Natural Halogenated Alkaloids

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Abstract

Structures of more than 230 natural halogenated (chlorine-, bromine- and iodine-containing) alkaloids isolated from cyanobacteria, plants, fungi, sea algae and invertebrates, and data on their biological activity are presented.

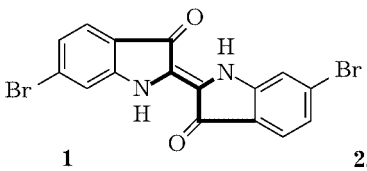
Contents

INTRODUCTION

Bromine-containing alkaloids make up one of the widest groups of halogenated alkaloids. Earlier, we have already considered chlorine-containing alkaloids [1], as well as bromine- and iodine-containing alkaloids of sea microorganisms and sponges [2]. Bromine-containing alkaloids are produced mainly by the sea invertebrates, such as sponges (Porifera type), ascidia (Tunicata type), bivalved (type Mollusca, class Bivalvia), gastropode (class Gastropoda) and nudibranchiate (class Gastropoda, subclass Nudibranchia) molluscs, Bryozoa, soft corals (Coelenterata type, class Anthozoa), *etc.* These compounds have also been detected in blue-green algae (cyanobacteria) and macrophytic algae [3–11]. Bromine-containing alkaloids may be divided into five basic types – indole, indole-carbazole, carboline, pyrrole and quinoline alkaloids. Alkaloids of other structural types may contain chlorine, bromine or iodine, but their number is not large. Some alkaloids isolated mainly from sea algae contain two different haloids, *e.g.*, Br^- and Cl^-.

INDOLE ALKALOIDS

Indole alkaloids are the most widespread type of halogenized nitrogen-containing metabolites. One of the well-known indole alkaloids is 6,6′-dibromoindigo (**1**) called “Antique Purple”. Since ancient times, it has been iso-



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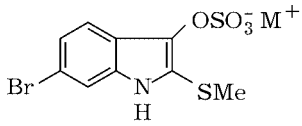
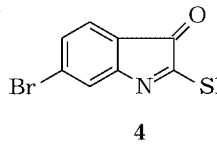


2. M = $Me_3\overset{+}{N}CH_2CH_2OH$
3. M = $Me_3\overset{+}{N}CH_2CH_2OCOCH{=}CHMe_2$



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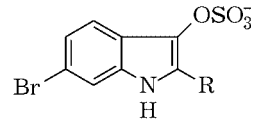
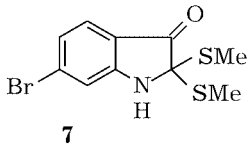


5. R = H
6. R = SO_2Me



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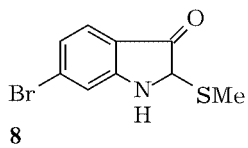

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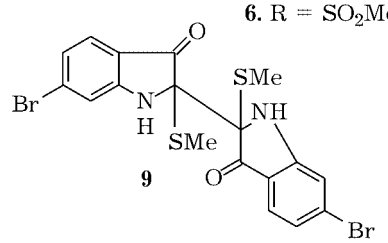

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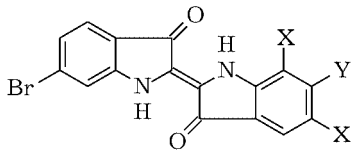
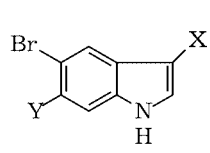
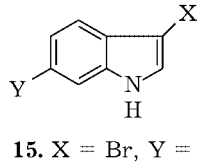


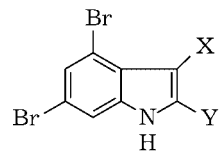
10. X = Br, Y = OMe
11. X = H, Y = Br



12. X = H, Y = OMe
13. X = Br, Y = H
14. X = Br, Y = OMe



15. X = Br, Y = H
16. X = Y = Br
17. X = Cl, Y = Br
18. X = Cl, Y = H



19. X = Br, Y = H
20. X = Y = H
21. X = H, Y = Me

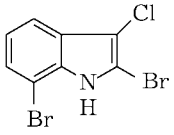
lated in Egypt from the Mediterranean mollusc *Murex bandaris* and used for staining tissues purple. The structure of this alkaloid was determined by Friedlander in 1909 [12]. He isolated 1.4 g of the "Antique Purple" from 12 000 molluscs *Murex bandaris* [12], and in 1922 he detected the alkaloid in two other sea mollusc species – *Purpura aperta* and *Purpura lapillus* [13]. Friedlander established that compounds containing the chromophore group (designated by a solid line in (**1**)) were, as a rule, stainable with dyes. These dyes were called indigoids [12, 13].

Much attention has been paid to biogenesis of 6,6′-dibromoindigo in works carried out in subsequent years. Thus, several possible precursors of the "Antique Purple" have been isolated from other molluscs: indoxylsulphates (**2**), (**3**) and (**4**) from *Dicathais orbita* [14], and (**5**) and (**6**) from *Murex trunculus*, *M. brandis*, *M.erinaceus* and *Purpura haemastoma* [15]. Metabolite (**4**) and its possible precursor (**7**) have been detected in molluscs *Dicathais orbita,Mancinella bufo, M. keineri, M. distinguenda* (another name *M. ancinella*) [16, 17]. Salts of choline (**2**) and of its ester (**3**) are presented, apart from the mollusc *Dicathais orbita* [14, 18], also in the mollusc *Mancinella keineri* [18]. Tyriverdin A (**9**) and its isomer tyriverdin B (not shown) isolated from molluscs *Nucela lepilus* [19] and *Thais clavigera* [20] are intermediate precursors of the "Antique Purple" [20–22]. These isomers seem to be formed from tyrindoxyl sulphate (2) *via* the intermediate tyrindoxyl (**8**) [19].

The acorn barnacle *Phychodera flava laysanica* contained "Antique Purple" (**1**) and two new 6,6`-dibromoindigotins similar in their structure – (**10**) and (**11**), and dibromoindole (**12**) [23]. Subsequent studies of this mollusc showed that it also produced brominated indole (**13**) [24], 3-chloro- (**15**), 3-bromo- (**16**) and 6-bromo-3-chloroindole (**17**) [25], and metabolites (**14**) and (**18**) [26]. Another mollusc species – *Phychodera* sp. – found in a deep-water cave Maoui contained alkaloid (**19**) [27] that had earlier been isolated from the acorn barnacle *Balanoglossus carnosus* [26]. The acorn barnacle *Galanobalanus* sp. produces metabolites (**16**), (**20**) and (**21**) [26, 28].

The sea alga *Rhodophyllis membranacea* growing off the shores of New Zealand synthesises nine new alkaloids (**22**)–(**30**) containing two halogen atoms – bromine and chlorine – in their molecules [29].

