Natural Halogenated Polyacetylenides

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Abstract

The review is dedicated to a group of natural compounds of a new type – halogenated polyacetylenides. These compounds are synthesized mainly by plants and by some sea organisms. Structures of 71 compounds are considered. Data on the biological activity of some of their representatives are discussed.

Contents

INTRODUCTION

Natural polyacetylene compounds containing two and more triple bonds are rather widespread in nature. More than 1000 compounds isolated from plants, fungi, lichens and sea invertebrates have been described [1–3]. Over 70 % of polyacetylene compounds have been isolated from plants of Apiacea, Araliaceae, Asteraceae [4, 5], Anthemidae [6], Helianthеae [7], Astereae [8] and Cynareae [9] families. Polyacetylenides produced by these plants are aliphatic compounds with a C_{17} chain length. Plants of Apiacea family contain polyacetylenides with a chain length of C_{11} to C_{18} [4, 5]. Biosynthesis of polyacetylenides begins, as a rule, with oleic acid [10].

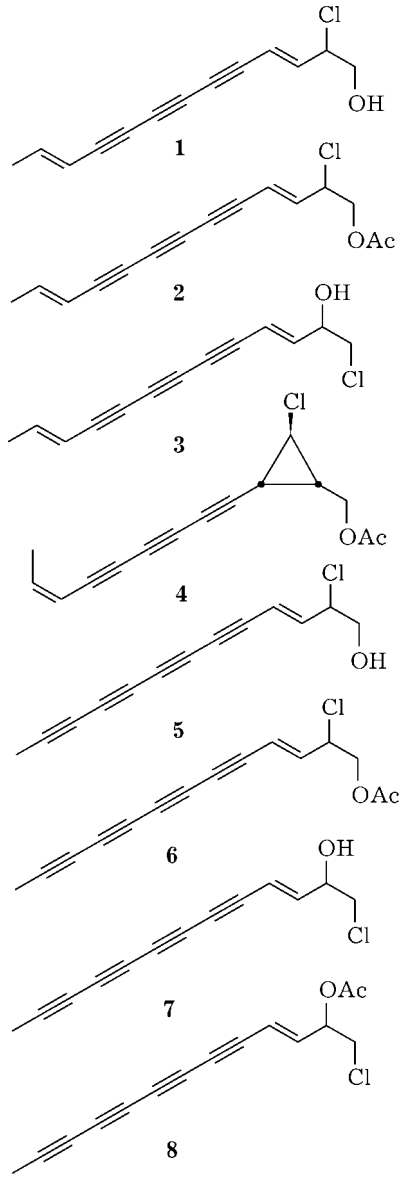
From a New Zealand plant *Aciphylla scott-thoumsonii* (Fam. Apiaceae), polyacetylenides with a chain length of C_{34} have been isolated [11]. Sea sponges can contain polyacetylenides as long as C_{46} [12].

Among acetylene compounds, thiophene derivatives are often found. Formation of the thiophene cycle can be imagined as a result of enzymatic thiylation of a diyne fragment contained in polyacetylenide molecules.

Halogenized polyacetylenides are a new, comparatively small group of natural compounds. Their producers are usually plants and

sea invertebrates. [13]. Up to recently, it was believed that chlorine was the only halogen participating in the formation of plant polyacetylenides. However, the studies of the last years have resulted in demonstrating that plants can produce bromine-containing acetylenides with structures similar to those of bromoacetylenides isolated from sea organisms. In the late 1980-ies, data appeared on cyclic diacetylene antibiotics of so-called endiyne type whose formation was associated with life activity of some bacteria. Among these wonderful compounds, very promising antitumor agents have been found.

Antifungal activity of aliphatic polyacetylene compounds has been found since very long. It is just this circumstance that has become the cause of the fact that natural polyacetylenides have served as a model for development of medicinal preparations used in the modern treatment of fungal diseases [14].



