Natural Halogenated Macrolides, Tetracyclines and Quinones

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Abstract

Natural halogenated macrolides, tetracyclines and quinones comprise three small groups of natural antibiotics which were isolated from microorganisms, plants, fungi and marine organisms. The structures of about 86 compounds are considered and the data on their biological activity are described.

Contents

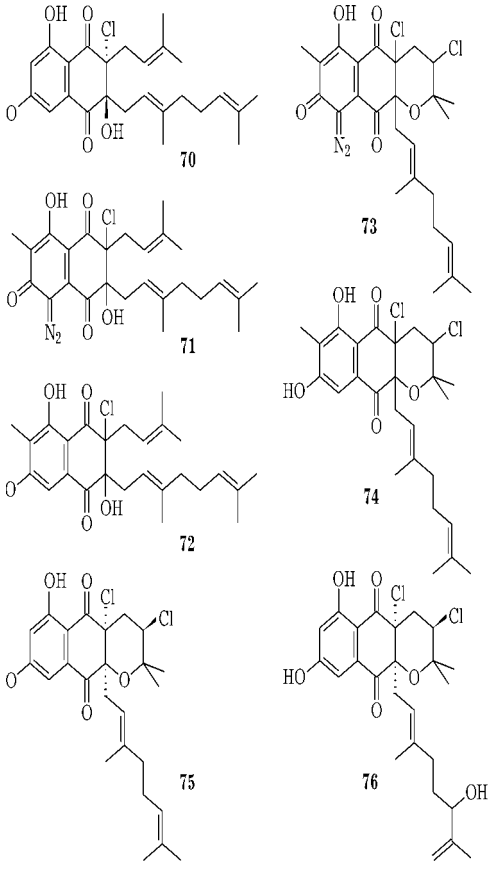
INTRODUCTION

The three groups of halogenated natural metabolites (macrolides, tetracyclines and quinones) have been united in the present review because almost all of them are antibiotics. However, antimicrobial activity inherent to these compounds does not imply the absence of other very valuable properties. In particular, strong toxins and carcinostatics were revealed among these compounds.

The first group of metabolites to be discussed in this review is macrolides. It is a very representative class of compounds generated by actinomycetes, cyanobacteria, fungi, plants and marine organisms [1–6]. Characteristic structural fragment of macrolides is a lactone macrocycle. The structures exhibit extreme variety: peptides, oligosaccharides, polyene structures, phenols or quinones of complicated structure. The examples involving binding with amino saccharides are not rare. As regards halogenated macrolides, the number of their discoveries is growing [7, 8].

The review also includes tetracyclines, among which halogenated compounds occur frequently.

The quinone compounds are widely represented in nature [9]. Halogenated representatives are being investigated since late 1960-ies. Not only the compounds of new structural types but also the substances with very valuable biological activity have been revealed among them.



