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NAPHTHOQUINONE METABOLITES OF THE FUNGI

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Key Word Index—Fungi; naphthoquinones; structure; physico-chemical properties; biosynthesis; biogenesis; biological activity; physiological role.

Abstract—Structures and physico-chemical properties of 100 naphthoquinone metabolites produced by filamentous fungi are reviewed. The conditions of pigment formation, biogenesis and the mechanism of biosynthesis of pigments by fungi are described. Sixty-three fungi cultures able to produce naphthoquinone are listed. The biological activities of the main pigments and the mechanism of fungal resistance to their own metabolites are described. The physiological role of the naphthoquinones in producers is discussed. © 1998 Elsevier Science Ltd. All rights reserved

INTRODUCTION

Interaction of species in an ecosystem is known to be determined by many factors, including the ability of the microorganisms to excrete substances which affect the development of other species. Such metabolites called allelotic metabolites play an important role in species adaptation, formation and functioning of communities [1]. The allelotic metabolites cover a broad range of metabolites, including both simple (organic acids, alcohols, sugars etc.) and complex (antibiotics, toxins, hormones etc.) compounds inhibiting and stimulating metabolic processes. This paper presents data on the naphthoquinone secondary metabolites of fungi.

Naphthoquinones are widespread in nature and have been found in higher plants [2], fungi [2, 3] and actinomycetes [4]. The interest of many investigators to this class of compounds is due to their broad-range biological action: phytotoxic [5–8], insecticidal [9], antibacterial [10–17] and fungicidal [12–15]. Besides, some of them also have cytostatic [13] and anticarcinogenic [18–20] properties. Nevertheless, as for most secondary fungal metabolites, at present there is no generally accepted view of the physiological role of naphthoquinones for the producers. In our opinion, it is the high biological activity of the fungal naphthoquinone metabolites with respect to the microorganisms, plants and other species that determines their ecological significance. We consider here the following aspects: (1) structural formulae and available information on the physico-chemical properties of naphthoquinones; (2) biosynthesis and the biogenetic relations of the pigments; and (3) biological activity and the mechanism of action of naphthoquinones. The structures and physico-chemical properties of naphthoquinone metabolites are given in Table 1.

The literature data given in Table 1 indicate that the ability for naphthoquinone biosynthesis is widespread among fungal organisms. It will suffice to note that the list of fungi producers includes 63 cultures (Table 2). Most fungi in this list belong to the genus *Fusarium*. However, it does not mean that other representatives are less active in producing naphthoquinone pigments; they have yet to be examined.

Naphthoquinone metabolites of fungi differ markedly in their chemical composition. Suffice is to compare the simplest of them, juglone, with bicaverine or dimeric naphthoquinones.

CONDITIONS OF NAPHTHOQUINONE BIOSYNTHESIS

The data on the dependence of pigment formation in the fungi on the composition of the medium used have been obtained in studies of naphthoquinone biosynthesis in *Fusarium* [6, 9, 82, 112]. Most of these workers aimed to obtain maximal amounts of various pigments and to study their structure. As a rule, rich complex media were used. Some papers [6, 9, 112] indicate that one of the conditions of naphthoquinone formation is the presence of ammonium nitrogen in the medium. Substitution of nitrate for ammonium

* Author to whom correspondence should be addressed.

Table 1. Structures and physico-chemical properties of the Naphthoquinone metabolites of fungi

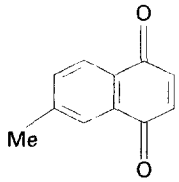
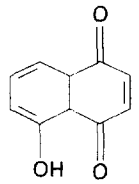
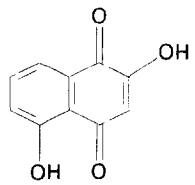
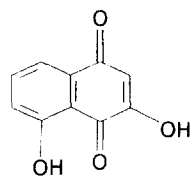
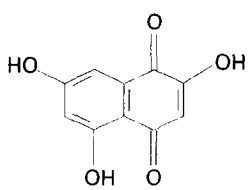
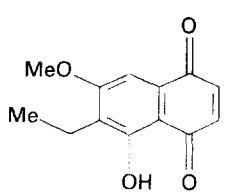
Naphthoquinone	Same physico-chemical properties
 (**1**) 6-methyl-1,4-NQ	$C_{11}H_8O_2$ M_r: 172 mp: 90–91° UV λ_{max}^{EtOH} nm (log ε): 249 (4.39), 255.5 (4.29), 342.5 (3.44). IR ν^{KBr} cm^{-1}: 1160, 1599. Source: *Marasmius graminum* [21].
 (**2**) Juglone	$C_{10}H_6O_3$ M_r: 174 mp: 164–165° UV λ_{max}^{EtOH} nm (log ε): 249 (4.09), 345sh (3.08), 422 (3.56). IR ν^{KBr} cm^{-1}: 1666, 1645, 1603. Source: *Verticillium dahliae* [22, 23].
 (**3**) 2-hydroxyjuglone	$C_{10}H_6O_4$ M_r: 190.0 UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 284 (4.08), 429 (3.54). $\lambda_{max}^{MeOH-HCl}$ nm (log ε): 282.5 (3.84), 411 (3.36). $\lambda_{max}^{MeOH-Na}$ nm (log ε): 261 (4.15), 386 (3.20), 470 (3.32). ^{1}H NMR [$(CD_3)_2CO$]: 4.34 (1H), 6.27 (1H), 7.25–7.45 (1H), 7.60–7.81 (2H), 12.70 (1H). Sources: *Pyricularia oryzae* [24], *V. dahliae* [25], *Cladosporium* sp., *Stemphylium* [26].
 (**4**) 3-hydroxyjuglone	$C_{10}H_6O_4$ M_r: 190.0 UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 284 (4.08), 429 (3.54). ^{1}H NMR [$(CD_3)_2CO$]: 4.34 (1H), 6.27 (1H), 7.25–7.45 (1H), 7.60–7.81 (2H), 12.70 (1H). Source: *V. dahliae* [25].
 (**5**) Flavioline	$C_{10}H_6O_5$ M_r: 206 mp: 164.5–168.5° UV λ_{max}^{Et-HCl} nm (log ε): 213 (4.33), 264 (4.18), 309 (3.86), 399 (2.30), 450 (3.38). UV λ_{max}^{Et-ONa} nm (log ε): 284.5 (4.38) 63 (3.78) 554 (3.34). IR ν^{KBr} cm^{-1}: 1592, 1385, 1240, 1175. ^{1}H NMR [$(CD_3)_2CO$]: 6.15 (1H, *s*), 6.68 (1H, *d*), 7.15 (1H, *d*), 12.65 (1H, *s*). Sources: *Aspergillus niger* [27], *A. citricus* [28], *Foma vasabiae* [23], *V. dahliae* [25], *Cladosporium* sp. [26], *Stemphylium* sp. [26].
 (**6**) 6-ethyl-7-methoxyjuglone	$C_{13}H_{12}O_4$ M_r: 232.0 mp: 103–104° UV λ_{max}^{MeOH} nm (log ε): 262 (4.56), 68sh (4.56), 426 (4.01). IR ν^{KBr} cm^{-1}: 2940, 1665, 1635, 1595. ^{1}H NMR ($CDCl_3$): 1.02 (*t*, Me), 2.64 (*q*, 2H), 3.85 (*s*, OMe), 6.73 (*s*, 2H), 7.05 (*s*, 1H), 12.10 (*s*, OH). Source: *Aspergillus parvulus* [29].

Table 1—*continued.*

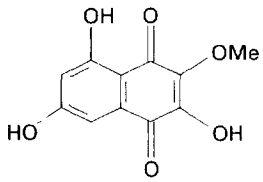
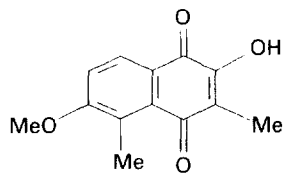
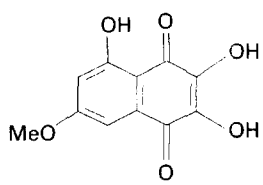
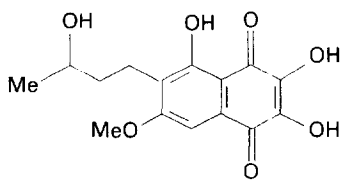
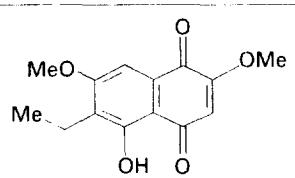
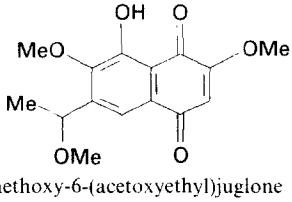
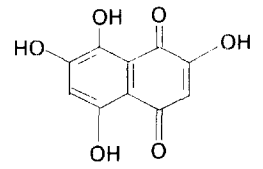
Naphthoquinone	Same physico-chemical properties
 (**7**) 2-methoxy-3,6,8-trihydroxy-1,4-NQ	$C_{11}H_8O_6$ M_r: 236 mp: 255 UV λ_{max}^{EtOH} nm (log ε): 225 (4.10), 269.5 (4.1), 320 (3.82), 384 (3.50), 470sh (3.08). UV $\lambda_{max}^{Et\text{-}ONa}$ nm: 227, 291, 374, 580. IR ν^{KBr} cm^{-1}: 3360, 1650, 1615. ^{1}H NMR (DMSO-d_6): 3.88 (*s*, OMe), 6.50 (*s*, H-Ar), 6.94 (*s*, H-Ar), 12.20 (*s*, OH). Source: *Cercospora melonis* [30].
 (**8**) 2-hydroxy-6-methoxy-3,5-dimethyl-1,4-NQ	$C_{13}H_{12}O_4$ M_r: 232 mp: 116–117° UV λ_{max}^{EtOH} nm (log ε): 217 (4.0), 287 (4.17), 410 (2.61). IR ν^{KBr} cm^{-1}: 3360, 1660, 1625, 1615. Source: *Foma wasabiae* [31].
 (**9**) 7-methylspinochrome B	$C_{11}H_8O_6$ M_r: 236 mp: 267° UV λ_{max}^{EtOH} nm (log ε): 272 (4.33), 285sh, 322 (3.99), 385 (3.56), 485 (3.26). IR ν^{KBr} cm^{-1}: 3480, 1660, 1620. Source: *Corynespora casiocala* [32].
 (**10**) 7-(3-hydroxy-*n*-butyl)-6-methyl-spinochrome B	$C_{15}H_{16}O_7$ M_r: 308 mp: 202 UV λ_{max}^{EtOH} nm (log ε): 273 (4.26), 286sh, 331 (3.87), 400 (3.44). IR ν^{KBr} cm^{-1}: 3400, 1650, 1610. Source: *Corinespora casiocala* [32].
 (**11**) 2,7-dimethoxy-5-hydroxy-6-ethyl-1,4-NQ	$C_{14}H_{14}O_5$ M_r: 262 mp: 187° UV λ_{max}^{MeOH} nm: 221, 256, 262, 305, 422. IR ν^{KBr} cm^{-1}: 1672, 1628, 1590. ^{1}H NMR ($CDCl_3$): 1.13 (*t*, Me), 2.75 (*q*, CH_2), 3.92 (*s*, OMe), 4.00 (*s*, OMe), 6.04 (*s*, H-Ar), 7.30 (*s*, H-Ar), 12.50 (*s*, OH). Source: *Hendersonula toruloidea* [33].
 (**12**) 2,7-dimethoxy-6-(acetoxyethyl)juglone	$C_{16}H_{16}O_7$ M_r: 320 mp: 160–163° UV λ_{max}^{MeOH} nm (log ε): 220 (4.51), 57sh (4.14), 263 (4.15), 306 (3.97), 425 (3.55). IR ν^{CCl_4} cm^{-1}: 1742, 1690, 1632. Source: *Hendersonula toruloidea* [34].
 (**13**) Mompain	$C_{10}H_6O_6$ M_r: 222 mp: >300°-decomp. UV λ_{max}^{EtOH} nm (log ε): 228 (4.43), 272 (4.06), 318 (3.93), 486 (3.75), 517 (3.80). IR ν^{KBr} cm^{-1}: 3240, 1660, 1625, 1602. ^{1}H NMR (DMSO-d_6): 6.31 (*s*, H-Ar), 6.31 (*s*, H-Ar), 13.1 (*s*, 2OH). Source: *Helicobasidium mompa* [35].

Table 1—*continued.*

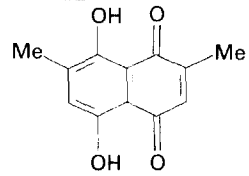
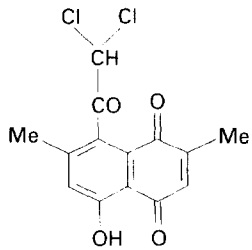
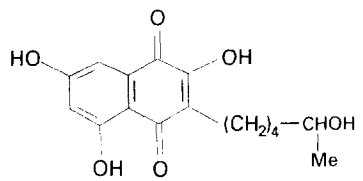
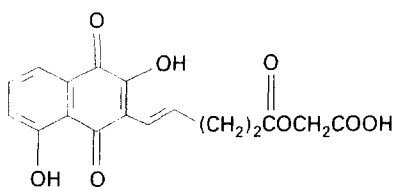
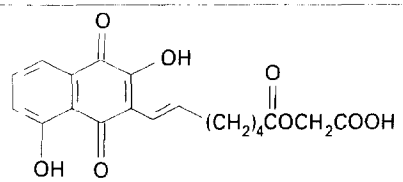
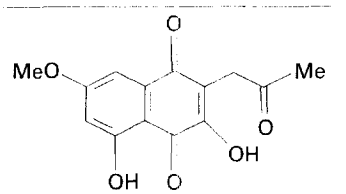
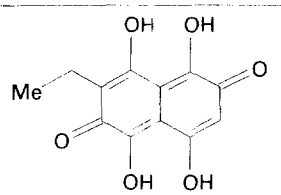
Naphthoquinone	Same physico-chemical properties
 (**14**) 2,7-dimethylnaphtazarin	$C_{12}H_{10}O_4$ M_r: 194 mp: 125–126 UV λ_{max}^{EtOH} nm (log ε): 217 (4.55), 280 (3.30), 480 (3.77), 510 (3.79), 550 (3.58). IR ν^{KBr} cm^{-1}: 1611. Source: *Mollisia caesia* [36].
 (**15**) Mollisin	$C_{14}H_{10}O_4Cl_2$ M_r: 313 mp: 202–203 UV λ_{max}^{EtOH} nm (log ε): 259 (4.26), 280 (3.90), 420 (3.52). IR ν^{KBr} cm^{-1}: 1720, 1649, 1618. ^{1}H NMR ($CDCl_3$) (τ): −2.05 (OH), 2.81 (H-Ar), 3.67 ($COCHCl_2$), 7.58 (CH-Ar), 7.84 (CH-Q), 2.81 (H-Q). Sources: *Mollisia caesia*, *M. fallens* [36–38].
 (**16**) 2,5,7-trihydroxy-3-(5-hydroxyhexyl)-1,4-NQ	$C_{16}H_{18}O_6$ M_r: 306 mp: 166–168 UV λ_{max}^{EtOH} nm (log ε): 214, 263, 314, 382, 460. IR ν^{KBr} cm^{-1}: 3370, 1650–1630, 1340. ^{1}H NMR (acetone-d_6): 1.09 (*s*, Me), 1.04 (2Me), 2.54 (2H), 3.70 (1H), 6.59 (H-Ar), 7.06 (H-Ar), 12.68 (OH). Source: *Penicillium* sp. [39].
 (**17**) Trichione	$C_{17}H_{14}O_6$ M_r: 346 Source: *Trichia floriformis* [40].
 (**18**) Homotrichione	$C_{19}H_{18}O_8$ M_r: 374 Source: *Metatrichia vespasiarum* [40].
 (**19**) 2-acetonyl-3,5-dihydroxy-7-methoxy-1,4-NQ	$C_{14}H_{12}O_6$ M_r: 276 mp: 208 UV λ_{max}^{EtOH} nm (log ε): 208 (4.4), 227 (4.3), 272 (4.2), 313 (4.1), 380 (3.7). IR ν^{KCl} cm^{-1}: 3340, 2980, 1705, 1635, 1610. ^{1}H NMR (pyridine-d_5): 2.30 (*s*, Me), 3.70 (*s*, OMe), 3.95 (*s*, CH_2), 6.70 (*d*, H-Ar), 7.35 (*d*, H-Ar), 10.7 (*s*, OH). Source: *Cylindrocarpon* sp. [41].
 (**20**) 1,4,5,8-tetrahydroxy-3-ethylnaphthalene-2,6-dione	$C_{12}H_{10}O_6$ M_r: 250 mp: 183–185 UV λ_{max}^{MeOH} nm (log ε): 217, 241sh, 266, 485sh, 517, 555. IR ν^{KBr} cm^{-1}: 3527, 3400, 2968–2872, 1598, 1460. ^{1}H NMR ($CDCl_3$): 1.23 (*t*, 3H, Me), 2.66 (*q*, 2H, CH_2), 11.33 (*s*, OH). Source: *Cetraria cucullata* [42].