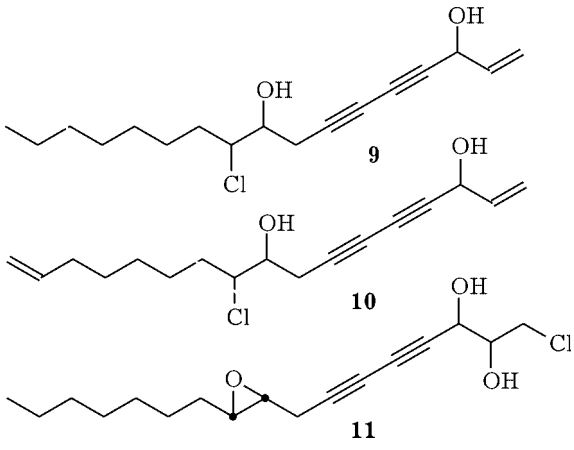
PLANT POLYACETYLENIDES

A comparatively small number of chlorine-containing polyacetylenides has been isolated from various plant species. So, metabolite (**1**) has been isolated from plants of Centaurea family (*C. alpina* [2], *C. ruthenica* [15], *C. scabiosa* [16], *C. tagana* [2]), Garthamus family (*C. coerules* [17], *C. glaucus* [2], *C. lanatus* [9], *C. tinctorius* [16]) and also from plants *Carduncellus coerulus* [2], *Dicoma zeyheri* [18] and *Dicoma argyrophylla* [19]. Acetylated metabolite (**2**) and compound (**3**) were isolated from plants *Centaurea alpina* [2], *C. rutenica* [4], *C. tagana* [2], *Carthamus coerules* [17], *C. lanatus* [9], *C. tinctorius* [17], *Dicoma argirophylla* [19] and *Coreopsis nodosa* [20].

It is considered that the cyclopropane compound (**4**) found only in the plant *Centaurea ruthenica* (Compositae) is a photolysis product of metabolite (**2**) [21]. The same plant contains polyacetylenides (**5**)–(**8**) [22, 23]. Metabolite (**5**) has been detected also in plants *Centaurea scabiosa* [16], *Carduncellus coerullus* [2] and *Carduncellus tinctorius* [17].

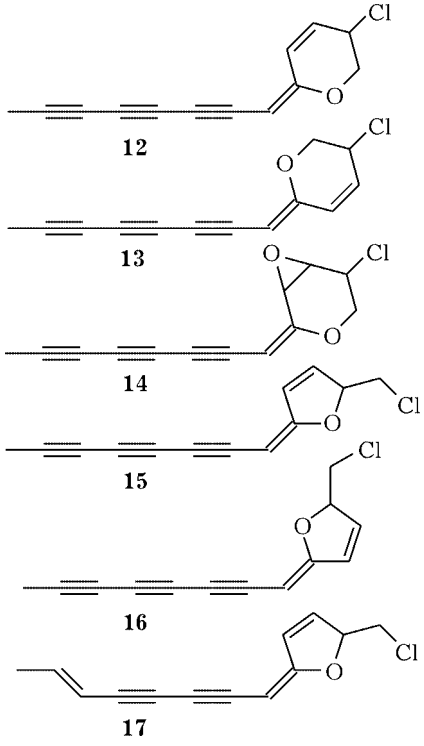
The famous ginseng (*Panax*) well-known for its unique properties contains, among other biologically active compounds, also chloropanaxydiol (**9**), panaxydol chlorohydrine (**10**) and ginsengoin B (**11**) [24, 25].

Dihydropyrane derivatives (**12**)–(**14**) have been isolated from plant *Anaphalis triplinervis* [26]. It is noteworthy that polyacetylenide (**12**) is contained in many plant species, such as *Anaphalis cinnamomea*, *A. yeodensis* [3], *A. margaritacea* [27], *Gnaphalium obstusifolium* [26], *G. sprengelii* [3] as well as in plants of *Helichrysum genus: H. allioides*, *H. arenarium*, *H. argenteum*, *H. argirophyllum*, *H. diosmaefolium*, *H. lanatum*, *H. nudiflolium*, *H. latifolium*, *H. serotium*, *H. stoechas*, *H. tianschanicum*, *H. petiolatum*, *H. paniculatum* and *H. odoratis-*