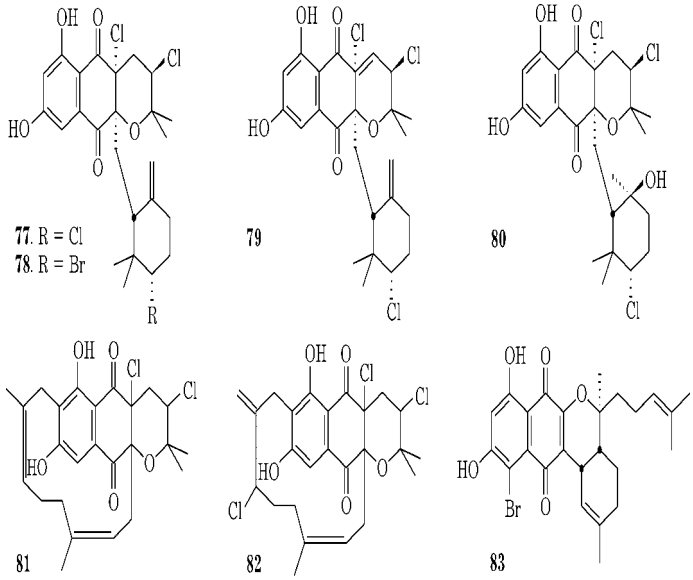
MACROLIDES

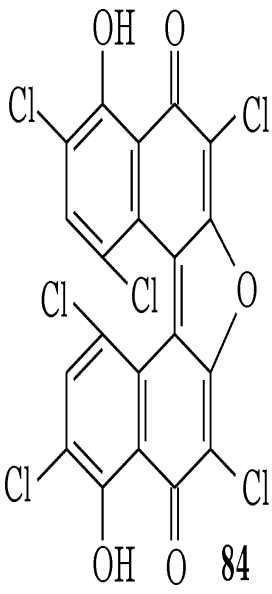
A number of new compounds was discovered when investigating the biosynthesis of antibiotics in *Streptomyces antibioticus* [10–12]. One of these compounds, chlorothricin (**1**), contained chlorine [13, 14]. Structurally similar compounds: hydroxychlorothricin (**2**), MC-031 (**3**), MC-032 (**4**), MC-033 (**5**) and MC-034 (**6**) are generated by *Streptomyces* sp. [15, 16].

Bromine-containing macrolide oscillariolide (**7**) is generated by *Oscillatoria* sp. cyanobacteria [17]. A series of macrolides (**8**)–(**12**) also containing bromine was isolated from the extracts of marine cyanobacteria *Lyngbya majuscula, Oscillatoria nigroviridis* and *Schizothrix calciola* [18, 19]. The compound (**12**) exhibits high activity against leukemia cells [20]. Two metabolites, aplysiatoxin (**12**) and its acetate (**13**) possessing high toxicity (LD_{100} = 0.3 mg/kg) were discovered in sea-mollusca *Stylocheilus longicauda* [20–22].

A number of halogenated macrolides was isolated from sea-sponges. For instance, altochyrtins A (**14**) and B (**15**) and 5-desacetylaltochyrtin A (**16**) exhibiting high activity against cancer are generated by *Hyrtios altum* sponge [23, 24]. Altochyrtin A (**14**) in the concentration of 0.01 ng/ml inhibits the growth of KB cancer cells [23]. Metabolite cinachyrolide (**17**), which is structurally similar to altochyrtin A (**14**), was discovered in *Cinachyra* sp. sponge [25].

Spongistatins 1(**18**), 3 (**19**) [26, 27], 4 (**20**), 5 (**21**) [28] and 9 (**22**) [29], which are even more active against cancer than altochyrtin A (**14**) were isolated from *Spongia* sp. sponge [26, 27] which lives in the Indian ocean, and from *Spirastella spinispirulifera* sponge [28, 29] which lives near the coast of South Africa.





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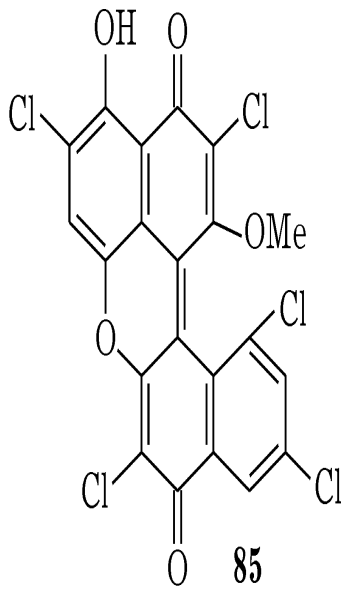

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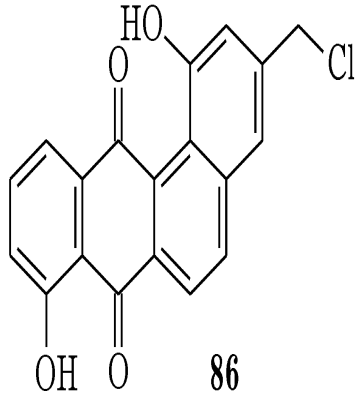

