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Supplementary Information

The 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one alkaloids. Results of 20 years of research, uncovering a new family of natural products

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Table 1. Chronology of the most relevant reports related to the isolation of members of the family of 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one alkaloids and related compounds.

Year	Isolated Compounds (Name/number)	Microorganism	Source of the microorganism and/or culture conditions	Reference
1995	NTC-47A (**1**) and NTC-47B (**2**)	*Penicillium sp.* NTC-47	Cultured on an okara medium	29
1996	Penigequinolones A (**3**) and B (**4**)	*Penicillium* sp. No. 410	Cultured in a malt medium	31
1997	Quinolinones A (**6**) and B (**5**)	*Penicillium sp.* NTC-47	Soil sample, cultured on okara medium	34
1999	Penigequinolones A (**3**) and B (**4**)	*Penicillium scabrosum, isolates* IBT 3740, 4030, 6635, 6637, 6815, 12258, 13671, 16088, 16106, 16246, 16395, 17219, 18318, 19284, 19286, 19422	Culture collection, Department of Biotechnology (IBT), Technical University of Denmark, grown on Czapek Yeast Extract agar	37
2000	Penigequinolones A (**3**) and B (**4**) Quinolinones A (**6**) and B (**5**) Peniprequinolone (**7**)	*Penicillium* cf. *simplicissimum* (Oudemans) Thom	Spores previously grown on solid potato dextrose agar were inoculated to a malt extract medium	38
2005	Quinolinones A (**6**) and B (**5**) *epi*-Quinolinone B Peniprequinolone (**7**)	*Penicillium janczewskii* Zalessky H-TW5/869	North Sea, surface water of German Bight Northeast of the Island of Heligoland; cultured in glucose/potato extract broth	40
2005	Peniprequinolone (**7**)	*Penicillium janczewskii* Zalessky	Phloem of *Prumnopitys andina* (Poepp. ex Endl.) de Laub (Lleuque); Las Trancas, Chillian, Chile. Cultured in potato dextrose medium	42
2005	Yaequinolones J1 (**15**) and J2 (**16**)	*Penicillium* sp. FKI-2140	Soil sample, Ishigakijima Island, Okinawa Prefecture, Japan	41a
2006	Aspoquinolones A-D (**17-20**)	*Aspergillus nidulans* HKI 0410	Cultured on a rice medium	47
2006	Penigequinolones A (**3**) and B (**4**) Quinolinones A (**6**) and B (**5**) Peniprequinolone (**7**) Yaequinolones A1 (**13**), A2 (**14**), B-F (**22-26**) Yaequinolones J1 (**15**) and J2 (**16**)	*Penicillium sp.* FKI-2140	Soil isolate, subtropical Okinawa, Japan	35 41b 50a
2007	Aspoquinolones A-D (**17-20**)	*Aspergillus nidulans* DSM 17772	Cultured on a rice medium	48
2009	Penigequinolones A (**3**) and B (**4**) Yaequinolones C (**23**) and E (**25**)	*Penicillium scabrosum* CBS-305.97	Cultured on a rice medium or liquid medium of soymeal	33 51a,c
2012	Aflaquinolones A-G (**27-33**)	*1-Aspergillus sp.* (MYC-2048 = NRRL 58570) ID as *Aspergillus flavipes* *2-Aspergillus sp.* SF-5044	1- Basidioma of *Rigidoporus microspores*, dead hardwood branch, alien wet forest, Hawaii 2- Intertidal sediment sample, Dadaepo Beach, Busan, Korea	52
2013	Aniduquinolones A-C (**34-36**) 6-Deoxyaflaquinolone E (**37**) Isoaflaquinolone E (**38**) 14-Hydroxyaflaquinolone F (**39**) Aflaquinolone A (**27**)	*Aspergillus nidulans* MA-143	Fresh leaves of the mangrove *Rhizophora stylosa*; cultured in liquid potato-dextrose broth medium	53
2013	Peniprequinolone (**7**)	*Penicillium namyslowskii*	*Rhododendron tomentosum* Harmaja; cultured in malt extract broth growth medium	54
2014	22-*O*-(*N*-Me-L-valinyl) Aflaquinolone B (**40**) 22-*O*-(*N*-Me-L-valinyl)- 21-*epi*-Aflaquinolone B (**41**) Aflaquinolones A (**27**) and D (**30**)	*Aspergillus sp.* XS-20090B15	*Muricella abnormaliz* collected from the Xisha Islands coral reef, South China Sea; cultured on a rice medium	56
2016	Aspoquinolones A (**17**) and B (**18**)	*Aspergillus nidulans* *Aspergillus fumigatus*	Cultured on glucose minimal medium (GMM)	57

Table 2. Stereochemical aspects of the 3,4-dioxygenated-4-aryl-quinolin-2(1*H*)-one alkaloids. Configuration of the olefin moieties and the stereogenic centers at C-3 and C-4 and centers in isoprenoid chain along with the analytical methods employed for their determination.