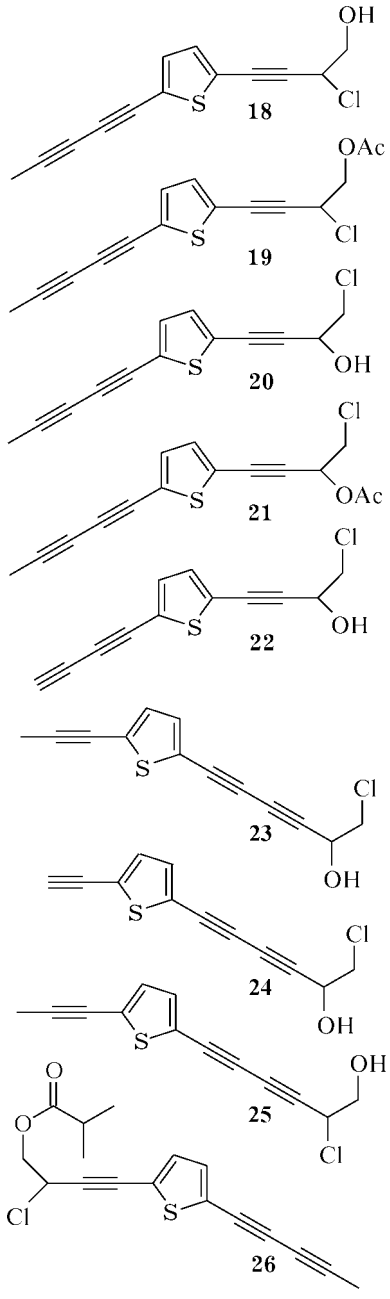


simum [3]. Epoxide (**14**) is presented in five of the above mentioned plants of Helichrysum genus and in *Gnaphalium sprengelii* [3]. Polyacetylenides (**15**) and (**17**) have been detected in extracts of a few plants. Thus, compounds (**15**) and (**17**) were isolated from *Achyrocline satureoides* [3], and (**15**) and (**16**) from *Gnaphalium obtusifolium* [26]. Brominated polyacetylenic acids are produced by lichens. The structures of these compounds are discussed in the review [28].

Chlorinated acetylenides with sulphur-containing heterocyclic fragments. The high reaction capacity of conjugated polyinic systems contributes to enzymatic thiylation reactions.

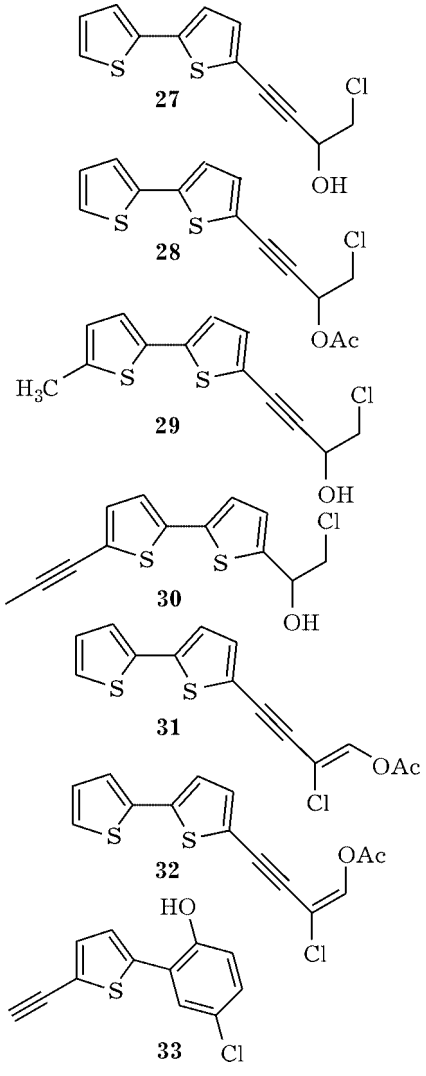


Depending on the conditions, compounds which contain one or two α-bound thiophene cycles can be formed. Isolation of about 20 chlorinated acetylenides of thiophene series has been described. The most widespread are triynic chlorohydrin (**18**) and its acetate (**19**). These compounds have been found in plants of Echinops genus *(E. commutatus, E. dahuricus* [29], *E. ellenbeckii* [30], *E. exaltus, E. giganteus* [29] *E. hispidus* [30], *E. horridus* [9, 29], *E. humilis, E. longisetus* [30], *E. macrochaetus* [30], *E. persicus* [9, 29], *E. ritro* [9, 29], *E. spaerocephalus* [9], *E. strigosus* [29], *E. viscosus* [9], in plants *Plu-*



chea dioscorides, *P. indica* и *Rudbeckia fulgida* [3]. Acetate of alcohol (**19**) has been isolated also from *Centaurea cristata* [31]. Metabolites (**20**)–(**22**) are synthesized by plants *Eclipta erecta* and *E. prostata* [7, 32]. Chlorohydrins (**23**), (**24**) have been isolated from plant *Pterocaulon virgatum* [33], and metabolites (**25**) and (**26**) from *Ambrosia chamissonis* [34] and *Pluchea dioscorides* [35].