The red alga *Laurencia brongniartii* from the Caribbean Sea [30] contains some new polyhaloindoles (**31**)–(**34**). Among them only tetrabromoindole (**33**) showed a high antimicrobial activity. Alkaloids (**32**) and (**34**) have also been found in the sea hare *Aplysia dactylomela* [31]. The soft coral *Dendrophyllia* sp. produces alde-



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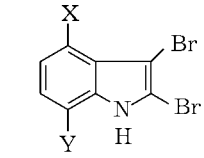
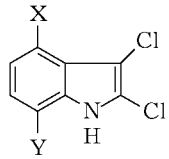
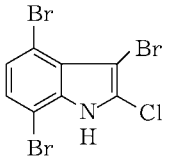


23. X = H, Y = Br
24. X = Y = Br



25. X = Y = Br
26. X = H, Y = Br
27. X = Cl, Y = Br
28. X = H, Y = Cl
29. X = Y = Cl



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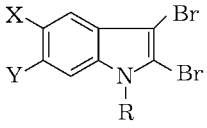
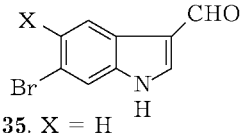
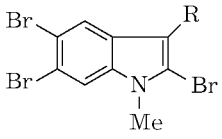


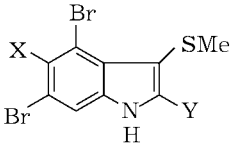
31. R = Me, X = H, Y = Br
32. R = Me, X = Br, Y = H
33. R = H, X = Y = Br
34. R = Me, X = Y = Br



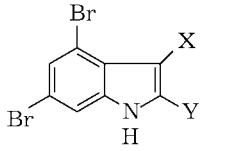
35. X = H
36. X = OH



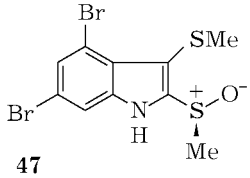
37. R = CH_2NMe_2
38. R = $CH_2N(O)Me_2$
39. R = CHO



40. X = H, Y = Br
41. X = Y = Br
42. X = H, Y = SMe
43. X = Br, Y = SMe



44. X = H, Y = Br
45. X = Y = Br
46. X = H, Y = SMe



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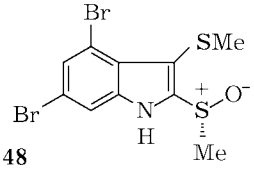

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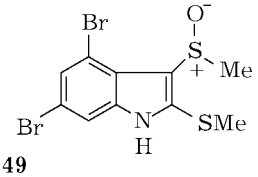

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hydes (**35**) and (**36**) [32]. The same compounds have been detected in sea sponges *Pleroma menoui* [33], *Plocamissma igzo* [34] and *Pseudosuberites hyalinus* [35].

Sea bryozoan *Zoobotryon verticillatum* synthesizes gramine (**37**) and N-oxide of gramine (**38**) and aldehyde (**39**) [36]. The latter hinders the development of sea urchin eggs.

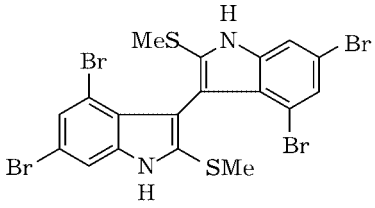
The alga *Laurencia brongniartii* from the Japanese Sea contains di-, tri- and tetrabromoindoles (**40**)–(**46**) [37, 38], three new sulphur-containing itomanindoles (**47**)–(**49**), and bisindole (**50**) [39].

The blue-green alga *Rivularia firma* produces a number of brominated indoles (**51**)–(**57**), among which (**52**)–(**55**) are optically active [40, 41]. Ascidia *Eudistoma fragum* [42] and *Didemnum candidum* [43] contain alkaloids (**58**) and (**59**), respectively. The ascidia *Polyandrocarpa* sp. that lives off the coasts of Philippines synthesises polyandrocarpamide A (**60**) and iodine-containing polyandrocarpamide B (**61**) [44], and the ascidia *Polycitorella mariae* (Fiji Isls) produces citorellamine (**62**) which has a high cytotoxic and antibacterial activity [45, 46].

The Mediterranean coral *Astroides calycularis* contains alkaloid (63) [47], the coral *Tubastraea* sp. contains new bromoaplysinopses (**64**) and (**65**), and the coral *Dendrophyllia* sp. produces alkaloids (**66**)–(**68**) [48].

The Californian ascidia *Dudemnum candidum* synthesizes metabolites (**69**) and (**82**) [43], and the ascidia *Eusynstyela misakiensis* produces alkaloid eusynstyelamide (**70**) [49].

It is known that many sea molluscs produce toxins, including such well-known ones as tetrodotoxin, saxitoxin, ciguatera toxins, palytoxin, brevetoxins, *etc.* [50]. All these toxins do not contain halogen atoms, and the bivalve mollusc *Babylonia japonica* living in the Japanese Sea produces surugatoxin (**71**) which contains bromine [27]. This toxin provokes a disease in people inhabiting the Suruga haven (Japan). Two other toxins – prosurugatoxin (**72**) and neosurugatoxin (**73**) – have also been iso-



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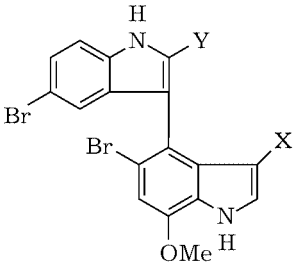
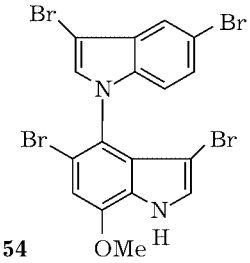


51. X = Y = Br
52. X = Br, Y = H
53. X = H, Y = Br



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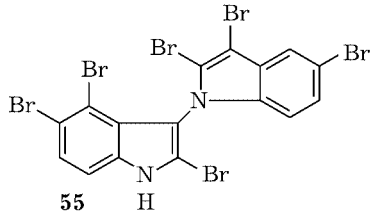

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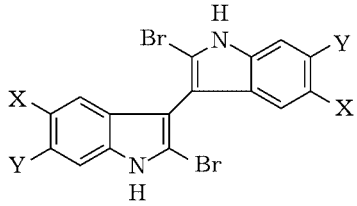
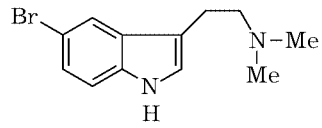


56. X = Br, Y = H
57. X = H, Y = Br



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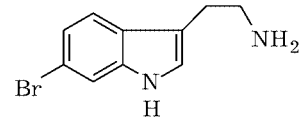

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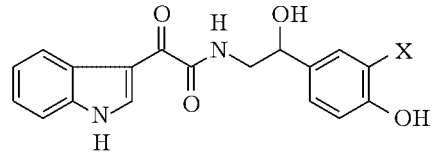
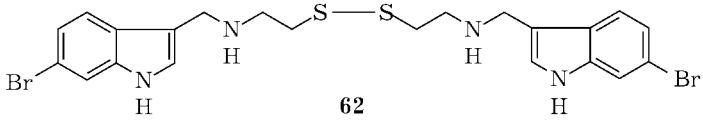


60. X = Br
61. X = I



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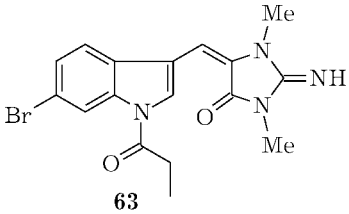

