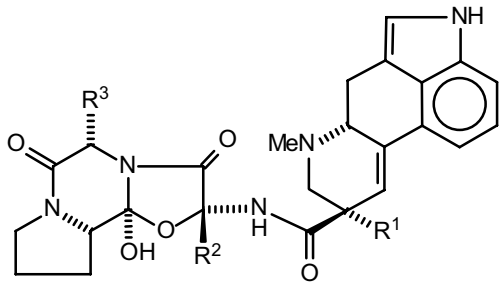
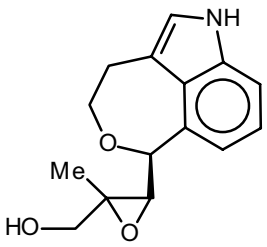


9a–c

	R^1	R^2	R^3
9a	OH	iPr	iBu
9b	H	iPr	CH_2-CH_2-SMe
9c	H	sBu	Bz



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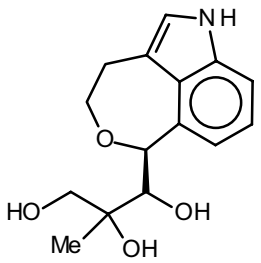

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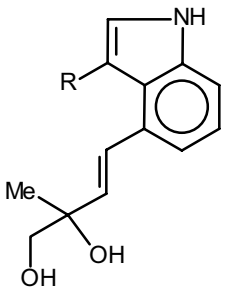
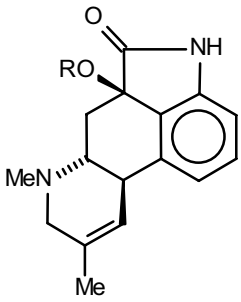


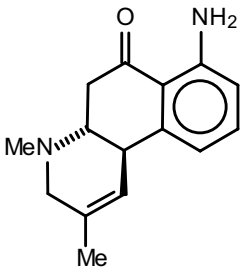
12a,b

	R
12a	CH_2-CH_2OH
12b	CHO



13a,b

	R
13a	Ac
13b	H



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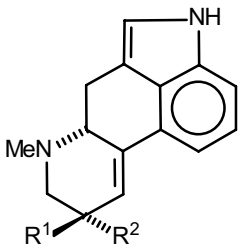
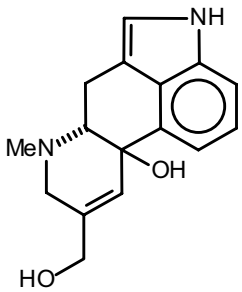


15a–d

	R^1	R^2
15a	Me	OH
15b	OH	Me
15c	CH_2OH	OH
15d	OH	CH_2OH



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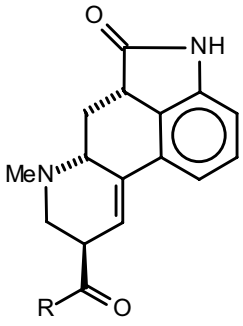

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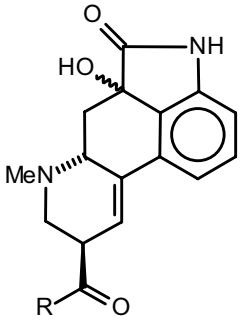

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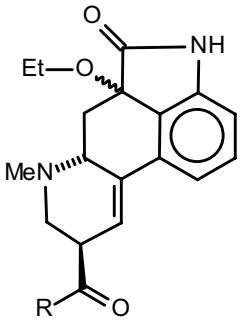
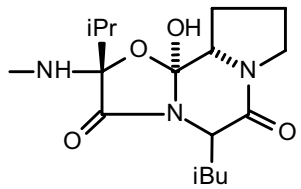
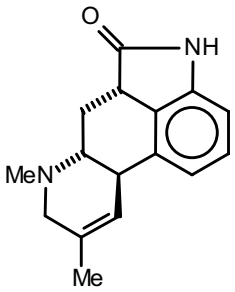


19

R =





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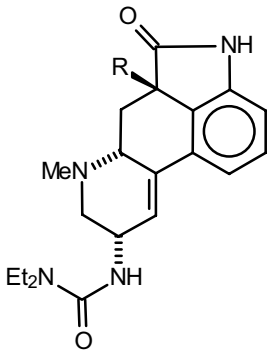
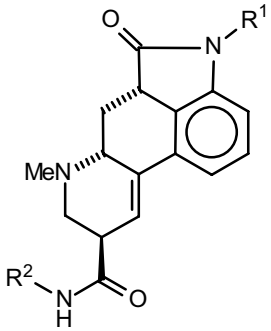


21a,b

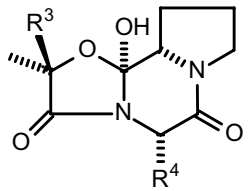
	R
21a	H
21b	OH

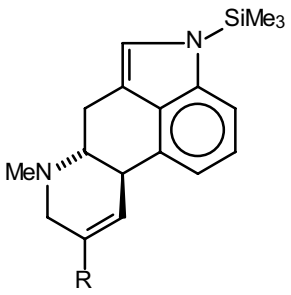


22a–e

	R^1	R^2	R^3	R^4
22a	H	$CH(CH_2OH)CH_2$-CH_3		
22b	Me	$CH(CH_2OH)CH_2$-CH_3		
22c	H	Z	Me	Bz
22d	H	Z	iPr	Bz
22e	H	Z	iPr	iBu

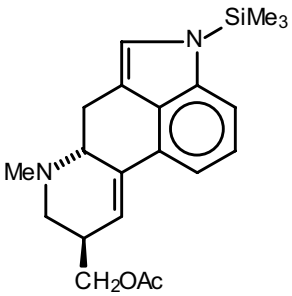
Z =





23a,b

	R
23a	Me
23b	CH_2OAc



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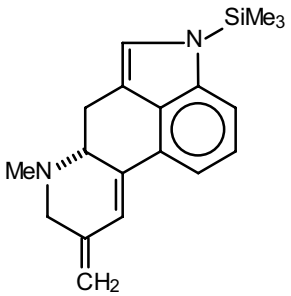

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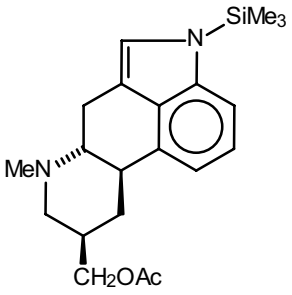

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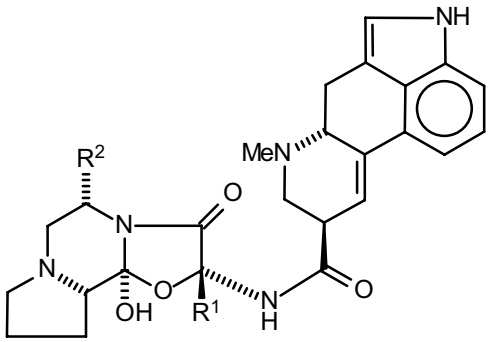
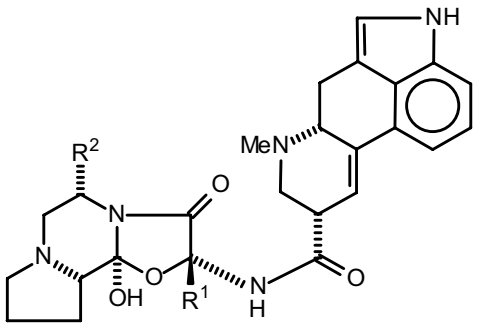


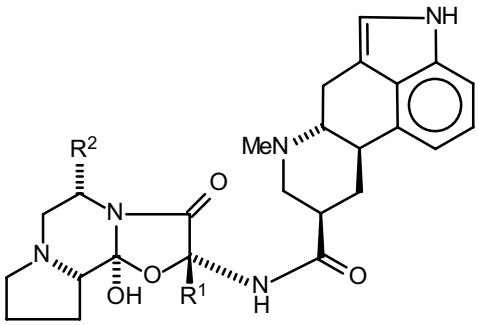
27a,b

	R^1	R^2
27a	iPr	iBu
27b	iPr	Bz



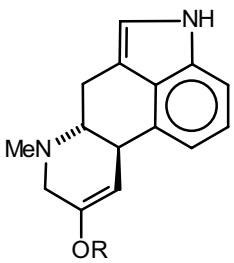
28

	R^1	R^2
28	iPr	Bz



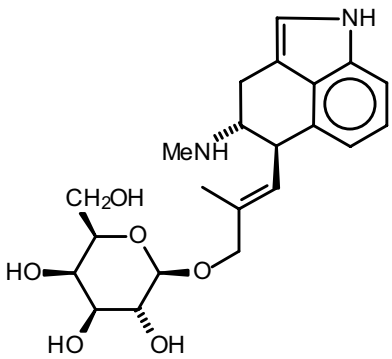
29a–c

	R^1	R^2
29a	iPr	iBu
29b	iPr	Bz
29c	Me	Bz



30a,b

	R
30a	β-D-Gal
30b	β-D-Gal-(1→6)-β-D-Fru



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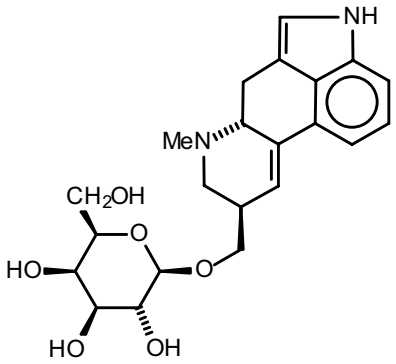

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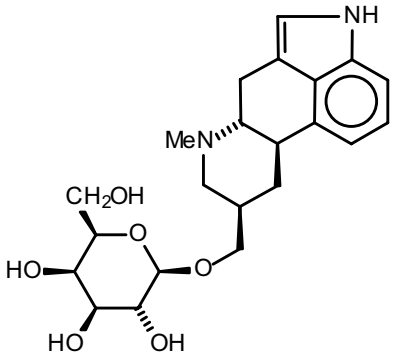

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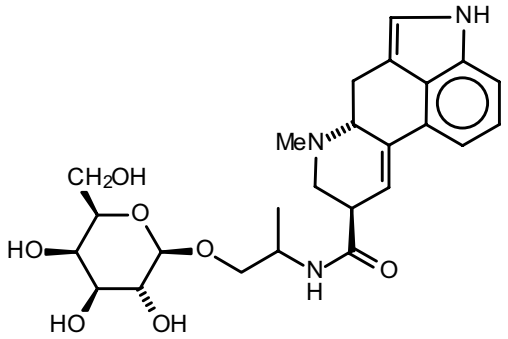
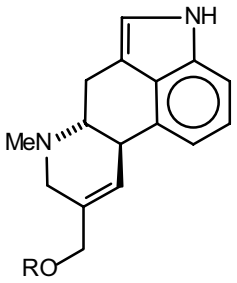
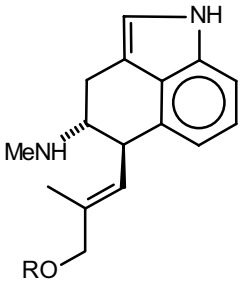


34



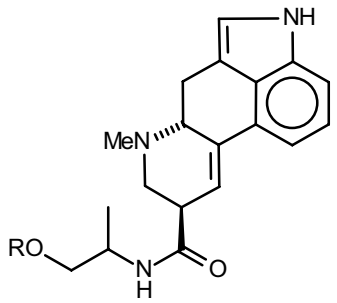
35a,b

	R
35a	β-D-GalNAc
35b	β-D-GlcNAc



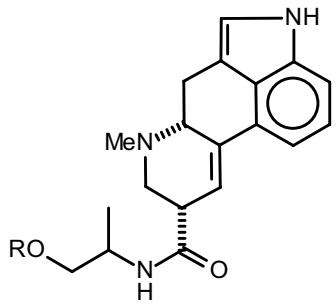
36a,b

	R
36a	β-D-GalNAc
36b	β-D-GlcNAc



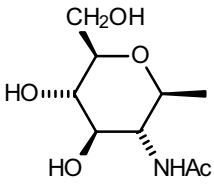
37a,b

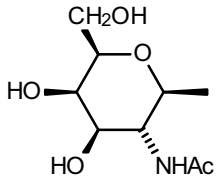
	R
37a	β-D-GalNAc
37b	β-D-GlcNAc

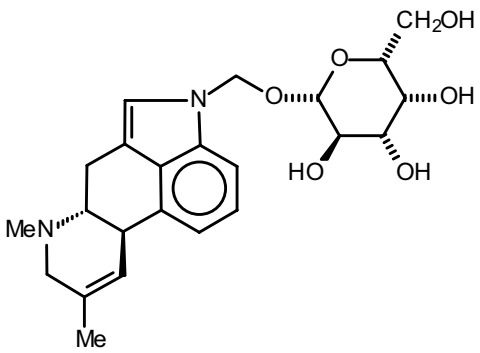


38

	R
38	β-D-GalNAc







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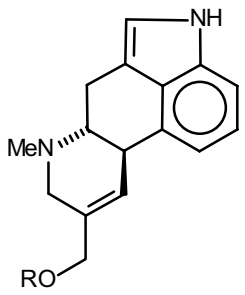
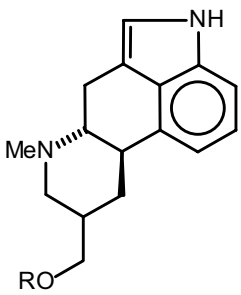