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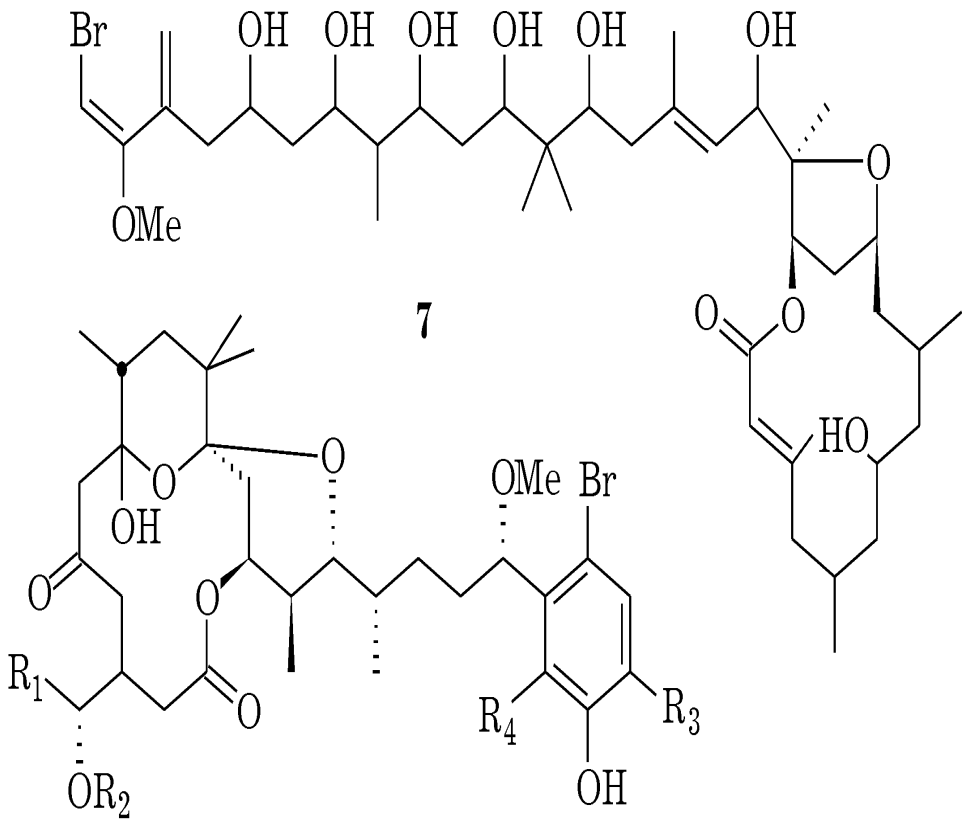
Hypocreic fungi (Hypocreales order) relate to typical saprotrophs and live on fallen or mortified branches of bushes and trees. Two representatives of this order – *Nactria radicicola* [30, 31] and *Monosporium bonorden* [32, 33] – generate monorden (radicicol) (**23**). This metabolite was also discovered in such fungi species as *Monocillium nordinii* [34] and *Neocosmospora tenuicristata* [35]. 6-Chlorodehydrocurvularine (**24**) is generated by *Cochliobolus spicifer* [36]. Two iodine-containing macrolides (**25**) and (**26**) are formed as a result of the reaction of arachidonic acid with lactoperoxidase in the presence of iodine and hydrogen peroxide [37].

A large group of macrolides (**27**)–(**47**) including maytansinoids and their derivative ansamitocides, exhibits clear activity against cancer [38]. They were isolated from the plants of Celastraceae family: *Maytenus serrata*, *M. buchananii* and *Putterilinckia verrucosa*. This group of compounds includes maytansinol (**27**), maytanacin (**28**), ansamitocin P-2 (**29**), ansamitocin P-3 (**30**), ansamitocin P-3[1] (**31**), ansamitocin P-4 (**32**), maytansine (**33**), maytanprine (**34**), maytanbutine (**35**), maytanvaline (**36**), maytanbutacine (**37**), a metabolite which has not got its name yet (**38**), colubrinol (**39**), normaytansine (**40**), normaytanciprine (**41**), trewiasine (**42**), dehydrotrewiasine (**43**), demethyltrewiasine (**43**), metabolite (**44**), maysine (**45**), normaysine (**46**) and maysenine (**47**).

Compounds (**35**), (**38**), (**39**) were also discovered in *Colubrina texensis* [39], metabolite (**40**) in *M. buchananii* [40], (**41**) in *Putterilinckia verrucosa* [41], compounds (**28**)–(**32**) in *Nocardia* sp. [42, 43].