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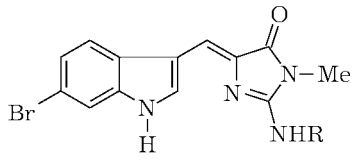
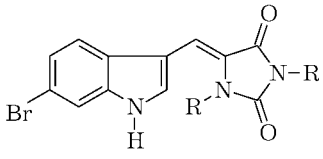
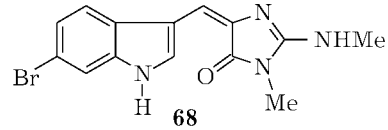


66. R = H
67. R = Me



64. R = Me
65. R = H



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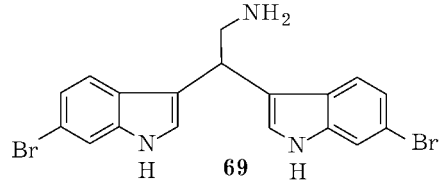

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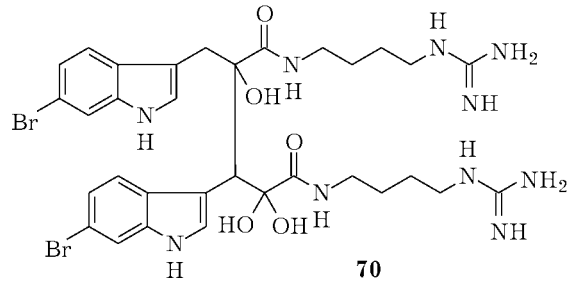

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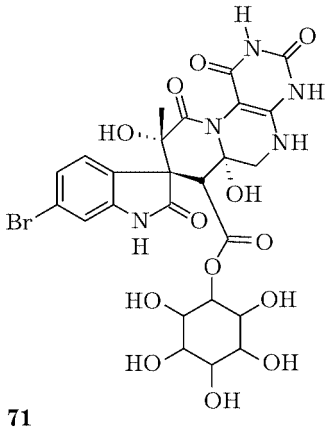
lated from this mollusc [51–53], the neosurugatoxin (**73**) being by 100 times more poisonous than the surugatoxin (**71**) and prosurugatoxin (**72**).

Two alkaloids – urochordamine A (**74**) and its epimer urochordamine B (**75**) – which promote the development of crustacean larvae have been isolated from ascidia *Ciona savignyi* [54]. Bryozoan *Hincksinoflustra denticulata* contains hinckdentine A (**76**), and bryozoan *Chartella papyracea* produces indole-β-lactam: chartelline A (**77**), B (**78**), C (**79**) [56, 57], as well as chartellamides A (**80**) and B (**81**) [58].

Bryozoan *Flustra foliacea* produces a series of brominated indoles (**83**)–(**98**), including flustrabromine (**83**) [59,60], flustramines A (**84**), B



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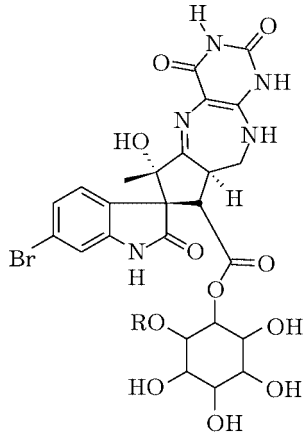
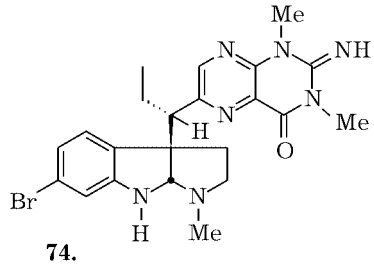
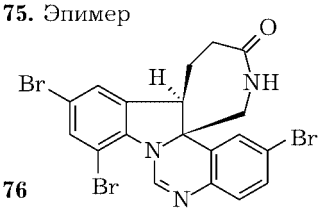


72. R = H
73. R =



74.
75. Эпимер



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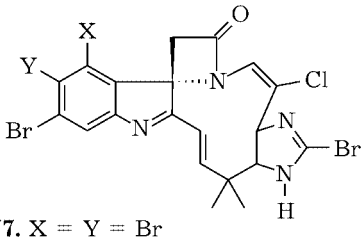
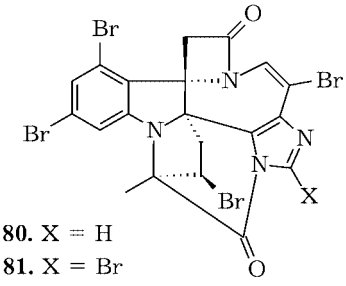
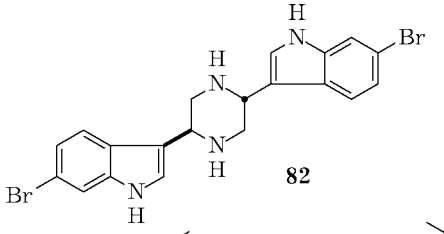


77. X = Y = Br
78. X = Br, Y = H
79. X = Y = H



80. X = H
81. X = Br



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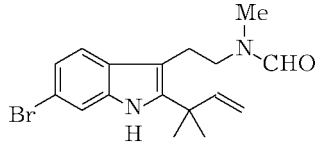

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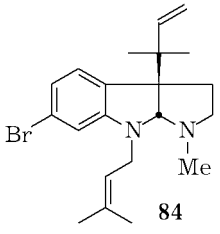

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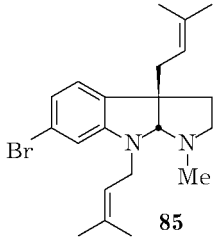

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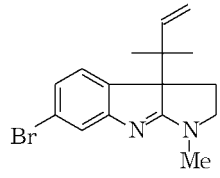

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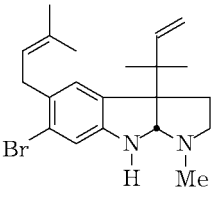

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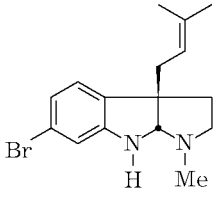

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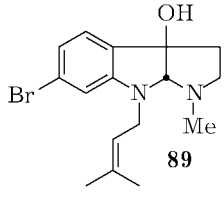

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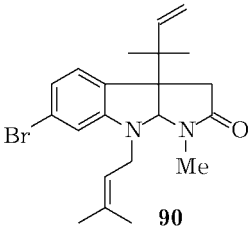

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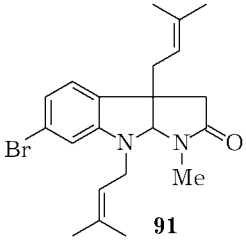

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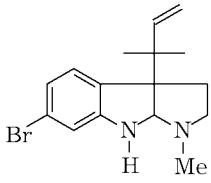

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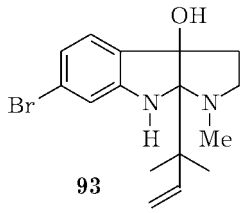

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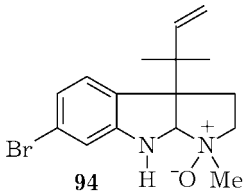

