SUPERCYTOSTATICS AND SUPERCYTOTOXINS

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Natural compounds are considered which in concentrations of $5 \cdot 10^{-8}$ M inhibit the proliferation of culturable malignant mammalian cells. It is proposed to call them supercytostatics and supercytotoxins. Their cytotoxic activities are based on various biochemical mechanisms. Among the supercytostatics there are mitotic poisons, inhibitors of protein and nucleic acid synthesis, and membrane and cytoplasmic enzymes. However, in many cases there are grounds for assuming that the critical cell targets do not coincide with the observed biochemical effects of the supercytostatics. In spite of their diverse chemical structures, the majority of substances contain similar structural fragments which may be complementary to unknown receptors participating in the regulation of cell proliferation.

The action of a large number of natural and synthetic substances on culturable tumor cells of mammals has been tested. As a quantitative characteristic the magnitude ED_{50} — a number expressing the concentration of a chemical compound in the culture medium at which the rate of proliferation of the cells is halved — has been used. On analyzing the available information, it is possible to single out a range of substances distinguished by a very powerful action on proliferating cells. It is desirable to call them supercytostatics or supercytotoxins, denoting by these terms preparations with biological activities equal to or exceeding those of the widely known cytostatics colchicine and vinblastine. On this definition, substances with $ED_{50} < 5 \cdot 10^{-8}$ or $8 \cdot 10^{-3}$ μg/ml will be assigned to the group under consideration.

It is important to concentrate attention on these compounds for two reasons. In the first place, among them the probability of finding biologically active substances of practical use is high. In the second place, the supercytostatics interact with very important cell regulatory systems the study of which is one of the most important current problems of biochemistry and molecular biology.

CHEMICAL STRUCTURE

The chemical structure of the known low-molecular-weight supercytostatics are given in Table 1. This also includes information on the cytotoxic properties of some protein compounds. As we can see from this list, all the supercytostatics belong to substances isolated from living nature. Not one of the many thousands of synthetic compounds tested has shown such a high biological activity as natural cell poisons. At the same time, among the supercytostatics no tendency to some particular section of chemical classification is observed. They can be found among the alkaloids, the terpenoids, steroids, lignans, peptides, etc., and different structures are also observed among these classes.

BIOCHEMICAL ACTION MECHANISMS

The inclusion of substances in the group of supercytostatics is done by a formal characteristic. It may therefore be expected that they should possess very diverse mechanisms of their biochemical action on the cell. In actual fact, this diversity is not so great. Furthermore, in many cases there are grounds for doubting whether observed biochemical effects act as the primary cause of the high cytotoxic activity.

Many supercytostatics possess the capacity for interacting noncovalently with the protein tubulin. This protein — an invariable ingredient of eucaryotic cells — plays a number of cytoplasmic functions. It participates in the formation of the spindle and the divergence