Ansamitocin P-3 (**30**) was isolated from the extracts of *Claopodium crispifolium* and *Anomodon attenuatus* mosses growing in the



8. R_1 = Me, R_2 = R_4 = H, R_3 = Br

9. R_1 = R_2 = R_3 = R_4 = H

10. R_1 = R_2 = R_4 = H, R_3 = Br

11. R_1 = Me, R_2 = H, R_3 = R_4 = Br

12. R_1 = Me, R_2 = R_3 = R_4 = H

13. R_1 = Me, R_2 = Ac, R_3 = R_4 = H

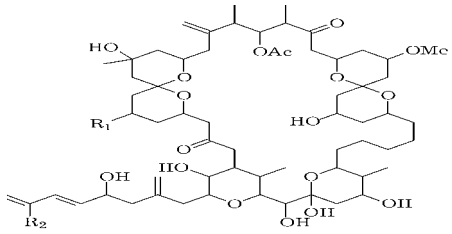
forests of Oregon (USA) [44]. This metabolite is highly active against the human «solid» cancer cells [44].

The *Isothecium subdiversiforme* and *Thamnobryum sandei* mosses growing on Japanese Isls generate metabolites (**30**), (**35**), (**42**) and (**44**) [45].

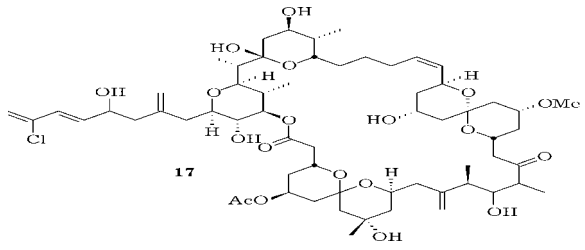
The seeds of the plant species *Trewia nudiflora* (Euphorbiaceae family) contain new macrolides: trenudine (**48**), treflorine (**49**) and *N*-methyltrenudone (**50**), as well as already known ones (**42**)–(**44**) [46, 47]. All the isolated metabolites exhibit evident activity against cancer [46, 47].

TETRACYCLINES

Several chlorinated tetracycline antibiotics (**51**)–(**63**) were isolated. The most widely known among them is aureomycin (**51**); it is generated by *Streptomyces aureofaciens* microorganism [48, 49]. The structure of this antibiotic was confirmed by several research teams [50–53]. Other derivatives of tetracyclines (**52**)–(**56**) are generated by different strains of *Streptomyces aureofaciens* [54–57]. Brominated derivatives of the metabolites (**51**)–(**56**) can be formed in the presence of bromine ions [58]. Other



14. R_1 = OAc, R_2 = Cl
15. R_1 = OAc, R_2 = Br
16. R_1 = OH, R_2 = Cl



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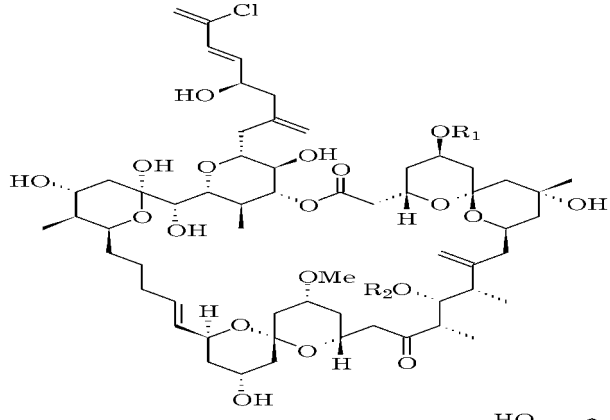
microorganisms, for example *Actinomadura brunnea* and *Dactylosporangium* sp., also generate chlortetracyclines (**57**) [59], (**58**) [60] and (**59**) [61], respectively. Dactylocyclines A (**60**), B (**61**), D (**62**) and E (**63**), which were isolated from *Dactylosporangium* sp. [62–65] exhibit activity towards tetracycline-resistant bacteria.