Table 1—*continued.*

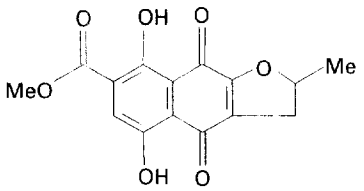
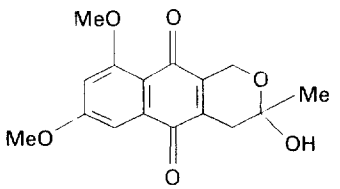
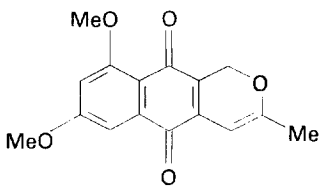
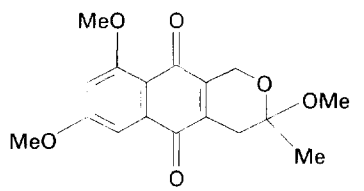
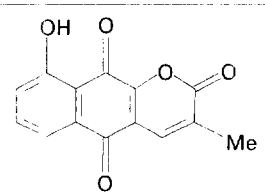
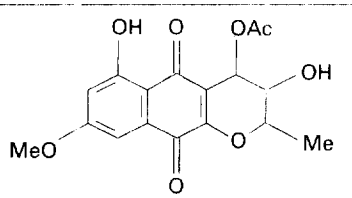
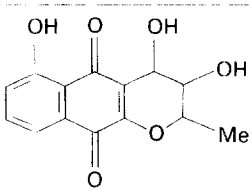
Naphthoquinone	Same physico-chemical properties
 (**21**) Homoventosin	$C_{15}H_{14}O_7$ M_r: 306 mp: 180° decomp. UV λ_{max}^{EtOH} nm (log ε): 235 (4.43), 294 (3.98), 505 (3.90). IR ν^{KBr} cm^{-1}: 1725, 1662, 1610, 1570. Source: *Haematomma ventosum* [43].
 (**22**) Herbarin	$C_{16}H_{16}O_6$ M_r: 304 mp: 192–193° IR ν^{KBr} cm^{-1}: 3325, 1678, 1650, 1607, 1572, 1567. ^{1}H NMR (pyridine-d_5) (τ): 2.61 (*d*, 1H), 3.18 (*d*, 1H), 4.9–5.0 (*m*, 2H), 5.4 (*s*, 1H), 6.17 (*s*, 3H), 6.21 (*s*, 3H), 6.86 (*m*, 1H), 7.33 (*m*, 1H), 8.26 (*s*, 3H). Source: *Torula herbarum* [44].
 (**23**) Dehydroherbarin	$C_{16}H_{14}O_5$ M_r: 286 mp: 189–190° UV λ_{max}^{EtOH} nm (log ε): 217 (4.12), 250 (3.85), 272 (3.85), 335 (3.28), 400 (3.15), 485 (3.15). IR ν^{KBr} cm^{-1}: 1675, 1632, 1610, 1600, 1565. ^{1}H NMR ($CDCl_3$) (τ): 2.75 (1H, *d*), 3.30 (1H, *d*), 4.18 (1H, *d*), 4.88 (2H, *s*), 6.05 (3H, *s*), 6.07 (3H, *s*), 8.02 (3H, *s*). Source: *Torula herbarum* [44].
 (**24**) *O*-methylherbarin	$C_{17}H_{18}O_6$ M_r: 318 mp: 188–190° UV λ_{max}^{EtOH} nm: 218, 267, 285sh, 415. ^{1}H NMR ($CDCl_3$) (τ): 2.73 (H-Ar), 3.29 (H-Ar), 5.25–5.65 (2H), 7.2–7.55 (2H), 6.06–6.08 (2OMe-Ar), 6.72 (OMe), 8.52 (Me). Source: *Torula herbarum* [45].
 (**25**) Lambertellin	$C_{14}H_8O_5$ M_r: 256 mp: 253–254° UV λ_{max}^{EtOH} nm (log ε): 284 (4.08), 290 (4.10), 430 (3.68). IR ν^{Nujol} cm^{-1}: 1746, 1665, 1657, 1620. ^{1}H NMR (D_2O) (τ): 1.74–2.58 (*m*, Me), 3.23 (*q*, 1H), 7.29 (*d*, 3H). Sources: *Lambertella* sp. [46], *Pseudospirones simplex* [47].
 (**26**) Gunacin	$C_{17}H_{16}O_8$ M_r: 348 UV λ_{max}^{EtOH} nm: 228, 267, 311–317, 430–445. λ_{max}^{EtONa} nm: 238, 290, 310–320, 520–545. IR ν^{KBr} cm^{-1}: 1730–1740, 1635, 1250. ^{1}H NMR ($CDCl_3$): 7.17 (1K, *d*), 6.65 (1H, *d*), 6.2 (1H, *d*), 4.4 (1H, *m*), 4.15 (1H, *m*), 3.9 (3H, *s*), 2.1 (3H, *s*), 1.7 (3H, *d*). Source: *Ustilago* sp. [15].
 (**27**) Cryptosporin	$C_{14}H_{12}O_6$ M_r: 276 mp: 244 UV λ_{max}^{MeOH} nm (log ε): 240 (4.08), 287 (4.00), 408 (3.65). IR ν^{KBr} cm^{-1}: 3550, 3500, 3300, 1660, 1635. Source: *Cryptosporium pinicola* [48].

Table 1—*continued.*

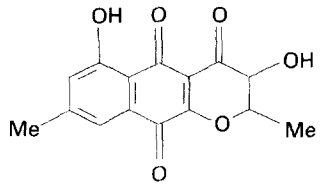
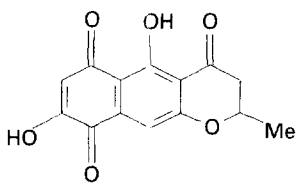
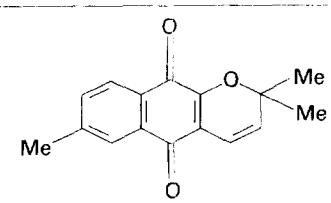
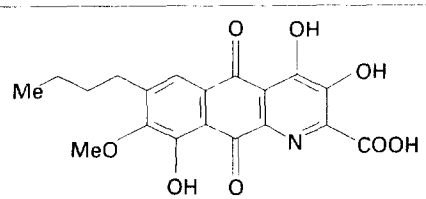
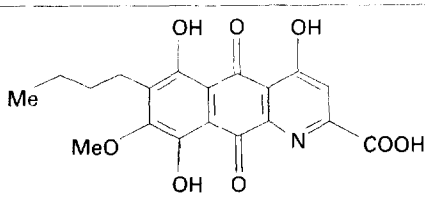
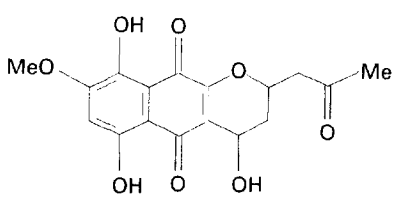
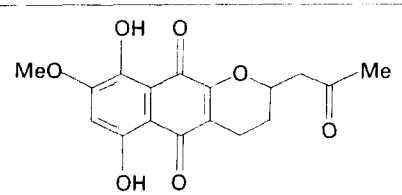
Naphthoquinone	Same physico-chemical properties
 (**28**) Rodocladonic acid	$C_{15}H_{10}O_8$ M_r: 318 mp: >300° decomp. UV λ_{max}^{EtOH} nm (log ε): 294 (4.37), 318 (4.18), 328 (3.99), 449 (3.65). IR ν^{KBr} cm^{-1}: 3385, 3300, 1660, 1630. Source: *Cladonia* sp. (lichens) [49].
 (**29**) Kanarion	$C_{14}H_8O_5$ M_r: 272 mp: 192–197° UV λ_{max}^{MeOH} nm (log ε): 241 (4.15), 267 (4.03), 370 (3.43), 430 (3.40). λ_{max}^{MeONa} nm: 279, 384, 520. IR ν^{KBr} cm^{-1}: 3450, 2940, 2850, 1650, 1595. Sources: *Usnea canariensis*, *Usnea nookeri* (lichens) [50].
 (**30**) 6-methyl-dehydro-a-lapachone	$C_{16}H_{14}O_3$ M_r: 254 mp: 130–132° UV λ_{max}^{EtOH} nm (log ε): 204 (4.52), 265 (4.30), 275 (4.26), 333 (3.76), 444 (3.14). IR ν^{KBr} cm^{-1}: 1668, 1648. ^{1}H NMR ($CDCl_3$): 1.57 (*s*, 2Me), 2.51 (*s*, Me), 5.75 (*d*, 1H), 6.70 (*d*, 1H), 7.93 (*s*, 1H), 7.55 (*d*, 1H), 8.02 (*d*, 1H). Source: *Fomes annosus* [51].
 (**31**) Phomasarin	$C_{19}H_{16}O_8N$ M_r: 387 mp: 196° UV λ_{max}^{EtOH} nm (log ε): 231 (4.54), 277 (4.77), 430 (3.92). IR ν^{CHCl_3} cm^{-1}: 1633, 1694. ^{1}H NMR (CF_3COOD) (τ): 1.95 (*s*, 1H), 5.75 (*s*, OMe), 7.06 (*t*, 2H, CH_2), 8.4 (*m*, 4H, $2CH_2$), −2.48 (*s*, OH), 8.95 (*t*, Me). Source: *Pyrenochaeta cerestris* [52].
 (**32**) Isophomasarin	$C_{18}H_{17}O_8N$ M_r: 387 mp: 215–216° UV λ_{max}^{EtOH} nm (log ε): 231 (4.54), 277 (4.77), 430 (3.92). IR ν^{CHCl_3} cm^{-1}: 1615, 1730. ^{1}H NMR (CF_3COOD): 1.72 (*s*, 1H), 5.86 (*s*, OMe), 7.06 (2H, CH_2), 8.4 (4H, $2CH_2$), 8.97 (*t*, Me). Source: *Pyrenochaeta cerestris* [53].
 (**33**) Erythrostominone	$C_{17}H_{16}O_8$ M_r: 348 mp: 184–185° UV λ_{max}^{EtOH} nm (log ε): 231.5 (4.54), 280 (3.89), 315 (3.9), 480 (3.86), 509 (3.93), 546 (3.72). IR ν^{CHBr_3} cm^{-1}: 3580, 1720, 1604. ^{1}H NMR ($CDCl_3$) (τ): 5.15 (*m*, 1H), 5.38 (*m*, 1H), 8.25 (*m*, 2H), 3.73 (*s*, H-Ar), 7.1 (*s*, 2H), 7.77 (*s*, 3H), 6.16 (*s*, OMe), −2.6 (*s*, OH), −3.9 (*s*, OH). Source: *Gnomonia erythrostoma* [54].
 (**34**) Deoxyerythrostominone	$C_{17}H_{16}O_7$ M_r: 332 mp: 148–150° UV λ_{max}^{EtOH} nm (log ε): 234 (4.49), 275 (3.83), 317 (3.88), 477 (3.84), 505 (3.91), 542 (3.73). IR ν^{CHBr_3} cm^{-1}: 1713, 1601. ^{1}H NMR ($CDCl_3$) (τ): 5.47 (*m*, 1H), 8.3 (*m*, 2H), 7.4 (*m*, 2H), 7.1 (*m*, 2H), 7.74 (*s*, Me), 3.72 (*s*, H-Ar), 6.16 (*s*, Me), −2.6 (*s*, OH), −3.9 (*s*, OH). Source: *Gnomonia erythrostoma* [54].