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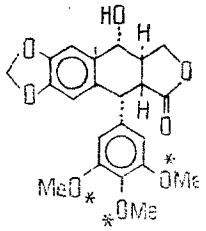
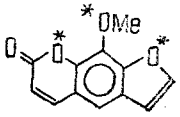
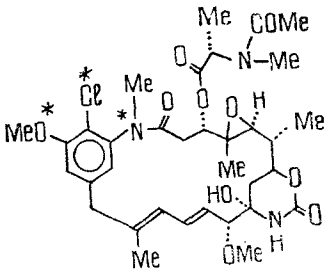
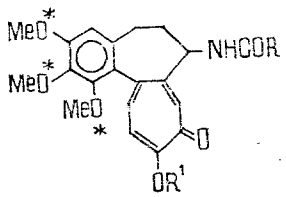
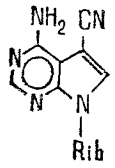
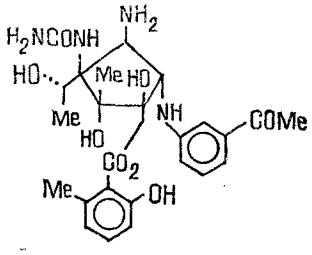
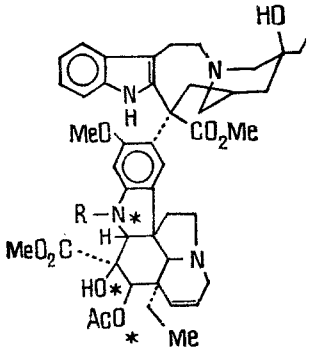
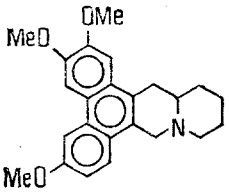
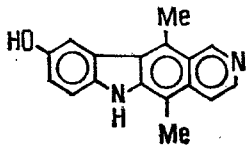
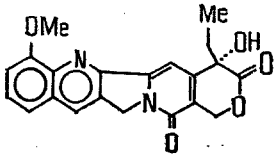
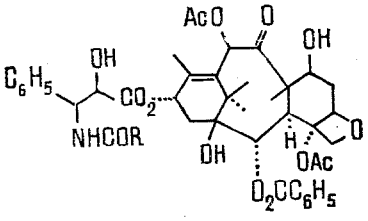
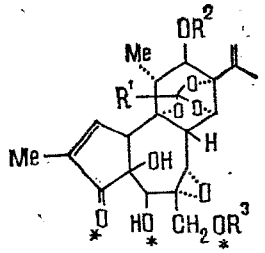
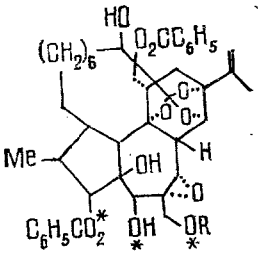
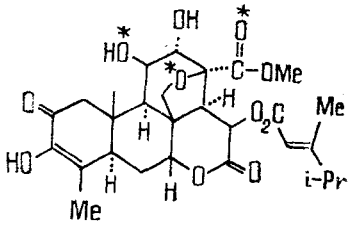
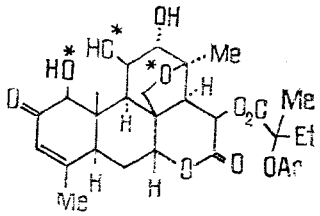
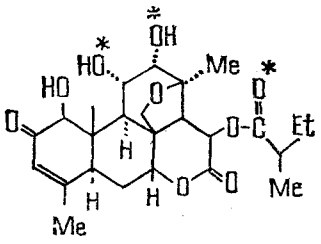
TABLE 1. Supercytostatics and Supercytotoxins

Name	Chemical structure	Cells	ED_{50}, μg/ml (M)	Literature
I. Podophyllotoxin		P 815	$5 \cdot 10^{-3}$ ($1.3 \cdot 10^{-8}$)	1 2
II. 8-Methoxypsoralen		Human lymphocytes	(10^{-10})	3
III. Maytansine and maytansinoids		KB	$10^{-5}-10^{-6}$ ($10^{-10}-10^{-11}$)	5,6
IV. Colchicine, R = R^1 = Me; N-(trifluoroacetyl)methylthio-IV, R = CF_3, R^1 = SMe.		L1210	($2.5 \cdot 10^{-8}$) ($2 \cdot 10^{-9}$)	7,8 8
V. Toyocamycin		L1210	($4 \cdot 10^{-8}$)	9
VI. Pactamycin		KB	$3 \cdot 10^{-3}$	4

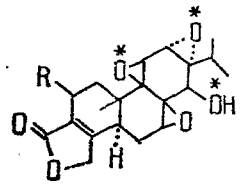
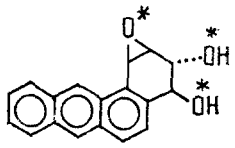
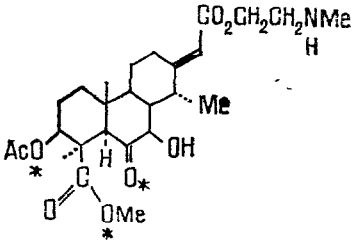
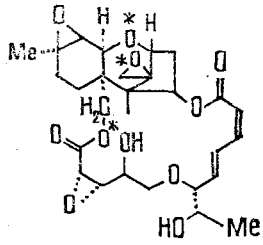
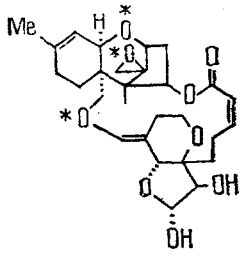
Continuation of Table 1