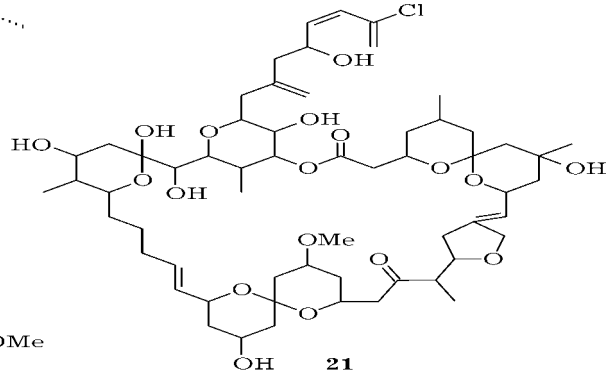
QUINONES

Among natural naphthoquinones and higher quinones, chlorine- and bromine-containing metabolites were discovered. *Ansa*-macrocyclic naphthomycin A (**64**) was first discovered in 1969 in the extracts of *Streptomyces* sp. [66]. However, the structure of that compound was not established then, though identification of the metabolite was carried out in part [67, 68]. Fifteen years ago the structure of naphthomycin was established [69]. Naphthomycin H (**65**) [70] and its geometric isomer naphthomycin B (**66**) [71] were also isolated from other representatives of *Streptomyces* sp.

3-Chloronaphthoquinone (plumbagin) (**67**) was discovered in different species of peren-



18. R_1 = R_2 = COMe
19. R_1 = H, R_2 = COMe
20. R_1 = COMe, R_2 = H



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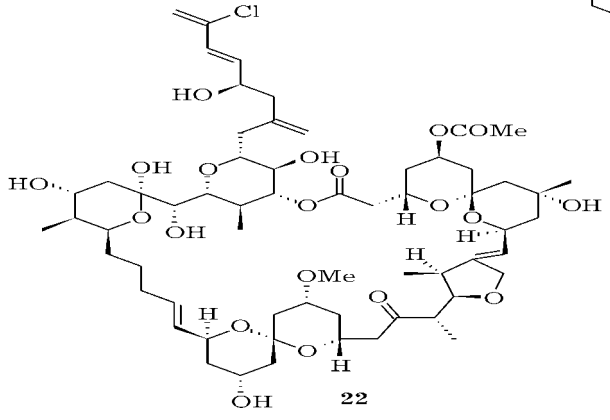

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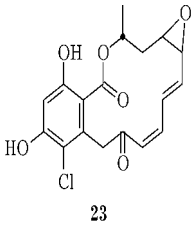

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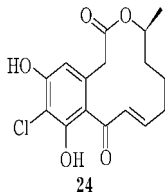

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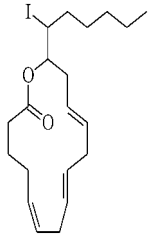

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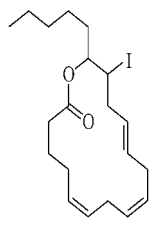

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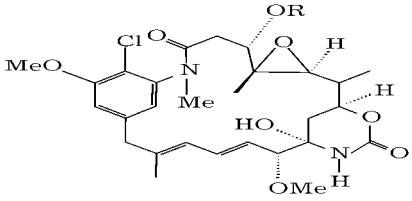
nial carnivores growing in Australia and New Zealand: *Drosera anglica*, *D. intermedia* and *D. musci pula* (Droseraceae family) [72, 73], *Plumbago zealanica* Plumnaginaceae family) [74]. Quinone (**74**) and its brominated analog (**68**) were isolated from the fruit of Asian plant *Diospyros maritime* (Ebenaceae family) [75].

The *Mollisia caesia* and *M. fallens* fungi generate antibiotic mollicine (**69**) [76–78]. It was demonstrated in the studies of its metabolism that only chlorine can get included into the structure of this naphthoquinone. The enzymatic system of these fungi is not intended for bromine inclusion [79].