Microorganism	Isolated Compounds Name(number)	Configuration at C-3 and C-4,[e] $[\alpha]_D$ and double bond	Analytical Method(s) Employed (other than OD)	Ref.
Penicillium sp. NTC-47	NTC-47A (**1**), NTC-47B (**2**)	Not determined	-	11
Penicillium sp. No. 410	Penigequinolones A (**3**) and B (**4**)	3*R*,4R** $[\alpha]_D$ (mixture)= +60 (*c* = 1.0, MeOH) Config. of the double bond: *E*	PFG-1D-ROESY ^{1}H NMR (2:1 mixture) Double bond config.: ^{1}H NMR (*J* values)	13
Penicillium sp. NTC-47	Quinolinone B (**5**)	3*R*,4R** $[\alpha]_D$= –55 (*c* = 0.02, MeOH)	XRD	16
	Quinolinone A (**6**)	3*S*,4S** $[\alpha]_D$= –62 (*c* = 0.3, MeOH)	Relationship with quinolinone B	
Penicillium cf. *simplicissimum* (Oudemans) Thom	Peniprequinolone (**7**)	3*R*,4R** $[\alpha]_D$= –0.3 (*c* ~ 0.6, $CHCl_3$)	NMR (nOe); CD (Cotton effect)	20
	Penigequinolones A (**3**) and B (**4**)	3*R*,4R** $[\alpha]_D$ (mixt.)= +97.8 (*c* = 0.4, EtOH)	CD (Cotton effect similar to peniprequinolone) ^{1}H NMR (2:1 mixture) Double bond config.: ^{1}H NMR (*J* values)	
	Quinolinone B (**5**)	3*R*,4R** $[\alpha]_D$= +17.1 (*c* = 0.2, EtOH)	Sugested as a 5-OH quinolinone A derivative	
	Quinolinone A (**6**)	3*R*,4R** $[\alpha]_D$= –54.7 (*c* = 0.5, $CHCl_3$)	CD (Cotton effect similar to peniprequinolone)	
Penicillium janczewskii Zalessky (strain H-TW5/869)	Yaequinolone A1 (**14**)	3*S*,4R** $[\alpha]_D$= –12.9 (*c* = 0.7, MeOH)	Conformational analysis Quantitative nOe from NOESY spectrum	22
	Yaequinolone A2 (**13**)	3*R*,4R** $[\alpha]_D$= –4.2 (*c* = 0.5, MeOH)	Conformational analysis Quantitative nOe from NOESY spectrum	
	Peniprequinolone (**7**)	3*R*,4R**	Comparison with literature data	
	Quinolinone A (**6**)	3*R*,4R**		
Penicillium janczewskii K.M. Zalessky	Peniprequinolone (**7**)	3*R*,4R** $[\alpha]_D$= –1.0 (*c* = 1.6, $CHCl_3$)	Comparison of NOESY data with ref. 38	24
Penicillium sp. FKI-2140	Yaequinolone J1 (**15**)	3*R*4R*3"S** $[\alpha]_D$= –65.6 (*c* = 0.1, EtOH)	Stereochemistry at C-3 and C-4: nOe Stereochemistry of C-3": nOe	23
	Yaequinolone J2 (**16**)	3*R*,4R*,3"R** $[\alpha]_D$= +181.7 (*c* = 0.1, EtOH)		
Aspergillus nidulans HKI 0410	Aspoquinolones A (**17**) and B (**18**)	3*R*,4R**	nOe	29
Penicillium sp. FKI-2140	Yaequinolone A1 (**14**)	3*R*,4S**[b] $[\alpha]_D$= –32.2 (*c* = 0.1, EtOH)	nOe	32a 17
	Yaequinolone A2 (**13**)	3*R*,4R** $[\alpha]_D$= –50.9 (*c* = 0.1, EtOH)		
	Yaequinolone B (**22**)	3*R*,4R** $[\alpha]_D$= +41.2 (*c* = 0.1, EtOH) Config. of the double bond: *E*	Stereochemistry at C-3 and C-4: nOe Double bond config.: ^{1}H NMR (*J* values)	
	Yaequinolone C (**23**)	3*R*,4R** $[\alpha]_D$= +32.4 (*c* = 0.1, EtOH) Config. of the double bond: *E*		
	Yaequinolone D (**24**)	3*R*,4R** $[\alpha]_D$= +56.1 (*c* = 0.1, EtOH) Config. of the double bond: *E*		
	Yaequinolone E (**25**)	3*R*,4R** $[\alpha]_D$= +51.2 (*c* = 0.1, EtOH) Config. of the double bond: *E*		
	Yaequinolone F (**26**)	3*R*,4R** $[\alpha]_D$= +76.9 (*c* = 0.1, EtOH) Config. of the double bond: *E*		
	Yaequinolone J1 (**15**)	3*R*4R*3"S**	Stereochemistry at C-3 and C-4: nOe Stereochemistry at C-3": nOe	
	Yaequinolone J2 (**16**)	3*R*4R*3"R**		
	Quinolinone A (**6**)	3*R*,4R**	nOe Comparison with the literature	
	Quinolinone B (**5**)	3*R*,4R**		
	Peniprequinolone (**7**)	3*R*,4R**		
	Penigequinolone A (**3**)	3*R*,4R**	Separated by HPLC with chiral column Stereochemistry at C-3 and C-4: nOe	
	Penigequinolone B (**4**)			