Name	Chemical structure	Cells	ED_{50}, μg/ml (M)	Literature
VII. Vinblastine, R = CH_3 –; vincristine, R = CHO —		P815	$8 \cdot 10^{-3}$ (10^{-8})	10
VIII. Cryptopleurine		KB	10^{-5}	11
IX. 9-Hydroxyellipticine		L1210	$3{,}9 \cdot 10^{-3}$	122
X. 9-Methoxycamptothecin		P388	$3{,}6 \cdot 10^{-3}$	13
XI. Taxol, R = C_6H_5—; cephalomannine, R = MeCH=CH(Me)–		KB	$5{,}5 \cdot 10^{-5}$ $3{,}8 \cdot 10^{-3}$	14 123

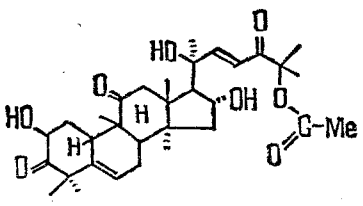
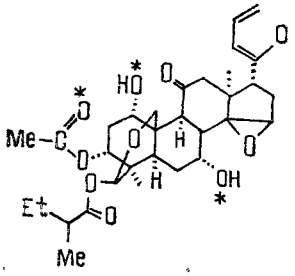
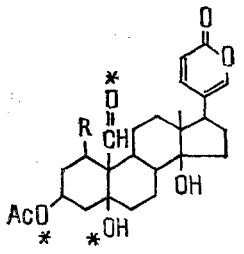
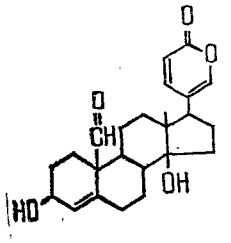
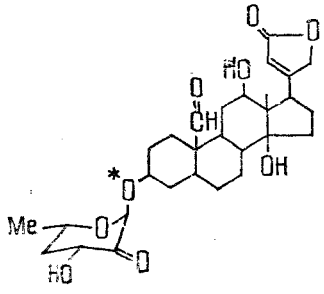
Continuation of Table 1

Name	Chemical structure	Cells	ED_{50}, μg/ml (M)	Literature
XII. Analogs of daphnetoxin: mezerein, gnidinin, gnidicin, gniditrin, etc.	 R^1 = phenyl, alkyenyl; R^2 = alkenoxyl; R^3 = H, acyl	KB	10^{-3}	15—18
XIII. Gnidimacrin, R = H–; palmitate of XIII, R = $C_{15}H_{31}CO$–		KB	10^{-3}	19
XIV. Bruceantin		KB	10^{-3}	20
XV. Quassimarin		KB	10^{-3}	21
XVI. Ailanthinone		KB	10^{-3}	22

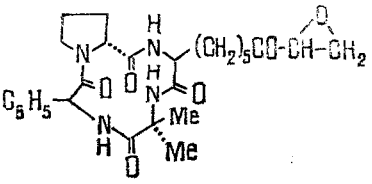
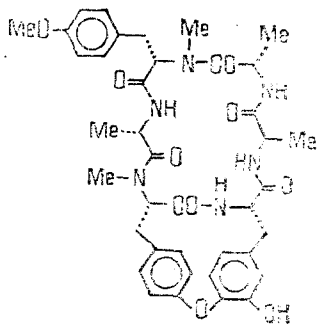
Continuation of Table 1