Table 1—*continued.*

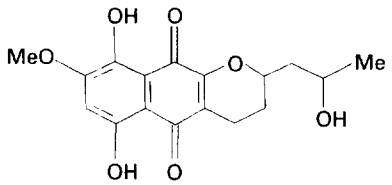
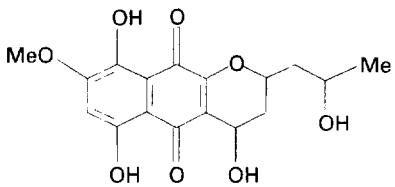
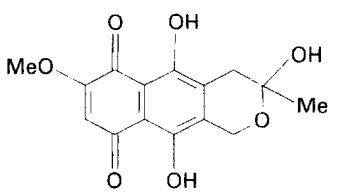
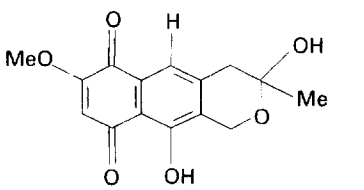
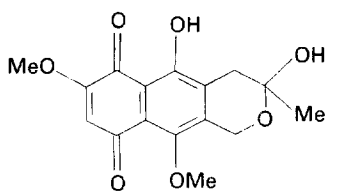
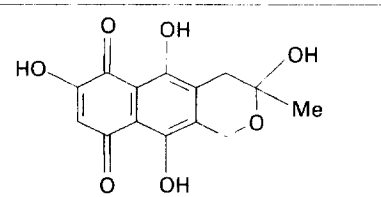
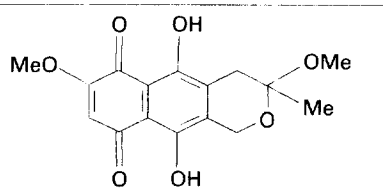
Naphthoquinone	Same physico-chemical properties
 (**35**) Deoxyerythrostominol	$C_{17}H_{18}O_7$ M_r: 334 mp: 139–141° UV λ_{max}^{EtOH} nm (log ε): 234 (4.46), 275 (3.85), 317 (3.89), 475sh (3.84), 505 (3.92), 541 (3.73). IR ν^{Nujol} cm^{-1}: 3580, 1603. ^1H NMR ($CDCl_3$) (τ): 5.59 (*m*, 1H), 8.12 (*m*, 2H), 7.37 (*m*, 1H), 3.65 (*s*, H-Ar), 7.1 (*m*, 2H), 5.82 (*m*, 1H), 8.72 (3H), 6.16 (*s*, OMe), −2.6 (*s*, OH), −3.9 (OH). Source: *Gnomonia erythrostoma* [54].
 (**36**) Epierythrostominol	$C_{17}H_{18}O_8$ M_r: 350 mp: 187–191° UV λ_{max}^{EtOH} nm (log ε): 231 (4.51), 277 (3.91), 317 (3.90), 482 (3.84), 514 (3.93), 551 (3.73). IR ν^{Nujol} cm^{-1}: 3570, 1605. ^1H NMR ($CDCl_3$) (τ): 8.67 (*d*, Me), 7.97 (*m*, $2CH_2$), 6.05 (*s*, OMe), 5.72 (*m*, 2H), 5.04 (*m*, 1H), 3.58 (*s*, 1H), −2.63 (*s*, OH), −3.21 (*s*, OH). Source: *Gnomonia erythrostoma* [55].
 (**37**) Fusarubin	$C_{15}H_{14}O_7$ M_r: 306 mp: 218 UV λ_{max}^{EtOH} nm: 224, 304, 475, 500, 535. IR ν^{CDCl_3} cm : 3550, 3425, 2900, 2825, 1600, 1570. ^1H NMR ($CDCl_3$): 1.80 (3H, *s*, Me), 3.05 (2H, *m*), 3.80 (3H, *s*, OMe), 5.15 (2H, *m*), 6.33 (1H, *s*, H-Ar), 12.69 (1H, *s*, OH), 12.95 (1H, *s*, OH). Sources: *Fusarium solani* [7, 11, 58, 59], *Neocosmospora vasinfectun*, *N. africana* [57], *Nectria haematococca* [56], *F. decemcellulare* [60], *F. moniliforme* [61].
 (**38**) Deoxyfusarubin	$C_{15}H_{14}O_6$ M_r: 290 mp: 208–212° UV λ_{max}^{EtOH} nm (log ε): 218 (3.95), 250 (3.84), 295 (3.72), 410 (3.33), 423 (3.34), 445 (3.22). IR ν^{KBr} cm^{-1}: 1680, 1620. ^1H NMR ($CDCl_3$): 1.65 (3H, *s*), 2.96 (2H, *s*), 3.94 (3H, *s*), 4.92 (2H, *s*), 6.04 (1H, *s*), 7.43 (1H, *s*), 12.25 (1H, *s*). Source: *Nectria haematococca* [62].
 (**39**) *O*-methylfusarubin	$C_{16}H_{16}O_7$ M_r: 320 mp: 138–139° UV λ_{max}^{MeOH} nm (log ε): 226 (4.48), 282.5 (4.05), 484 (3.83), 510 (3.80), 550 (3.49). IR ν^{KBr} cm^{-1}: 3470, 3240, 1605, 1550, 1460 [63]. ^1H NMR ($CDCl_3$): 1.56 (3H, Me), 2.50–2.78 (2H), 4.01 (3H, OMe), 4.05 (3H, OMe), 4.66 (2H), 6.85 (1H, H-Ar), 13.16 (1H, OH). Sources: *Fusarium moniliforme* [61], *F. oxysporum* [63].
 (**40**) *O*-demethylfusarubin	$C_{14}H_{12}O_7$ M_r: 292 mp: 195–197° UV λ_{max}^{EtOH} nm: 230, 305, 475, 505, 540. IR ν^{KBr} cm^{-1}: 3450, 3380, 1620, 1575. ^1H NMR ($CDCl_3$): 1.65 (3H, Me), 2.67–2.96 (2H), 4.85–4.91 (2H), 6.34 (1H, H-Ar), 13.01 (1H, OH), 11.88 (1H, OH). Source: *F. decemcellulare* [64].
 (**41**) *O*-methylfusarubin	$C_{16}H_{16}O_7$ M_r: 320 mp: 188–190° UV λ_{max}^{EtOH} nm: 225 (4.49), 302 (3.95), 470 (3.78), 495 (3.83), 532 (3.64). IR ν^{KBr} cm $^{-1}$: 3425, 1600. ^1H NMR ($CDCl_3$): 1.54 (3H, *s*, Me), 3.04–2.64 (2H, *dd*), 3.31 (3H, *s*, OMe), 3.92 (3H, *s*, OMe), 4.90–4.53 (2H, *dd*), 6.17 (1H, *s*, H-Ar), 12.63 (1H, *s*, OH), 12.91 (1H, *s*, OH). Sources: *F. martii* [13], *F. solani* [65].

Table 1—*continued.*

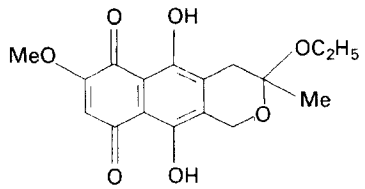
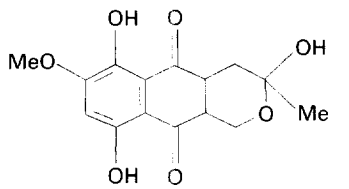
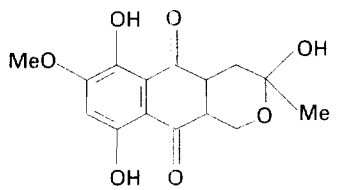
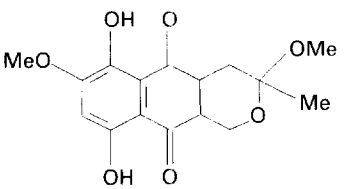
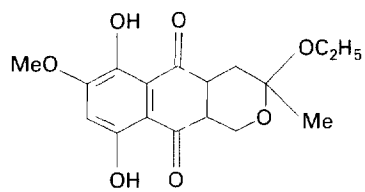
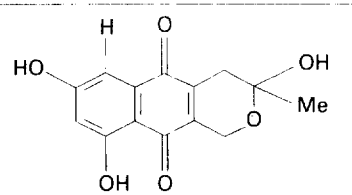
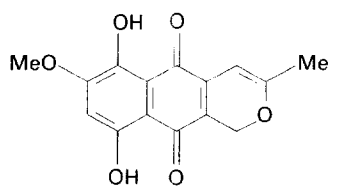
Naphthoquinone	Same physico-chemical properties
 (**42**) *O*-ethylfusarubin	$C_{17}H_{18}O_7$ M_r: 334 mp: 138–139° UV λ_{max}^{EtOH} nm (log ε): 225 (4.44), 302 (3.91), 470 (3.78). IR ν^{KBr} cm^{-1}: 3425, 1625. ^{1}H NMR ($CDCl_3$): 1.55 (3H, *s*, Me), 3.04–2.64 (2H, *dd*), 3.61–1.55 (5H, *q*, *t*, OCH_2CH_3), 3.92 (3H, *s*, OMe), 4.88–4.52 (2H, *dd*), 6.17 (1H, *s*, H-Ar), 12.63 (1H, *s*, OH), 12.91 (1H, *s*, OH). Sources: *F. martii* [13], *F. solani* [66].
 (**43**) Dihydrofusarubin (stereoisomer 1)	$C_{15}H_{16}O_7$ M_r: 308 mp: 153–154° UV λ_{max}^{EtOH} nm (log ε): 231 (4.17), 243 (4.30), 273 (3.97), 300 (3.71), 391 (3.94). ^{1}H NMR ($CDCl_3$): 1.75 (*s*, Me), 3.87 (*s*, OMe), 6.98 (*s*, H-Ar), 7.96 (*bs*, OH), 12.58 (*bs*, OH), 12.83 (*bs*, OH), 4.45–4.46 (*m*, CH_2), 2.72–1.92 (*dd*, CH_2), 3.37 (*m*, 1H), 3.97 (*m*, 1H). Source: *F. solani* [13, 65, 67].
 (**44**) Dihydrofusarubin (stereoisomer 2)	$C_{15}H_{16}O_7$ M_r: 308 mp: 117–118° UV λ_{max}^{EtOH} nm (log ε): 213 (4.15), 243 (4.31), 273 (3.89), 300 (3.70), 391 (3.96). ^{1}H NMR ($CDCl_3$): 1.38 (*s*, Me), 3.94 (*s*, OMe), 6.72 (*s*, H-Ar), 2.50 (*s*, OH), 12.34 (*s*, OH), 2.69 (*s*, OH), 4.51–4.00 (*dd*, CH_2), 1.97–1.59 (*dd*, CH_2), 3.55 (*m*, 1H), 3.0 (*m*, 1H). Source: *F. solani* [13, 65, 67].
 (**45**) *O*-methyldihydrofusarubin	$C_{16}H_{18}O_7$ M_r: 322 mp: 134–135° UV λ_{max}^{EtOH} nm (log ε): 242 (4.17), 273 (3.79), 300 (3.7), 390 (3.82). IR ν^{KBr} cm^{-1}: 3425, 1625. ^{1}H NMR ($CDCl_3$): 3.81–22 (*dd*, CH_2), 1.68–2.41 (*dd*, CH_2), 3.43 (*ddd*, 1H), 2.94 (*ddd*, 1H), 1.41 (*s*, Me), 6.65 (*s*, H-Ar), 3.95 (*s*, OMe), 3.23 (*s*, OMe), 12.02 (*s*, OH), 12.17 (*s*, OH). Source: *F. solani* [13, 65].
 (**46**) *O*-ethyldihydrofusarubin	$C_{17}H_{20}O_7$ M_r: 336 mp: 138–139° UV λ_{max}^{EtOH} nm (log ε): 242 (4.11), 273 (3.74), 300 (3.70), 390 (3.67). IR ν^{KBr} cm^{-1}: 3425 (OH), 1625 (CO). ^{1}H NMR ($CDCl_3$): 3.79–34 (*dd*, CH_2), 1.76–2.45 (*dd*, CH_2), 3.42 (*ddd*, 1H), 2.97 (*ddd*, 1H), 6.65 (*s*, H-Ar), 1.41 (*s*, Me), 3.95 (*s*, OMe), 11.92 (*s*, OH), 12.16 (*s*, OH). 5.05 (*q*, OCH_2CH_3), 1.38 (*t*, OCH_2CH_3). Sources: *F. solani* [13], *N. haematococca* [68].
 (**47**) 6-*O*-demethyl-5-deoxyfusarubin	$C_{14}H_{12}O_6$ M_r: 276 mp: 194–196° UV λ_{max}^{MeOH} nm (log ε): 2.15 (4.20), 268 (3.89), 288 (3.73), 442 (3.34). IR ν^{KBr} cm^{-1}: 3429, 1649, 1620. ^{1}H NMR (DMSO-d_6): 1.43 (*s*, Me), 6.10 (*s*, OH), 2.33–2.60 (*dd*, 1H), 6.93 (*d*, 1H), 11.20 (*s*, OH), 6.50 (*d*, 1H), 12.0 (*s*, OH), 4.53 (*s*, 1H). Source: *N. haematococca* [69].
 (**48**) Anhydrofusarubin	$C_{15}H_{12}O_6$ M_r: 272 mp: 193–198° UV λ_{max}^{EtOH} nm: 235, 290, 537. IR ν^{KBr} cm^{-1}: 2970, 2920, 2830, 1590, 1435. ^{1}H NMR ($CDCl_3$): 1.95 (*s*, Me), 3.94 (*s*, OMe), 5.22 (*s*, 2H), 5.94 (*s*, 1H), 6.14 (*s*, H-Ar), 12.74 (*s*, OH), 13.10 (*s*, OH). Sources: *F. solani* [7, 56, 65, 70], *Neocosmospora vasinfectum*, *N. africana* [57], *F. decemcellulare* [60].

Table 1—*continued.*

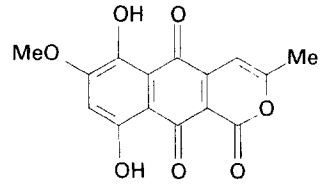
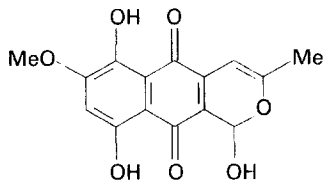
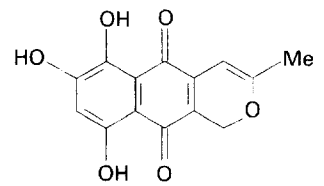
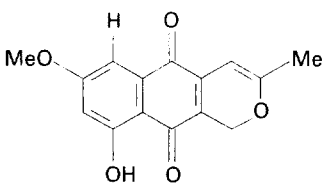
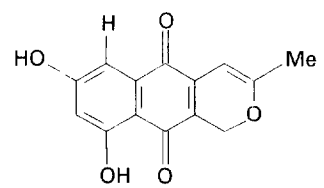
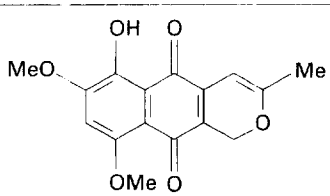
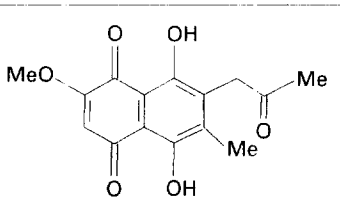
Naphthoquinone	Same physico-chemical properties
 (**49**) Anhydrofusarubin-lacton	$C_{15}H_{10}O_7$ M_r: 302 mp: 300° UV λ_{max}^{EtOH} nm: 240, 285, 355, 500. λ_{max}^{MeOH} nm (log ε): 255 (4.25), 312 (3.55), 330 (3.46), 508 (3.72), 536 (3.77), 576 (3.72), 612 (3.49). IR ν^{KBr} cm^{-1}: 1745, 1650, 1610, 1582. ^{1}H NMR ($CDCl_3$): 2.40 (*s*, Me), 3.95 (*s*, OMe), 6.30 (*s*, H-Ar), 6.84 (*s*, 1H), 12.76 (*s*, OH), 14.30 (*s*, OH) [71]. Sources: *F. solani* [71], *N. haematococca* [72].
 (**50**) Anhydrofusarubin lactol	$C_{15}H_{12}O_7$ M_r: 304 mp: 245° UV λ_{max}^{MeOH} nm (log ε): 228 (4.06), 263 (4.05), 278 (4.0), 343 (3.23), 509 (3.80), 535 (3.87), 572 (3.71). IR ν^{KBr} cm^{-1}: 3425, 1600, 1580, 1440. ^{1}H NMR ($CDCl_3$): 2.18 (*s*, Me), 3.94 (*s*, OMe), 6.26 (*s*, 1H), 6.45 (*s*, 1H), 6.73 (*s*, 1H), 12.85 (*s*, OH), 13.25 (*s*, OH). Sources: *F. solani* [71], *N. haematococca* [73].
 (**51**) *O*-demethylanhydrofusarubin	$C_{14}H_{10}O_6$ M_r: 274 mp: 202–204° UV λ_{max}^{EtOH} nm: 237, 285, 353, 492sh, 546. IR ν^{KBr} cm^{-1}: 3345, 1660, 1607. ^{1}H NMR ($CDCl_3$) (*t*): 8.01 (*s*, Me), 4.79 (*s*, 2H), 4.03 (*s*, 1H), 3.69 (*s*, H-Ar), −1.87 (*s*, OH), −3.10 (*s*, OH). Source: *Gibberella fujikuroi* [74].
 (**52**) Deoxyanhydrofusarubin	$C_{15}H_{12}O_5$ M_r: 272 mp: 210–213° UV λ_{max}^{EtOH} nm (log ε): 235 (3.39), 295 (5.2), 340 (0.95), 450 (1.02). IR ν^{KBr} cm^{-1}: 1680, 1630. ^{1}H NMR ($CDCl_3$): 1.97 (*s*, Me), 3.94 (*s*, OMe), 5.25 (*s*, 2H), 5.60 (*s*, 1H), 5.98 (*s*, H-Ar), 7.12 (*s*, 1H), 12.2 (*s*, OH). Source: *N. haematococca* [62, 70].
 (**53**) 6-*O*-demethyl-5-deoxyanhydrofusarubin	$C_{14}H_{10}O_5$ M_r: 258 mp: 181–184° UV λ_{max}^{MeOH} nm: 279, 355, 509. IR ν^{KBr} cm^{-1}: 3437, 1644, 1613. ^{1}H NMR (DMSO-d_6): 2.03 (*s*, Me), 5.07 (*s*, 1H), 5.85 (*s*, 1H), 6.50 (*d*, 1H), 6.93 (*d*, 1H), 11.72 (*s*, OH), 12.88 (*s*, OH). Source: *N. haematococca* [69].
 (**54**) *O*-methylanhydrofusarubin	$C_{16}H_{14}O_6$ M_r: 302 mp: 175–177° UV λ_{max}^{EtOH} nm (log ε): 208 (4.3), 222 (4.4), 273 (4.2), 503 (3.6). IR ν^{KBr} cm^{-1}: 3450, 1620, 1570, 1460, 1425. ^{1}H NMR ($CDCl_3$): 2.00 (*s*, Me), 3.97 (*s*, OMe) 4.00 (*s*, OMe), 5.15 (*s*, 2H), 5.83 (*s*, 1H), 6.74 (*s*, 1H), 13.14 (*s*, OH). Source: *F. oxysporum* [63].
 (**55**) Javanicin	$C_{15}H_{14}O_6$ M_r: 290 mp: 207–208° UV λ_{max}^{EtOH} nm: 227, 305, 478sh, 504, 541sh. IR ν^{KBr} cm^{-1}: 1720, 1600. ^{1}H NMR ($CDCl_3$): 2.28 (*s*, Me), 2.22–3.88 (*gh*, 2H), 3.91 (*s*, OMe), 6.18 (*s*, H), 12.82 (*s*, OH), 13.21 (*s*, OH). Sources: *F. javanicum* [11, 57], *F. solani* [5, 65], *F. martii* [5, 12], *Neocosmospora vasinfecta*, *N. africana* [57], *N. haematococca* [56, 70], *F. decemcellulare* [60].