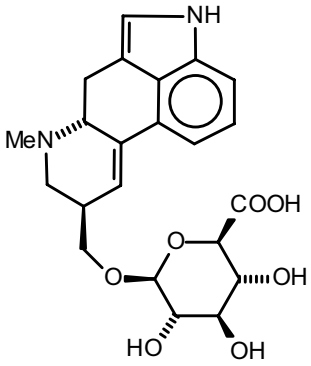
40a,b

	R
40a	β-D-Gal-(1→4)-β-D-Glc
40b	α-D-Neu5Ac-(2→6)-β-D-Gal-(1→4)-β-D-GlcNAc

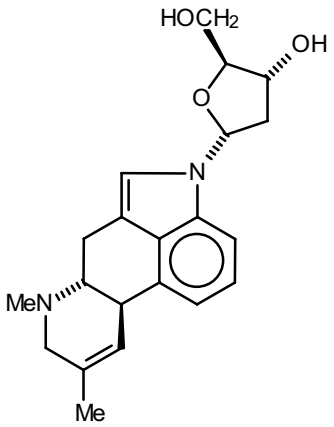


41

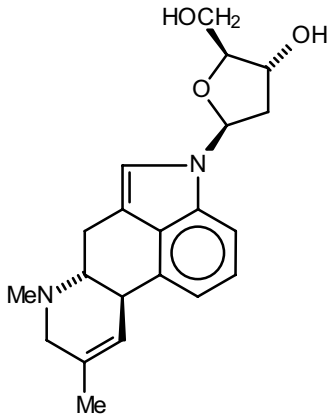
	R
41	β-D-Gal-(1→4)-β-D-Glc


NH
MeN
COOH
O
O
OH
HO
OH

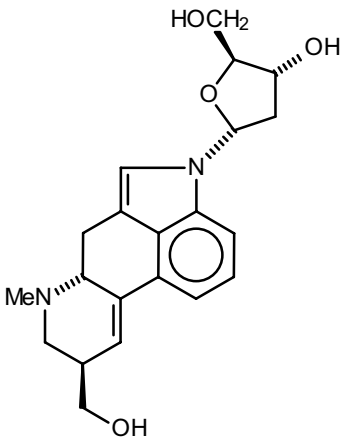
42


HOCH2
OH
O
N
MeN
Me

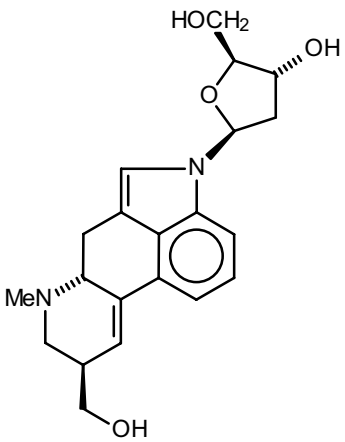
43


HOCH2
OH
O
N
MeN
Me

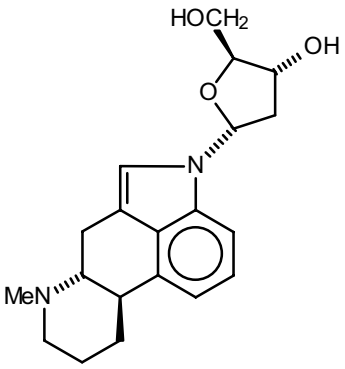
44


HOCH2
OH
O
N
MeN
OH

45


HOCH2
OH
O
N
MeN
OH

46



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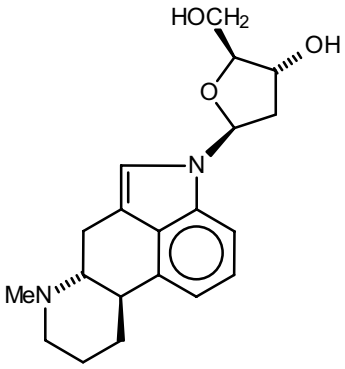

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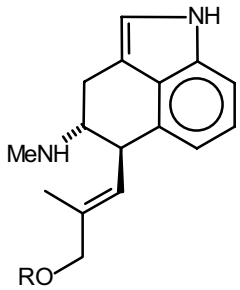
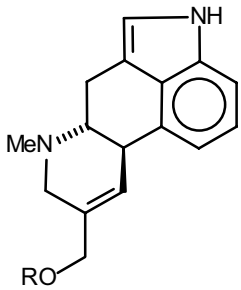


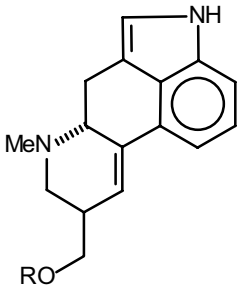
49a–d

	R
49a	α-D-Gal
49b	α-D-Glc
49c	α-D-Man
49d	α-D-Fuc



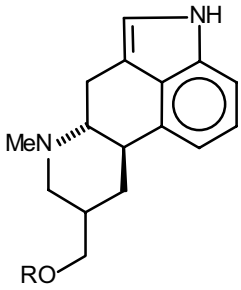
50a–c

	R
50a	α-D-Gal
50b	α-D-Gal-(1→3)-α-D-Gal
50c	α-D-Man



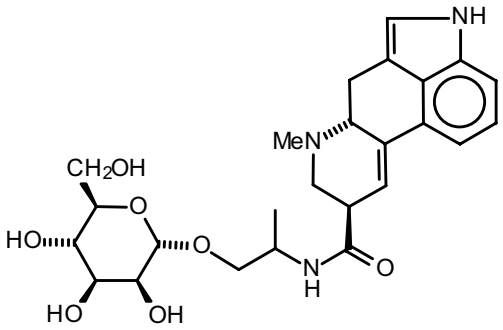
51a,b

	R
51a	α-D-Gal
51b	α-D-Man



52a–c

	R
52a	α-D-Gal
52b	α-D-Glc
52c	α-D-Man



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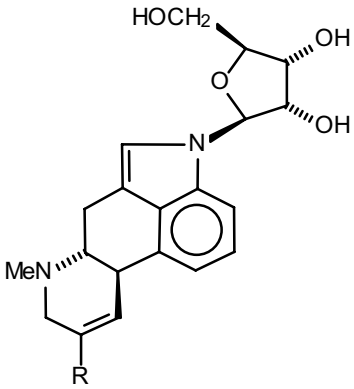
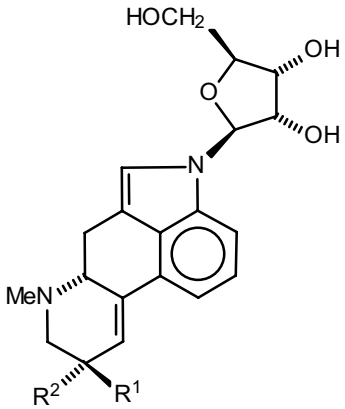


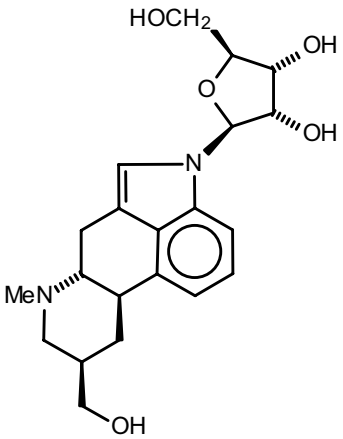
54a,b

	R
54a	CH_3
54b	CH_2OH



55a,b

	R^1	R^2
55a	CH_2OH	H
55b	CH_3	CH_3



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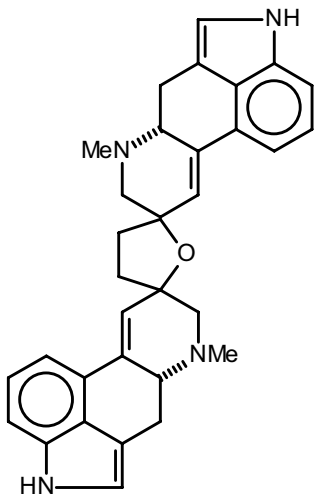

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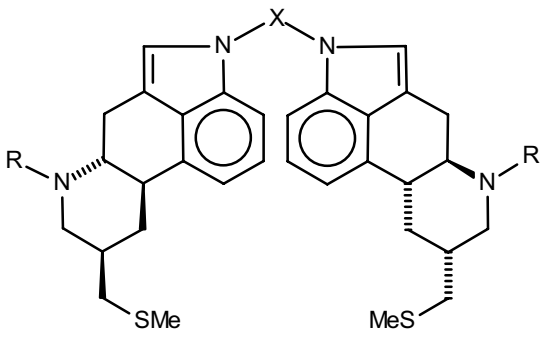
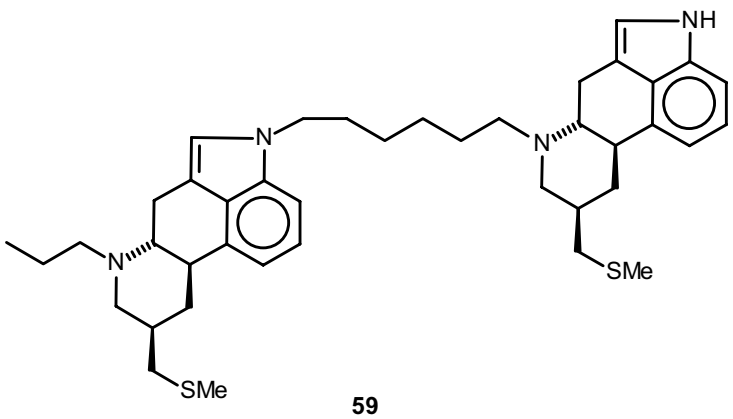


58a–c

	X	R
58a	$-(CH_2)_6-$	Pr
58b	**$-CH_2-C_6H_4-CH_2-$**	Pr
58c	$-(CH_2)_6-$	H



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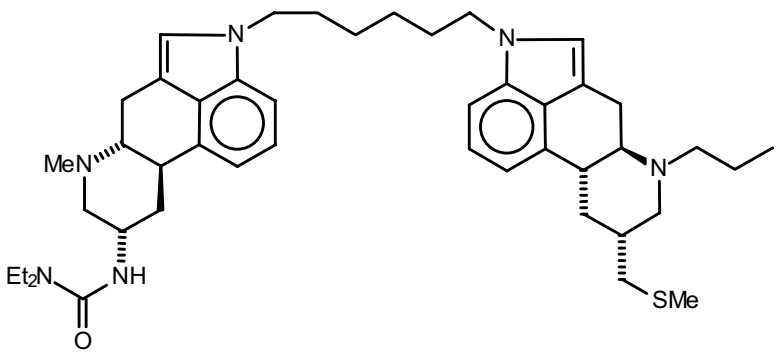

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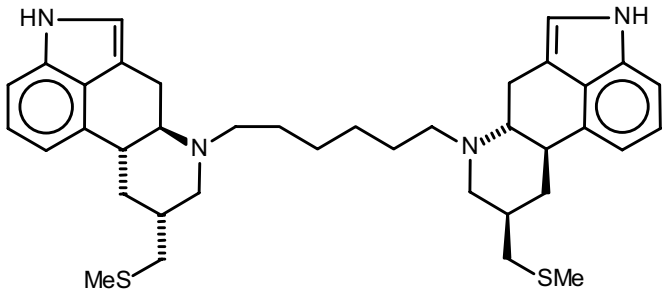

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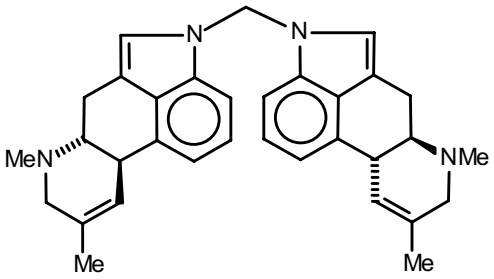

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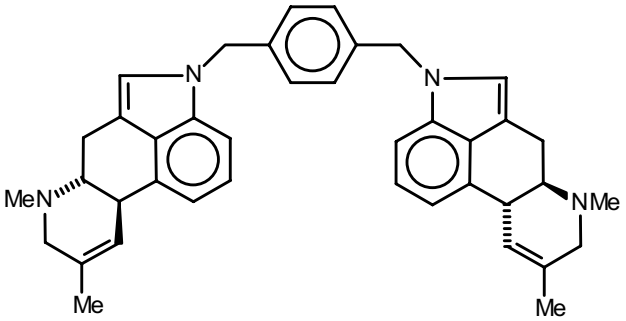

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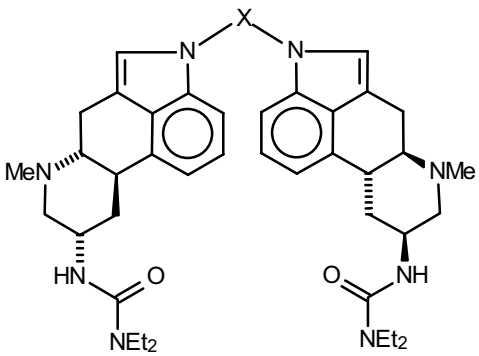
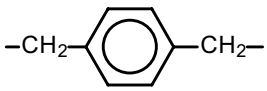


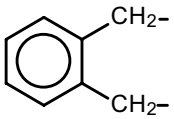
64a–e

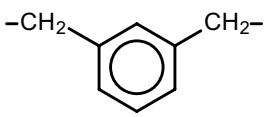
X

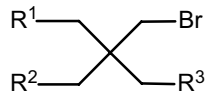
64a –CH_2–

64b –$(CH_2)_6$–

64c 

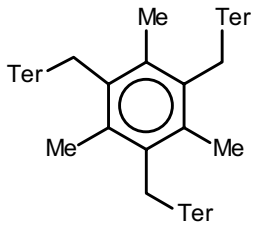
64d 

64e 



65a–c

	R^1	R^2	R^3
65a	Ter	Br	Br
65b	Ter	Ter	Br
65c	Ter	Ter	Ter



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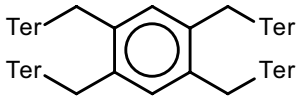

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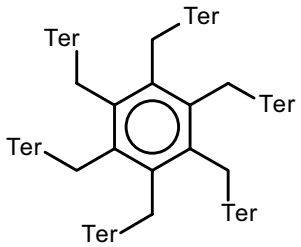

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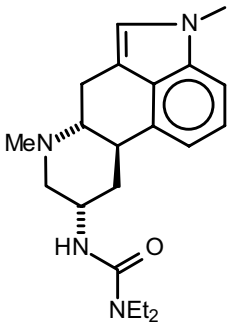
Ter =



3 CYCLIC OLIGOPEPTIDES

All these compounds (Table II) exhibit strong physiological effects in mammals including man. Havlíček *et al.* (1993, 2000) determined the MS sequence of amino acids in cyclosporins using FAB. The general fragmentation scheme was derived from the spectra of cyclosporins A, B, C, D, F, G, L and [DH-MeBmt(1)]CS (dihydro-N-methyl-butenylthreonine-cyclosporin). This fragmentation scheme was used for amino acid sequence determination in four new natural cyclosporins, [MeLeu(1)]CS (**69a**), [Ile(4)]CS (**69b**), [Leu(5)]CS (**69c**) and [Leu(4)]CS (**69d**).

New natural cyclosporins were isolated from the mycelium of the surface-cultivated fungus *Tolypocladium terricola* (Jegorov *et al.* 1995*a*). The chemical structures of [Leu(4)]CS and [MeLeu(1)]CS, *i.e.* cyclosporin J, were deduced from the spectral data. The proliferative mitogen stimulation test was used to determine the biological activity of new cyclosporins.

The structure of cyclo(3-hydroxy-7-hydroperoxy-4-methyl-2-methylamino-5*E*-octenoic acid(1)-Val(2)-Sar(3)-MeLeu(4)-Val(5)-MeLeu(6)-Ala(7)-D-Ala(8)-MeLeu(9)-MeLeu(10)-MeVal(11)-) (**69e**) was assigned to a new metabolite of the fungus *T. terricola* (Sedmera *et al.* 1995).