Name	Chemical structure	Cells	ED_{50}, μg/ml (M)	Literature
XVII. Triptolide, R = H⁻; triptodiolide, R = OH⁻		KB	10^{-3} —10^{-4}	23
XVIII. 3,4-Dihydroxy-1,2-epoxybenzanthracene*		V-79	$(1,2 \cdot 10^{-9})$	12
XIX. 3β-Acetoxynorerythrosuamine		KB	$3 \cdot 10^{-4}$	24
XX. Baccharin		KB	10^{-3} —10^{-4}	25
XXI. Vertisporin		HeLa	$1 \cdot 10^{-3}$	26

Continuation of Table 1

Name	Chemical structure	Cells	ED_{50}, μg/ml (M)	Literature
XXII. Cucurbitacin B		KB	$5 \cdot 10^{-3}$	27
XXIII. Amurastatin		P 388	$1 \cdot 10^{-3}$	28
XXIV. Hellibrigenin 3-acetate, R = H; bersaldegenin acetate, R = OH		KB KB	$2{,}4 \cdot 10^{-7}$ $3{,}6 \cdot 10^{-5}$	29 30
XXV. Scillaglaucosidin		KB	$2 \cdot 10^{-3}$	31
XXVI. Calotropin		KB	$3{,}7 \cdot 10^{-3}$	32

Continuation of Table 1

Name	Chemical structure	Cells	ED_{50}, μg/ml (M)	Literature
XXVII. Chlamydocin		P 815	$10^{-6,4}$	33
XXVIII. Bouvardin, R = OH–; deoxybouvardin, R= H–		KB	$4,3 \cdot 10^{-7}$	34
		KB	$1,9 \cdot 10^{-8}$	34
XXIX. Neocarzinostatin	For primary structure, see [35]	HeLa	$2 \cdot 10^{-2}$ (10^{-9})	36
XXX. Cesalin		KB	$9 \cdot 10^{-7}$	37
XXXI. Ricin	[38–40]	BW.5147	$5 \cdot 10^{-3}$ (10^{-9})†	41 42
XXXII. Macromomycin				
XXXIII. Modeccin			$2 \cdot 10^{-7}$†	43
XXXIV. Diphtheria toxin			$3 \cdot 10^{-4}$†	43

*Metabolite of benzanthracene.
†Concentration inhibiting the formation of colonies by 84%.

of the chromosomes in the metaphase of mitosis [44] and in the organization of the cytoplasm and of the membrane receptors [45]. Its molecule consists of two nonidentical subunits, α and β, and it is soluble in the cytoplasm. In the presence of specific protein factors and GTP, the dimeric molecules of tubulin polymerize into microtubes. On both subunits of the protein there are receptor sections with which the supercytostatics interact, after which the tubulin loses its capacity for polymerization. Since microtubes exist in dynamic equilibrium with the dimers, there is not only a prevention of the formation of new ones but also the dissolution of the polymeric structures that have already been formed, including the mitotic spindle. Consequently, such substances have acquired the name of mitotic poisons. Of the compounds under consideration here, the maytansinoids (III), podophyllotoxin (I), vinblastine and vincristine (VII), and colchicine (IV), and their analogs belong to this group.

The antimitotic action of colchicine has been studied in the greatest detail [46]. The receptor of this alkaloid, one to a dimer, is located in a hydrophobic pocket of the molecule. Binding is noncovalent, although the complex dissociates very slowly. Lignan I and some of its analogs displace colchicine in competition for the receptors. At the same time, the podophyllotoxin-tubulin complex dissociates more readily than the colchicine complex. The receptors of these two substances are largely similar but not identical. They probably represent overlapping sections of the protein molecule [47-49].

For the alkaloids of *Vinca rosea* (VII) there are two types of receptors. At low concentrations of vinblastine, two molecules of the alkaloid interact with each molecule of tubulin. The capacity for polymerization is then lost and disintegration of the microtubes takes place. At higher concentrations of (VII), receptors with a lower affinity are also saturated, which causes the formation of crystal-like tubulin aggregates. Colchicine does not displace vinblastine in experiments on competitive binding. At the same time, the addition of the latter stabilizes the colchicine-tubulin complex, which shows the existence of a definite link between the receptors of these two substances. Both (IV) and (VII) interact only with tubulin dimers, and not with intact microtubes. It may be concluded from this that both receptors participate directly in the polymerization of the protein [47, 50, 51].