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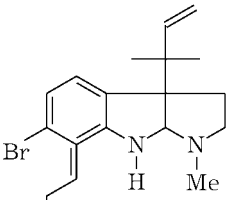

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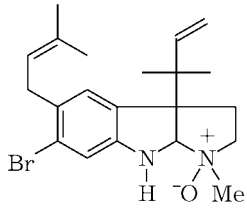

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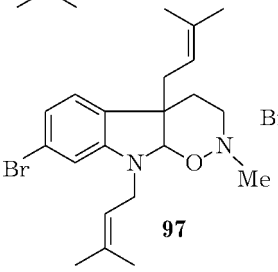

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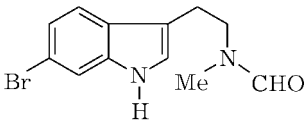
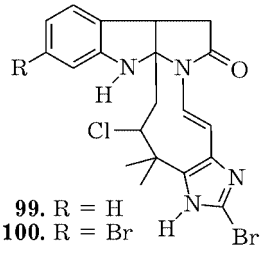


98

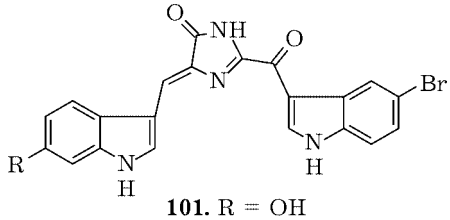
(**85**), C (**86**), D (**87**), E (**88**) [64], flustraminoles A (**93**) [65] and B (**89**) [62], flustramides A (**90**) [65] and B (**91**) [66], dihydroflustramine C (**92**) [67] and its *N*-oxide (**94**) [63], isoflustrarine D (**95**) and its *N*-oxide (**96**) [63]. Flustrarine B (**97**) and flustrabromine (**98**) have also been found in this bryozoa species [59, 66]. Although the biological role of these alkaloids has not still been established, one of these metabolites – flustramine E (**88**) – has shown a high activity against parasitic fungi *Botrytis cinera* and *Rhizotonia solani* [64]. Halogenated indole-imidazole alkaloids securamine A (**99**) and B (**100**) have been isolated from bryozoan *Securiflustra securifrons* inhabiting the North Sea [68].

Ascidia *Rhopalaea* sp. lived near the Japanese island Okinawa produces new indole alkaloids – rhopaladines A – D, two of which – rhopaladines B (**101**) and C (**102**) – contain a bromine atom [69]. Rhopaladine C (**102**) has shown an antibacterial activity against pathogenic bacteria *Sarcia lutea* and *Corybebacterium xerosis*, and rhopaladine B (**101**) inhibited cycline-dependent kinase 4 and C-erb-2 kinase [69]. Another ascidia species – *Aplidium meridianum* lived near the Argentinian island Southern George (South Atlantic) produces new indole alkaloids (**103**)–(**109**) four of which are called meridianine B (**103**), meridianine C (**104**), meridianine D (**105**) and meridianine E (**106**) [70]. Metabolites (**103**)–(**106**) have shown activity against adenocarcinoma cells.

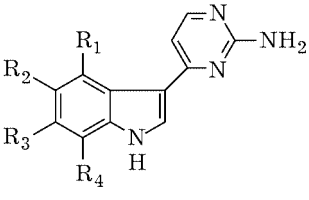
A series of sulphur-containing halogenated alkaloids has been isolated from pathogenic fungi provoking eczema in domestic animals [71]. Thus, sporidesmin A (**110**) has been isolat-



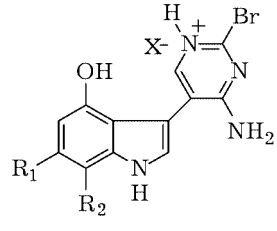
99. R = H
100. R = Br



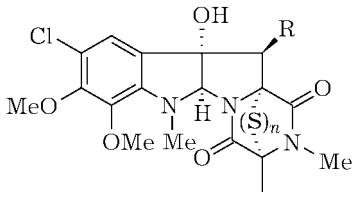
101. R = OH
102. R = H



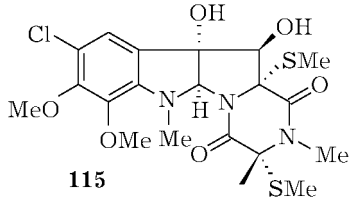
103. R_1 = OH, R_2 = R_4 = H, R_3 = Br
104. R_1 = R_3 = R_4 = H, R_2 = Br
105. R_1 = R_2 = R_4 = H, R_3 = Br
106. R_1 = OH, R_2 = R_3 = H, R_4 = Br



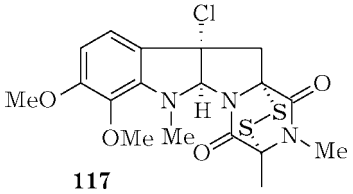
107. R_1 = R_2 =H
108. R_1 = H, R_2 = Br
109. R_1 = Br, R_2 = H



110. R = OH, n = 2
111. R = H, n = 2
112. R = OH, n = 3
113. R = OH, n = 4



115



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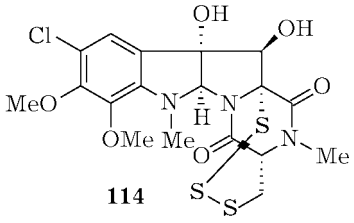

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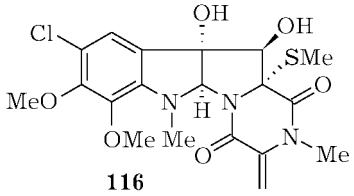
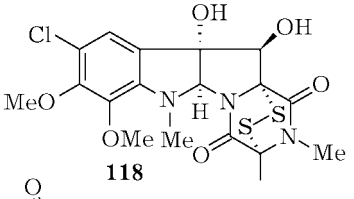
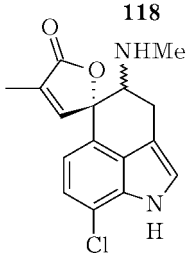


116



118



119. α-Эпимер
120. β-Эпимер

ed from *Sporidesmium bakeri* [72–74], sporidesmins A (**110**), B (**111**) and C (**114**), from the fungus *Pithomyces chartarum* that provokes eczema and liver disorders in New Zealand sheep [75–77]. Subsequent studies demonstrated that this pathogenic fungus *P. chartarum* produced also sporidesmins D (**115**) [78], E (**112**) [79], F (**116**) [78], G (**113**) [80, 81], H (**117**) [82] and J (**118**) [82].

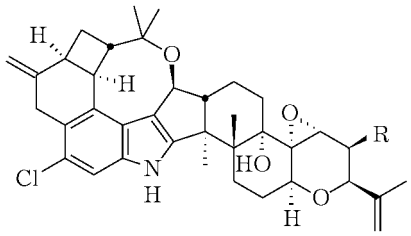
The fungus *Penicillium islandicum* produces highly toxic alkaloids – 8-chlororugulovasines A (**119**) and B (**120**) [83, 84].

The fungus *Penicillium crustosum* produces highly toxic, especially for domestic animals, chlorine-containing metabolites – penitrems A (**121**), C (**122**) and F (**123**) [85–87]. Pennigritrim (**124**) has been isolated from fungus *P. nugricans* [88]. Besides, penitrem A (**121**) has been detected in *P. verrucosum* var. *cyclopium* [89].