MS analysis of cyclosporins was used for identifying isobaric amino acids (Havlíček *et al.* 1995*b*). The use of this analysis was illustrated by the structure elucidation of a novel natural cyclosporin,

[Leu(9)]CS (**69f**). Another new natural [Ala(2),Val(11)] cyclosporin (**69g**) was isolated from the submerged culture of mycelium sterilae MS 2929 (Buchta *et al.* 1998).

Cyclosporin H was isolated as the acid-catalyzed degradation product of cyclosporin A (**69h**) (Jegorov *et al.* 2000). This degradative process involves the conversion of L-MeVal(11) to D-MeVal(11) as demonstrated by chiral capillary chromatography with MS identification.

A new cyclosporin, [Sar(1)]CS (**69i**), containing the atypical amino acid (4*R*)-4-(2-(*E*)-butenyl)-N^4-dimethyl-L-threonine (MeBmt) and resulting from the side chain cleavage of MeBmt was identified by HPLC-FAB/MS (Jegorov *et al.* 1996).

^{3}H-Cyclosporin A (**69j**) labeled in the first amino acid ([ω-^{3}H-MeBmt(1)]CS) was prepared (Černý *et al.* 1998) by tritium gas hydrogenolysis of [O-acetyl-ω-bromo-MeBmt(1)]CS.

The fungi *Metarhizium anisopliae* and *Trichothecium roseum* produced cyclic hexadepsipeptides destruxins (Jegorov *et al.* 1998*a*,*b*). In addition to 22 known destruxins, two new representatives were identified, *i.e.* roseotoxin A (**70a**) and destruxin Ed (**70b**). Dihydrodestruxin A (**70c**) was produced by the fungus *M. anisopliae* grown in media containing 2-amino-4-pentenoic acid or norvaline (Jegorov *et al.* 1992).

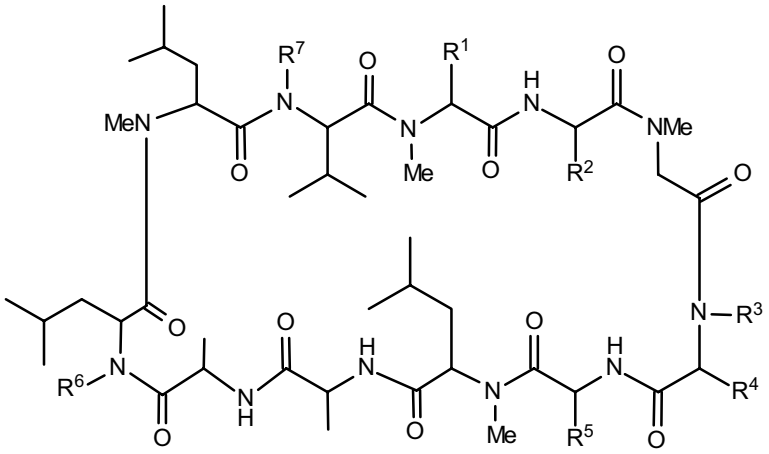
New beauverolides L (**71a**) and L_a (**71b**) were isolated and identified from the entomopathogenic fungi *Beauveria tenella* and *Paecilomyces fumosoroseus* (Jegorov *et al.* 1994).

BF_3-catalyzed methanolysis was employed for cyclic peptide cleavage using cyclosporins as model compounds (Havlíček *et al.* 1995*a*). The resulting secocyclosporins were analyzed by FAB-MS that determined the complete sequence of all prepared oligopeptides.

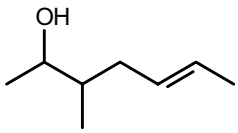
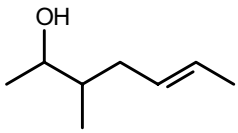
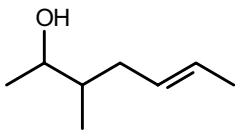
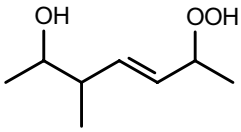
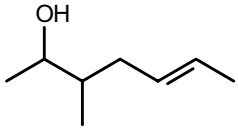
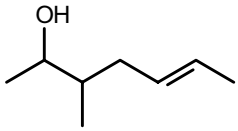
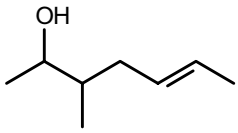
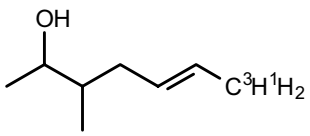
Table II. Cyclic oligopeptides

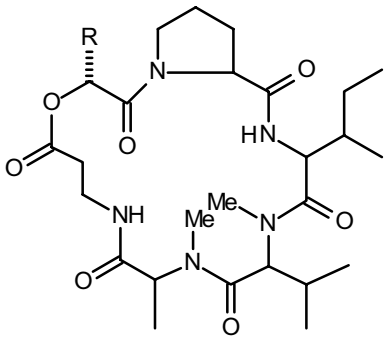
Compound[a]	Formula	Origin[b]	Note	Reference
[MeLeu(1)]CS	**69a**	*Tolypocladium terricola*	immunosuppressivum	Havlíček *et al.* 1993
[Ile(4)]CS	**69b**	*ditto*	*ditto*	*ditto*
[Leu(5)]CS	**69c**	*ditto*	*ditto*	*ditto*
[Leu(4)]CS	**69d**	*ditto*	*ditto*	Jegorov *et al.* 1995*a*
[3-hydroxy-7-hydroperoxy-4-methyl-2-methylamino-5*E*-octenoic acid]CS	**69e**	*ditto*	*ditto*	Sedmera *et al.* 1995
[Leu(9)] CS	**69f**	*ditto*	*ditto*	Havlíček *et al.* 1995*b*
[Ala(2),Val(11)]CS	**69g**	mycelia sterila	*ditto*	Buchta *et al.* 1998
[D-MeVal(11)]CS	**69h**	SC	epimerization from [L-MeVal(11)]CS	Jegorov *et al.* 2000
[Sar(1)]CS	**69i**	*ditto*	synthesis from cyclosporin A	Jegorov *et al.* 1996
^{3}H-Cyclosporin A	**69j**	*ditto*	*ditto*	Černý *et al.* 1998
Roseotoxin A	**70a**	*Trichothecium roseum*	insecticides and/or immunomodulators	Jegorov *et al.* 1998
Destruxin Ed	**70b**	*Metarhizium anisopliae*	*ditto*	Jegorov *et al.* 1998
Dihydrodestruxin A	**70c**	*ditto*	–	Jegorov *et al.* 1992
Beauverolides L and L_a	**71a,b**	*Beauveria tenella* and *Paecilomyces fumosoroseus*	immunomodulator	Jegorov *et al.* 1994

[a]CS – cyclosporin. [b]For abbreviations *see* footnote to Table I.



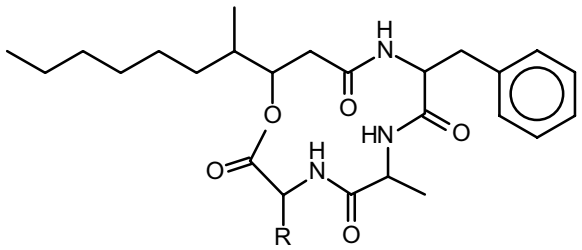
69a–j

	R^1	R^2	R^3	R^4	R^5	R^6	R^7
69a	iBu	Et	Me	iBu	iPr	Me	Me
69b		Et	H	sPe	iPr	Me	Me
69c		Et	Me	iBu	iBu	Me	Me
69d		Et	H	iBu	iPr	Me	Me
69e		iPr	Me	iBu	iPr	Me	Me
69f		Et	Me	iBu	iPr	H	Me
69g		Me	Me	iBu	iPr	Me	H
69h		Et	Me	iBu	iPr	Me	Me
69i	H	Et	Me	iBu	iPr	Me	Me
69j		Et	Me	iBu	iPr	Me	Me



70a–c

	R
70a	iBu
70b	CH_2-CH(OH)-CH_2OH
70c	Pr



71a,b

	R
71a	iPe
71b	sPe

4 ENZYMES AND SUGAR COMPOUNDS

Enzymes, saccharides and other derivatives of glycosidic nature, except for glycosides of ergot alkaloids are shown in Table III. Pyranose oxidase and pyranosone dehydratase, which were isolated from *Agaricus bisporus* and partially characterized, catalyzed the conversion of D-glucose *via* D-glucosone to the antibiotic β-pyrone, cortalcerone (Volc *et al.* 1991). Pyranose oxidase and pyranosone dehydratase converted D-glucose to cortalcerone during idiophasic growth of *Phanerochaete chrysosporium* (Gabriel *et al.* 1993). Pyranose oxidase catalyzed enzyme reactions of dihydrate of D-*erythro*-hexos-2,3-diulose (**72**) (Sedmera *et al.* 1997), and also the oxidation of gentibiose (**74a**), melibiose (**74b**) and isomaltose (**73**, **75**) at C-2 of their reducing moiety (Volc *et al.* 1999). Further pyranose dehydrogenase from *A. bisporus* catalyzed the oxidation of D-xylose at C-2 and C-3 (Volc *et al.* 2000), and also catalyzed C-2 and C-3 oxidation of D-Glc to 2-oxo-D-Glc and 3-oxo-D-Glc and eventually to the same end-product 2,3-dioxo-D-Glc.

Cell cultures of *Papaver somniferum* var. *setigerum* were shown to carry out the biotransformation of silybin (enzymic glycosylation of the silybin aglycone) to silybin 7-O-β-D-glucopyranoside (**76**) (Křen *et al.* 1998*b*).

Starting from 23-O-β-D-glucopyranosylsilybin and 23-O-β-D-galactopyranosylsilybin, α-D-oligoglucosides of silybin (**77a–d**, **78**, **79**) were synthesized by employing cyclodextrin glucanotransferase (EC 2.4.1.19) from *Bacillus stearothermophilus*. Oligoglycosides of silybin were tested for the low-density lipoprotein (LDL) antioxidant activity *in vitro* (Kubisch *et al.* 2001).

Silybin glycosides, *i.e.* 23-O-β-glucoside (**80a**), β-galactoside (**80b**), β-lactoside (**80c**) and β-maltoside (**80d**) were synthesized and the separation of two silybin diastereoisomers in the form of acetylated monoglycosides was performed for the first time. These new silybin glycosides have a hepatoprotective activity (Křen *et al.* 1997*c*).

Optically pure silybin A was obtained by using ovine liver glucuronyltransferase and afforded three β-D-glucuronides of silybin. It was shown that the main silybin conjugate in humans is its 20-β-D-glucuronate (**81a**), while the C-7 regioisomer (**81b**) was formed in a lower proportion. The rate of conjugation of individual silybin diastereoisomers (**81c**. *i.e.* 10*S*, 11*S* and 10*R*, 11*R*) and therefore also their metabolism in humans was found to differ, as shown in a pharmacological study using optically pure silybin (Křen *et al.* 2000).

The disaccharide GlcNAc-β(1→4)ManNAc (**82a**) shows a high affinity towards NKR-P1 protein acting as a crucial activating receptor of rat natural killer cells. Also GlcNAc-β(1→4)GlcNAc-β(1→4)ManNAc (**82b**) exhibited strong binding to NKR-P1 (Sedmera *et al.* 1998).

β-N-Acetylhexosaminidase (EC 3.2.1.52) from *A. oryzae* catalyzed the transfer of N-acetylglucosamine moiety to mannose giving the major product GlcNAc-β(1→1)-β-Man (**83**), and GlcNAc-β(1→3)Man (**84**) and GlcNAc-β(1→6)Man (**85**) as two minor products (Křen *et al.* 1996*b*).

Its counterpart from *Penicillium brasilianum* catalyzed the glycosylation of GlcNAc yielding 6′-O,N,N′-triacetylchitobiose (**88**). Transglycosylation reaction catalyzed by the same enzyme yielded 6-O,N,N′-triacetylchitobiose (**87**) (Hušáková *et al.* 2001).

4-Nitrophenyl β-chitobioside was prepared using β-N-acetylhexosaminidase from *A. oryzae*. As a minor by-product (1→6)-linked regioisomer was formed (Kubisch *et al.* 1999).

The same enzyme was used to prepare a new thiamin β-D-2-deoxy-2-acetamidoglucopyranoside (**89**) by transglycosylation (Křen *et al.* 1998*a*).

Three glycosidases, α-mannosidase from Jack beans, β-galactosidase and β-N-acetylhexosaminidase from *A. oryzae* were evaluated for their ability to catalyze the glycosylation of non-saccharidic polyols (**90a–c**, **91a,b**, **92a,b**) (Kieburg *et al.* 1998).

Galactosyltransferase from bovine milk was found to be able to utilize UDP-Glc to transfer Glc onto GlcNAc and chitooligomers [-β-GlcNAc-(1→4)-]$_n$, n = 2–4 (**86a–c**). β-Glucosylated products were used in binding studies with NKR-P1A protein cloned from rat natural killer cells (Křen *et al.* 1997*a*).

The reactions of thirty-five glycosidases with pyridoxine were used for testing their ability to form new glycosidic bonds. Pyridoxine (**93a–e**) was used as a new substrate for screening glycosidases having a synthetic potential (Weignerová *et al.* 1999*a*). β-Glycosidases were used as tools for chirality (Zarevúcka *et al.* 1999) while fungal α-galactosidases were used to synthesize α-galactopyranosides (Weignerová *et al.* 2001*a*).

6′-O-Acyl-lactose derivatives (**94a–d**) were used as acceptors for enzymic transglycosylations catalyzed by β-galactosidase from *Talaromyces flavus* forming iso-globotriose (Weignerová *et al.* 1999*b*).

Two new heterocyclic derivatives (**95a,b**) were prepared by the fungal enzyme pyranosone dehydratase and by condensation of 1,2-benzenediamine and 4-deoxy-2,3-aldodiuloses (Gabriel *et al.* 1995). The compounds inhibited the growth of *Escherichia coli*, *Bacillus subtilis* and *Candida pseudotropicalis*.

4′-O-Methylsucrose and α-D-glucopyranosyl-β-D-xylofuranoside 2,1′-anhydride and α-D-glucopyranosyl-1,3-anhydro-β-D-*xylo*-hexulofuranoside (**96**) were prepared by Čapek *et al.* (1993). These derivatives were prepared with the aim of obtaining readily degradable saccharide derivatives.

Semisynthetic derivatives of anthracycline glycosides (**97a,b**, **98a–d**, **99**) were also synthesized (Jizba *et al.* 1989). Derivatives of semisynthetic anthracyclines are known to exhibit considerable activity against various types of cancer. Therefore, derivatives with an increased absorption and biological activity against tumor diseases were synthesized in cooperation with a pharmaceutical company.