Table 1—*continued.*

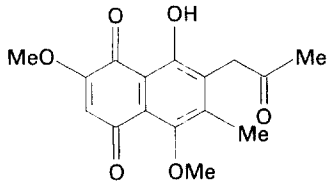
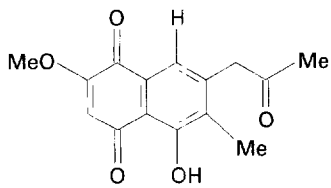
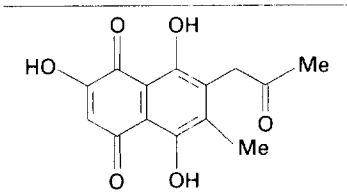
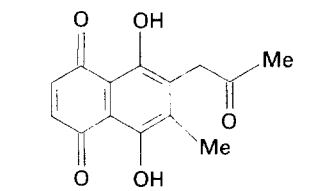
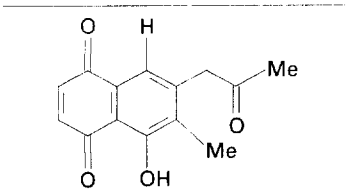
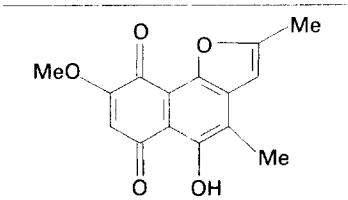
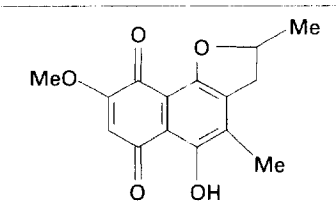
Naphthoquinone	Same physico-chemical properties
 (**56**) *O*-methyljavanicin	$C_{16}H_{14}O_6$ M_r: 304 mp: 197–198° UV λ_{max}^{MeOH} nm (log ε): 226 (4.56), 82.5 (4.04), 482 (3.8), 510 (3.75), 550 (3.80). IR ν^{CHCl_3} cm^{-1}: 1620, 1470, 1438, 1270. ^1H NMR ($CDCl_3$): 2.11–3.78 (*s*, 2H), 2.31 (*s*, Me), 3.99 (*s*, OMe), 4.02 (*s*, OMe), 6.74 (*s*, H), 13.02 (*s*, OH). Sources: *F. moniliforme* [61], *F. solani* [75], *F. oxysporum* [63].
 (**57**) Deoxyjavanicin	$C_{15}H_{14}O_5$ M_r: 274 mp: 121–124° UV λ_{max}^{EtOH} nm (log ε): 216 (4.33), 266 (3.97), 290sh (3.70), 428 (3.40). IR ν^{KBr} cm^{-1}: 3420, 2940, 2860, 1720, 1665, 1645, 1620, 1580, 1495. ^1H NMR ($CDCl_3$): 2.10 (*s*, Me), 2.28 (*s*, Me), 3.77 (*s*, 2H), 3.87 (*s*, OMe), 6.60 (*s*, 1H), 7.20 (*s*, 1H), 12.28 (*s*, OH). Sources: *Fusarium* sp. [76]. *N. haematococca* [70].
 (**58**) *O*-demethyljavanicin	$C_{14}H_{12}O_6$ M_r: 276 mp: 154–155° UV λ_{max}^{EtOH} nm: 230, 310, 475, 505, 544. IR ν^{KBr} cm^{-1}: 3425, 2940, 2870, 1740, 1635. ^1H NMR ($CDCl_3$): 2.25 (*s*, Me), 2.29 (*s*, Me), 3.80 (*s*, 2H), 3.90 (*s*, OMe), 6.34 (*s*, 1H), 13.32 (*s*, OH), 12.06 (*s*, OH). Source: *F. decemcellulare* [64].
 (**59**) 7-acetonyl-5,8-dihydroxy-6-methyl-1,4-NQ	$C_{14}H_{12}O_5$ M_r: 260 mp: 121–122° UV λ_{max}^{EtOH} nm: 212, 274, 476, 509, 546. IR ν^{KBr} cm^{-1}: 3415, 1715, 1610, 1575, 1465. ^1H NMR ($CDCl_3$): 2.15 (*s*, Me), 2.32 (*s*, Me), 3.83 (*s*, 2H), 7.20 (*s*, 2H-Ar), 12.42 (*s*, 1H-OH), 12.57 (*s*, 1H-OH). Source: *Fusarium* sp. [76].
 (**60**) 7-acetonyl-5-hydroxy-6-methyl-1,4-NQ	$C_{14}H_{12}O_4$ M_r: 244 mp: 120–122° UV λ_{max}^{EtOH} nm: 206, 247, 269, 420, 450. IR ν^{KBr} cm^{-1}: 3430, 1720, 1670, 1650, 1625. ^1H NMR ($CDCl_3$): 2.08 (*s*, Me), 2.27 (*s*, Me), 3.75 (*s*, 2H), 7.22 (*s*, H-Ar), 7.55 (*d*, 2H-Ar), 12.03 (*s*, OH). Source: *Fusarium* sp. [76].
 (**61**) Anhydrojavanicin	$C_{15}H_{12}O_5$ M_r: 272 mp: 215–217° UV λ_{max}^{EtOH} nm: 234, 257, 316, 448. IR ν^{KBr} cm^{-1}: 3430, 3130, 1685, 1465. ^1H NMR ($CDCl_3$): 2.37 (*s*, Me), 2.53 (*s*, Me), 3.93 (*s*, OMe), 6.06 (*s*, 1H), 6.40 (*s*, H-Ar), 12.85 (*s*, OH). Sources: *Fusarium* sp. [76], *N. haematococca* [56], *F. decemcellulare* [64], *N. vasinfecta* [57], *N. africana* [57].
 (**62**) Dihydroanhydrojavanicin	$C_{15}H_{14}O_5$ M_r: 274 mp: 225–228° UV λ_{max}^{EtOH} nm (log ε): 225 (4.43), 288 (4.08), 480 (3.81), 501 (3.80), 535 (3.51). IR ν^{KBr} cm^{-1}: 3420, 2980, 1670, 1635, 1585. ^1H NMR ($CDCl_3$): 1.40 (*d*, 3H), 2.13 (*s*, 3H), 2.50 (*dd*, 1H), 3.10 (*dd*, 1H), 3.70 (*s*, OMe), 5.07 (*m*, 1H), 6.23 (*s*, H-Ar), 12.90 (*s*, OH). Sources: *Fusarium* sp. [76], *F. solani* [71].

Table 1—*continued.*

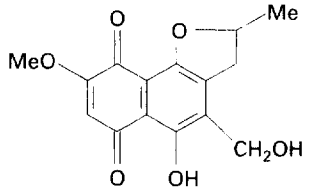
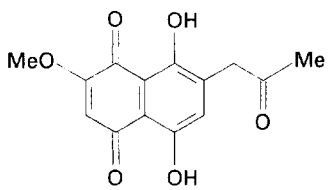
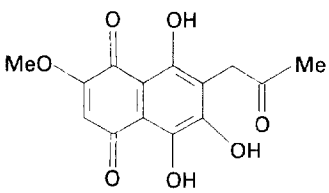
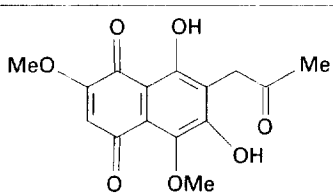
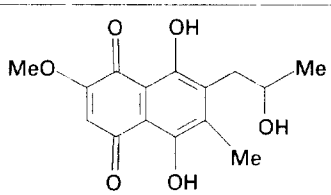
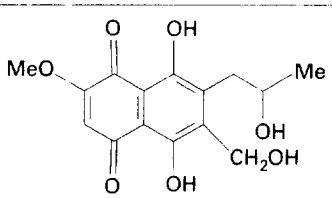
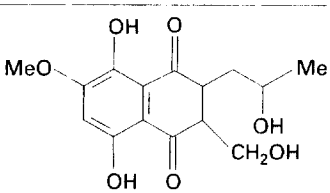
Naphthoquinone	Same physico-chemical properties
 (**63**) 2,3-dihydro-5-hydroxymethyl-anhydrojavanicin	$C_{15}H_{14}O_6$ M_r: 290 mp: 202–203° UV λ_{max}^{EtOH} nm (log ε): 223 (4.06), 297 (3.62), 485 (3.50), 502 (3.47), 538 (3.17). IR ν^{KBr} cm^{-1}: 3490, 1660, 1625, 1585, 1420. ^{1}H NMR ($CDCl_3$): 1.59 (*d*, Me), 2.67 (*t*, OH), 2.92 (*dd*, 1H), 3.46 (*dd*, 1H), 3.90 (*s*, OMe), 4.74 (*d*, 1H), 5.21 (*m*, 1H), 6.07 (*s*, H-Ar), 13.60 (*s*, OH) Source: *F. solani* [77].
 (**64**) Norjavanicin	$C_{14}H_{12}O_6$ M_r: 276 mp: 200–204° UV λ_{max}^{EtOH} nm: 225, 295, 477, 500, 537. IR ν^{KBr} cm^{-1}: 1725, 1610, 1580, 1440, 1360. ^{1}H NMR ($CDCl_3$): 2.28 (*g*, Me), 3.78 (*h*, 1H), 7.18 (*r*, 1H), 3.91 (*s*, OMe), 6.15 (*s*, H-Ar), 12.55 (*s*, OH), 12.59 (*s*, OH). Sources: *Fusarium* sp. [78], *F. martiela* [5, 12], *F. solani* [65], *F. decemcellulare* [60], *N. vasinfecta* [57], *N. africana* [57], *N. haematococca* [56].
 (**65**) 6-hydroxynorjavanicin	$C_{14}H_{12}O_7$ M_r: 292 mp: 231–234° UV λ_{max}^{EtOH} nm (log ε): 212 (4.22), 238 (4.14), 261 (4.07), 320 (3.88), 470 (3.84), 490 (3.82), 520 (3.66). IR ν^{KBr} cm^{-1}: 3300, 1710, 1630, 1600, 1570. ^{1}H NMR ($CDCl_3$): 2.30 (*s*, Me), 3.72 (*s*, 2H), 4.00 (*s*, OMe), 6.52 (*s*, H-Ar), 12.05 (*s*, OH), 13.20 (*s*, OH). Sources: *F. solani* [63], *N. haematococca* [79].
 (**66**) *O*-methyl-6-hydroxynorjavanicin	$C_{15}H_{14}O_7$ M_r: 306 mp: 226–229° UV λ_{max}^{EtOH} nm (log ε): 211 (4.3), 240 (4.2), 270 (4.2), 300 (4.0), 454 (3.9). IR ν^{KBr} cm^{-1}: 3200, 1705, 1635, 1610, 1570. ^{1}H NMR ($CDCl_3$): 2.28 (*s*, Me), 3.68 (*s*, 2H), 4.0 (*s*, OMe), 4.0 (*s*, OMe), 6.62 (*s*, H-Ar), 8.21 (*s*, OH), 13.60 (*s*, OH). Source: *F. oxysporum* [63].
 (**67**) Solaniol	$C_{15}H_{16}O_6$ M_r: 292 mp: 190–194° UV $\lambda_{max}^{dioxane}$ nm (log ε): 227 (4.53), 304 (3.97), 500 (3.91). IR ν^{KBr} cm^{-1}: 3350, 3280, 1602. ^{1}H NMR ($CDCl_3$) (τ): 3.85 (*s*, H-Ar), 6.08 (*s*, OMe), −3.28 (*s*, OH), −2.97 (*s*, OH), 7.67 (*s*, Me), 7.08 (*d*, 2H), 5.80 (*m*, 1H), 6.08 (*s*, OH), 8.67 (*s*, Me). Sources: *F. solani* [80], *Fusarium* sp. [76].
 (**68**) 6-hydroxymethylsolaniol	$C_{15}H_{16}O_7$ M_r: 308 mp: 206–212° UV λ_{max}^{EtOH} nm (log ε): 227 (4.38), 306 (3.87), 452 (3.56), 509 (3.80), 546 (3.59). IR ν^{KBr} cm^{-1}: 3330, 1615, 1550, 1450. ^{1}H NMR ($CDCl_3$): 1.39 (*d*, Me), 2.86 (*dd*, 1H), 3.13 (*dd*, 1H), 3.95 (*s*, OMe), 4.16 (*m*, 1H), 4.63 (*d*, 1H), 4.97 (*d*, 1H), 6.20 (*s*, 1H-Ar), 12.86 (*s*, OH), 13.35 (*s*, OH). Source: *F. solani* [77].
 (**69**) 2,3-dihydro-2-hydroxymethylsolaniol	$C_{15}H_{18}O_7$ M_r: 310 mp: 135° UV λ_{max}^{EtOH} nm (log ε): 213 (3.98), 244 (4.21), 277 (4.2), 303 (3.64), 391 (3.88), 400 (3.83). IR ν^{KBr} cm^{-1}: 3300, 1610, 1570, 1470, 1430. ^{1}H NMR ($CDCl_3$): 1.22 (*d*, Me), 1.79 (*m*, 1H), 1.96 (*m*, 1H), 2.42 (*s*, OH), 2.90 (*m*, 1H), 3.28 (*m*, 1H), 3.86 (*m*, 2H), 3.95 (*s*, Me), 4.24 (*dd*, 1H), 6.70 (*s*, H-Ar), 12.22 (*s*, OH), 12.58 (*s* OH). Source: *F. solani* [77].

Table 1—*continued*.