Acetylenides with two thiophene cycles are found in nature much more seldom. Compound (**27**) is synthesized by plants *Eclipta erecta* [32] and *E. prostata* [7], *Pterocaulon virgatum* [33] и *Tagetes minuta* [36]. Metabolites (**28**)–(**30**) have been found in plants *Porophylum scoparia* [37], *Pterocaulon virgatum* [32] and *Epaltes brasiliensis* [37]. Acetylenides (**31**), (**32**) have been found in plants of *Berkheya*: *B. adlamii*, *B. bergiana*, *B. echinata*, *B. maritima*, *B. macrocephala*, *B. onopordifolia*, *B. rhapontica* and *B. speciosa* [3, 38–40].

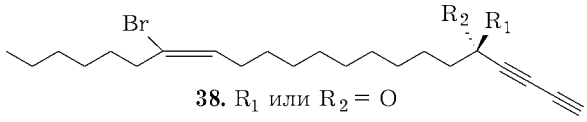


Cytotoxic capacity is possessed by thiophene metabolites (**33**), (**34**) produced by *Helichrysum tenuifolium* [41].

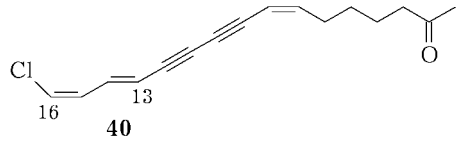
A wide range of biological activity, including antiviral, fungicide and antibacterial one, is characteristic of derivatives of 1,2-dithiocyclohexa-3,5-diene referred to as thiarubrines. The plants that contain these rare compounds are used in popular medicine of equatorial Africa as a remedy for abdominal infections. It has been noticed that leaves of one of these plants, *Aspilia africana*, are chewed by chimpanzees to get rid of endoparasites [42]. Chlorine-containing thiarubrines (**35**), (**36**) that display a high activity against mosquito larvae have been found only in *Ambrosia chamissinis* [33]. Another *Ambrosia* species contains nonhalogenated thiarubrins. One may suppose that in the plant hypochlorination of thiarubrin (**37**) takes place. Taking into account the structural peculiarity of thiarubrins, one has to admit that thiophene metabolites are formed by addition of S_2 particle to the diyne system which results in the formation of dithiacyclohexadienes and subsequent elimination of atomic sulphur.

POLYACETYLENIDES OF SEA INVERTEBRATES

A large group of polyacetylenides has been detached from sea invertebrates, among which sponges occupy a leading place with respect to



38. R_1 или $R_2 = O$
39. $R_1 = OH$, $R_2 = H$



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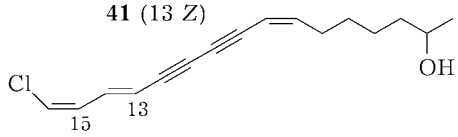
41 (13 *Z*)



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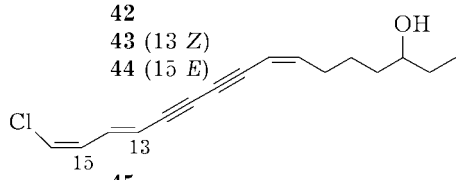
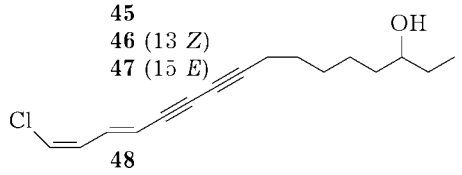
43 (13 *Z*)
44 (15 *E*)



45
46 (13 *Z*)
47 (15 *E*)



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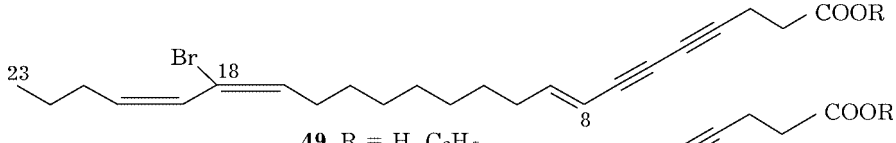
synthesis of these biologically active compounds [13, 43].