Table III. Enzymes and sugar compounds

Compound	Formula	Origin[a]	Note	Reference
Pyranose oxidase	–	*Phanerochaete chrysosporium*	new enzyme	Volc *et al.* 1991
Pyranosone dehydratase	–	*ditto*	*ditto*	*ditto*
D-*erythro*-Hexos-2,3-diulose	**72**	BT by pyranose oxidase	–	Sedmera *et al.* 1997
1-(N,N-Diphenylhydrazone) β-D-glucopyranosyl-(1→6)-D-*arabino*-hexos-2-uloside	**73**	BT by *T. multicolor*	–	Volc *et al.* 1999
1-(N,N-Diphenylhydrazone) α-D-galactopyranosyl-(1→6)-D-*arabino*-hexos-2-uloside	**74a**	*ditto*	–	*ditto*
1-(N,N-Diphenylhydrazone) α-D-glucopyranosyl-(1→6)-D-*arabino*-hexos-2-uloside	**74b**	*ditto*	–	*ditto*
1,2-Bis(N,N-diphenylhydrazone) α-D-glucopyranosyl-(1→6)-D-*arabino*-hexos-2-uloside	**75**	*ditto*	–	*ditto*
Silybin 7-O-β-D-glucopyranoside	**76**	*Papaver somniferum* var. *setigerum*	BT from silybin; hepatoprotectivum	Křen *et al.* 1998*b*
Silybin α-D-oligoglucosides	**77a**	*Bacillus stearothermophilus*	LDL activity	Kubisch *et al.* 2001
	77b	*ditto*	–	*ditto*
	77c	*ditto*	–	*ditto*
	77d	*ditto*	–	*ditto*
4-Nitrophenyl (1→4)-β-chitobioside	**78**	*A. oryzae*	–	Kubisch *et al.* 1999

Table III – *continued*

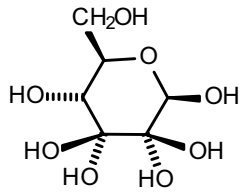
4-Nitrophenyl (1→6)-β-chitobioside	**79**	*ditto*	–	*ditto*
Silybin 23-O-β-glucoside	**80a**	SC	hepatoprotectivum	Křen *et al.* 1997*c*
Silybin 23-O-β-galactoside	**80b**	*ditto*	*ditto*	*ditto*
Silybin 23-O-β-lactoside	**80c**	*ditto*	*ditto*	*ditto*
Silybin 23-O-β-maltoside	**80d**	*ditto*	*ditto*	*ditto*
Silybin 20-β-D-glucuronate	**81a**	ovine liver	BT from silybin; hepatoprotectivum	Křen *et al.* 2000
Silybin 7-β-D-glucuronate	**81b**	*ditto*	*ditto*	*ditto*
Silybin 5-β-D-glucuronate	**81c**	*ditto*	*ditto*	*ditto*
GlcNAc-β-(1→4)-ManNAc	**82a**	SC	ligand of NK cell receptor	Sedmera *et al.* 1998
GlcNAc-β-(1→4)-GlcNAc-β-(1→4)-ManNAc	**82b**	*ditto*	–	*ditto*
GlcNAc-β-(1→1)-Man-β	**83**	*A. oryzae*	–	Křen *et al.* 1996*b*
GlcNAc-β-(1→3)-Man-α/β	**84**		–	*ditto*
GlcNAc-β-(1→6)-Man-α/β	**85**		–	*ditto*
β-GlcNAc-(1→4)$_n$ (n = 2–4)	**86a,b,c**	bovine milk	ligand of NK cell receptor of β-Glc	Křen *et al.* 1997*a*
6-O,N,N′-Triacetylchitobiose	**87**	by β-N-acetylhexosaminidase from *Penicillium brasilianum*	–	Hušáková *et al.* 2001
6′-O,N,N′-Triacetylchitobiose	**88**	*ditto*	–	*ditto*
Thiamin β-D-2-deoxy-2-acetamidoglucopyranoside	**89**	by β-N-acetylhexosaminidase from *A. oryzae*	–	Křen *et al.* 1998*a*
1-[(2-Acetamido-2-deoxy-β-D-glucopyranosylethyl)-3,5-bis(hydroxyethyl)]cyanuric acid	**90a**	ES by glycosidases	–	Kieburg *et al.* 1998
1-[(β-D-Galactopyranosylethyl)-3,5-bis(hydroxyethyl)]cyanuric acid	**90b**	*ditto*	–	*ditto*
1-[(α-D-Mannopyranosylethyl)-3,5-bis(hydroxyethyl)]cyanuric acid	**90c**	*ditto*	–	*ditto*
O-(1-β-D-Galactopyranosyl)pentaerythritol	**91a**	*ditto*	–	*ditto*
O-(1-α-D-Mannopyranosyl)pentaerythritol	**91b**	*ditto*	–	*ditto*
(2-Acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosylmethyl)-4-(O-acetylhydroxymethyl)benzene	**92a**	*ditto*	–	*ditto*
(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosylmethyl)-4-(O-acetylhydroxymethyl)benzene	**92b**	*ditto*	–	*ditto*
4*a*/5*a*-Pyridoxine 2-acetamido-2-deoxy-β-D-glucopyranosides	**93a,b**	35 different glycosidases	vitamers	Weignerová *et al.* 1999*a*
4*a*/5*a*-Pyridoxine α-D-mannopyranosides	**93c,d**		–	*ditto*
5*a*-Pyridoxine α-D-galactopyranoside	**93e**		–	*ditto*
6′′-O-Acylisoglobotrioses	**94a–d**	*Bacillus subtilis* and *Talaromyces flavus*	xenotransplantation	Weignerová *et al.* 1999*b*
6-(2-Hydroxypropyl)-13*H*-1,5-benzodiazepino[2,3-*b*]quinoxaline	**95a**	SC	antimicrobial activity	Gabriel *et al.* 1995
6-(2-Hydroxyethyl)-13*H*-1,5-benzodiazepino[2,3-*b*]quinoxaline	**95b**	*ditto*	–	*ditto*
α-D-Glucopyranosyl-1,3-anhydro-β-D-*xylo*-hexulofuranoside	**96**		–	Čapek *et al.* 1993
3-Amino-2,3,6-trideoxy-α-L-lyxopyranosyl-(7*R*)-O-(2-hydroxyethyl)daunomycinone	**97a**	*ditto*	anticancer drug	Jizba *et al.* 1989
3-Amino-2,3,6-trideoxy-β-L-lyxopyranosyl-(7*R*)-O-(2-hydroxyethyl)daunomycinone	**97b**	*ditto*	*ditto*	*ditto*
3-Amino-2,3,6-trideoxy-α-L-lyxopyranosyl-(7*S*)-O-(2-hydroxyethyl)daunomycinone	**98a**	*ditto*	*ditto*	*ditto*

continued

Table III – *continued*

3-Amino-2,3,6-trideoxy-β-L-lyxopyranosyl-(7*S*)-O-(2-hydroxyethyl)daunomycinone	**98b**	*ditto*	*ditto*	*ditto*
2,6-Dideoxy-α-L-arabinopyranosyl-(7*R*)-O-(2-hydroxyethyl)daunomycinone	**98c**	*ditto*	*ditto*	*ditto*
2,6-Dideoxy-β-L-arabinopyranosyl-(7*R*)-O-(2-hydroxyethyl)daunomycinone	**98d**	*ditto*	*ditto*	*ditto*
3-Amino-2,3,6-trideoxy-α-L-lyxopyranosyl-(7*S*)-O-(4-hydroxy-2-butinyl)daunomycinone	**99**	*ditto*	*ditto*	*ditto*

[a]For abbreviations *see* footnote to Table I.



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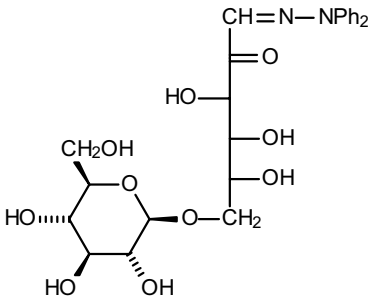

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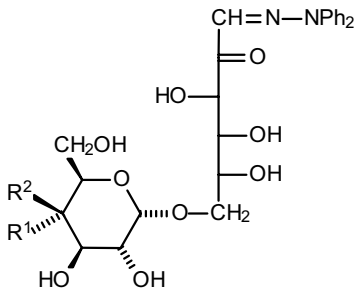
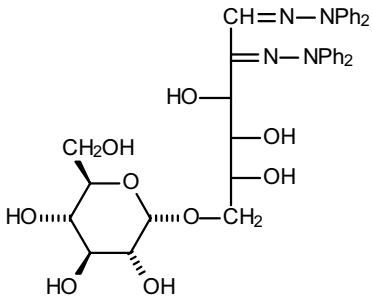
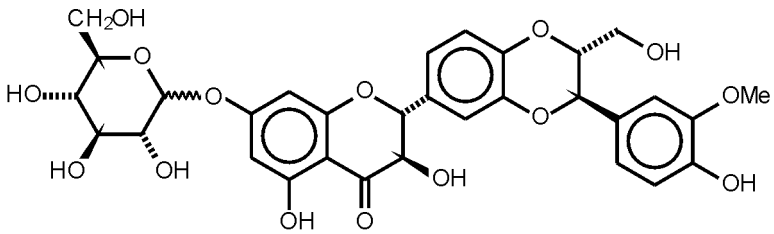


74a,b



75

	R^1	R^2
74a	H	OH
74b	OH	H



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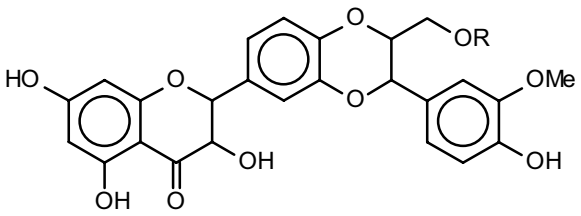
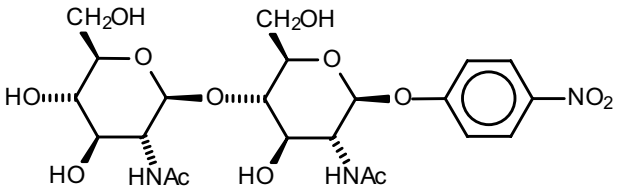


77a–d

	R
77a	α-D-Glc-(1→3)-β-D-Gal
77b	α-D-Glc-(1→4)-α-D-Glc-(1→3)-β-D-Gal
77c	α-D-Glc-(1→4)-β-D-Glc
77d	α-D-Glc-(1→4)-α-D-Glc-(1→4)-β-D-Glc



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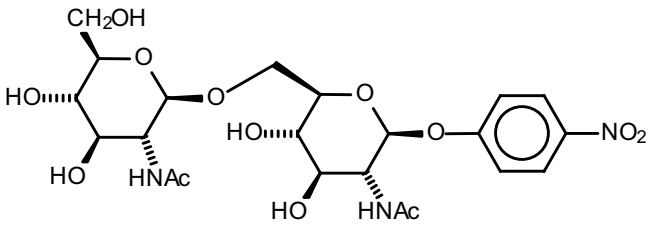

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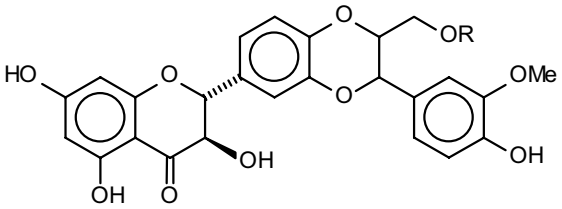
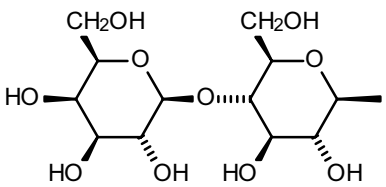


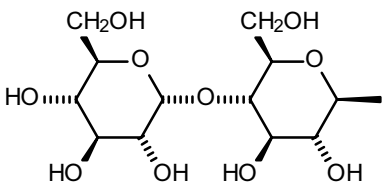
80a–d

	R
80a	β-Glc
80b	β-Gal
80c	β-Lac
80d	β-Mal

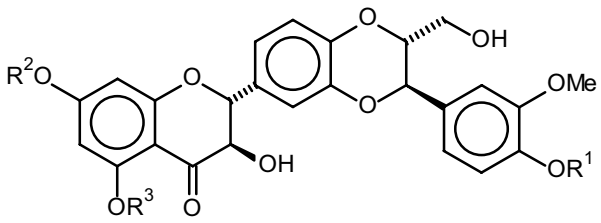
R



β-Lac



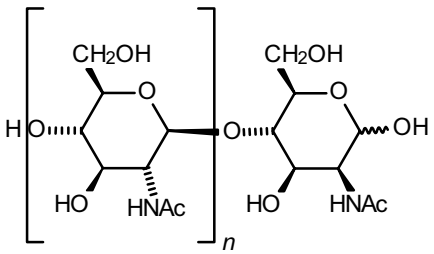
β-Mal



81a–c

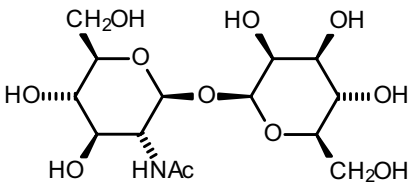
	R^1	R^2	R^3
81a	GA	H	H
81b	H	GA	H
81c	H	H	GA

GA = α-D-glucuronopyranosyl



82a,b

	n
82a	1
82b	2



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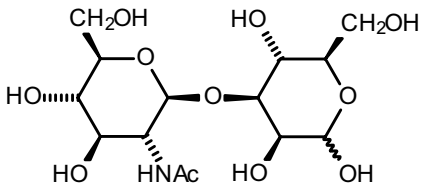

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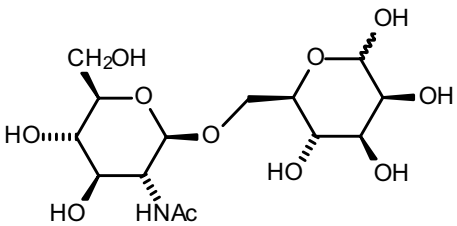

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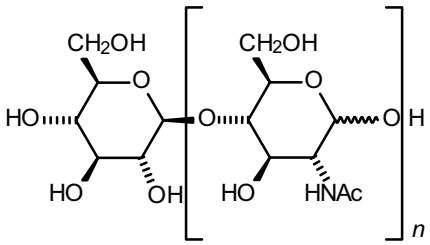
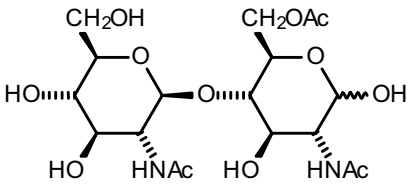


86a–c

	n
86a	2
86b	3
86c	4



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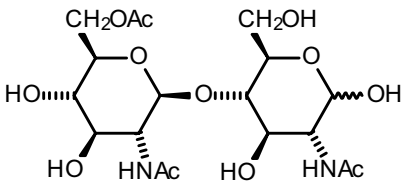