Naphthomevaline (**70**) was discovered in the soil microorganism *Streptomyces* sp. [80] which



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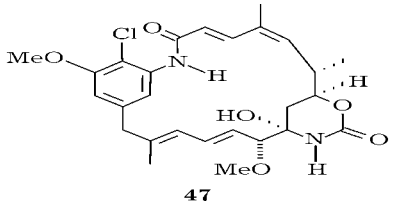
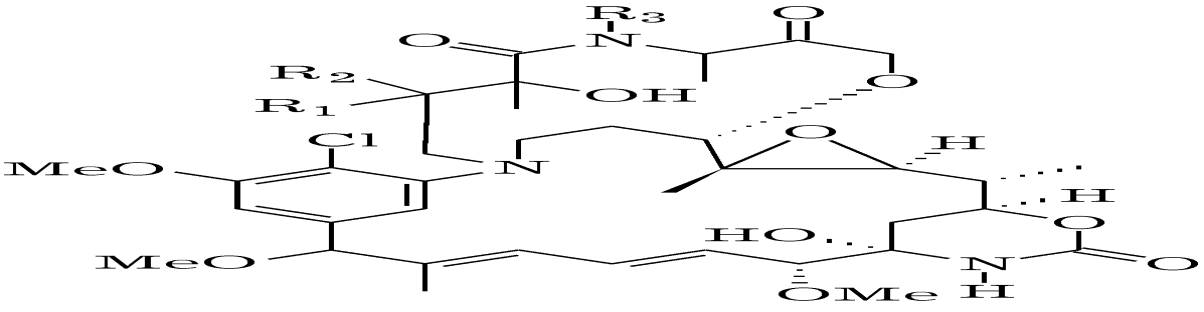
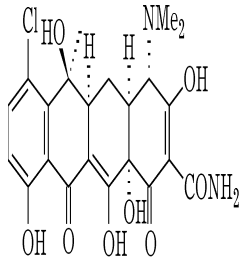


47

	R_1	R_3	R_2
27.	Me	H	H
28.	Me	H	Ac
29.	Me	H	COEt
30.	Me	H	$COCHMe_2$
31.	Me	H	COC_3H_7
32.	Me	H	$COCH_2CHMe_2$
33.	Me	H	COCHMeNMeCOMe
34.	Me	H	COCHMeNMeCOEt
35.	Me	H	$COCHMeNMeCOCHMe_2$
36.	Me	H	$COCHMeNMeCOCH_2CHMe_2$
37.	Me	OAc	$COCHMe_2$
38.	Me	OAc	$COCHMeNMeCOCHMe_2$
39.	Me	OH	$COCHMeNMeCOCHMe_2$
40.	H	H	COCHMeNMeCOMe
41.	H	H	COCHMeNMeCO 
42.	Me	OMe	$COCHMeNMeCOCHMe_2$
43.	Me	OMe	COCHMeNMeCO
44.	Me	OMe	$COCHMeNHCOCHMe_2$
45.	Me	OMe	$COCHMe_2$



48. $R_1 = OH$, $R_2 = R_3 = H$
49. $R_1 = R_2 = R_3 = H$
50. $R_1 = R_2 = O$, $R_3 = Me$



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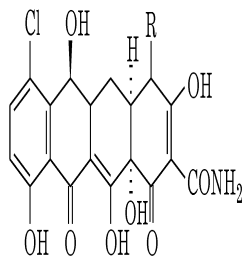
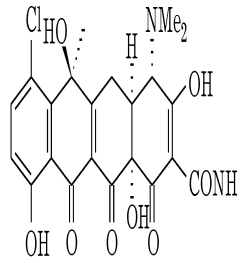


52. R = α-NMe_2
53. R = β-NMe_2



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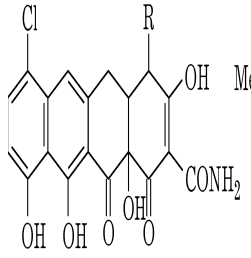
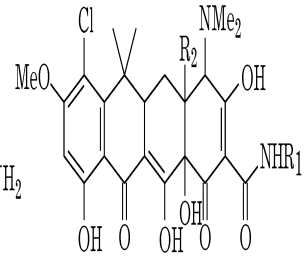
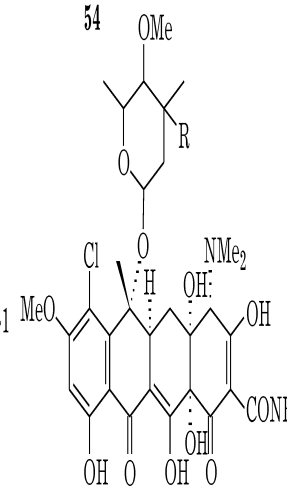