Brominated acetylenides renierin (**38**) and its derivative (**39**) have been isolated from the lipid extract of sea sponge *Reniera fulva* living near the coasts of Italy [44]. Nudibranchial mollusk *Diaulula sandiegensis* produces a large number of halometabolites among which chlorine-containing polyacetylenides (**40**)–(**48**) have been detected [45]. The mollusk uses these toxic metabolites for defense against eventual enemies. All the polyacetylenides (**40**)–(**48**) have been isolated from the mollusk's skin, the content of the main of them (**40**) making up 0.11 % of the dry mass.

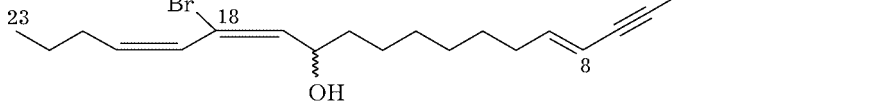
Acetylene acids (**49**), (**50**) and their ethyl ethers are contained in the sponge *Plakelia carduus* inhabiting the Great Barrier Reef of Australia [46]. These compounds have demonstrated a high activity against Gram-positive bacteria. Sea sponges of Xestospongia family produce mono- and dibromoacetylene acids. So, sponges of this family inhabiting the Red Sea contain acids (**51**)–(**53**) [47]. A series of polyacetylene acids (**54**)–(**63**) possessing a high antifungal activity is produced by the sponge *Petrosia volcano* living in the Japanese Sea [48]. About the structure of other brominated acetylene acids it is reported in the review [28].

ENDIINE ANTIBIOTICS

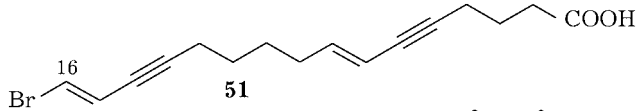
Antibiotics of new structural types with unique bicyclic skeletons containing an endiinic fragment have been enjoying a close attention of chemists during the last decade. One of these antibiotics – calicheamycin γ_1 – has displayed an extraordinary anticancer activity



49. R = H, C_2H_5



50. R = H, C_2H_5



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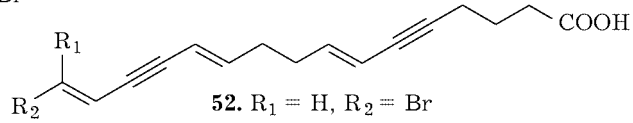
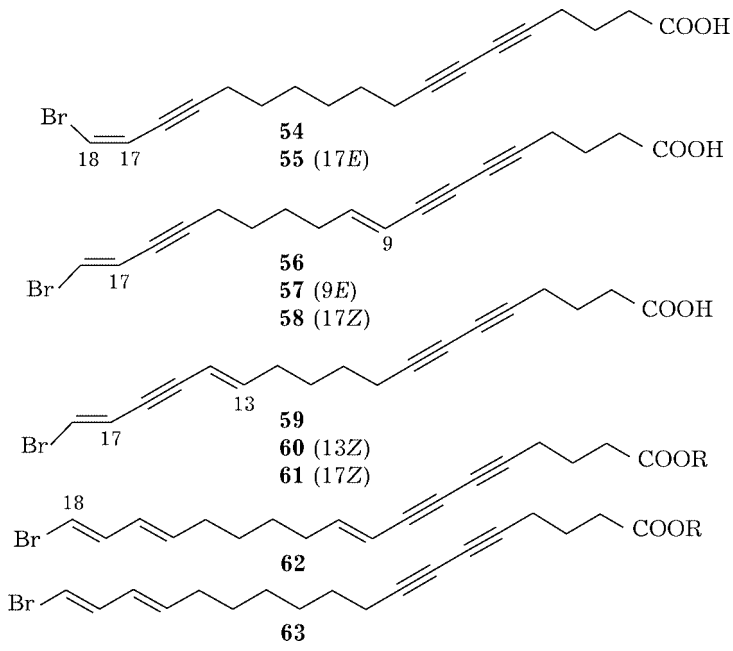
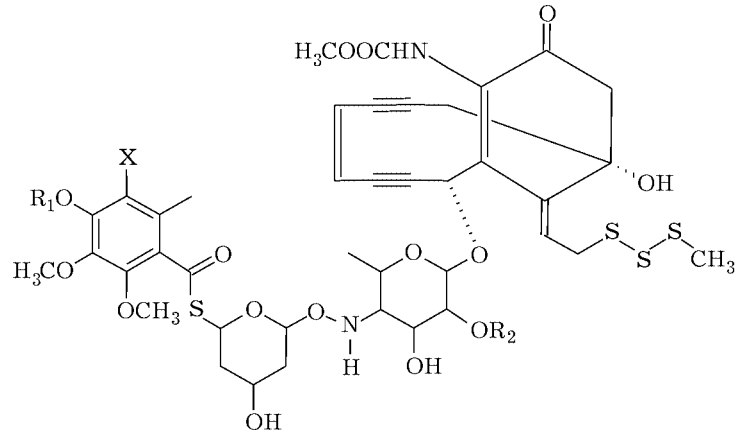
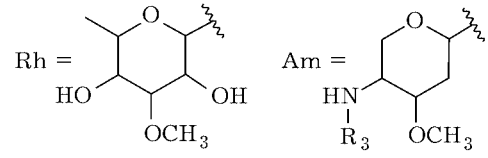