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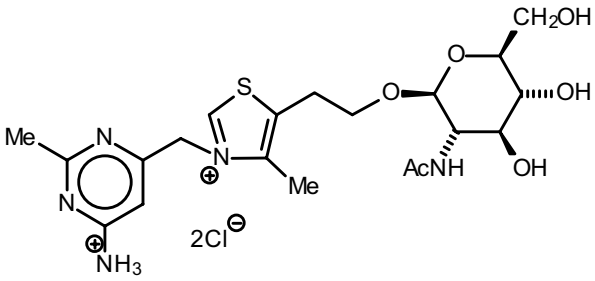

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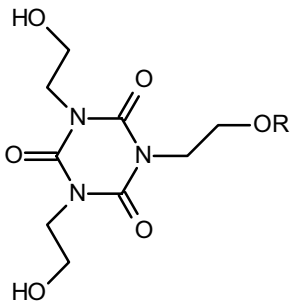
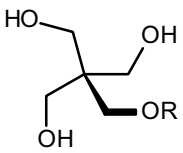


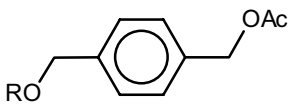
90a–c

	R
90a	β-D-GlcNAc
90b	β-D-Gal
90c	α-D-Man



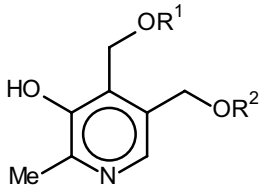
91a,b

	R
91a	β-D-Gal
91b	α-D-Man



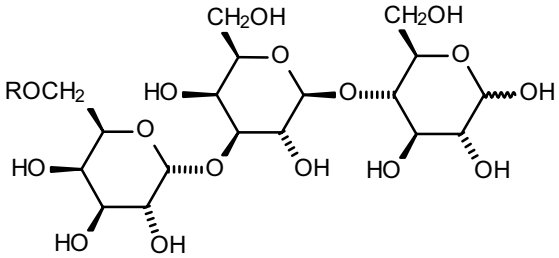
92a,b

	R
92a	β-D-GlcNAc(OAc)$_3$
92b	β-D-Gal(OAc)$_4$



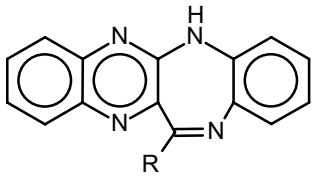
93a–e

	R^1	R^2
93a	β-D-GlcNAc	H
93b	H	β-D-GlcNAc
93c	α-D-Man	H
93d	H	α-D-Man
93e	H	α-D-Gal



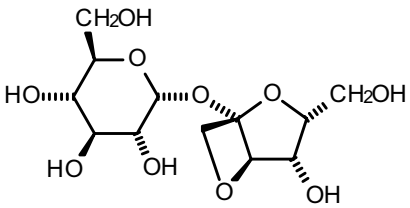
94a–d

	R
94a	H
94b	COMe
94c	COEt
94d	COPr



95a,b

	R
95a	CH_2-CH(OH)-CH_3
95b	CH_2-CH_2OH



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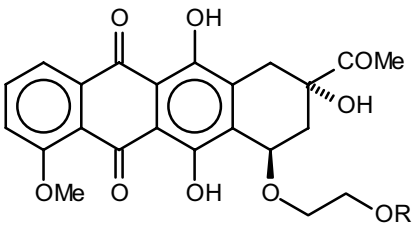
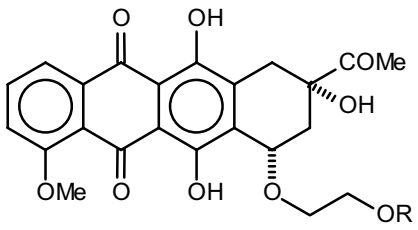


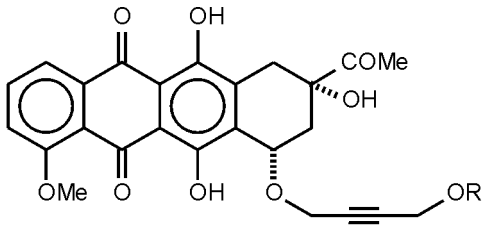
97a,b

	R
97a	α-Y
97b	β-Y

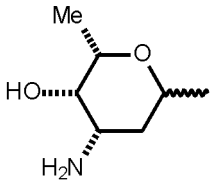


98a–d

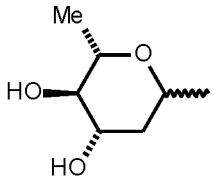
	R
98a	α-Y
98b	β-Y
98c	α-Z
98d	β-Z



99
R = α–Y



Y



Z

5 MISCELLANEOUS COMPOUNDS

New metabolites produced by microorganisms but also by lower and higher plants and animals and identified in our laboratories are listed in Table IV.

Addition of metyrapone to the culture of *Streptomyces cinnamonensis* induced the co-production of new metabolites, 26-deoxymonensins A (**100a**) and B (**100b**) (Pospíšil *et al.* 1994).

The mutant strain *S. cinnamonensis* TR-26 produced two new compounds (**101a,b**) (Pospíšil *et al.* 1998). Phenolic antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) at a concentration of 0.55 and 2.25 mmol/L, respectively, added to cultures of *Streptomyces cinnamonensis* C-100-5 caused up to a 380 % higher production of the oligoether antibiotic monensin. *S. cinnamonensis* exhibits a high tolerance to BHT, but it is more sensitive towards BHA. 5.5 mmol/L BHA practically stopped growth, while 45 mmol/L BHT still stimulated antibiotic production. Other antioxidants probucol and tocoferol acetate did not exert such positive effects. BHA was predominantly metabolized to 5-hydroxy-BHA. When BHA and BHT were applied simultaneously, the main transformation metabolite was 3,3′,5,5′-tetra-*tert*-butyl-stilbene-4,4′-quinone accompanied by 1,2-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane.

The structure of a furano-naphthoquinone derivative (**102**) was assigned to a new metabolite isolated from *S. cinnamonensis* (Sedmera *et al.* 1991). Additional biologically active derivatives were isolated as side products in the biosynthesis of monensins. The compound described here is closely similar to droserone a to other furaquinocin antibiotics and also exhibits similar biological effects.

Two new microbial metabolites (**103**, **104**) were isolated from submerged cultures of the macrotetrolide-producing strains *S. globisporus* and *S. griseus* (Jizba *et al.* 1993). Additional biologically active metabolites were isolated as side products in the biosynthesis of monensins. These compounds can play an important role in the initial steps of monensin biosynthesis and thus also influence its overproduction.

Lincomycin biotransformation was conducted by using *S. venezuelae* and *S. phaeochromogenes* cell-free extracts yielding lincomycin sulfoxide (**105a**) and lincomycin sulfone (**105b**). The same com-

pounds were also produced by chemical synthesis (Pospíšil *et al.* 2001). Lincomycin, a glycosidic antibiotic active against Gram-positive bacteria, was modified enzymically with the aim of improving its physico-chemical and biological properties. Its glycosylation using Jack bean α-mannosidase produced 7-O-α-D-manno-pyranosyl-lincomycin (Weignerová *et al.* 2001*b*).

The pyrenomycete *Melanconis flavovirens* was found to produce an antifungal antibiotic flavorinin (**106**) (Saidler *et al.* 1989), which possesses a strong activity against yeasts and a moderate activity against filamentous fungi.

A new derivative of hydroxamic acid (tolypocin, HL) (**107**) was isolated from the mycelium of the fungus *Tolypocladium geodes*. The iron(III)–Tris-chelate complex of this ligand [FeL3] was isolated from the mycelium of the fungus *T. terricola* (Jegorov *et al.* 1993).

A new chelator of di- and trivalent cations, tolypocladin (**108**), was isolated from the mycelium of *T. inflatum* strain DSM 915. Its production is dependent on zinc ions in the medium. It serves as an endogenous hydrogen acceptor under oxygen limitation in the producing strain, *T. inflatum* (Gräfe *et al.* 1990).

A minor peptidic chlorinated siderophore (**109**) was isolated (Hennard *et al.* 1997) in the course of the purification procedure of pyoverdins produced by *Pseudomonas aeruginosa* strain ATCC 15692 in large batch cultures. A mechanism for the formation of this compound was proposed and a procedure for its preparation was described.

A new homoaporphine alkaloid baytopine (**110**) was isolated from the leaves and flowers of *Merendera kurdica* (Hušek *et al.* 1989).

A new bisbenzylisoquinoline alkaloid (–)-(1*S*,1′*R*)-O,O′-dimethylgrisabine (**111**) was isolated from the leaves of *Phaeanthus vietnamensis* and its antibacterial activity was described by Sedmera *et al.* (1990).

The structure of leptocarpine (**112**), a new protopine alkaloid isolated from the whole plant of *Hypecoum leptocarpum* (Táborská *et al.* 1995), and fumaflorine (**113**), a new 1-benzylisoquinoline alkaloid, were isolated from the aerial mycelium of *Fumaria densiflora* (Táborská *et al.* 1996, 1997). Oplopanonyl acetate (**114**) was isolated from *Chamaecyparis pisifera* (De Bruyn *et al.* 1990).

Flobufen and its 3-methyl isomer (**115a,b**) were obtained by the Friedel–Crafts reaction of 2,4-difluorobiphenyl with itaconic or citraconic anhydride, respectively, followed by hydrogenation of the products (Jegorov *et al.* 1995*b*). The structures of both compounds have been elucidated by mass spectrometry and ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. The structure of flobufen has been confirmed by a single-crystal X-ray study. Metabolic transformations of flobufen, a non-steroid antiinflammatory agent, were studied *in vitro* using rat and mouse liver homogenates and liver subcellular fractions as biological models.

The complete covalent structure of a novel boar DQH sperm surface protein (designation in accordance with the N-terminal amino-acid sequence; Asp, Gln, His) (**116**) resistant to many classical procedures of enzymic cleavage was determined by Bezouška *et al.* (1999).

Whole cells of *Rhodococcus equi* strain A4 chemoselectively hydrolyzed methyl cyanobutanoates into methyl (*R*,*S*)-3-benzyloxyglutamine (**117a**) and methyl (*R*,*S*)-3-benzyloxyglutarate (**117b**), respectively (Martínková *et al.* 2001).

The structure of unusual compounds, *e.g.*, 2,3′-anhydrosucrose (**118**) obtained by organic synthesis was determined by Čapek *et al.* (1990). These derivatives were prepared within the frames of the directed research of biologically readily degradable derivatives of saccharides.

The compounds isolated from the extracts of Central Asian lichens comprised new glycosides (**119**–**123h**), glycoside esters (**124a–j**) and macrolactone glycosides (**125**–**127**) (Řezanka and Guschina 2000, 2001*a–c*). Many different metabolites containing predominantly bromo derivatives were isolated from the same lichens (**128**–**138b**) (*see* Řezanka and Dembitsky 1998, 1999*a*,*b*, 2001*a*; Řezanka and Guschina 1999). Halogen derivatives were isolated from the marine alga *Plocamium cartilagineum* (**139**–**142**) (Řezanka and Dembitsky 2001*c*). Fatty acids including dicarboxylic ones (**143**, **144**) were isolated from horse-tails (Řezanka 1998) and from brackish invertebrates (*Rhithropanopeus harrisii*, *Astacus leptodactylus eichwaldi* and *Mytilaster lineatus*) of the Caspian Sea (Dembitsky and Řezanka 1993) and identified as furan acids (**145a,b**). Unusual fatty acids were identified in the deep-lake invertebrate *Acanthogammarus grewingkii* living in Baikal Lake (**146a–h**) (Řezanka and Dembitsky 1994); fresh-water sponges (*Baicalospongia intermedia*, *B. bacilifera*, and *Lubomirskia baikalensis*) contained isoprenoid polyunsaturated fatty acids (**146i–n**) (Řezanka and Dembitsky 1993). Nine fungal species belonging to the *Ascomycetes* and *Basidiomycetes* were examined and some novel unusual hydroxy fatty acids were identified (**147a–d**) by Dembitsky *et al.* (1993). Six novel fatty acid derivatives (**148**–**153**) containing one γ-lactone ring and unusual unsaturated chains were isolated from two soft corals, *Sarcophyton trocheliophorum* and *Lithophyton arboreum*, collected in the Red Sea. The compounds gave positive results in a brine shrimp toxicity assay (Řezanka and Dembitsky 2001*b*).

Table IV. Miscellaneous compounds

Compound	Formula	Origin[a]	Note	Reference
26-Deoxymonensins A and B	**100a,b**	*Streptomyces cinnamonensis*	antibiotic activity	Pospíšil *et al.* 1994
2-Demethylmonensins A and B	**101a,b**	*ditto*	*ditto*	Pospíšil *et al.* 1998
Furanonaphthoquinone	**102**	*ditto*	*ditto*	Sedmera *et al.* 1991
5,6,7,7*a*-Tetrahydro-3*H*-pyrrolizin-7*a*-ol-3-one	**103**	*Streptomyces globisporus*	–	Jizba *et al.* 1993
N-[2-(1-hydroxy-4-methylpentyl)]acetamide	**104**	*Streptomyces griseus*	–	*ditto*
Lincomycin sulfoxide	**105a**	SS	*ditto*	Pospíšil *et al.* 2001
Lincomycin sulfone	**105b**	*ditto*	*ditto*	*ditto*
2-Amino-2-hydroxymethyl-3,4-*trans*-epoxy-14-oxoeicos-*trans*-enoic acid	**106**	*Melanconis flavovirens*	*ditto*	Saidler *et al.* 1989
Tolypocin	**107**	*Tolypocladium geodes*	–	Jegorov *et al.* 1993
Tolypocladin	**108**	*Tolypocladium inflatum*	metal-chelating compound	Gräfe *et al.* 1990
Pyoverdin	**109**	*Pseudomonas aeruginosa*	–	Hennard *et al.* 1997
Baytopine	**110**	*Merendera kurdica*	–	Hušek *et al.* 1989
(–)-(1*S*,1′*R*)-O,O′-Dimethylgrisabine	**111**	*Phaeanthus vietnamensis*	–	Sedmera *et al.* 1990
Leptocarpine	**112**	*Hypecoum leptocarpum*	alkaloid	Táborská *et al.* 1995
Fumaflorine	**113**	*Fumaria densiflora*	cytoprotective effect	Táborská *et al.* 1996, 1997
Oplopanonyl acetate	**114**	*Chamaecyparis pisifera*	–	De Bruyn *et al.* 1990
4-(2',4'-Difluorobiphenyl-4-y1)-2-methyl-4-oxobutanoic acid	**115a**	SC	–	Jegorov *et al.* 1995*b*
4-(2',4'-Difluorobiphenyl-4-y1)-3-methyl-4-oxobutanoic acid	**115b**	*ditto*	–	*ditto*
"O-Glycoprotein"	**116**	boar DQH sperm	–	Bezouška *et al.* 1999
Methyl (*R*,*S*)-3-benzyloxyglutamine	**117a**	BT by *Rhodococcus equi*	–	Martínková *et al.* 2001
Methyl (*R*,*S*)-3-benzyloxyglutarate	**117b**	BT by *R. equi*	–	*ditto*
2,3′-Anhydrosucrose	**118**	SC	–	Čapek *et al.* 1990
(18*R*)-18-Hydroxymurolic acid	**119**	*A.g.*, *X.e.*	–	Řezanka and Guschina 2000
(18*S*)-18-Hydroxyprotoconstipatic acid	**120**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
(18*R*)-18-Hydroxy-*allo*-murolic acid	**121**	*L.s.*, *P.c.*	–	*ditto*
Murolic acid (18*R*)-18-O-β-D-glucopyranoside	**122a**	*A.g., X.e.*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-β-D-glucopyranoside	**122b**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
allo-Murolic acid (18*R*)-18-O-1-β-D-xylopyranosyl-(1→6)-β-D-glucopyranoside	**122c**	*L.s.*, *P.c.*	–	*ditto*
Murolic acid (18*R*)-18-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside	**122d**	*ditto*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside	**122e**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-α-D-arabinofuranosyl-(1→6)-β-D-glucopyranoside	**122f**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
allo-Murolic acid (18*R*)-18-O-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	**122g**	*L.s.*, *P.c.*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-β-D-apiofuranosyl-(1→4)-β-D-glucopyranoside	**122h**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*