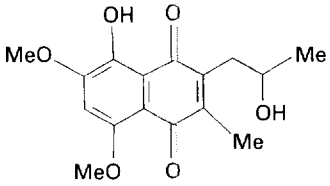
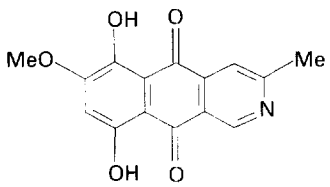
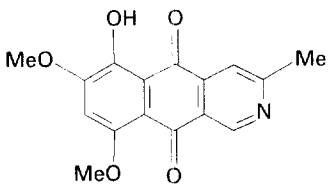
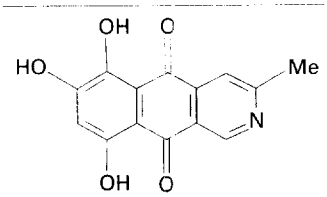
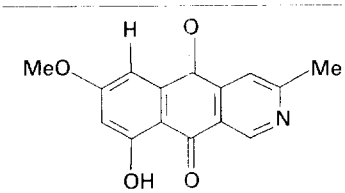
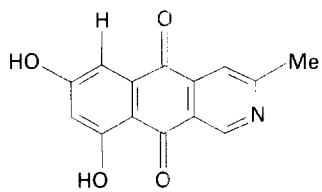
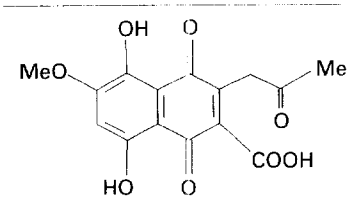
Naphthoquinone	Same physico-chemical properties
 (**70**) *O*-methylsolaniol	$C_{16}H_{18}O_6$ M_r: 306 mp: 152–154° UV λ_{max}^{MeOH} nm (log ε): 226 (4.49), 285 (4.02), 476 (3.82), 510sh (3.69). IR ν^{KBr} cm^{-1}: 3460, 1610, 1480, 1435, 1380 [63]. ^{1}H NMR ($CDCl_3$): 1.36 (*d*, Me), 2.12 (*s*, Me), 2.62–2.80 (*dd*, 2H), 3.41 (*d*, OH), 3.87 (*s*, OMe), 3.92 (*s*, OMe), 4.18 (*m*, 1H), 6.49 (*s*, H-Ar), 13.22 (*s*, OH). Sources: *Fusarium moniliforme* [61], *F. solani* [63].
 (**71**) Bostrycoidin	$C_{15}H_{11}NO_5$ M_r: 285 mp: 231–235° UV λ_{max}^{EtOH} nm (log ε): 253, 322, 476, 500, 530. IR ν^{CHCl_3} cm^{-1}: 1641, 1591, 1311. ^{1}H NMR ($CDCl_3$): 2.81 (*s*, Me), 7.96 (*s*, 1H), 4.02 (*s*, OMe), 9.50 (*s*, 1H), 6.75 (*s*, H-Ar), 13.10 (*s*, OH), 13.50 (*s*, OH). Sources: *F. bostrycoides* [81], *F. solani* [65, 82], *F. decemcellulare* [60].
 (**72**) *O*-methylbostrycoidin	$C_{16}H_{13}NO_5$ M_r: 299 mp: 215–216° UV λ_{max}^{MeOH} nm (log ε): 247 (4.50), 318 (3.92), 480 (3.83). $\lambda_{max}^{Me\text{-}HCl}$ nm (log ε): 227 (4.32), 262 (4.20), 310 (3.88), 510 (3.73). $\lambda_{max}^{Me\text{-}ONa}$ nm (log ε): 259 (4.44), 306 (3.82), 546 (4.0). IR ν^{KBr} cm^{-1}: 1641, 1591, 1311. ^{1}H NMR ($CDCl_3$): 9.44 (*s*, 1H), 7.85 (*s*, 1H), 6.86 (*s*, H-Ar), 2.76 (*s*, Me), 4.05 (*s*, OMe), 4.05 (*s*, OMe). Sources: *F. moniliforme* [61], *F. oxysporum* [63].
 (**73**) *O*-demethylbostrycoidin	$C_{14}H_9NO_5$ M_r: 271 mp: 221–223° UV λ_{max}^{EtOH} nm: 252, 340, 476, 496, 530. $\lambda_{max}^{Et\text{-}ONa}$ nm: 230, 290, 485sh, 525, 556. Source: *F. decemcellulare* [64].
 (**74**) 5-deoxybostricoidin	$C_{15}H_{11}NO_4$ M_r: 269 mp: 195–196° UV λ_{max}^{MeOH} nm: 237, 270, 322(sh), 414. IR ν^{KBr} cm^{-1}: 1680, 1635, 1590. ^{1}H NMR ($CDCl_3$): 2.78 (*s*, Me), 3.94 (*s*, OMe), 6.74 (*d*, 1H), 7.32 (*d*, 1H), 7.86 (*s*, 1H), 9.40 (*s*, 1H), 12.76 (*s*, OH). Source: *N. haematococca* [83].
 (**75**) 6-*O*-demethyl-5-deoxybostricoidin	$C_{14}H_7NO_4$ M_r: 255 mp: 300–305° UV λ_{max}^{MeOH} nm (log ε): 205 (4.40), 239 (4.42), 280 (4.12), 320 (sh, 383), 421 (3.75). IR ν^{KBr} cm^{-1}: 3200–2400, 1682, 1637, 1600. ^{1}H NMR [$(CD_3)_2SO$]: 2.70 (*s*, Me), 6.60 (*d*, 1H), 7.10 (*d*, 1H), 7.80 (*s*, 1H), 9.20 (*s*, 1H), 12.57 (*s*, OH). Source: *N. haematococca* [84].
 (**76**) Fusarubinoic acid	$C_{15}H_{12}O_6$ M_r: 302 mp: 200–210° IR ν^{KBr} cm^{-1}: 3300–2500. ^{1}H NMR (CD_3OD): 2.25 (*s*, Me), 3.98 (*s*, 2H), 4.04 (*s*, OMe), 6.46 (*s*, H-Ar). Source: *N. haematococca* [85].

Table 1—*continued.*

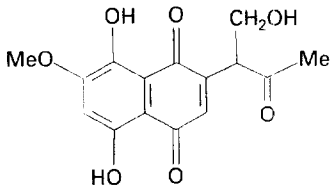
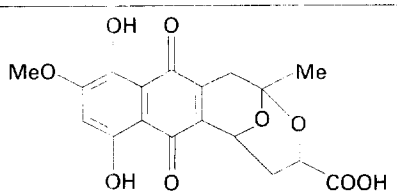
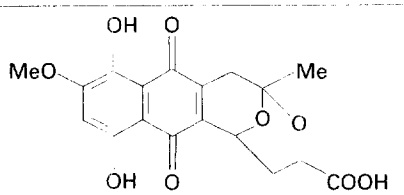
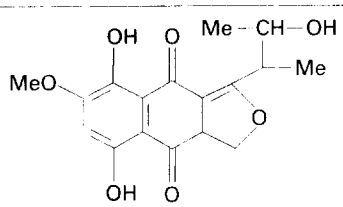
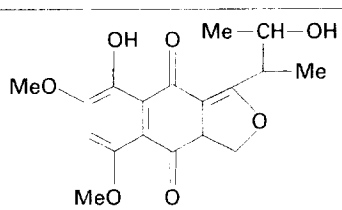
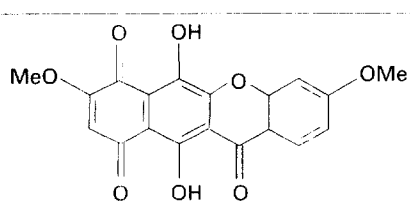
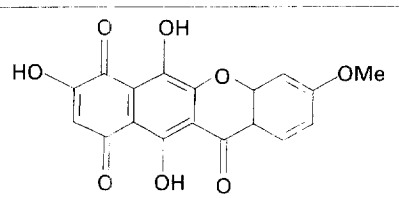
Naphthoquinone	Same physico-chemical properties
 (**77**) Novarubin	$C_{15}H_{14}O_7$ M_r: 306 mp: 162° UV λ_{max}^{EtOH} nm: 302, 477sh, 505, 542. Sources: *F. solani*, *F. martii* [12], *Neocosmospora vasinfectum*, *N. africana* [57], *F. decemcellulare* [60].
 (**78**) Marticin	$C_{18}H_{16}O_9$ M_r: 376 mp: 180–182 UV λ_{max}^{EtOH} nm: 229, 304, 474, 501, 536. IR ν^{KBr} cm^{-1}: 3600–2800, 1720. ^{1}H NMR ($CDCl_3$): 1.68 (*s*, Me), 2.73 (*d*, 1H), 3.12 (*d*, 1H), 2.10 (*m*, 1H), 5.42 (*d*, 1H), 2.86 (*m*, OH), 3.94 (*s*, OMe), 4.58 (*m*, 1H), 12.53 (*s*, OH), 12.93 (*s*, OH). Sources: *F. solani* [65], *F martii* [5, 12].
 (**79**) Isomarticin	$C_{18}H_{16}O_9$ M_r: 376 mp: 160–163 UV λ_{max}^{EtOH} nm: 229, 304, 474, 501, 536. IR ν^{KBr} cm^{-1}: 3430, 1720. ^{1}H NMR ($CDCl_3$): 1.70 (*s*, Me), 3.00 (*d*, 1H), 3.13 (*d*, 1H), 2.04 (*m*, 1H), 5.58 (*d*, 1H), 2.30 (*m*, OH), 4.31 (*dd*, 1H), 6.20 (*s*, H-Ar), 12.51 (*s*, OH), 12.91 (*s*, OH). Sources: *F. solani* [65], *F. martii* [5, 12].
 (**80**) Nectriafurone	$C_{15}H_{12}O_7$ M_r: 304 mp: 230 UV λ_{max}^{EtOH} nm: 255, 320, 443, 465. IR ν^{KBr} cm^{-1}: 3350, 3250–2500, 2840, 1735, 1605. ^{1}H NMR ($CDCl_3$): 1.67 (*s*, Me), 3.92 (*s*, OMe), 5.18 (*q*, 1H), 6.66 (*s*, H-Ar), 8.10 (*s*, 1H), 13.03 (*s*, OH), 13.35 (*s*, OH). Sources: *N. haematococca* [72], *F. oxysporum* [14].
 (**81**) *O*-methyl-nectriafurone	$C_{16}H_{14}O_7$ M_r: 318 mp: 214–222 UV λ_{max}^{EtOH} nm: 236 (4.37), 225sh (4.21), 322 (3.90), 443 (4.02). IR ν^{KBr} cm^{-1}: 3430, 3120, 1645, 1625, 1600. ^{1}H NMR ($CDCl_3$): 1.64 (*d*, Me), 4.00 (*s*, OMe), 4.03 (*s*, OMe), 4.78 (*d*, OH), 5.19 (*m*, 1H), 6.83 (*s*, H-Ar), 7.99 (*s*, 1H), 13.30 (*s*, OH). Source: *F. oxysporum* [14].
 (**82**) Bikaverin	$C_{20}H_{14}O_8$ M_r: 382 mp: 320–325° (decomp.) UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 253 (4.53), 271 (4.51), 320 (3.92), 510 (3.96), 550 (3.77). IR ν^{KBr} cm^{-1}: 1670, 1653, 1620. ^{1}H NMR ($CDCl_3$): 3.07 (3H, *s*-Me), 4.23 (*s*, 2OMe), 6.93 (1H, s-Ar), 7.44 (1H, *m*), 7.49 (1H, *d*). Sources: *Gibberella fujikuroi* [17, 89], *Fusarium bulbigenum* [86], *Fusarium oxysporum* [87], *Verticillium agaricinum* [88].
 (**83**) Norbikaverin	$C_{19}H_{12}O_8$ M_r: 368 mp: >300° (decomp.) UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 253 (4.51), 273 (4.51), 320 (3.92), 515 (3.96), 550 (3.78). IR ν^{Nujol} cm^{-1}: 3400, 1670, 1640, 1620–1560. ^{1}H NMR ($CDCl_3$): 3.02 (*s*, Me), 4.18 (*s*, OMe), 6.92 (*s*, 1H), 7.26 (*m*, 1H), 7.45 (*d*, 1H). Source: *Gibberella fujikuroi* [89].