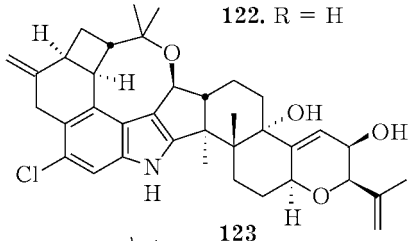
Anti-cancer antibiotics – pyrindamycins A (**125**) and B (**126**) – are synthesized by *Streptomyces* SF2582 [90, 91]. The same compounds have been detected in *Streptomyces* DO-89 [92, 93], but given the names of duocarmycin C_2 (**125**) and C_1 (**126**). Chloroisotin (**127**) is produced by fungus *Nicromonospora carbonacea* [94]. 4-Chloro-6-methoxyindole (**128**) which promotes rectal cancer has been isolated from the plant *Vicia faba* [95].

Two alkaloids of topsentin class (**129**) and (**130**) having a cytotoxic activity have been isolated from the sponge *Spongosorites genitrix* living off the coasts of South Korea [96], and the Australian sponge *Echinodictyum* sp. contains antibacterial metabolites – echinosulphonic acids A (**131**), B (**132**), C (**133**) and echinosulphone (**134**) [97].

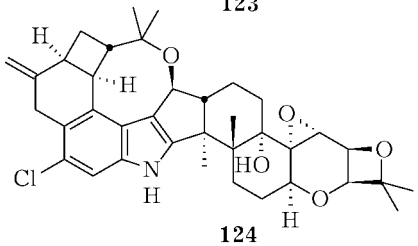
A series of 3-hydroxyindoles – convolutamydines A (**135**), B (**136**), C (**137**) and D (**138**) – are produced by sea bryozoan *Amathia convoluta* [98, 99] inhabiting the North Mexican gulf off the Florida shore. Racemic convolutamydine A (**135**) has been synthesized from 4,6-dibromoisatin [100, 101]. Convolutamydin A (**135**) inhibits the development of cancer HL-60 cells and decreases phagocytosis.



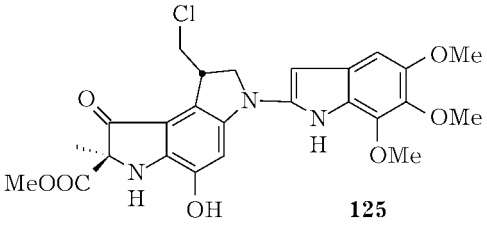
121. R = OH
122. R = H



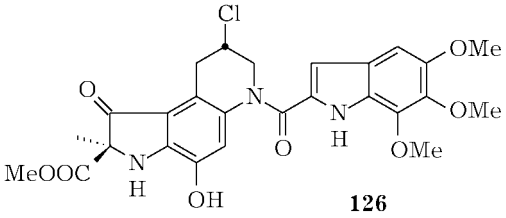
123



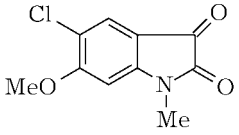
124



125



126



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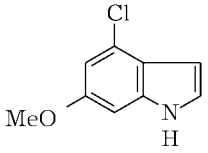

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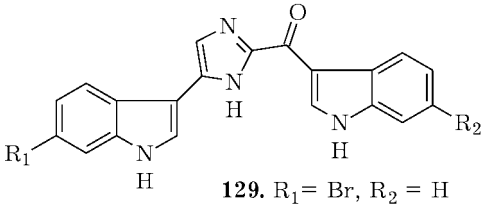
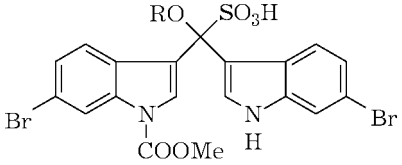
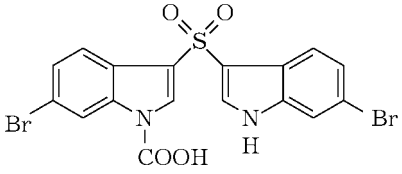


129. R_1= Br, R_2 = H
130. R_1= H, R_2 = Br



131. R = Et
132. R = Me
133. R = H



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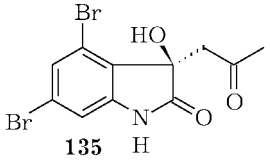
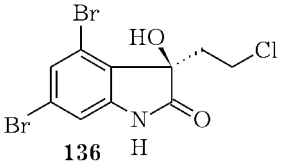
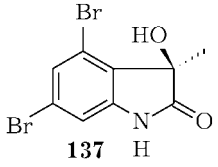


135



136



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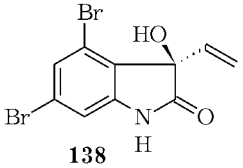

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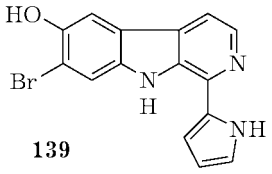

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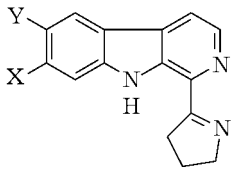
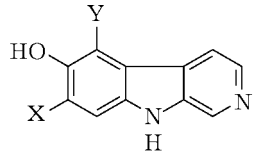
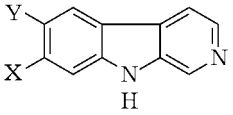


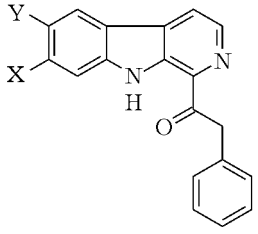
140. X = Br, Y = H
141. X = H, Y = Br
142. X = Br, Y = OH



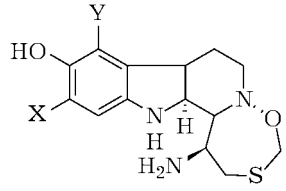
143. X = H, Y = Br
144. X = Br, Y = H



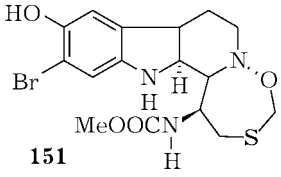
145. X = H, Y = Br
146. X = Br, Y = H



147. X = Br, Y = H
148. X = H, Y = Br



149. X = Br, Y = H
150. X = H, Y = Br



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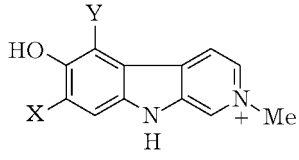
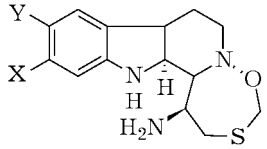
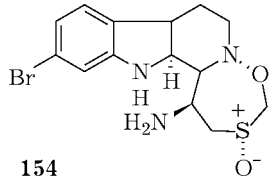


155. X = H, Y = Br
156. X = Br, Y = H



152. X = Br, Y = H
153. X = H, Y = Br



154

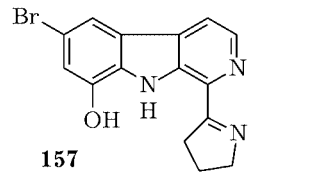
CARBOLINE ALKALOIDS

Carbolines, especially β-carbolines, are mainly plant alkaloids [102–194] and do not contain haloid atoms in their structure. Some β-carbolines isolated from plants growing in the Amazon tropics provoke psychosis which can pass to schizophrenia as a result of a long-term abuse of these compounds [105, 106]. It has also been demonstrated that some β-carbolines belonging to the group of hallucinogens [107] may provoke symptoms similar to those of Parkinson syndrome [108].