continued

Table IV – *continued*

Murolic acid (18*R*)-18-O-β-D-apiofuranosyl-(1→2)-β-D-glucopyranoside	**122i**	*A.g.*, *X.e.*	–	*ditto*
allo-Murolic acid (18*R*)-18-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside	**123a**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	Řezanka and Guschina 2001*a*
Murolic acid (18*R*)-O-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside	**123b**	*L.s.*, *P.c.*, *X.e.*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside	**123c**	*ditto*	–	*ditto*
allo-Murolic acid (18*R*)-18-O-β-D-glucopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→2)]-β-D-glucopyranoside	**123d**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
allo-Murolic acid (18*R*)-18-O-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranoside	**123e**	*ditto*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside	**123f**	*L.s.*, *P.c.*, *X.e.*	–	*ditto*
Murolic acid (18*R*)-18-O-β-D-glucopyranosyl-(1→3)-[β-D-glucopyranosyl(1→6)]-β-D-glucopyranoside	**123g**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
Protoconstipatic acid (18*S*)-18-O-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside	**123h**	*A.g.*, *X.t.*	–	*ditto*
18*R*-Hydroxydihydroalloprotolichesterinic acid	**124a**	*A.g.*, *X.t.*, *X.e.*	–	Řezanka and Guschina 2001
18*S*-Hydroxydihydroprotolichesterinic acid	**124b**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
18*S*-Hydroxyneodihydroprotolichesterinic acid	**124c**	*L.s.*, *P.c.*	–	*ditto*
21-O-α-L-Rhamnopyranosyl-18*R*-hydroxydihydroalloprotolichesterinate	**124d**	*A.g.*, *X.t.*, *X.e.*	–	*ditto*
21-O-β-D-Glucopyranosyl-18*S*-hydroxydihydroprotolichesterinate	**124e**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
21-O-β-D-Glucopyranosyl-18*S*-hydroxyneodihydrolichesterinate	**124f**	*L.s.*, *P.c.*	–	*ditto*
18-O-β-D-Glucopyranosyl-18*R*-hydroxydihydroalloprotolichesterinate 21-O-α-L-rhamnopyranoside	**124g**	*ditto*	–	*ditto*
18-O-β-D-Xylopyranosyl-18*S*-hydroxydihydroprotolichesterinate 21-O-β-D-glucopyranoside	**124h**	*C.f.*, *L.f.*, *R.p.*, *X.c.*	–	*ditto*
18-O-α-L-Rhamnopyranosyl-18*S*-hydroxyneodihydroprotolichesterinate 21-O-β-D-glucopyranoside	**124i**	*C.f.*, *L.f.*, *R.p.*, *X.c.*, *X.e.*	–	*ditto*
18-O-β-D-Glucopyranosyl-18*S*-hydroxyneodihydroprotolichesterinate 21-O-β-D-glucopyranoside	**124j**	*L.s.*, *P.c.*	–	*ditto*
Gobienine A	**125**	*Acarospora gobiensis*	–	Řezanka and Guschina 2001*c*
Gobienine B	**126**	*ditto*	–	*ditto*
Gobienine C	**127**	*ditto*	–	*ditto*
Methyl 18-bromo-(5*E*,17*E*)-octadeca-5,17-diene-15-ynoate	**128**	*ditto*	–	Řezanka and Dembitsky 1998
Methyl 18-bromooctadeca-5,7,17-triynoate	**129**	*ditto*	–	*ditto*
Methyl 16,18-dibromo-(15*E*,17*Z*)-octadeca-15,17-diene-5,7-diynoate	**130**	*L.f.*, *P.c.*, *R.p.*, *X.t.*	–	Řezanka and Dembitsky 1999*a*,*b*
Methyl 18,18-dibromo-17-octadecene-5,7-diynoate	**131**	*C.f.*, *L.s.*, *R.p.*, *X.c.*	–	*ditto*
Methyl 18-bromo-(5*E*,17*Z*)-octadeca-5,17-diene-15-ynoate	**132**	*C.f.*, *P.c.*, *X.e.*	–	*ditto*
Methyl 6-bromo-(5*E*,15*Z*)-octadeca-5,15-diene-11,13,17-triynoate	**133**	*R.p.*, *X.c.*	–	*ditto*
Methyl 18-bromo-9-hydroxy-12,13-*trans*-epoxy-(10*E*,15*Z*)-octadeca-10,15-diene-17-ynoate	**134**	*L.s.*, *X.c.*	–	*ditto*

Table IV – *continued*

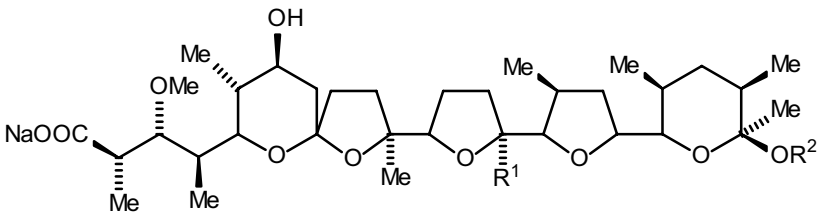
Methyl 18-bromo-5,6-*trans*-endomethylene-7,11,15-trimethyl-(8*E*,10*Z*)-octadeca-8,10-diene-17-ynoate	**135**	*X.t.*, *X.e.*	–	*ditto*
(12*Z*,15*S*,18*S*)-15-Hydroxy-18-bromo-12,16,17-octadecatrienoic acid	**136**	*A.g.*, *L.f.*, *L.s.*, *R.p.*, *X.e.*	–	Řezanka and Dembitsky 2001*a*
(13*E*,15*S*,18*S*)-15-Hydroxy-18-bromo-13,16,17-octadecatrienoic acid	**137**	*A.g.*, *L.s.*, *P.c.*, *X.c.*, *X.t.*	–	*ditto*
Acarogobien A	**138a**	*A. gobiensis*	–	Řezanka and Guschina 1999
Acarogobien B	**138b**	*ditto*	–	*ditto*
(6*E*,8*E*,12*E*)-3-Methylene-4-oxo-7,11-dimethyl-(10*S**,11*R**)-dichloro-13-bromo-trideca-6,8,12-trienoic acid	**139**	*Plocamium cartilagineum*	–	Řezanka and Dembitsky 2001*c*
(6*E*,8*E*,12*E*)-3-Methylene-4-oxo-7,11-dimethyl-(10*R**,11*R**)-dichloro-13-bromo-trideca-6,8,12-trienoic acid	**140**	*ditto*	–	*ditto*
(6*E*,8*E*,12*E*)-3-Methylene-(4*R*)-hydroxy-7,11-dimethyl-(10*R**,11*R**)-dichloro-13-bromo-trideca-6,8,12-trienoic acid	**141**	*ditto*	–	*ditto*
(6*E*,8*E*,12*E*)-3-Methylene-(4*R*)-hydroxy-7,11-dimethyl-(10*S**,11*R**)-dichloro-13-bromo-trideca-6,8,12-trienoic acid	**142**	*ditto*	–	*ditto*
Dimethyl 14,15-dimethyltriacontanedioate	**143a**	*Equisetum litorale*	–	Řezanka 1998
Dimethyl 14-methylnonacosanedioate	**143b**	*ditto*	–	*ditto*
Methyl 15-(3′-methyl-5′-pentyl-2′-furanyl)-pentadecanoate	**144a**	*Mytilaster lineatus*	–	Dembitsky and Řezanka 1993
Methyl 15-(3′,4′-dimethyl-5′-pentyl-2′-furanyl)-pentadecanoate	**144b**	*ditto*	–	*ditto*
cis,*cis*-11,12-14,15-Bis-methylene-*cis*-5-eicosenoic acid	**145a**	*Acanthogammarus grewingkii*	–	Řezanka and Dembitsky 1994
cis,*cis*-13,14-16,17-Bis-methylene-*cis*-5-docosenoic acid	**145b**	*ditto*	–	*ditto*
cis,*cis*-15,16-18,19-Bis-methylene-*cis*-5-tetracosenoic acid	**145c**	*ditto*	–	*ditto*
cis-11,12-Methylene-*cis*-5-eicosenoic acid	**145d**	*ditto*	–	*ditto*
cis-13,14-Methylene-*cis*-5-docosenoic acid	**145e**	*ditto*	–	*ditto*
cis-16,17-Methylene-*cis*-5-docosenoic acid	**145f**	*ditto*	–	*ditto*
cis-15,16-Methylene-*cis*-5-tetracosenoic acid	**145g**	*ditto*	–	*ditto*
cis-18,19-Methylene-*cis*-5-tetracosenoic acid	**145h**	*ditto*	–	*ditto*
9,13,17-Trimethyl-5-octadecenoic acid	**146a**	*Lubomirskia baikalensis*	–	Řezanka and Dembitsky 1993
11,15,19-Trimethyl-5-eicosenoic acid	**146b**	*ditto*	–	*ditto*
11,15,19-Trimethyl-5,9-eicosadienoic acid	**146c**	*Baicalospongia bacilifera*	–	*ditto*
11,15,19-Trimethyl-5,9,17-eicosatrienoic acid	**146d**	*ditto*	–	*ditto*
9,13,17,21-Tetramethyl-5-docosenoic acid	**146e**	*Lubomirskia baikalensis*	–	*ditto*
13,17,21-Trimethyl-5-docosenoic acid	**146f**	*ditto*	–	*ditto*
13,17,21-Trimethyl-5,9-docosadienoic acid	**146g**	*ditto*	–	*ditto*
13,17,21-Trimethyl-5,9,19-docosatrienoic acid	**146h**	*B. bacilifera*	–	*ditto*
11,15,19,23-Tetramethyl-5-tetracosenoic acid	**146i**	*ditto*	–	*ditto*
11,15,19,23-Tetramethyl-5,9-tetracosadienoic acid	**146j**	*ditto*	–	*ditto*
11,15,19,23-Tetramethyl-5,9,17-tetracosatrienoic acid	**146k**	*ditto*	–	*ditto*
15,19,23-Trimethyl-5,9,17-tetracosatrienoic acid	**146l**	*ditto*	–	*ditto*
13,17,21,25-Tetramethyl-5-hexacosenoic acid	**146m**	*L. baikalensis*	–	*ditto*
13,17,21,25-Tetramethyl-5,9-hexacosadienoic acid	**146n**	*ditto*	–	*ditto*
7-Hydroxy-8,14-dimethyl-9-hexadecenoic acid	**147a**	*Phellinus* sp.	–	Dembitsky *et al.* 1993

continued

Table IV – *continued*

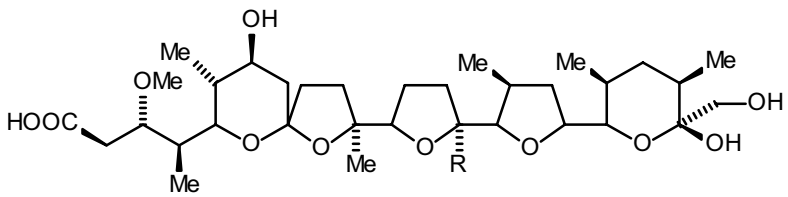
7-Hydroxy-8,16-dimethyl-9-octadecenoic acid	**147b**	*ditto*	–	*ditto*
7-Hydroxy-8,18-dimethyl-9-icosenoic acid	**147c**	*ditto*.	–	*ditto*
7-Hydroxy-8,20-dimethyl-9-docosenoic acid	**147d**	*ditto*	–	*ditto*
5*R*-Methyl-4-(2′-methylene-6′-methyl-5′-heptenyl-3′-ine)-2(5*H*)-furanone	**148**	*Sarcophyton trocheliophorum*	–	Řezanka and Dembitsky 2001*b*
5*R*-Methyl-4-(5′*S*-hydroxy-3′-heptenyl-6′-ine)-2(5*H*)-furanone	**149**	*ditto*	–	*ditto*
5*S*-Methyl-4-(4′*S*,9′*S*-dihydroxy-2′*Z*,11′-undecadienyl-5′,7′-diine)-2(5*H*)-furanone	**150**	*ditto*	–	*ditto*
5*S*-Methyl-4-(11′-hydroxy-2′*Z*-undecenyl-5′,7′,9′-triine)-2(5*H*)-furanone	**151**	*ditto*	–	*ditto*
5*R*-(1′*S*-Hydroxy-2′*Z*,4′*E*-decadienyl)-2-tetrahydrofuranone	**152**	*Lithophyton arboreum*	–	*ditto*
(5*R*)-5-Methyl-(1′*S*-hydroxy-4′,8′-dimethyl-4*Z*,8*Z*-tridecadienyl)-2-tetrahydrofuranone	**153**	*ditto*	–	*ditto*

[a]*A.g.* – *Acarospora gobiensis*; *C.f.* – *Cladonia furcata*; *L.f.* – *Lecanora fructulosa*; *L.s.* – *Leptogium saturninum*; *P.c.* – *Peltigera canina*; *R.p.* – *Rhizoplaca peltata*; *X.c.* – *Xanthoparmelia camtschadalis*, *X.t.* – *X. tinctina*; *X.e.* – *Xanthoria elegans*; for further abbreviations *see* footnote to Table I.