Table 1—*continued*

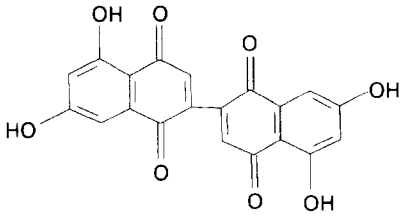
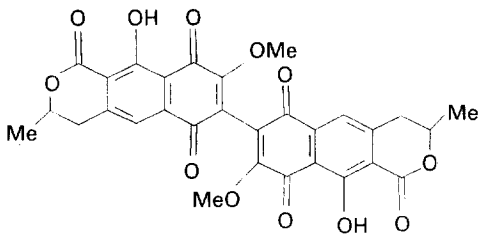
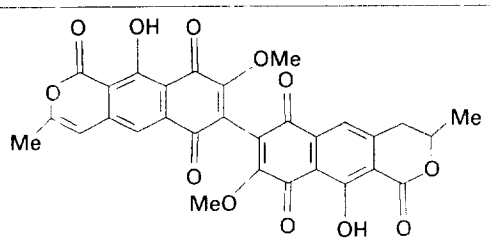
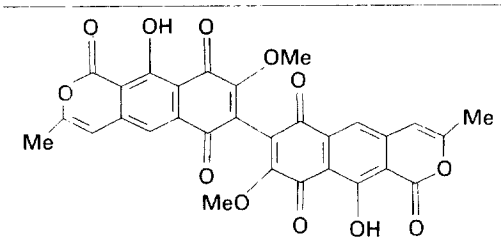
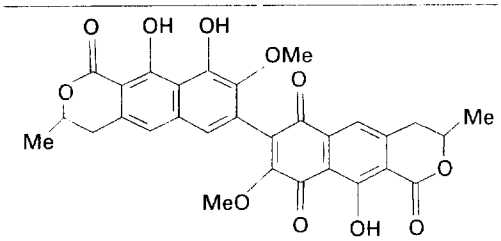
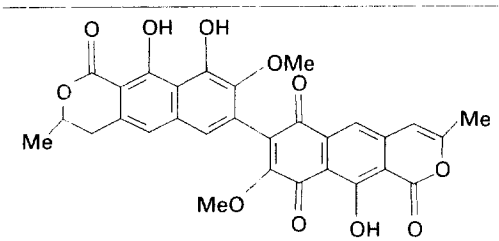
Naphthoquinone	Same physico-chemical properties
 (**84**) Biflaviolin	$C_{23}H_{20}O_{10}$ M_r: 410 UV λ_{max}^{EtONa} nm (log ε): 294 (4.68), 372 (4.02), 422sh, 560 (3.43). $\lambda_{max}^{Et\text{-}HCl}$ nm (log ε): 265 (4.48), 312 (4.15), 390 (3.81), 460sh. ^{1}H NMR [$(CD_3)_2CO$]: 6.68 (*d*, 2H), 7.18 (*d*, 2H), 12.5 (*s*, 2OH). Source: *Thielaviopsis basicola* [90].
 (**85**) Xanthomegnin	$C_{30}H_{26}O_{12}$ M_r: 578 mp: >260° (dec.) UV λ_{max}^{MeONa} nm (log ε): 222 (4.41), 264 (4.29), 380 (3.90). IR ν^{KBr} cm^{-1}: 3430, 1721, 1675, 1616, 1590. ^{1}H NMR ($CDCl_3$): 1.51 (*d*, Me), 3.02 (*d*, CH_2), 4.67 (*m*, 1H), 7.50 (*s*, 1H), 4.11 (*s*, OMe), 13.17 (*s*, OH). Sources: *Trichophyton rubrum* [91], *T. megnini* [92], *T. violaceum* [93], *Aspergillus sulphureus*, *A. melleus* [94], *Penicillium viridicatum* [95], *Microsporum cookei* [96], *Nannizzia cajetani* [97].
 (**86**) 3,4-dehydroxanthomegnin	$C_{30}H_{24}O_{12}$ M_r: 576 mp: >160° (dec.) UV λ_{max}^{MeOH} nm: 237, 275sh, 385, 436sh. λ_{max}^{MeONa} nm: 254, 275, 300, 394, 550. IR ν^{KBr} cm^{-1}: 3385, 1738, 1680, 1655, 1618. ^{1}H NMR ($CDCl_3$) (quinone part): 1.56 (*d*, Me), 4.68 (*m*, 1H), 3.05 (*d*, 2H), 7.51 (*s*, 1H), 4.16 (*s*, OMe), 13.17 (*s*, H); (phenolic part): 2.35 (*s*, Me), 6.39 (*s*, 2H), 7.48 (*s*, 1H), 4.16 (*s*, OMe), 13.7 (*s*, Me). Sources: *Nannizzia cajetani* [97], *P. citreoviride* [98].
 (**87**) 3,4,3′,4′-Bisdehydroxanthomegnin	$C_{30}H_{22}O_{12}$ M_r: 574 UV λ_{max}^{MeOH} nm: 231sh, 267sh, 364. λ_{max}^{MeONa} nm: 229, 282, 387, 530. ^{1}H NMR ($CDCl_3$): 2.37 (*s*, Me), 6.39 (*s*, 2H), 7.53 (*s*, 1H), 4.19 (*s*, OMe), 13.72 (*s*, OH). Source: *N. cajetani* [97].
 (**88**) Viomellein	$C_{30}H_{26}O_{11}$ M_r: 562 mp: >260° (dec.) UV λ_{max}^{MeOH} nm: 264, 366sh, 376. λ_{max}^{MeONa} nm: 265, 330, 372, 385, 536. IR ν^{KBr} cm^{-1}: 3445, 1735, 1675, 1640. ^{1}H NMR ($CDCl_3$) (quinone part): 1.54 (*s*, Me), 4.70 (*m*, 1H), 3.01 (*d*, 2H), 7.49 (*s*, 1H), 3.90 (*s*, OMe), 13.50 (*s*, OH); (phenolic part): 1.54 (*s*, Me), 4.70 (*m*, 1H), 3.01 (*d*, 2H), 6.96 (*s*, 1H), 6.66 (*s*, 1H), 3.86 (*s*, OMe), 9.80 (OH), 13.88 (OH). Sources: *N. cajetani* [97], *A. sulphureus*, *A. melleus* [94], *T. violaceum* [93], *P. viridicatum* [95], *P. citreoviride* [98].
 (**89**) 3′,4′-dehydroviomellein	$C_{30}H_{24}O_{11}$ M_r: 560 mp: >150° (dec.) UV λ_{max}^{MeOH} nm: 261, 365, 375, 446. λ_{max}^{MeONa} nm: 260, 372, 383, 547. IR ν^{KBr} cm^{-1}: 3390, 1752, 1675, 1648, 1618. ^{1}H NMR ($CDCl_3$) (quinone part): 2.33 (*s*, Me), 6.33 (*s*, 2H), 7.53 (*s*, 1H), 3.92 (*s*, OMe), 14.03 (*s*, OH); (phenolic part): 1.56 (*d*, Me), 4.72 (*m*, 1H), 3.02 (*dd*, 2H), 6.96 (*s*, 1H), 6.98 (*s*, 1H), 3.86 (*s*, OMe), 9.80 (*s*, OH), 13.88 (*s*, OH). Source: *N. cajetani* [97].

Table 1—*continued.*

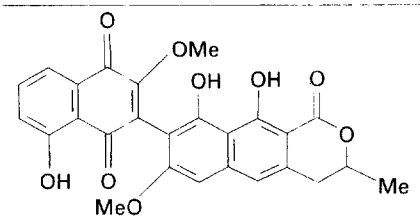
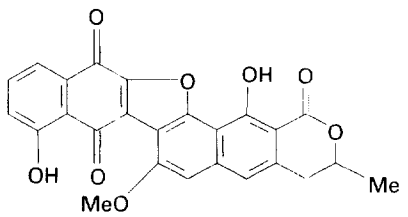
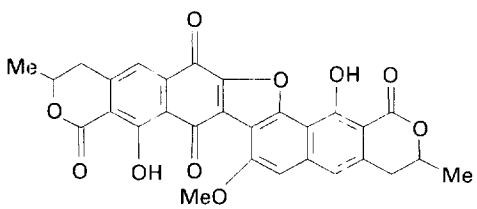
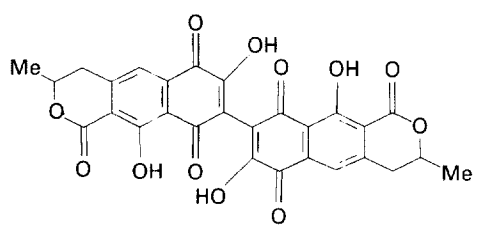
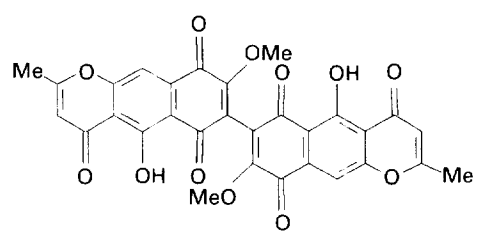
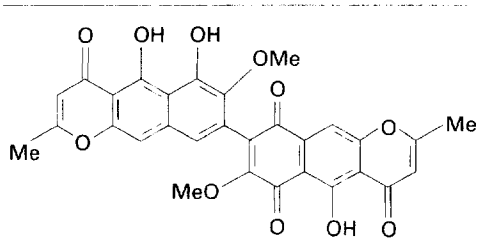
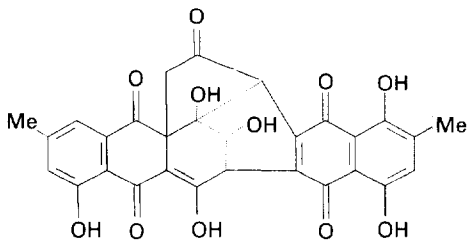
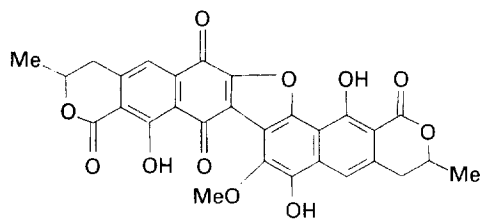
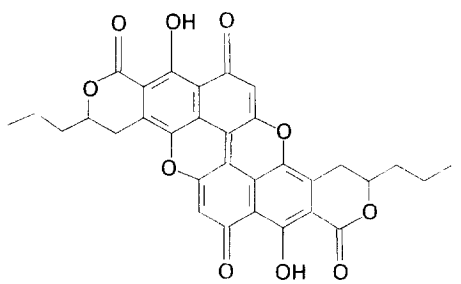
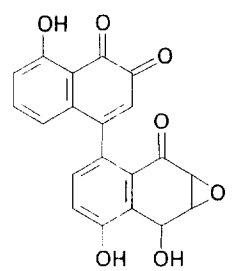
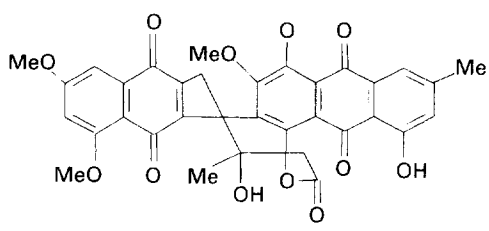
Naphthoquinone	Same physico-chemical properties
 (**90**) Xanthoviridicatin D	$C_{26}H_{20}O_9$ M_r: 476 mp: 133–136° UV λ_{max}^{MeOH} nm (log ε): 225 (4.06), 264 (4.3), 384 (3.91). IR ν^{KBr} cm^{-1}: 3420, 1725, 1590. ^{1}H NMR ($CDCl_3$): 1.50 (*d*, Me), 2.98 (*d*, 2H), 3.83 (*s*, OMe), 3.89 (*s*, OMe), 4.74 (*m*, 1H), 6.66 (*s*, 1H-Ar), 6.95 (*s*, 1H-Ar), 9.78 (*s*, OH), 12.30 (*s*, OH), 13.92 (*s*, OH). Source: *Penicillium veridicatum* [99].
 (**91**) Xanthoviridicatin G	$C_{25}H_{16}O_8$ M_r: 444 mp: 318–320° UV λ_{max}^{MeOH} nm (log ε): 280 (4.47), 355 (3.51), 440 (3.64). IR ν^{KBr} cm^{-1}: 3390, 1737, 1664, 1580. ^{1}H NMR ($CDCl_3$): 1.53 (*d*, Me), 2.98 (*d*, 2H), 4.10 (*s*, OMe), 4.72 (*m*, 1H), 6.87 (*s*, H-Ar), 7.37 (*s*, H-Ar), 7.44 (*dd*, H-Ar), 7.80 (*t*, H-Ar), 8.19 (*dd*, H-Ar), 12.30–13.92 (*s*, 2OH). Source: *Penicillium veridicatum* [99].
 (**92**) Rubrosulphin	$C_{29}H_{20}O_{10}$ M_r: 528 mp: 280 UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 280 (4.50), 357 (3.58), 415 (3.69). IR ν^{KBr} cm^{-1}: 3278, 2910, 1729, 1670, 1640, 1600. Sources: *P. viridicatum* [95], *A. sulphureus*, *A. melleus* [94].
 (**93**) Luteosporin	$C_{28}H_{18}O_{12}$ M_r: 546 Source: *Microsporium cookei* [100].
 (**94**) Aurofusarin	$C_{30}H_{18}O_{12}$ M_r: 570 mp: >330° (dec.) UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 248 (4.62), 268 (4.48), 381 (3.94). IR ν^{KBr} cm^{-1}: 1660, 1600, 1470, 1438. ^{1}H NMR (CF_3COOD) (τ): 7.13 (*s*, Me), 5.63 (*s*, OMe), 1.87 (*s*, H-Ar), 2.91 (*s*, 2H). Sources: *Hypomyces rosellus* [101], *Dactylium dendroides* [101], *F. culmorum* [102, 103], *F. graminearum* [102, 104, 105], *F. decemcellulare* [106, 107].
 (**95**) Fuscofusarin	$C_{30}H_{20}O_{10}$ M_r: 556 mp: >300° UV λ_{max}^{EtOH} nm (log ε): 225 (4.50), 281 (4.63), 346 (3.89), 405 (4.01). IR ν^{CHCl_3} cm^{-1}: 1665, 1650, 1620, 1603. ^{1}H NMR ($CDCl_3$) (τ): 7.76 (*s*, MeCOO), 7.60 (*s*, MeCOO, Me, Me), 6.10 (*s*, OMe), 3.97 (*s*, H), 3.86 (*s*, H), 3.05 (*s*, H), 2.93 (*s*, H), 1.90 (*s*, H), 4.74 (*s*, OH). Source: *Fusarium culmorum* [106].

Table 1—*continued.*

Naphthoquinone	*Same physico-chemical properties*
 (**96**) Purpurogenone	$C_{29}H_{20}O_{11}$ M_r: 544 mp: 310° (dec.) UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 252 (4.18), 306 (3.73), 387 (3.80), 498 (3.42), 528 (347), 568 (3.27). Source: *Penicillium purpurogenum* [108].
 (**97**) Viopurpurin	$C_{29}H_{20}O_{11}$ M_r: 544 mp: 310° UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 272 (4.58), 280 (4.59), 375 (3.92). IR ν^{KBr} cm^{-1}: 3420, 1730, 1670, 1635, 1600, 1560, 1545. Sources: *P. viridicatum* [95], *T. violaceum* [93], *A. melleus*, *A. sulphureus* [94].
 (**98**) Xylindein	$C_{32}H_{24}O_{10}$ M_r: 564 mp: >300° UV λ_{max}^{EtOH} nm: 380, 405, 423, 603, 647. IR ν^{KBr} cm^{-1}: 1720, 1625. Sources: *Chlorociboria aeruginose*, *Lophyostoma viridarium* [109].
 (**99**) Mycochrison	$C_{20}H_{12}O_7$ M_r: 364 mp: 195° (dec.) UV λ_{max}^{EtOH} nm (log ε): 236 (4.49), 303 (4.75), 438 (3.80). IR ν^{KBr} cm^{-1}: 1689, 1666, 1637. ^{1}H NMR [$(CD_3)_2CO$] (τ): 5.88 (*m*, 1H), 6.38 (*m*, 1H), 3.5 (*d*, 1H), 3.6 (*s*, 1H), 3.57 (*d*, 1H), 3.78 (*d*, 1H). Source: cultures an unidentified inopercolate discomycete [110].
 (**100**) Dermocanarin 2	$C_{33}H_{26}O_{11}$ M_r: 598 mp: 235–240° UV λ^{EtOH} nm (log ε): 216 (4.80), 272 (4.51), 302sh (4.21), 420 (3.82). $\lambda^{E\text{-}ONa}$ nm (log ε): 515 (3.75). IR ν^{KBr} cm^{-1}: 3457, 1771, 1651, 1633, 1593. ^{1}H NMR ($CDCl_3$): 7.12 (*br*, *s*, 1H), 7.64 (*br*, *s*, 1H), 7.83 (*s*, 1H), 2.47 (*s*, Me), 3.98 (*s*, OMe), 12.38 (*s*, OH), 2.47 (*d*, $1H^A$), 1.97 (*d*, $1H^A$), 2.71 (*d*, $1H^B$), 3.36 (*d*, $1H^B$), 7.32 (*d*, 1H), 6.75 (*d*, 1H), 1.39 (*s*, Me), 3.03 (*s*, OH), 3.96 (*s*, OMe), 3.92 (*s*, OMe). Source: *Dermocybe canaria* [111].

UV-wavelength are in nm. and log ε or ε values are given in parentheses. Only values for λ max are quoted. IR values are in cm^{-1}. Melting points (MP) are in degrees centigrade and are uncorrected. ^{1}H NMR chemical shifts are in ppm on the σ scale.