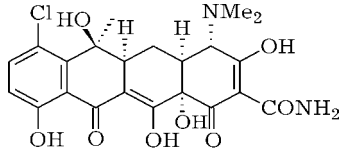
55. R = NH_2
56. R = NMe_2



57. R_1 = Me, R_2 = H
58. R_1 = R_2 = H
59. R_1 = H, R_2 = OH



60. R = NHOH
61. R = NO_2
62. R = NHOAc



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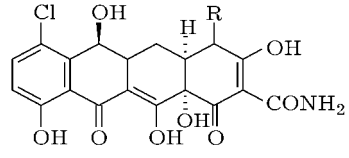
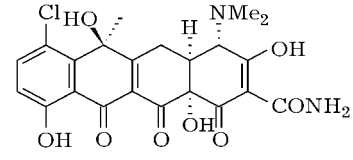


52. R = α-NMe_2
53. R = β-NMe_2



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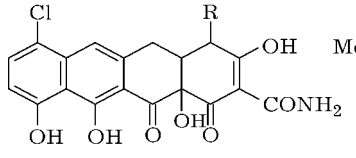
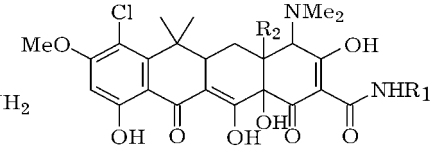
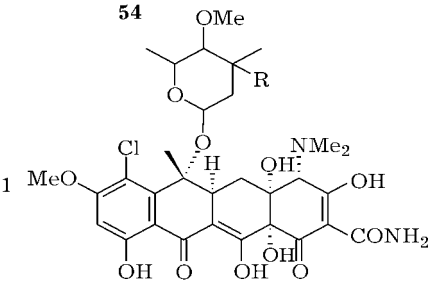


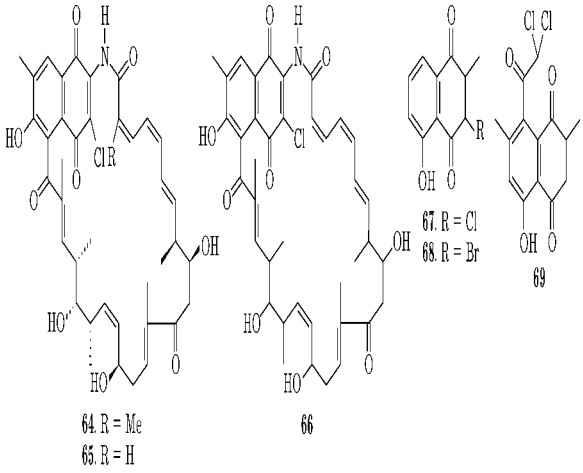
55. R = NH_2
56. R = NMe_2



57. R_1 = Me, R_2 = H
58. R_1 = R_2 = H
59. R_1 = H, R_2 = OH



60. R = NHOH
61. R = NO_2
62. R = NHOAc
63. R = OH



grows in Australia. Several structurally similar antibiotics called SF2415-A1 (**71**), SF2415-B1 (**72**), SF2415-A3 (**73**) and SF-2415-B3 (**74**) were isolated from *Streptomyces aculeolatus* [81, 82]. Attention should be paid to quinones (**71**) and (**73**) containing diazo group. A series of chlorine-containing napuradiomycins (**75**)–(**83**) is generated by *Chainia rubra* microorganism [83–85]. Napuradiomycin A (75) and napuradiomycin B1 (**77**) inhibit estrogenic receptor [86], while brominated marinone (**82**) exhibits high anti-bacterial activity [87].

The soil fungus (the species of which was not established) isolated from the green soil (Australia) generates a new purple pigment dinaphthofuranedione (**84**) which is a quinone of the new structural type [88, 89]. However, the authors assume that this quinone was isolated previously during the hydrolysis of extract from the roots of *Eucalyptus oblique* plant [90]. It is likely to be included into a more complicated compound. Quinone (**85**) was also isolated from this fungus [88, 89]. The fungus belonging to the Actinomycetes order generates chlorotetrangulol (**86**) [91].

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