In the mechanism of its action on mitosis, the strong cytostatic maytansine (III) is similar to vinblastine and vincristine. The available information indicates an identity of the receptors of these substances, although in the case of (III), saturation of the low-affinity receptors does not cause aggregation of the protein [52-56].

Taxol (XI) also interferes with mitosis, but its action is accompanied by a stabilization of the microtubules and increases their resistance to depolymerizing effects [57, 58].

Some supercytostatics attack nucleic acids and inhibit the processes of their biosynthesis. In the presence of glutathione or of mercaptoethanol, the protein neocarzinostatin (XXIX) causes the cleavage of DNA at linker sites and its degradation to small double-stranded fragments [59, 60]. A low-molecular-weight cofactor without which the protein does not exhibit biological activity is present in the molecule of (XXIX) [36, 61]. The protein antibiotic macromomycin (XXXII) is similar to (XXIX) in the mechanism of its action on DNA and in its structure [62].

8-Methoxypsoralen (II) and many other coumarins [3] possess a disrupting action on DNA and chromatin structures, as does the alkaloid camptothecin [63], the supercytotoxic analog of which, (X), probably acts in the same way.

The nucleoside antibiotic toyocamycin (V) destroys cells, acting by the mechanism of lethal synthesis. *In vivo*, (V) and a number of antimetabolites similar to it are phosphorylated to triphosphates and are included in the composition of the DNA, making it incapable of normal functioning [65-67]. Cucurbitacin B (XXII) and other curcurbitacins inhibit the synthesis of DNA by an unknown mechanism [68].

Another fundamental biochemical process — the biosynthesis of protein — is also subject to the action of the supercytostatics. The molecule of ricin (XXXI) consists of two subunits, A and B, linked by a disulfide bond. Subunit B is responsible for the adsorption of protein on galactose-containing receptors of the cell surface. Then the molecules of (XXXI) diffuse in the lateral plane and are collected into a limited number of aggregates undergoing endocytosis. In the cytoplasm, an interaction of the A-chain with the 60S ribosomal subunit takes place, as a consequence of which the capacity for forming functionally active ribosomes is lost and the synthesis of new peptide chains ceases [40, 69-71]. Cytotoxins (XXXIII) and (XXXIV) are also powerful inhibitors of the new formation of proteins. The mechanism of the inhibiting action of modeccin [43] has not been established. One of the two subunits of diphtheria toxin exhibits an enzymatic activity, transferring an ADP-ribose residue from NAD^+ to elongation factor EF-2. After this, the factor loses its functional activity [72].

The properties of a peptide synthesis inhibitor have been detected in bouvardin (XXVIII) [73]. Baccharin and vertisporin (XX and XXI) also probably suppress the functioning of the protein-synthesizing apparatus. The mechanism of the action of these substances has not been studied. However, they belong to a group of chemically related mycotoxins forming derivatives of epoxytrichothecene, which, on entering the cytoplasm, interact with the peptidyl transferase centers of the ribosomes and interfere with the elongation or initiation of the synthesis of the peptide chain [74, 75]. Pactamycin (VI) [83] and bruceantin (XIV) inhibit initiation by a different mechanism [76, 77]. The alkaloid cryptopleurine (VIII) binds with the 40S subunit of the eucaryotic ribosome and prevents translocation — a cooperative function of both subunits. This effect is reversed by GTP, by factor EF-2, and by ribosomal GTPase [78, 84].

The targets of the action of a number of supercytostatics are enzymes. Steroidal bufadienolides and cardenolides (XXIV-XXVI) are known as inhibitors of membrane Na,K-ATPase [79, 80]. The diterpenene alkaloid (XIX) is probably endowed with the same property. The

mechanism of the action of this substance has not been investigated but its analog cassaine is well known as an inhibitor of this enzyme [80, 81]. The protein cesalin (XXX) strongly inhibits the activity of Na,K-ATPase. Its simultaneously exhibits two other, independent, effects: It inhibits the synthesis of DNA and mitosis [37]. In so doing, (XXX) does not penetrate into the cytoplasm.