Table 2. Fungi producers of naphthoquinone metabolites

Culture of fungi	Metabolites (N in Tab. 1)	Culture of fungi	Metabolites (N in Tab. 1)
1. *Aspergillus citricus*	**5**	33. *Hypomyces rosellus*	**94**
2. *A. melleus*	**85, 88, 92, 97**	34. *Lambertella* spp.	**25**
3. *A niger*	**5**	35. *Lophyostoma viridarium*	**98**
4. *A. parvulus*	**6**	36. *Marasmius graminum*	**1**
5. *A. sulfureus*	**85, 88, 92, 97**	37. *Microsporium cookei*	**85, 93**
6. *Cercospora melonis*	**7**	38. *Metatrichia vespasiarum*	**17, 18**
7. *Cetraria cucullata*	**20**	39. *Mollisia caesia*	**14, 15**
8. *Chlorociboria aeruginose*	**98**	40. *Mollisia fallens*	**15**
9. *Cladosporium* sp.	**3, 4, 5**	41. *Nannizzia cajetani*	**81, 85–89**
10. *Cladonia* spp.	**28**	42. *Neocosmospora africana*	**37, 48, 55, 61, 64, 77**
11. *Corinespora cassiocola*	**9, 10**	43. *Neocosmospora vasinfectum*	**37, 48, 55, 61, 64, 77**
12. *Criptosporium pinicola*	**27**	44. *Nectria haematococca*	**37, 38, 46, 47, 49, 50, 52, 53, 55, 57, 61, 64, 65, 74–76, 80**
13. *Cylindrocarpon* sp.	**19**		
14. *Dactilium dendroides*	**94**		
15. *Dermocybe canaria*	**100**	45. *Penicillium* spp.	**16**
16. *Foma wasabiae*	**8**	46. *P. ceterioviride*	**86, 88**
17. *Fomes annosus*	**30**	47. *P. purpurogenum*	**96**
18. *Fusarium bostricoideas*	**71**	48. *P. viridicatum*	**85, 88, 80, 97**
19. *F. bulbigenum*	**82**	49. *Pirenocheta cerestris*	**31, 32**
20. *F. culmorum*	**94, 95**	50. *Pirex coccifera*	**28**
21. *F. decemcellulare*	**37, 40, 48, 58, 61, 62, 73, 77, 94**	51. *Pseudospirones simplex*	**25**
		52. *Stemphyllium* spp.	**3, 4, 5**
22. *F. graminearum*	**94**	53. *Thielaviopsis basicola*	**84**
23. *F. javanicum*	**55**	54. *Torula herbarum*	**22, 23, 24**
24. *F. moniliforme*	**37, 39, 56, 70**	55. *Trichia floriformis*	**17, 18**
25. *F. martii*	**12, 13, 64**	56. *Trichophyton megnini*	**85**
26. *F. oxisporum*	**39, 54, 56, 66, 80, 82**	57. *T. rubrum*	**85**
27. *F. solani*	**37, 42–50, 55–71, 79–79**	58. *T. violaceum*	**85, 88, 97**
28. *Gibberella fujicuroi*	**51, 82, 83**	59. *Ushnea canariensis*	**29**
29. *Gnomonia eristoma*	**33, 34, 35, 36**	60. *Ushnea nookeri*	**29**
30. *Helicobasidium mompa*	**13**	61. *Ustilago* spp.	**26**
31. *Hematoma ventosum*	**31**	62. *Verticillium agaricinum*	**82, 83**
32. *Hendersonula toruloidea*	**11, 12**	63. *Verticillium dahliae*	**2, 3, 4, 5**

nitrogen led to the inhibition of naphthoquinone biosynthesis.

Kurobane *et al.* [82] noted that the composition of naphthoquinones can be determined by the initial ratio of the carbon and nitrogen sources in the culture medium. Thus, when grown on maltose (at a concentration of 20–50 g/l) the fungus *F. solani* synthesized dihydrofusarubins and javanicin if ammonium tartrate was added at 4.6 g/l. An increase in the concentration of the nitrogen source to 6.9 g/l led to the synthesis of bostricoidin, the molecule of which contains a nitrogen atom. A significant role in the increase of pigment formation was played by Fe, Mg and Zn ions [112]. A study of the effect of the cultivation conditions on the biosynthesis of naphthoquinones by the fungus *F. decemcellulare*, showed that the major condition of pigment formation is the inhibition or total cessation of the fungal growth with an excess carbon source and energy [107]. The factor regulating the composition of naphthoquinones proves to be the pH of the cultivation medium. Thus, during the inhibition of fungal growth by a high concentration of hydrogen ions in the medium (pH 4.0 and lower) and excess carbon, we observed synthesis of naphthasarins (fusarubin, javanicin, bostricoidin etc.) [107].

On the other hand, inhibition of fungal growth as a result of a pH increase in the medium to 8.0 was accompanied by the formation of only the dimeric naphthoquinone, aurofusarin [107]. Formation of aurofusarin was also observed during the limitation of fungal growth by nitrogen and phosphorous sources (optimal pH being maintained). It proved that during the growth on a medium containing ammonium sulphate as a nitrogen source there occurred the physiological acidification of the cultivation medium to pH 4.0 and lower, due to the consumption of ammonium and accumulation of the acid. Under these conditions, naphthasarin metabolites were formed.

In contrast, in growth with sodium nitrate (Chapek's medium), the pH of the medium was increased to 8.0 and aurofusarin accumulated. In the

limitation of fungal growth by a phosphorous source at excess ammonium sulphate and the optimal pH, dimeric naphthoquinone, aurofusarin was formed and no synthesis of naphthasarins was observed. Based on these data, it was concluded that pH of the medium, but not the nature of the nitrogen source, determined the composition of naphthoquinones.

A pH decrease as a necessary factor of naphthoquinone synthesis was earlier reported by Backer *et al.* [6], Claydon *et al.* [9] and Kurobane *et al.* [82]. The key role of pH in naphthoquinone synthesis is probably due to the fact that at pHs close to the neutral value, naphthoquinones exhibit a strong cytotoxic action against the microorganisms, plants and the fungal producers themselves [60, 113–115].

In contrast, at low pH the activity of the pigments, as auto-oxidative compounds, sharply decreases [60]. We suggest that, depending on the ambient conditions, the fungal producers are capable of changing the nature of the end product synthesized, thus protecting themselves from the harmful effects of their own metabolites.

Among other factors which lead to the synthesis of naphthoquinones, we should note the following [56]: (1) the presence of inhibitors capable of inhibiting the growth of the fungi (5-fluorouracil, ethidium bromide, sodium azide, nystatin); (2) temperature not optimal for the growth (30–32° instead of 26°); (3) oxidation of the incubation medium (pH lower than 3.5); and (4) the presence of microbial antagonists (*Bacillus subtilis*) or their products.

All the above enables one to consider naphthoquinones of the fungi (exemplified by the genus *Fusarium*) as a classical example of the secondary metabolites which are synthesized under conditions of growth inhibition or total cessation of growth [116].

THE MECHANISM OF NAPHTHOQUINONE SYNTHESIS

Detailed studies of the mechanism of naphthoquinone synthesis by fungi began in 1965 [117, 118]. The authors using ^{14}C-labelled acetate showed the synthesis of javanicin by the fungus *F. javanicum* to proceed via the polyketide route. Experiments with the ^{14}C-labelled methyl group of methionine showed that the methoxy group of javanicin originated from this source as a result of the interaction of the alkylating agent *S*-adensyolmethionine with the aromatic nucleus. Formation of the methyl group of the pigment occurs as a result of the reduction of the end carboxyl group. Subsequently, these results were supported by the data of NMR spectroscopy obtained by Kurobane *et al.* [37] in studies of dihydrofusarubin synthesis by *F. solani* using ^{14}C- and ^{3}H-labelled acetate compounds. Similar data were obtained in studies of 5-deoxyfusarubin synthesis by a mutant strain *N. haematococca* by Parisot *et al.* [62] and by Holenstein [117] for marticin synthesis. The data cited indicate that synthesis of naphthoquinones by fungi proceeds via the formation of a common precursor—a product of the acetate malonate pathway. Figure 1 summarizes the data on the biogenic relations of various naphthoquinones synthesized by *Fusarium* fungi [37, 80, 82, 85, 118].

Gatenbeck and Bentley [118] and later Arsenault [80] suggested that the primary metabolite in pigment synthesis is an aromatic acid (Fig. 1), which is then methylated to fusarubinic acid. This metabolite was not found for over 20 years. Only in 1988, was it isolated from the culture medium of *N. haematococca* and characterized [85]. As a result of successive reduction, fusarubinic acid was subsequently transformed to the aromatic aldehyde (not yet found), to the primary alcohol fusarubin and then to javanicin, solaniol and bostricoidin [80, 118]. Anhydrofusarubin and anhydrojavanicin were formed as a result of dehydration of, respectively, fusarubin and javanicin. Fusarubinic acid can also be directly converted into anhydrofusarubin lactone which, in turn, is reduced to anhydrofusarubin lactol [3, 85].

A slightly different scheme of naphthoquinone biogenesis was proposed by Kurobane *et al.* [37, 82]. They postulated that the next product synthesized after the aromatic acid is dihydrofusarubin (4). Under alkaline conditions, dihydrofusarubin is converted to fusarubin as a result of nonenzymatic oxidation. Similarly, norjavanicin and bostricoidin are formed (for bostricoidin to be formed, ammonium ions have to be present in the medium). Javanicin found in the medium at the early stages of cultivation is believed by the authors [82] to be a co-metabolite of dihydrofusarubin, but not a product of its conversion.

The polyketide route of synthesis has been also demonstrated for other metabolites: mollisin [36], mompain [59], fomasarin [52], flaviolin [27].

THE BIOLOGICAL ACTIVITY OF NAPHTHOQUINONE METABOLITES

As we noted in the Introduction, naphthoquinones have a broad range of biological action. The fungal pigments are found to be active against bacteria, yeasts, fungi [5, 10–13, 15, 119–121], protozoa *Leishmania brasiliensis* [17], insects *Calliphora erythrocephala* [9]. The cytotoxic activity of naphthoquinones against mouse leukemia [13] and HeLa cells [15] has been noted. Along with the antibiotic and toxic activities, naphthoquinones revealed mutagenic and carcinogenic properties [122].

One should note that the antibiotic activity of naphthoquinones is of selective character and is manifest mainly against Gram-positive bacteria. This effect is suggested [15] to be due to the lipophilic properties of naphthoquinones and their inability to penetrate the outer membrane of Gram-positive bacteria. This is supported by a relatively strong inhibitory effect of naphthoquinones against *Escherichia coli*, the permeability barrier being decreased for antibiotics [15].

Of special interest from the biological and medical points of view are dimeric naphthoquinones of the

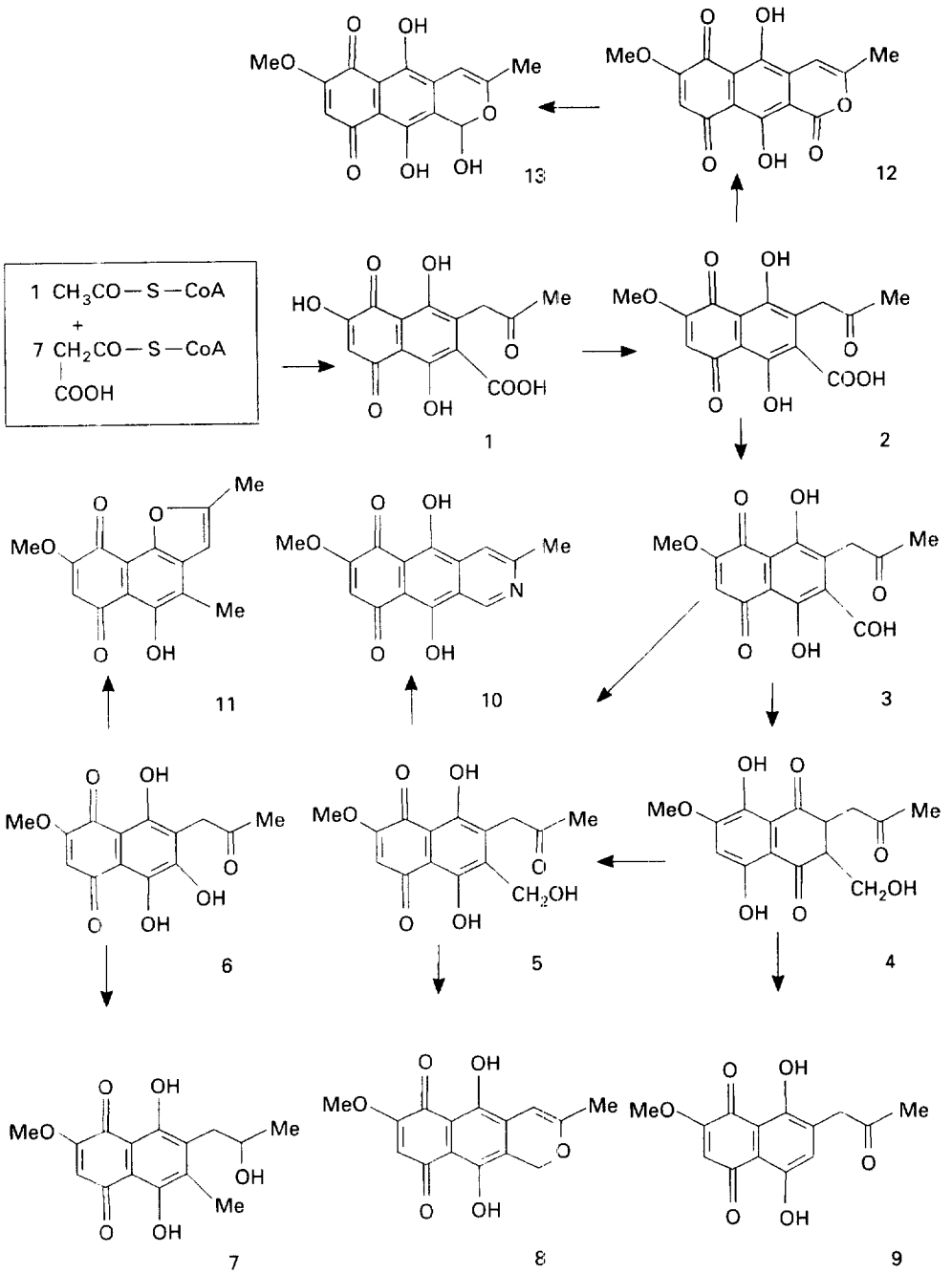


Fig. 1. Proposed route for the formation of naphthoquinone metabolites in fungi genus *Fusarium*. 1—aromatic acid; 2—fusarubinic acid; 3—aromatic aldehyde; 4—dihydrofusarubin; 5—fusarubin; 6—javanicin; 7—solaniol; 8—anhydrofusarubin; 9—norjavanicin; 10—bostricoidin; 11—anhydrojavanicin; 12—anhydrofusarubin lacton; 13—anhydrofusarubin lactol.

fungi. Besides the antibiotic activity against Gram-positive and Gram-negative bacteria, fungi and yeasts [97, 98, 107], many of them exhibit the properties of mycotoxins [123]. Thus, the best known xanthomegnin and viomellein, synthesized by *Penicillium*, *Aspergillus*, *Microsporium*, *Trichophyton* fungi, affected liver and kidney in laboratory animals [123].

Most naphthoquinone metabolites are synthesized by phytopathogenic fungi *Fusarium*, and their phytotoxic effects have been studied the most intensively [5–8, 12, 57, 75, 76, 124, 128].

Already the first studies on pea seedlings showed the symptoms of a disease during the treatment of the seedlings with solutions of purified naphthoquinones [5, 8, 12]. Subsequently, naphthoquinones were found to be able to inhibit the growth of the roots of the

radish, lemon [6, 8], and lettuce seedlings [75], to suppress the growth of the tomato culture *Licopersicon esculentum* [39], to slow down the germination of the pine-tree (*Pinus thunbergii*) pollen [76].

Treatment of the developing rough lemon seedlings with naphthoquinones caused leaf roll, which occurred between 48–72 hr, followed by leaf dehydration, wilt and veinal chlorosis [8]. Characteristically, the pea and lemon sprouts infected by *F. solani* isolates, exhibited similar features [8]. Interestingly, in the incubation of the pea and lemon seedlings in a medium with isomatricin and fusarubin, these pigments were found in stems and leaves in 4 hr [8, 124].

The phytotoxic activity as the antibiotic effects, depended on the structure of the naphthoquinones. Marticin and isomarticin were more toxic to peas and lemon than fusarubin, javanicin, norjavanicin and anhydrofusarubin [5, 8].