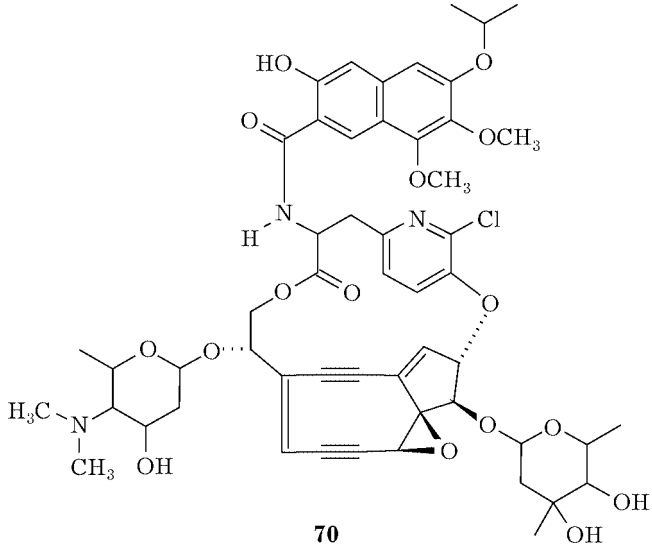
52. R_1 = H, R_2 = Br
53. R_1 = Br, R_2 = H







64. X = Br, R_1 = Rh, R_2 = Am, R_3 = *i*-Pr
65. X = Br, R_1 = Rh, R_2 = Am, R_3 = Et
66. X = I, R_1 = H, R_2 = Am, R_3 = Et
67. X = I, R_1 = Rh, R_2 = H, R_3 = H
68. X = I, R_1 = Rh, R_2 = Am, R_3 = *i*-Pr
69. X = I, R_1 = Rh, R_2 = Am, R_3 = CH_3



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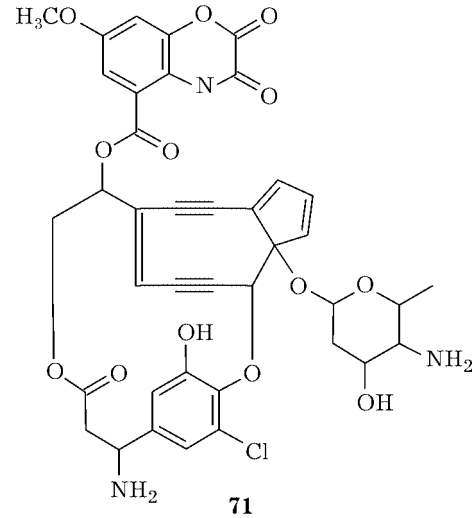

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exceeding by 4000 times that of adriamycin used in oncology [49–52]. Calicheamycins β_1-bromine (**64**), γ_1-bromine (**65**), α_2-iodine (**66**), α_3-iodine (**67**), β_1-iodine (**68**) and γ_1-iodine (**69**) differing not only in the nature of the halogen, but also in the structure of the glycoside moiety of the molecule are powerful antitumor agents.

Actinomycetes produce antibiotic kedarcidin (**70**) that inhibits *in vivo* the development of cancer [53–56]. The soil microbe *Streptomyces globisporus* synthesizes antibiotic C-1027 (**71**) displaying an extremely high activity against cancer cells KB [57–62].

Complete synthesis of endiin metabolites and of their analogs is becoming progressively more often the object of attention of large schools of synthesis [63]. Obviously, halogenated polyacetylenides have rather quickly become an object of thorough investigation of their biological activity, and also an object that extends the possibility of designing molecules promising for chemotherapy.

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