Triptolide (XVII) is a representation of a large group of alkylating terpenoids containing acceptor Michael functions and epoxide rings which react with the SH groups of enzymes [82]. The key enzymes of glycolysis, DNA polymerase, the proteins of chromatin, and of membranes, etc., may be the targets of their action [85, 86]. A similar activity is also characteristic of quassinoids and simaroubolides [64], of which bruceantin (XIV) has been mentioned above as an inhibitor of protein synthesis.

A widespread opinion exists that the object of the action of the majority of cell poisons is DNA. Of course, in many cases this is actually so. However, for the supercytostatics the functioning of the nucleic acids is not the most sensitive target in the cell. In actual fact, only (V), (IX), (XXIX), and (XXXII) act directly on the intracellular polynucleotides. At the same time there is information according to which other, possible more vulnerable links of the cell organization exist for the last two. Neocarzinostatin (XXIX) interacts with the proteins of the microtubules [124] and changes the structure of the cytoskeleton [88], and both proteins may exert a cytotoxic action without penetrating through the membranes [59, 87], when contact with the cell DNA is excluded.

It is also doubtful whether the biosynthesis of protein is the critical link for the protein-synthesis inhibitors considered above. For example, (VIII) inhibits translocation *in vitro* in a concentration of 10^{-5}-10^{-6} M, while its cytotoxic concentration is 3-4 orders of magnitude lower [11, 78]. It has been found that some trichothecene toxins, analogs of (XX) and (XXI), exhibit a colchicine-like action [125]. The many-sided biochemical activity of bruceantin (XIV) has already been mentioned.

On the surface of a cell there are glycoprotein receptors the topography of which determines their proliferative potential. The diffuse arrangement of the receptors is associated with a state of rest, and their aggregation with mitotic activity. Normal cells in the phase of mitosis are analogous, in relation to the structure of the cell surface, to malignant cells [89, 90]. In its turn, the localization of the membrane receptors is controlled by cytoplasmic structures — microtubules and active microfilaments. These fibrous structures form a cytoplasmic tubulin-actin chain — a cytoskeleton. Its structure, well expressed in normal cells, simplifies on malignization [89, 90-93]. The organization of the tubulin component of the cytoskeleton is under the control of microtubule-organizing centers (MTOCs) — limited sections of cytoplasm fulfilling the function of tubulin polymerization initiators. The nature of the MTOCs is unknown. Geometrically, they are connected with the cell center, the pericentriolar material, and the mitotic poles [94-97]. Their functional state changes in the course of cell cycle. Only the MTOCs from mitotic cells are capable of initiating the formation of the spindle [97-99].

The cytoskeleton is also in contact with the nuclear membrane and regulates the position of the nucleus in the cytoplasm [95, 99]. It is assumed [100-102] that the tubulin-actin network participates in the mediation of the transfer of hormonal and other proliferative stimuli from the surface of the cell to the nucleus. In other words, the synthesis of DNA and the mitotic activity of the cell are under the control of the cytoplasmic structures. Exogenous actions on the cytoskeleton and the surface receptors connected with it may lead to uncontrollable growth, to the stimulation of biochemical mechanisms, or to the death of the cell [103-105].

A fairly large amount of information exists according to which the critical target of the supercytotoxic mitotic poisons is not the spindle of mitosis but the tubulin components of the cytoskeleton. For example, the greatest sensitivity to vincristine (VII) is observed in the S phase of the cell cycle and is connected with the disturbance in the functioning of the centrioles and mitotic poles [106-108].

The actin component of the cytoskeleton also undergoes structural changes on transformation [109]. For the subject of the present paper, it is interesting to observe [110] that the tumor promotor 12-O-tetradecanoylphorbol 13-acetate in a concentration of $7.3 \cdot 10^{-10}$ M changes the organization of the cytoskeleton actin in a mediated manner. The daphnetoxins (XII-XIV) are chemically related to this diterpenoid.