[a]The asterisk means that only the relative configuration was established or proposed.

[b]The relative stereochemistry of side chain could not be defined for all the yaequinolones.

Table 3. Stereochemical aspects of the aflaquinolones and aniduquinolones. Configuration of the olefin moieties and the stereogenic centers, along with the analytical methods employed for their determination.

Isolated Compounds (Name/number)	Microorganism	Configuration at C-3 and C-4,[a] $[\alpha]_D$ and double bond	Analytical Method(s) Employed (other than OD)	Ref.
Aflaquinolone A (**27**)	*Aspergillus sp.* MYC-2048	3*S*,4*S*,2″*S*,4″*R* $[\alpha]_D$= +14 (*c* = 0.19, MeOH) Config. of the double bond: *E*	^{1}H NMR (*J* values) and NOESY, ECD-TDDFT Double bond config.: ^{1}H NMR (*J* values) Cyclohexanone ring: Comparison with Afla-B	34
Aflaquinolone B (**28**)		3*S*,4*S*,1″*R*,2″*S*,4″*R* $[\alpha]_D$= +20 (*c* = 0.14, MeOH) Config. of the double bond: *E*	ECD-TDDFT ^{1}H NMR of Mosher esters (prenyl moiety) Double bond config.: ^{1}H NMR (*J* values)	
Aflaquinolone D (**30**)		3*S*,4*S*,2″*S*,4″*S* $[\alpha]_D$= –10 (*c* = 0.10, MeOH) Config. of the double bond: *E*	ECD, NOESY Comparison with aflaquinolones A and B Double bond config.: ^{1}H NMR (*J* values)	
Aflaquinolone C (**29**)		3*S*,4*S*,2″*R*,4″*S* $[\alpha]_D$= –33 (*c* = 0.30, MeOH) Config. of the double bond: *E*	Holistic analysis of $[\alpha]_D$, ECD, NOESY and HPLC data. Comparison with aflaquinolones A and B Double bond config.: ^{1}H NMR (*J* values)	
Aflaquinolone E (**31**)		3*S*,4*S* $[\alpha]_D$= –41 (*c* = 1.1, MeOH)	ECD, NOESY Comparison with aflaquinolones A-D	
Aflaquinolone F (**32**)		3*S*,4*S* $[\alpha]_D$= +33 (*c* = 0.19, MeOH)	Comparison with aflaquinolones A-E	
Aflaquinolone G (**33**)		3*R*,4*S* $[\alpha]_D$= –6 (*c* = 0.18, MeOH)	ECD-TDDFT, NOESY	
Aniduquinolone A (**34**)	*Aspergillus nidulans* MA-143	3*S*,4*S*,2″*R*,5″*R* $[\alpha]_D$= +50 (*c* = 0.10, MeOH) Config. of the double bond: *E*	Relative config: XRD; NOESY Absolute config. of the heterocycle: ECD Double bond config.: ^{1}H NMR (*J* values)	35
Aniduquinolone B (**35**)		3*S*,4*S*,2″*R**,5″*R** $[\alpha]_D$= +31 (*c* = 0.13, MeOH) Config. of the double bond: *E*	ECD, NOESY Absolute config. not fully assigned Double bond config.: ^{1}H NMR (*J* values)	
Aniduquinolone C (**36**)		3*S*,4*S* $[\alpha]_D$= +11 (*c* = 0.28, MeOH)	ECD, NOESY	
6-Deoxyaflaquinolone E (**37**)[b]		3*S*,4*S* $[\alpha]_D$= –80 (*c* = 0.15, MeOH)	nOe CD (Identical shape to aniduquinolones), shifted due to the absence of olefins attached to C-6	