Lately, more than thirty of halogenated β-carbolines have been isolated from sea invertebrates. They are produced mainly by ascidia [109]. Ascidia *Eudistoma olivaceum* from the Caribbean Sea contains some halogenated β-carbolines of various types: (**139**)–(**154**) and (**157**), (**158**). Eudistomins A (**139**), G (**140**), H (**141**), P (**142**), D (**143**), J (**144**), N (**145**), O (**146**), C (**149**), E (**150**), F (**151**), K (**152**), L (**153**) [110] and eudistomins R (**147**) and S (**148**) have been isolated from the same ascidia species living near the Bermudas [111]. The alkaloids possess a high antiviral and antimicrobial activity [110]. The New Zealand ascidia *Ratella signillinoides* contains eudistomin K sulphoxide (**154**) [112, 113] and eudistomins O (**146**) and C (**149**) [114, 115]. Metabolite (**154**) shows activity against *Polio* and *Herpes* viruses [114], and the synthetically produced D (**143**) stimulates muscular contraction by 100 times than caffeine does [116].

N-methylated β-carbolines 2-methyleudistomin D (**155**) and 2-methyleudistomin J (**156**), as well as eudistomins D (**143**), J (**144**), C (**149**), E (**150**), K (**152**), L (**153**) and 14-methyleudistomin C (**160**) have been isolated from ascidia *Eudistoma gilboverde* [117]. 14-Methyleudistomin C (**160**) has a high cytotoxic activity against four various cancer cell types [117].

Ascidia *Eudistoma glaucum* lived in the Japanese Sea near the Okinawa produces eudistomidins A (**157**) [118], B (**158**), D (**159**), C (**160**) [119], E (**161**) and F (**162**) [120], and ascidia *E. album* contains new alkaloids – eudistalbines A (**163**), B (**164**) – and eudistomin C (**149**) [121].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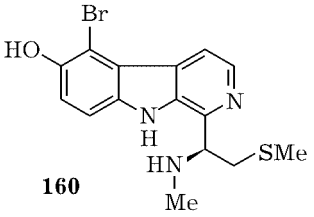
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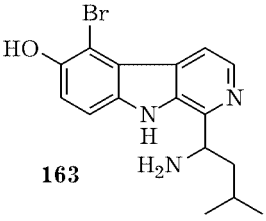
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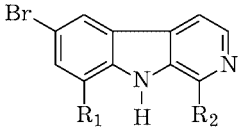
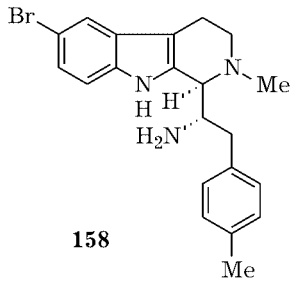

166. R_1=H, R_2 = Et
167. R_1=H, R_2 = Me
168. R_1=Br, R_2 = Et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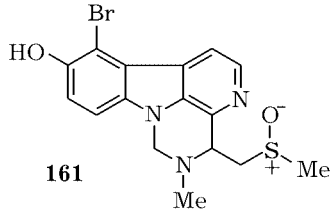
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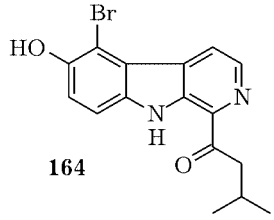
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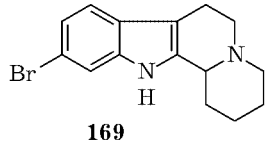
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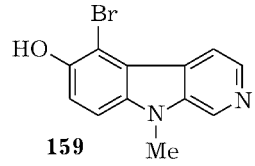
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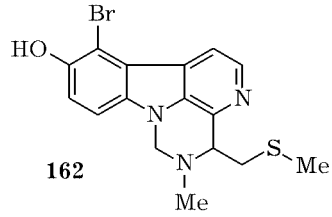
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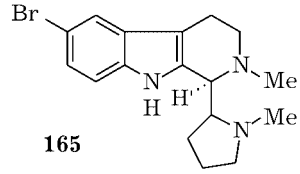
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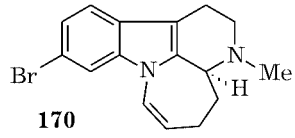
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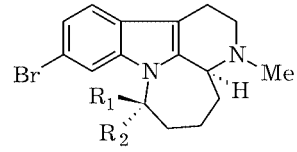
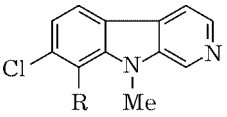
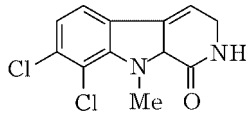

171. R_1 = OH, R_2 = H
172. R_1 = H, R_2 = OH

Eudistalbine A (**163**) has shown a weak activity against cancerous KB cells, and eudistalbine B (**164**) was inactive. Ascidia *E. fragum* (coastal zone of New Caledonia) contains a new metabolite woodinine (**165**) [42], and hydroid *Aglaophenia pluma* produces β-carbolines (**166**)–(**168**) [122]. Four new metabolites – arborescidines A (**169**), B (**170**), C (**171**) and D (**172**) – have been found in another ascidia species – *Pseudodistoma arborescens* from New Caledonia [123].

Terrestrial cyanobacterium *Dichothrix baueriana* produces chlorine-containing alkaloids – bauerines A (**173**), B (**174**) and C (**175**) [124]. All these metabolites were active against *Herpes* virus [124]. Bromine-containing β-carbolines (**176**) and (**177**) have been detected in ascidia *Didemnum* sp. [125].


173. R = H
174. R = Cl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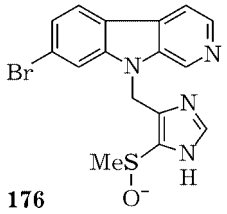
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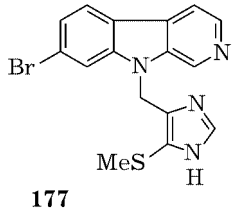
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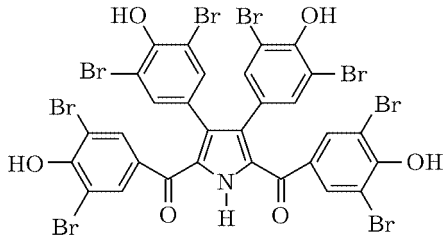
PYRROLE ALKALOIDS

Alkaloids containing a pyrrole ring in their structure are widespread in nature [126–128]. Halogenated pyrrole alkaloids containing chlorine, bromine and iodine have been isolated from microorganisms, fungi, plants and sea invertebrates [129–133].