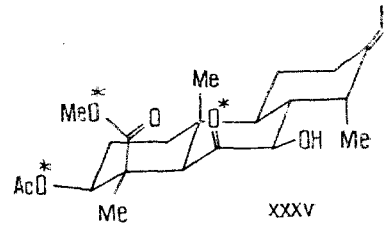
Thus, it can be stated with different degrees of confidence that the critical biochemical targets for the majority of supercytostatics are components of the cytoskeleton and of structures connected with them: the surface receptors for the Na,K-ATPase inhibitors (XIV, XXIV-XXVI) and for the proteins (XXIX, XXX, XXXII, XXXIII), the tubulin structures and MTOCs for mitotic poisons and taxol, and the actin microfilaments for the diterpenoids (XII and XIII).

COMMON STRUCTURAL FEATURES

From the point of view of the existence of a limited number of receptors for supercytostatics, particular interest is presented by the presence of common structural fragments in their molecules. These include three p-electronic heteroatoms arranged identically in space, and an α-dicarbonyl or an α-hydroxycarbonyl or pyrocatechol fragment. (The first grouping is denoted by asterisks attached to the formulas in Table 1.) It is frequently represented by an aromatic nucleus with three vicinal atoms bearing free electron pairs (O, N, Cl). In other cases, this fragment is not obvious in a planar illustration of the structure, but the necessary geometric relationships exist in stable conformations, as has been shown for the cases of (XXXV-XXXVIII).

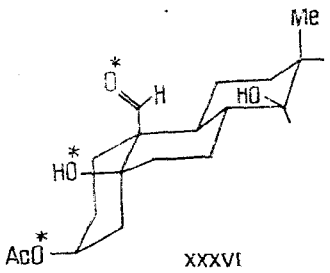
A multitude of other biologically active compounds include a three-oxygen fragment in their molecules. Its various carriers are capable of interacting with tubulin [44, 111].

Another very obvious feature of the chemical structures of the supercytostatics is the presence of α-dicarbonyl, α-hydrocarbonyl, or pyrocatechol fragments. The last two groupings can be converted into the first as the result of metabolic reactions. In some cases, the carbonyl function is masked. For example, in maytansine (III) it is present in the form of a carbinolamide.



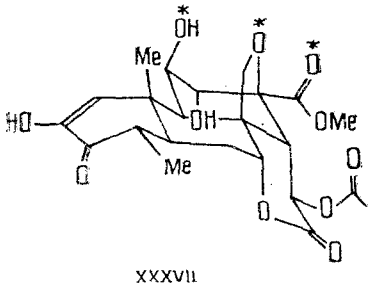
XXXV

3-β – Acetoxynorerythrosuamine



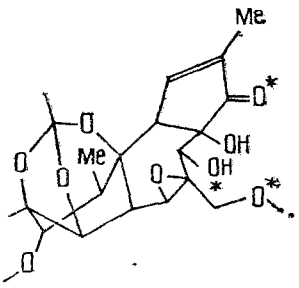
XXXVI

Hellebrigenin 3-acetate



XXXVII

Bruceantin [112]



XXXVIII

Daphnetoxin analogs [113]

The conclusion suggests itself of the existence of a link between this fragment of the supercytotoxic molecules and Szent-Györgyi's concept of the role of bicarbonyl functions in the processes of regulation of cell division [114]. According to this author, in the course of evolution living matter acquired the capacity for controlling the proliferative activity thanks to an increase in the reactivity of proteins as the result of their passage into the free-radical state. The acceptance of an electron necessary for this is achieved by the formation of charge-transfer complexes with the participation of methylglyoxal or other dicarbonyl compounds. In such a state, the protein acquires the reactivity that is necessary for the response to regulating signals. The absence of protein charge-transfer complexes is associated with unorganized proliferation. If this hypothesis is correct and

α-dicarbonyl regulators of mitotic activity exist, then supercytostatics with vicinal oxygen functional groups may act as antimetabolites to them.