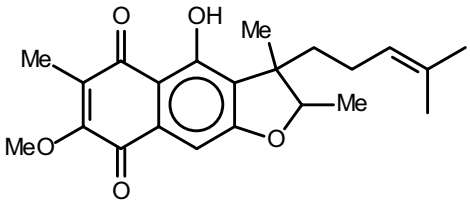
100a,b

	R^1	R^2
100a	Et	H
100b	Me	Me

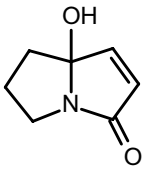


101a,b

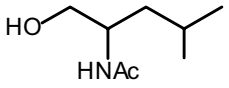
	R
101a	Et
101b	Me



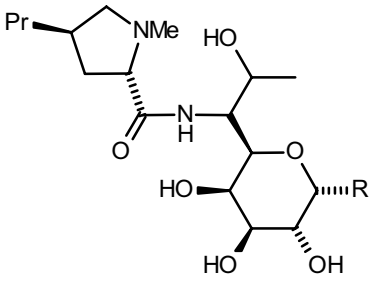
102



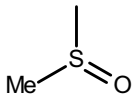
103

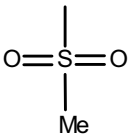


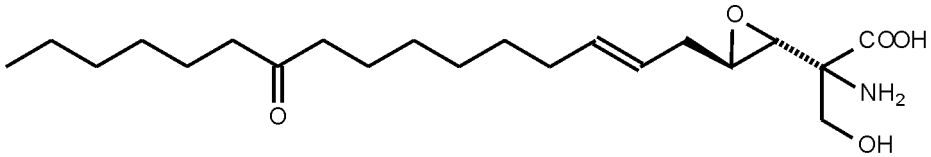
104



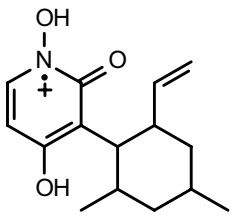
105a,b

105a R= 

105b R= 



106



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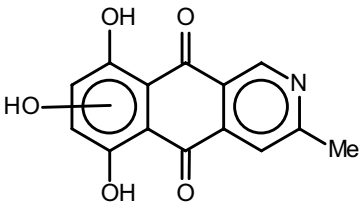
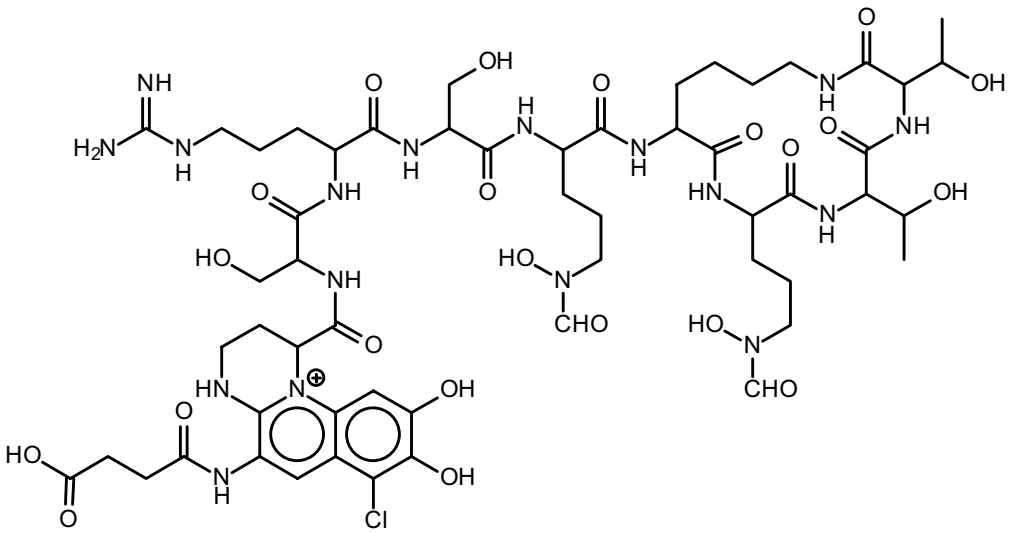


108



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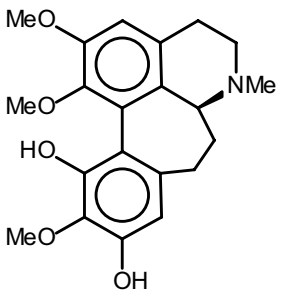

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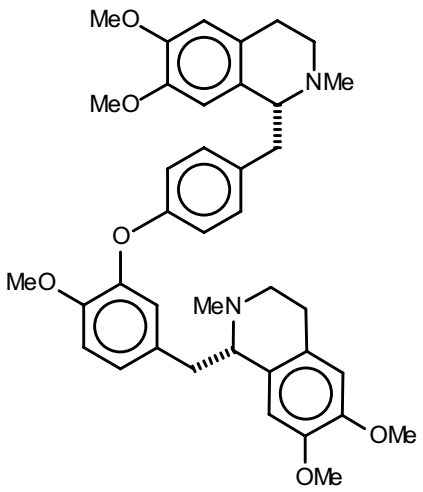

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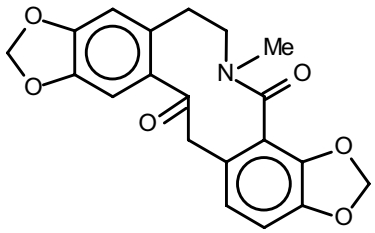

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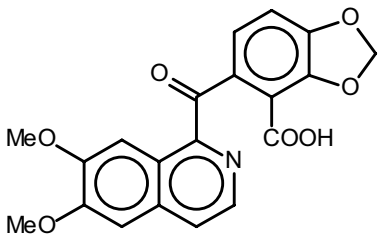
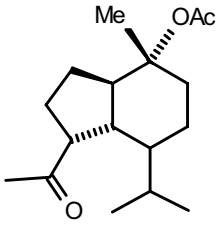
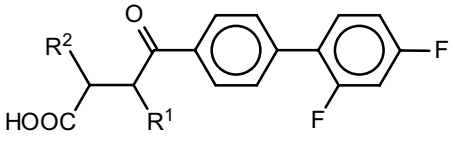


113



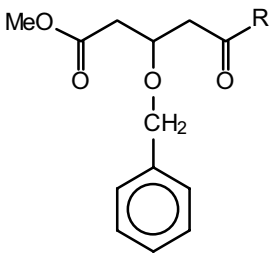
114



115a,b

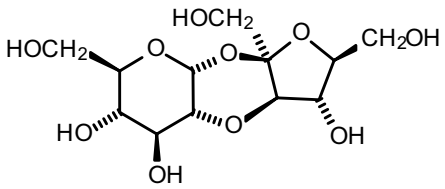
	R^1	R^2
115a	H	Me
115b	Me	H

116

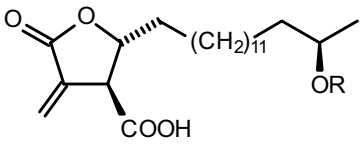


117a,b

	R
117a	NH_2
117b	OH



118



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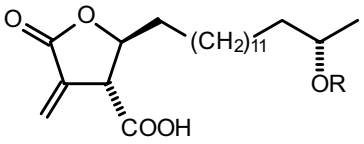

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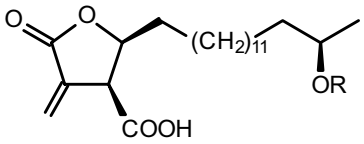
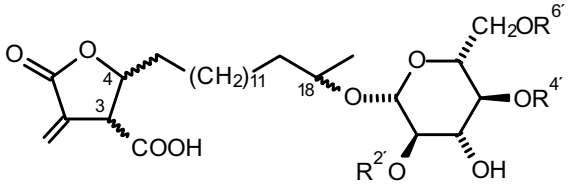


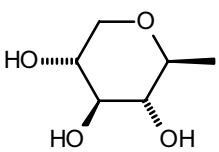
121

R = H or MTPA
MTPA = (*S*)- or (*R*,*S*)- or (*R*)-α-methoxy-α-trifluoromethylphenylacetyl

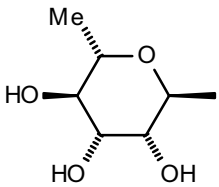


122 a–i

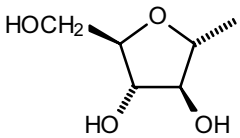
	$R^{2'}$	$R^{4'}$	$R^{6'}$	C-3	C-4	C-18
122a	H	H	H	*S*	*R*	*R*
122b	H	H	H	*S*	*S*	*S*
122c	H	H	Xyl	*S*	*S*	*R*
122d	H	H	Rha	*S*	*S*	*R*
122e	H	Rha	H	*R*	*S*	*S*
122f	H	H	Ara	*S*	*S*	*R*
122g	H	H	Api	*S*	*S*	*R*
122h	H	Api	H	*R*	*S*	*S*
122i	Api	H	H	*S*	*R*	*R*



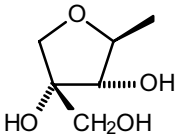
β-D-Xyl



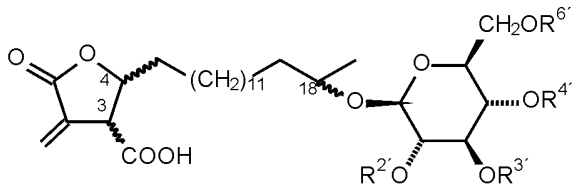
α-L-Rha



α-D-Ara

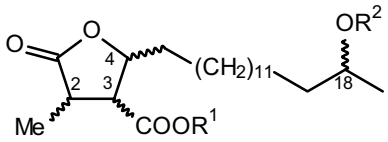


β-D-Api



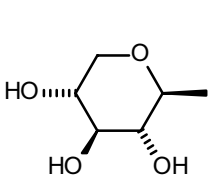
123a–h

	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{6'}$	C-3	C-4	C-18
123a	Glc	H	H	H	*S*	*S*	*R*
123b	H	Glc	H	H	*S*	*R*	*R*
123c	H	H	H	Glc	*R*	*S*	*S*
123d	Glc	Glc	H	H	*S*	*S*	*R*
123e	Glc	H	H	Glc	*S*	*S*	*R*
123f	Glc´´-(2→1)-Glc´´´	H	H	H	*R*	*S*	*S*
123g	H	Glc	H	Glc	*S*	*R*	*R*
123h	Glc´´-(6→1)-Glc´´´	Glc	H	H	*R*	*S*	*S*

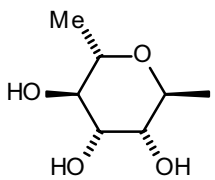


124a–j

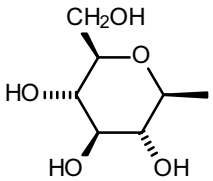
	R^1	R^2	C-2	C-3	C-4	C-18
124a	H	H	*R*	*S*	*S*	*R*
124b	H	H	*S*	*R*	*S*	*S*
124c	H	H	*R*	*R*	*S*	*S*
124d	Rha	H	*R*	*S*	*S*	*R*
124e	Glc	H	*S*	*R*	*S*	*S*
124f	Glc	H	*R*	*R*	*S*	*S*
124g	Rha	Glc	*R*	*S*	*S*	*R*
124h	Glc	Xyl	*S*	*R*	*S*	*S*
124i	Glc	Rha	*R*	*R*	*S*	*S*
124j	Glc	Glc	*R*	*R*	*S*	*S*



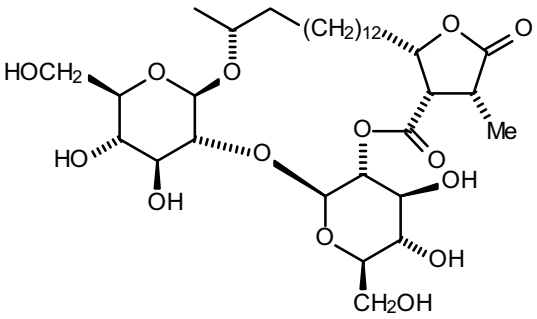
β-D-Xyl



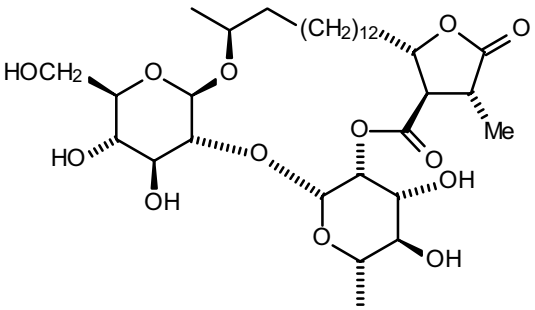
α-L-Rha



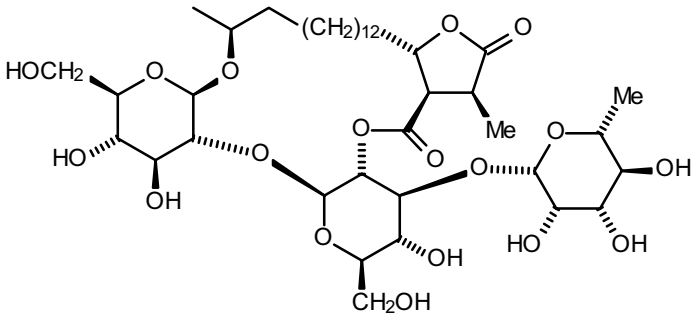
β-D-Glc



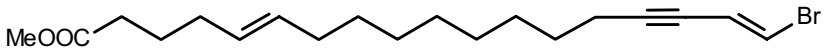
125



126



127



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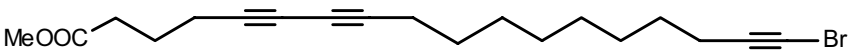

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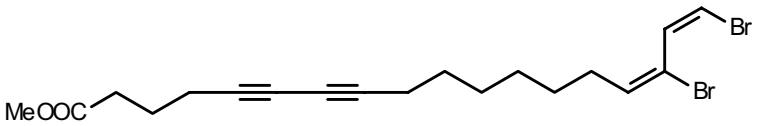
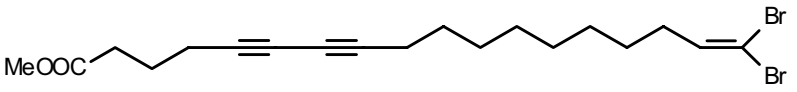


130



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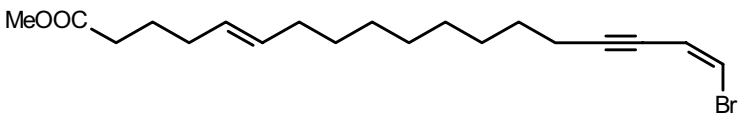

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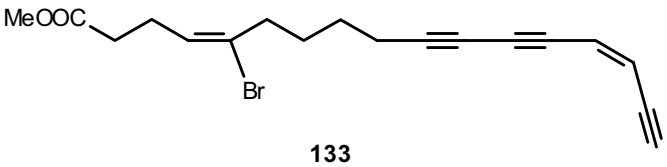