THE MECHANISM OF TOXIC ACTION

Studies of the mechanism of the antibiotic and phytotoxic action of naphthoquinones were started by Kern *et al.* [5, 125, 126]. Experiments on the action of the pigments on the subcellular level showed [125] that the naphthoquinone metabolites inhibited the aerobic decarboxylation of α-ketoglutarate and the anaerobic decarboxylation of pyruvate. Since the inhibitory effect was partially eliminated in the presence of excess thiamine pyrophosphate (TPP), the authors concluded that the pigments reacted directly with TPP.

The toxicity of the pigments for bacteria and plants was found to be decreased in the presence of some metal ions (Cu, Fe, Al) [5, 126, 127]. Thus, the presence of fusarubin and javanicin in the medium with the increased amount of Cu had no effect on the growth of plants and bacteria. The increase in the content of Cu ions in the growth medium did not affect the formation of the pigments [5, 127]. This effect of detoxication of naphthoquinones, in the opinion of the authors, was a result of formation of chelate complexes with metal ions. It is not impossible that the ability to form complexes with metals also determines their toxicity.

Further studies have found that the toxic effect of marticins on the development of pea sprouts decreases in the presence of glutamine [128]. It was suggested that the toxins inhibit glutamine synthetase. This hypothesis was supported in *in vitro* experiments on the direct inhibition of glutamine synthetase as well as on the reconstitution of the effect of isomarticin by nethionine sulphoximine, a known inhibitor of glutamine synthetase [5, 128].

It was shown [5, 13, 125] that the antibacterial activity of the fungal pigments depended on their chemical structure. Thus, in the metabolites synthesized by *Fusarium solani*, the activity against *Bacillus subtilis* decreased as follows: novarubin > norjavanicin > javanicin > fusarubin > marticin [5]. The activity of novarubin exceeded that of marticin ten-fold. The fungicidal activity changed in the same order but differed a 100-fold [5].

The dependence of the activity on the structure of a metabolite was also shown by Kurobane *et al.* [13]. Dihydrofusarubin proved to be more active than fusarubin; in turn, dihydrofusarubin and fusarubin were more active than their *O*-methyl and ethyl derivatives. The authors believe this to be due to the decrease in their solubility in water [13].

Besides the above effects, marticin and isomarticin evoked a pronounced disturbance of the selective permeability of plant cell membranes. Similar changes were observed in pea cells infected by a pathogenic strain *F. martii* which synthesizes large amounts of marticin and isomarticin. In both cases, the cytoplasmic membrane and chloroplast membrane were disrupted which led to the release of the nucleotides, amino acids, chlorophyll, proteins and mineral salts from the cells [5, 57, 128].

This picture of the consequences of the effect of naphthoquinones on the plant and microbial cells may reflect their ability to uncouple oxidative phosphorylation. It is just the property of uncoupling oxidative phosphorylation that is, in the opinion of the Japanese investigators, a cause of the high antibiotic activity of simple and dimeric naphthoquinones [100, 129, 130]. It was shown that a dimeric naphthoquinone xanthomegnin and juglone at low concentrations uncoupled oxidative phosphorylation of intact rat liver mitochondria [129, 130]. The uncoupling action of naphthoquinones was determined by phenolic hydroxyl groups because the methylated analogues lost their uncoupling properties [130]. Interestingly, the most bacterially active naphthoquinones (viomellein and dihydroviomellein) contained more hydroxyl groups [97], which can be a reflection of their uncoupling activity.

Of the other metabolites with antibiotic activities, the mechanism of action was investigated for gunacin and 2-hydroxyjuglone. Gunacin synthesized by the fungus *Ustilago* sp. [15] features a high antibacterial activity against Gram-positive bacteria, fungi and mycoplasmas. It was found that gunacin inhibited the inclusion of ^{14}C-labelled thiamine and uracil into DNA and RNA and did not inhibit the induction of interferon in fibroblasts. Based on these results, the authors concluded that the mechanism of the cytotoxic action of the naphthoquinone is related to the disturbance of DNA synthesis [15].

The mechanism of the cytotoxic action of 2-hydroxyjuglone [131] a metabolite of the fungi *Pyricularia oryzae* [24], *Verticillium dahliae* [22] and others [26], is slightly different from that of gunacin. It was shown [131] that 2-hydroxyjuglone inhibited the respiration of fungal spheroplasts and mitochondria, suppressed the biosynthesis of RNA, proteins, lipids and transport of glucose. These results, in the opinion of the authors, indicate that 2-hydroxyjuglone has an inhibi-

tory effect on the basic biochemical processes and membrane systems of the cells [131].

Considering the fact that the metabolites of the naphthoquinone structure are potentially capable of redox conversions, we suggested and then showed [60, 113–115, 121, 132, 133] that their antibiotic and phytotoxic effects are due to the interaction with the oxidative systems of microbial and plant cells. We have investigated the naphthoquinones of the fungi *Fusarium decemcellulare* (fusarubin, anhydrofusarubin, javanicin, anhydrojavanicin, bostricoidin, norjavanicin) and *Verticillium dahliae* (flaviolin and 2-hydroxyjuglone) [60, 113, 114, 121].

It has been found that the respiration of the Gram-positive bacteria, yeasts and fungi is noticeably activated by naphthoquinones after its suppression by cyanide [60, 113, 121]. These data indicate that naphthoquinones are capable of interacting with the redox systems of sensitive cells. Naphthoquinones accepted the reducing equivalents from the redox enzymes and transferred them directly to oxygen.

Studies of the subcellular components of bacterial, yeast and fungal cells showed that such systems are soluble cytoplasmic, flavin-containing NAD(P)H-dependent diaphorases [121]. Interestingly, respiration of Gram-negative bacteria was not activated by the pigments. However, naphthoquinones catalysed the oxidation of NAD(P)H by the cytoplasmic fraction of the Gram-negative bacteria [121]. This indicates that the resistance of the Gram-negative bacteria to the pigments is due to the absence of their transport across the cytoplasmic membrane.

In yeasts and fungi, the pigments actively catalysed the oxidation of the exogenous NAD(P)H by mitochondria in the presence of cyanide. It proved that the naphthoquinones accepted the reducing equivalents from flavin of the exogenous NADH dehydrogenase and transferred them to oxygen, bypassing the respiratory chain [113, 121].

We should also note that some of the naphthoquinones(2-hydroxyjuglone) exhibited an inhibitory effect on NADH:ferricyanide-reductase activity of complex I of the respiratory chain of rat liver mitochondria [133]. These data indicate that the pigments are capable of disturbing ATP synthesis in mitochondria at the oxidation of NAD-dependent substrates.

The mechanism of the phytotoxic action of the fungal naphthoquinones was investigated on pea seedlings [114, 115]. It was shown that, as in the case of eucaryotic organisms, the metabolites of the *Fusarium* (javanicin, fusarubin, anhydrofusarubin, bostricoidin) and *Verticillium* (2-hydroxyjuglone, flaviolin) fungi actively catalysed the oxidation of NADH and NADPH by the soluble, mitochondrial and microsomal fractions of the cells in the presence of oxygen. As a result of the transfer of the reducing equivalents by the naphthoquinone pigments from the flavine NAD(P)H-dependent dehydrogenases to oxygen there occurred the formation of superoxide radicals [114, 115].

It is known [122, 134, 135] that the one-electron reduction of quinone compounds is accompanied by the formation of semiquinone radicals. The subsequent auto-oxidation of the quinone radicals in the presence of molecular oxygen is coupled with the formation of superoxide anion radicals, potentially toxic species. Thus, the one-electron reduction of quinones to semiquinones and the subsequent auto-oxidation of semiquinones to quinones leads to the formation of a large amount of superoxide anions. This redox process, known as the quinone "redox cycle", determines the oxidative stress caused by naphthoquinones [122].

The quinone "redox cycle" is catalysed by various flavine enzymes. In bacteria, these are soluble DT diaphorases [60]. In yeasts, fungi and plants the reduction of naphthoquinones was performed by cytoplasmic soluble NADH and NADPH diaphorases, microsomal flavine NAD(P)H-dependent dehydrogenases and mitochondrial exogenous NADH dehydrogenase localized at the outer side of the inner membrane [60, 113–115]. In animal cells the naphthoquinone "redox cycle" is maintained by NADPH cytochrome P-450 reductase, NADH cytochrome *b*-5 reductase and NADH ubiquinone oxidoreductase [122]. A relative ability of each of these enzymes to catalyse one-electron reduction is determined by the redox potential of naphthoquinone.

Besides the enzyme, naphthoquinones are capable of being directly reduced by intracellular electron carriers. Thus, for instance, menadione and other naphthoquinones react with the reduced glutathione and SH groups of membrane proteins. In this case, compounds are formed that preserve the ability to perform the "redox cycle" to form superoxide radicals and other active oxygen forms [135]. Spontaneous or enzymatic dismutation of superoxide radicals is accompanied by the formation of oxygen peroxide and molecular oxygen. Besides, the superoxide radicals in the presence of some metal ions can react with oxygen peroxide to form more reactive compounds—hydroxyl radicals and singlet oxygen [134, 136]. Thus, getting into the cell, as a result of the flavoprotein-catalysed or nonenzymatic "redox cycle", naphthoquinones rapidly lead to oxidative stress. Formation of active oxygen forms is accompanied by damage to the DNAs, proteins and membranes [122, 134–136].

Further studies showed that naphthoquinones were capable of inhibiting the activity of glutathione reductase [132]. This enzyme responsible for the maintenance of a high concentration of reduced glutathione in the cell is crucial in the protection against the "oxidative stress"—an increased concentration of superoxide radicals and other active oxygen forms. Moreover, it proved [137] that the superoxide-generating quinones (1,4- and 1,2-naphthoquinones) inhibit the activity of superoxide dismutase—an

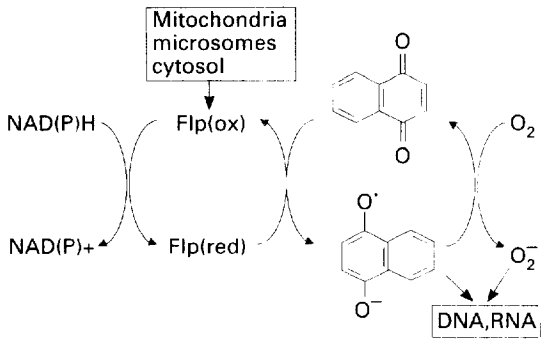


Fig. 2. Proposed mechanism of cytotoxic action of the naphthoquinone metabolites of fungi. Naphthoquinones interact with mitochondria, microsomes and cytosolic proteins and function as free radical carriers. They augment the flow of electrons from NAD(P)H to molecular oxygen. This reaction is catalysed by flavoproteins and produces a free radical intermediate form pigment. As free radicals, these pigments, because of their high affinity and selective binding to nucleic acids, have the potential to be "site-specific free radicals" that bind to DNA or RNA, and either react directly or generate oxygen-dependent free radicals such as superoxide radical or hydroxyl radical to cause the damage associated with their cytotoxic actions.

enzyme responsible for the decrease in the concentration of superoxide radicals.

On the whole, we believe the following two aspects to be characteristic of the mechanism of the cytotoxic action of the auto-oxidative naphthoquinone fungal metabolites (Fig. 2).

Firstly, the disturbance of the energy metabolism due to the uncontrollable oxidation of NADH and NADPH and, thus, their removal from the oxidative phosphorylation system as potential sources of reducing equivalents for the respiratory chain. Second, the disturbance of the constructive metabolism determined by the formation of chemically active forms of reduced oxygen and free-radical forms of the pigments capable of interaction with DNA and RNA.

In a sense, the mechanism of action of naphthoquinones can be called universal. In nature, there is a great number of compounds (benzoquinones, naphthoquinones, etc.) which possess auto-oxidative properties and are capable of evoking the "oxidative stress" when they get into a living cell.

THE MECHANISM OF RESISTANCE OF THE FUNGI TO THEIR OWN METABOLITES

Resistance of microbial producers to their own metabolites possessing a high biological activity is described in detail in a review by Vining [138]. The insensitivity of the organisms-producers to the toxic metabolites is noted to be achieved in two ways. Firstly, by the change of the sensitivity of the target or its absence in the cells of the producer. Second, by the change of the toxicity of the metabolite by phosphorylation, acetylation etc. This section presents the results of our studies on the mechanism of the tolerance of the fungus *F. decemcellulare* to its own naphthoquinones.

Biosynthesis and accumulation of naphthoquinones in the culture medium is observed under conditions of fungal growth inhibition due to the decrease of pH of the medium to 3.5 and lower [60, 107]. Under these conditions, the pigments formed had no effect on the metabolism of the producer [60]. An increase in pH of the medium to 6.0 resulted in an effect of the pigment on the fungi, which was manifest in the increase of the cyanide-insensitive respiration due to the interaction of the auto-oxidative pigments with the redox systems of the cells [60]. As it was to be expected, under conditions optimal for growth (pH of the cultivation medium, 5.5–6.5) naphthoquinones inhibited fungal growth. In the presence of purified individual pigments the lag phase noticeably increased—up to 20–22 hr as against 6 hr in their absence [64]. In this period the respiration of the fungi was almost twice as active as compared with the control and by 40–60% insensitive to cyanide. Besides, the cells in the presence of the pigment have 3 times as high superoxide dismutase activity and 2 times as high catalase activity. The fact that these enzymes are responsible for the decrease of the level of the active oxygen forms in the cells in oxidative stress suggests that under these conditions naphthoquinones actively function as auto-oxidative acceptors of reducing equivalents [60, 121].

By the beginning of the active fungal growth (the end of the lag phase) the pigments added were transformed by 80–90% to the inactive metabolites [64]. According to the data of mass, IR and UV spectroscopy, the transformation was due to the demethylation of the 7-methoxy group of the quinone ring. In *O*-demethyl derivatives of naphthoquinones the ability to accept the reducing equivalents from the flavine dehydrogenases of the fungi and bacteria decreases [64]. The decrease in the acceptor properties is, probably, due to the decrease in their redox potential as it was noted for other naphthoquinones [139].

It should be pointed out that the decrease in the activity by way of changing the nature of the substituent in the quinone ring can be of crucial importance in the protection of the producer from the toxic effect of the metabolites during their biosynthesis. As it was already noted, the synthesis of naphthoquinones is coupled at a certain stage with the formation of nonmethylated derivatives [118], which are not toxic for the producer. Presumably, methylation (i.e. activation) of naphthoquinones is the last reaction in their biosynthesis and is performed at the stage of excretion.

CONCLUSION

Fungal naphthoquinones are typical representatives of the secondary metabolites and are synthesized under conditions of inhibition or total cess-

ation of fungal growth [108, 116]. As for many other secondary metabolites, their physiological role for producers is still a matter of dispute and there is no common view on this problem [140, 141]. Since naphthoquinones possess a broad-range biological activity and a universal mechanism of action, they can play a significant ecological role as protectors by providing a selective advantage for the producer in its survival in a natural ecosystem. In this sense they are largely similar to the phytoalexins of plants (some of which are also of naphthoquinone structure) whose protective function is generally accepted [142]. The secondary metabolites in fungi, as phytoalexins in plants, are induced by factors of biotic and abiotic origin including the foreign competitive organisms, toxic compounds etc. [56, 142]. In other words, formation of biologically active metabolites is a reaction to unfavourable factors in the environment.

Most naphthoquinones are synthesized by phytopathogenic fungi (Table 2). At first glance, one should have expected that they shall play a significant role in the pathogenicity of the fungi with respect to plants. However, no direct evidence of this has been obtained as of today. Nevertheless, the compounds can actively change the metabolism of plant cells by suppressing their protection mechanisms.

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