Polycitone B (**178**), polycetone A (**179**) and polycitine A (**181**) have been detected in ascidia *Polycitor africanus* living near the Comora Isls [134], while polycetone A (**179**), and poly-



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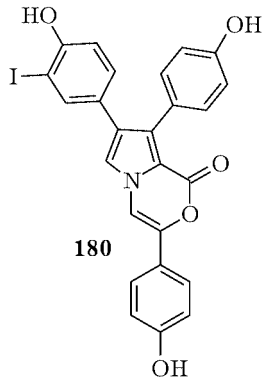

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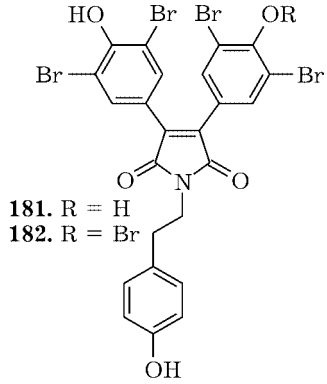
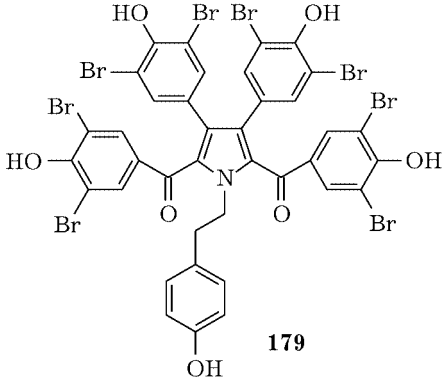


181. R = H
182. R = Br



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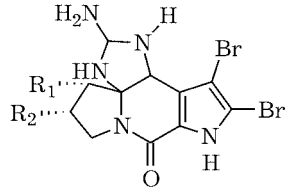
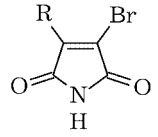
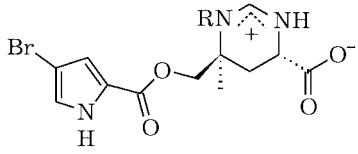


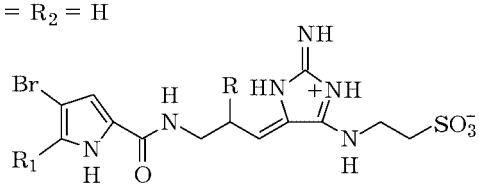
183. R_1 = OH, R_2 = Cl
184. R_1 = R_2 = H



185. R = H
186. R = Br



187. R = Me
188. R = H



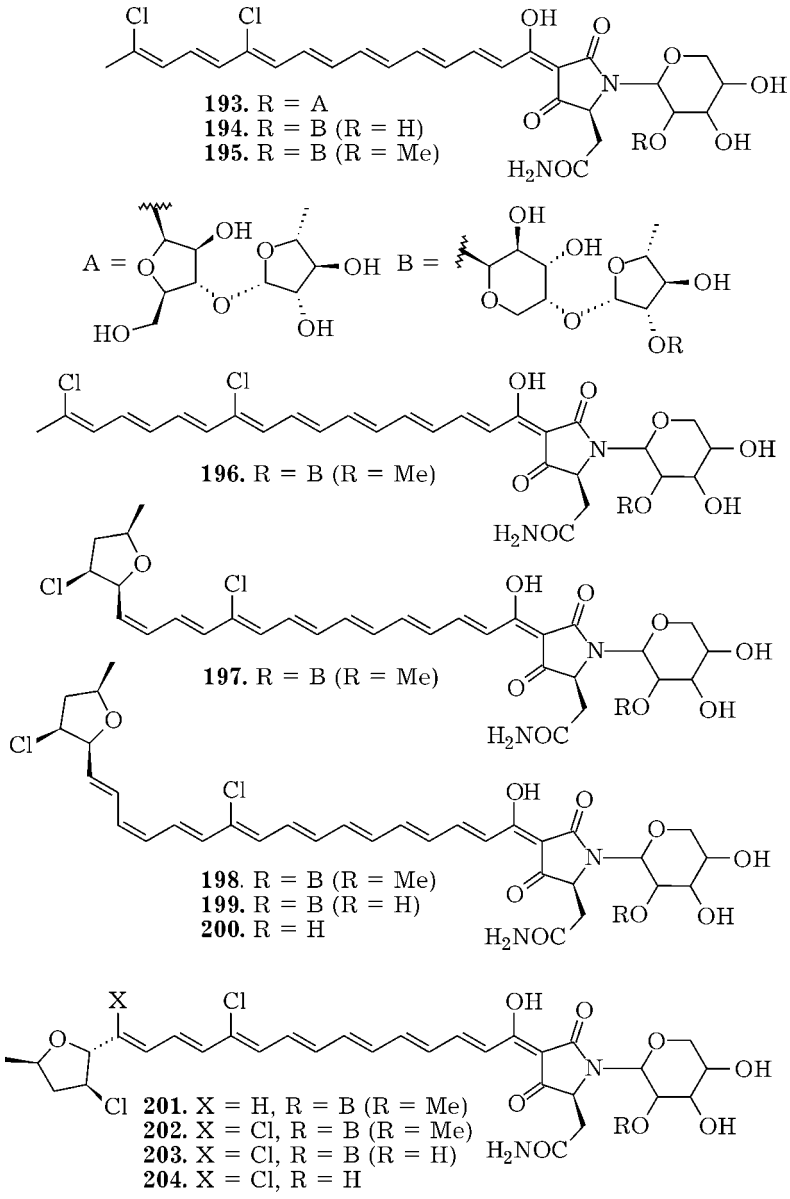
189. R = OH, R_1 = Br
190. R = H, R_1 = Br
191. R = R_1 = H
192. R = OH, R_1 = H

citines A (**181**) and B (**182**) are found also in ascidia belonging to Polycitor family (South Africa) [135]. Polycetone A (**179**) inhibits DNA polymerase [134]. Lucianole B (**180**) – a rare iodine-containing alkaloid – has been isolated from ascidia of a non-established species [136]. New pyrrole alkaloids (**183**)–(**190**) have been isolated from the sponge *Axinella brevistyla* [137], and tauroascidines A (**191**) and B (192) – from the sponge *Hymeniacidon* sp. [138]. Metabolites (**183**)–(**190**) have demonstrated a high activity against *Saccharomyces cerevisiae* [137], and tauroascidines A (**191**) and B (**192**) inhibit the EGF receptor of kinase and of C-erb-2 kinase [138].

A series of halogenated polyene glycosides (**193**)–(**204**) have been isolated from methanol extracts of sea sponges. Thus, aurantoside C (**193**) has been found in the sponge *Homophymia conferta* [139] living near the Philippines, and aurantosides D (**194**), E (**195**) and F (**196**) possessing an antifungal activity have been detected in the sponge *Siliquariaspongia japonica* [140] from the Japanese Sea. Rubrosides A – H (**197**)–(**204**) have been isolated from the same sponge species *S. japonica* [141].