The daphnetoxin analogs (XII-XIV) contain an orthoester grouping, which is rarely found among natural compounds. Whether this is significant for the cytotoxic properties of the substances is unknown. It is interesting to note that orthoacid fragments are also present in other highly active substances, such as the nerve poisons tetrodotoxin [115], 2,6,7-trioxabicyclo[2.2.2]octane [116], and the orthosomycin antibiotics [117].

In addition to the structural features mentioned, the molecules of the supercytostatics may contain other fragments important for biological activity the role of which is more or less clear. In many cases, they are provided with alkylating functions, i.e., functional groups capable of reacting with biological nucleophilic targets with the formation of covalent chemical bonds. The main alkylating functional groups are epoxide and α,β-unsaturated carbonyl groups. Their reactivities are frequently raised as the result of the effect of anchimeric cooperation. At the same time, an intramolecular hydrogen bond plays the role of a factor repelling electrons and increasing the electrophilicity of the reaction center [22, 118, 119].

The molecules of some supercytostatics and supercytotoxins are provided with ester groupings the removal of which by hydrolysis causes a marked, by 2-5 orders of magnitude, fall in their cytotoxic properties. This phenomenon has been observed for taxol [14], quassinoids, and simaroubolides [20, 76, 120], maytansinoids [5, 21], and daphnetoxin analogs [16-18]. The chemical structure of the acyl moiety of the ester is of value for the quassinoids [120], but is quite unimportant for the maytansine analogs [121]. To it is ascribed the role of "carrier," facilitating the penetration of the substance through the cell membranes. In actual fact, after saponification, bruceantin (XV) loses its capacity for inhibiting protein synthesis in intact reticulocytes, but the molecule deprived of the ester grouping is active in lysates [76].

The natural substances called here supercytostatics and supercytotoxins are toxic for dividing eucaryotic cells in very low concentrations. The mechanisms of their action have been studied inadequately, but it can be stated that in the majority of cases the biochemical targets that are attacked are localized at the boundaries of the cell nucleus.

The importance of the further study of supercytostatics consists in the fact that their receptors may play a key role in yet undiscovered mechanisms of membrane and cytoplasmic actions on the functioning of the genome. The elucidation of these mechanisms will open up new prospects in chemotherapy, pharmacology, and other sciences studying the control of the processes of vital activity.

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SYNTHESIS OF SOME L-IDOSE DERIVATIVES

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UDC 547.917

The synthesis of 3-O-benzyl- and 3-O-mesyl-1,2-O-isopropylidene-β'-L-iodofuranose has been effected on the basis of the intramolecular nucleophilic exchange of a mesyloxy group at C_5 in derivatives of 1,2-O-isopropylidene-α-D-glucofuranose. It has been found that in a system of vicinal primary and secondary mesyloxy groups a selective replacement of the primary mesyloxy group by an acetyl group is possible. It has been shown in benzyl and mesyl ethers of 5,6-anhydro-1,2-O - isopropylidene-β-L-idofuranose the opening of the oxide ring under conditions of acid hydrolysis with the retention of the isopropylidene group is possible.

In the course of work on the synthesis of methyl ethers of monosaccharides, we have come up against the necessity of obtaining the difficulty accessible L-idose. We propose a new variant of the synthesis of some of its derivatives starting from D-glucose.

A number of methods of passing from the D-gluco- to the L-ido-configuration of sugars based on the nucleophilic replacement of C_5-O-sulfonic esters of the corresponding derivatives of 1,2-isopropylidene-α-D-glucofuranose with the isolation of 5-O-acyl- or 5,6-anhydro-derivatives of L-idose have been described in the literature. Potassium acetate in acetic anhydride [1, 2] and sodium benzoate in dimethyl formamide [3] have been proposed as nucleophilic agents for bimolecular substitution with the inversion of the configuration at C_5.

In recent years, in place of potassium acetate, an anion-exchange resin in the acetate form has been used [4, 5], which considerably increases the yield of L-idose derivatives. The synthesis of 5,6-anhydro derivatives of L-idose is based on intramolecular nucleophilic substitution on the treatment of the sulfonic esters having the D-gluco-configuration with

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