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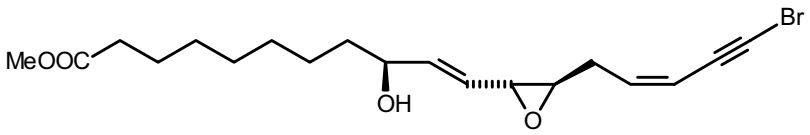

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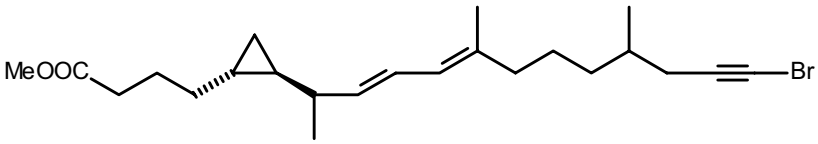

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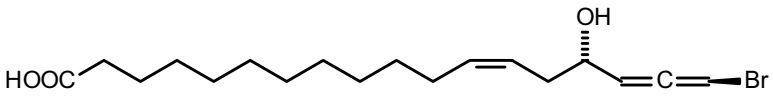

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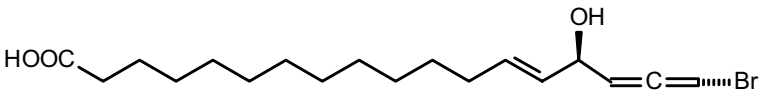

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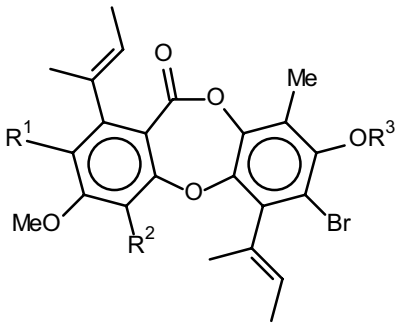
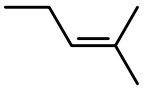
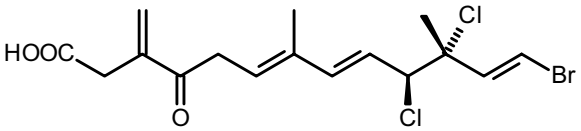


138a,b

	R^1	R^2	R^3
138a	H	Me	H
138b	Br	CHO	



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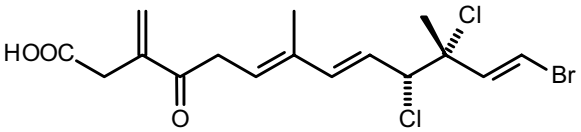

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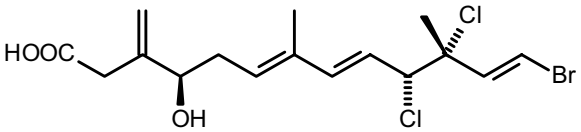
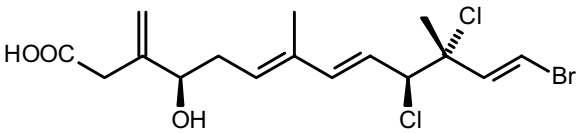
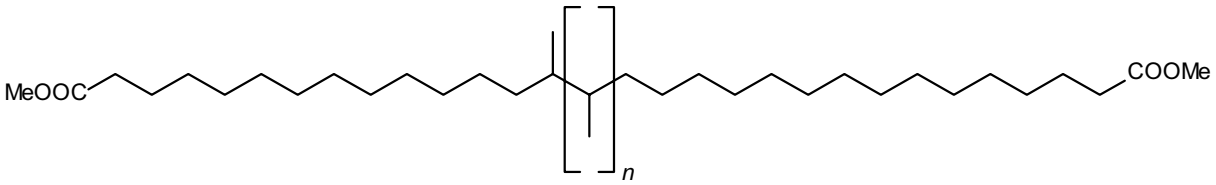


141

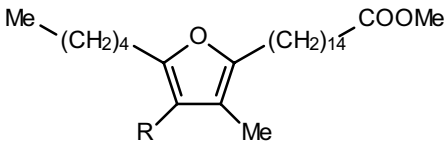


142



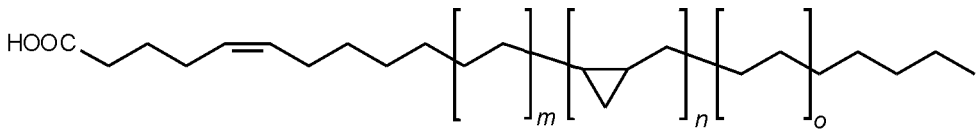
143a,b

	n
143a	1
143b	0



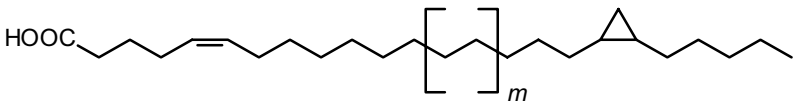
144a,b

	R
144a	H
144b	Me



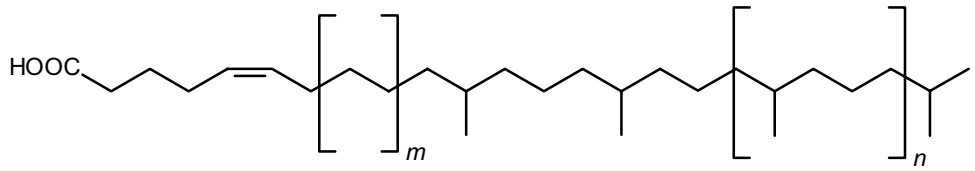
145a–f

	m	*n*	*o*
145a	0	2	0
145b	1	2	0
145c	2	2	0
145d	0	1	1
145e	1	1	1
145f	2	1	1



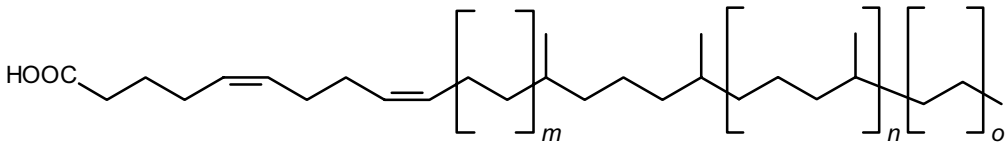
145g,h

	m
145g	0
145h	1



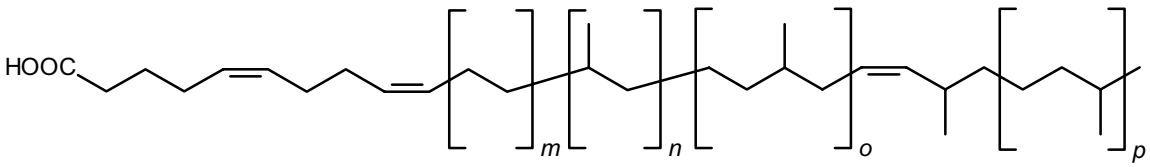
146a–f

	m	*n*
146a	0	0
146b	0	1
146c	1	0
146d	2	0
146e	1	1
146f	2	1



146g–j

	m	*n*	*o*
146g	0	1	0
146h	0	2	0
146i	1	0	1
146j	1	2	0



146k–n

	m	*n*	*o*	*p*
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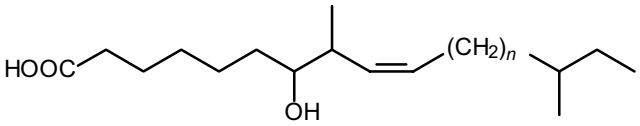
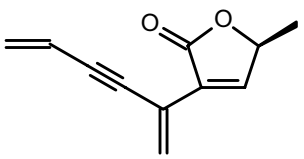
146l	0	0	2	0
146m	1	0	1	1
146n	0	1	1	1

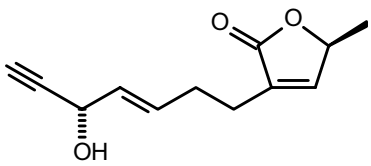


147a–d

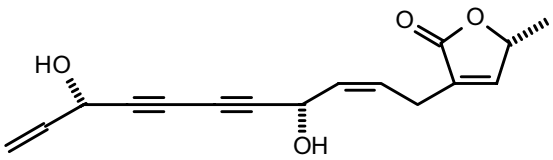
	n
147a	3
147b	5
147c	7
147d	9



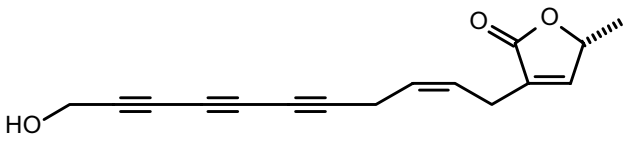
148



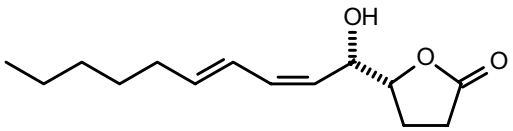
149



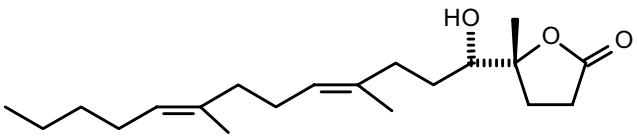
150



151



152



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6 FUTURE PERSPECTIVES

More than 10 000 antibiotics and similar biologically active compounds from microorganisms, plants and other producers have so far been described and more than 100 000 semisynthetic and synthetic derivatives have been derived from the basic natural structures. Thousands of natural compounds exhibiting biological activity are described every year; however, only a very small proportion is practically used, mainly due to their low efficacy and sometimes even toxicity and, last but not least, to their laborious and costly commercial production.

At first glance the search for new biologically active compounds does not seem to have brought anything new, at least in recent years. It is now relatively commonly accepted that only new derivatives rather than entirely new groups of compounds have recently been isolated and that thus the research aimed at isolating practically applicable natural compounds will hardly be successful.

However, the pharmaceutical industry needs new compounds to treat cancer, autoimmune, cardiovascular and other diseases. Infectious diseases that represent a serious medical problem include viral agents such as HIV, Ebola, West Nile, *etc.*, and bacterial infections caused mainly by antibiotic resistant bacteria and new resistant strains of the malaria causative agent *Plasmodium falciparum* and *P. malariae*. The clinical need for new classes of antibiotics and other biologically active compounds continues to grow, driven by drug resistance which erodes the efficacy of current therapies. What future can then be expected in the search for new biologically active compounds, or, even better, of new classes of biologically active compounds? The authors of this review assume that the future research will be highly accelerated both by the adoption of sophisticated analytical techniques such as mass spectrometry and nuclear magnetic resonance which enable the identification of new compounds in terms of days rather than months and years, and by automated screening procedures. Both have been successfully used by academia and pharmaceutical companies and are rapidly further developing.

In addition, more imaginative strategies will be used. One of those is apparently genomics whose advent has provided information necessary to extend our knowledge into areas of microbial physiology and to build the tools that will facilitate investigation (Allsop and Illingworth 2002). Genomics aims at deciphering the complete genetic basis (genome) of the most varied organisms. Due to the extremely rapid development of DNA sequencing techniques the human genome structure was completed much sooner than originally expected (Collins *et al*. 2001; Venter *et al*. 2001). Currently, there are over 70 bacterial strains, about 16 species of *Archaea* and 13 eukaryotic species including man for which complete sequence data are available, and in excess of 50 ongoing sequencing projects, many of them in microbial pathogens, for which data are available to help determine target conservation across species of importance. Comparison of both the human and pathogen genomes has a great impact on our ability to determine whether targets are likely to be selective for bacteria over the human host.

The genome structure of *Streptomyces coelicolor*, a model representative of actinomycetes, the most efficient group of microbial antibiotic producers, has also been completed (Bentley *et al.* 2002). This will certainly lead to the discovery of new metabolic pathways and consequently to new groups of biologically active secondary metabolites. The sequence of a small-to-medium genome can be established in terms of months rather than years as previously. The acquired knowledge of the genomes of various organisms has already been applied to several areas:

(*1*) gene therapy;
(*2*) search for new targets for new biologically active compounds including antibiotics, anticancer drugs, industrial catalysts and other types of interesting products;
(*3*) knowledge of genomic structures indicates that many new metabolic pathways exist in microorganisms that can either be used as new targets for therapeutics or for isolation of new drugs.

It should be kept in mind that not all genes are expressed under a single set of conditions. The genomic data provide an insight into the genetic apparatus of organisms but may not always necessarily bring information on the regulation of gene expression. Proteomics using two-dimensional electrophoresis with a subsequent automated evaluation and sophisticated software has already yielded information on what proteins are synthesized under different outer and inner conditions and will certainly help to find conditions for overproduction of selected proteins and biologically active metabolites. Proteomic data should facilitate:

(*1*) overproduction of therapeutically important proteins including recombinant proteins in heterologous hosts;
(*2*) overproduction of therapeutically interesting low-molar-mass compounds;
(*3*) comparison of the proteome of healthy individuals with that of the patients in the search for new compounds and therapeutical procedures.

Combinatorial chemistry will apparently play an immense role in the search for new biologically active compounds in the future. It is hoped that the time required for organic synthesis and "organic chemistry *in silico*" will be substantially reduced. An extensive screening of new compounds will thus be possible even without their previous synthesis.

Biosynthesis of a number of biologically active compounds is catalyzed by modular enzymes. Such compounds include some important antibiotics such as erythromycin, avermectins, *etc.* By means of genetic manipulation it is possible to change individual modules and replace them with modules of biosynthetic enzymes from other producers and thus produce immense numbers of new compounds that can exhibit new biological activities or be endowed with other advantageous features such as decreased or no toxicity, higher stability, better pharmacological properties, higher water solubility, *etc.* (Hutchinson 1994, 1997). Together with combinatorial chemistry this approach can substantially contribute to the search for new compounds for

the treatment of cancer, metabolic and autoimmune diseases, as well as to the treatment of infectious diseases caused by resistant bacteria and some viruses.

The search for new biologically active natural compounds has been traditional in the *Institute of Microbiology of the Academy Sciences of the Czech Republic*. Some of the compounds isolated and described below reflect that tradition. The authors hope sincerely that those modern methods of isolation and structure elucidation, as well as the use of highly imaginative new strategies also available at this Institute will help to discover many new compounds to be described in the near future.

This work was supported by the *Grant Agency of the Czech Republic* (grant no. 204/01/1004) and by the *Institutional Research Concept* no. AV 0Z 5020 903. The authors express their appreciation to Miss J. Jáchymová for drawing a great numbers of chemical formulas. We are also indebted to Mr. P. Řezanka (student of *Institute of Chemical Technology* and *Faculty of Science at Charles University*, Prague) for technical assistance.

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