Fungus *Auxarthron umbrinum* produces antibiotic rubrin (**205**) that prevents peroxide oxidation of biomembrane lipids [142]. It has been proposed to use rubrin for the treatment of consequences of myocardial infarction and cerebral ischemia [142, 143]. Thiazochalostatin (**206**) has been found in the culture of fungus *Actinomadura* sp. [144, 145]. Sea ciliate *Pseudokeronopsis rubra* contains new bromopyrrole alkaloids keronopsines A_1 (**207**), A_2 (**208**), B_1 (**209**) and B_2 (**210**) [146].

Bromopyrrole alkaloids slagelines A (**211**) and B (**212**) have been isolated from the Okinawa sponge *Agelas nakamurai* [147, 148], and axillamides of an unusual structure – A (**213**) and B (**214**) – found in the Australian sponge *Ax-*



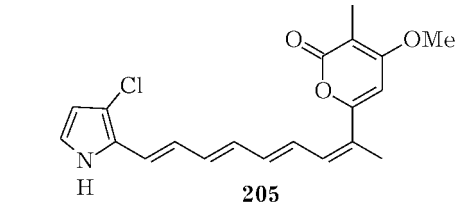
inella sp. [149]. Sponge *Homaxinella* sp. contains three new alkaloids (**215**)–(**217**) [150].

ALKALOIDS OF OTHER STRUCTURAL TYPES

7-Bromoquinoline (**218**) has been isolated from the sea bryozoa *Flustra foliacea* [151], and the ascidia *Pyura sacciformis* produces quinazolidione (**219**) [152]. Sea sponge *Echinodictyum* sp. contains pyrrolopyrimidine (**220**), and a iodine-containing nucleoside – tubercidine (**221**) – has been found in the Australian red alga *Hypnea valendiae* [153]. Bryozoa *Amathia wilsoni* synthesizes amathamides A (**222**) and B (**223**) [154], and the coral *Tubastraea micrantha* contains tubastraine (**224**) [155].

A series of halogenated pyridoacridine alkaloids was first isolated from sea organisms. Thus, 2-bromoleptoclinidinone (**225**) was discovered in ascidia *Leptoclinides* sp. [150]; pantheridine (**226**) possessing a high activity against cancer cells P388 was found in the Australian ascidia *Aplidium pantherium* [157], and shermillamine A (**227**) was isolated from ascidia *Tridemnum* sp. [158].

The deep-water sponge *Batzella* sp. inhabiting the Caribbean Sea contains secobatzelines



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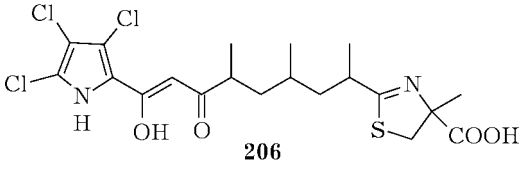

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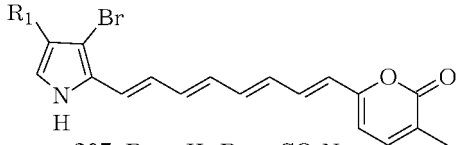
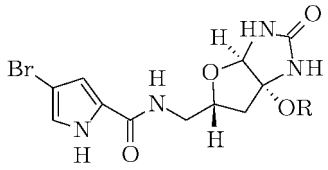
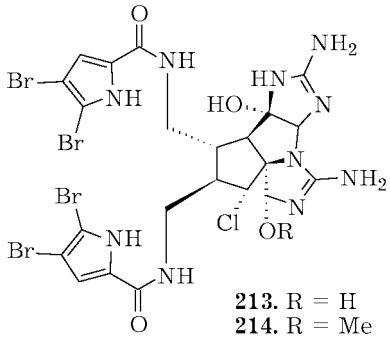


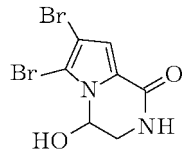
207. R_1 = H, R_2 = SO_3Na
208. R_1 = Br, R_2 = SO_3Na
209. R_1 = R_2 = H
210. R_1 = Br, R_2 = H



211. R = H
212. R = Me



213. R = H
214. R = Me



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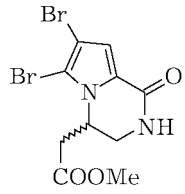
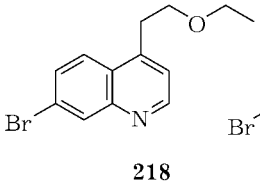


216. (*R*)
217. (*S*)



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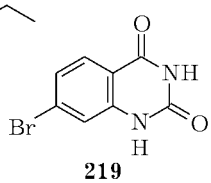

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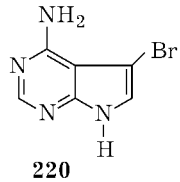

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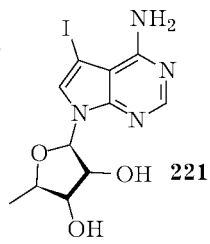
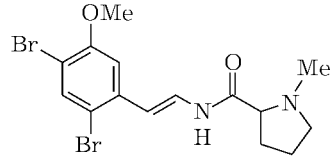
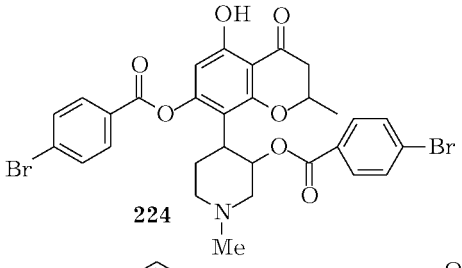


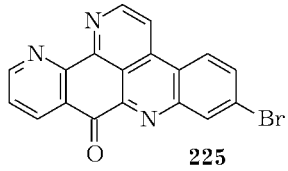
221



222. *E*-изомер
223. *Z*-изомер



224



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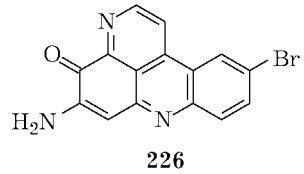
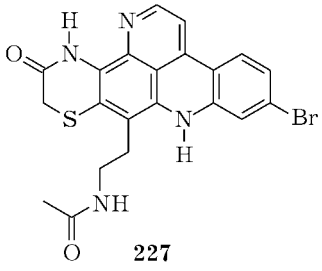
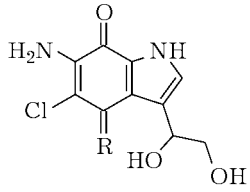


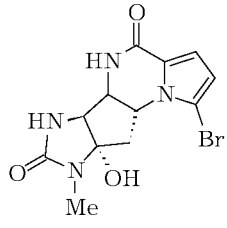
226



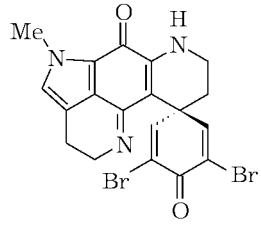
227



228. R = NH
229. R = O



230



231

A (**228**) and B (*229*) [159] which have a high cytotoxic activity and inhibit pepsidase CPP32. Cytotoxic metabolite agelastatine (**230**) has been isolated from the sponge *Agelas dendromorpha* [160], and discorchabdine P (**231**) having an activity similar to that of secobatzelines A (**228**) and B (**229**) was found in the deep-water sponge *Batzella* sp. lived near the Bahamas [161].

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