Isoaflaquinolone E (**38**)		3*S*,4*S* $[\alpha]_D$= –26 (*c* = 0.35, MeOH)		
14-Hydroxyaflaquinolone F (**39**)[b]		3*S*,4*S* $[\alpha]_D$= –33 (*c* = 0.15, MeOH)		
Aflaquinolone A (**27**)		3*S*,4*S*,2″*S*,4″*R* $[\alpha]_D$= +20 (*c* = 0.5, MeOH) Config. of the double bond: *E*	^{1}H NMR, NOESY Comparison with data of ref. 53 Double bond config.: ^{1}H NMR (*J* values) Config. of the double bond: *E*	
22-*O*-(*N*-Me-L-valyl)-aflaquinolone B (**40**)[b]	*Aspergillus sp.* XS-20090B15	3*S*,4*S*,1″*R* ,2″*S*, 4″*R*. Aminoacid: *S* $[\alpha]_D$= +50 (*c* = 0.1, MeOH) Config. of the double bond: *E*	^{1}H NMR, NOESY, ECD Aminoacid config.: Marfey's method	38
Aflaquinolone B (**28**)		$[\alpha]_D$= +28 (*c* = 0.17, MeOH)	Comparison of $[\alpha]_D$, ^{1}H NMR, data of ref. 52	
22-*O*-(*N*-Me-L-valinyl)-21-*epi*-Aflaquinolone B (**41**)[b]		3*S*,4*S*,1″*R* ,2″*S*, 4″*R* (Proposed) Aminoacid: *S* $[\alpha]_D$= +15 (*c* = 0.20, MeOH) Config. of the double bond: *E*	^{1}H NMR, NOESY, ECD Aminoacid config.: Marfey's method Comparison with data of its epimer Config. of the double bond: *E*	
Aflaquinolone A (**27**)		$[\alpha]_D$= +16 (*c* = 0.20, MeOH)	Comparison of $[\alpha]_D$, ^{1}H NMR, and data of ref. 52	
Aflaquinolone D (**30**, tentative)		$[\alpha]_D$= –18 (*c* = 0.15, MeOH)		

[a]The asterisk means that only the relative configuration was established or proposed.

[b]Original name contains a different ring numbering system.

Table 4. Chronological summary of the observed biological activities of the 5-hydroxy-4-aryl-quinolin-2(1*H*)-one natural products and related compounds in 20 years of discovery.

Year	Compound	Biological activity	Ref.
1995	NTC-47A (**1**) NTC-47B (**2**)	Toxic to brine shrimp	11
1996	Penigequinolones A and B (**3** and **4**)	Inhibition of pollen-growth	13
1997	Quinolinone A (**6**)	Toxic to brine shrimp	16
2000	Peniprequinolone (**7**) Penigequinolones A and B (**3** and **4**)	Nematicidal against *Pratylenchus penetrans* Toxic to *C. elegans* Growth stimulant of root of rice seedlings	20
2005	Yaequinolone A1 (**14**)	Cytotoxic specificity on SKOV-3 cells	22
2005	Peniprequinolone (**7**)	Cytotoxic (non-selective) AGS cells and fibroblasts Antineoplastic (MDA-MB 231, HT-29, SKOV-3, DU-145)	22 24
2005	Yaequinolones J1 (**15**) and J2 (**16**)	Toxic to brine shrimp	23a
2006	Aspoquinolones A (**17**) and B (**18**)	Cytotoxic (L-929 mouse fibroblasts) Antiproliferative (human leukaemia K-562)	29
2006	Yaequinolones A2, A1, B-F, J1 and J2 (**13-16**; **22-26**)	Toxic to brine shrimp Inactive against *C. elegans* and other 14 microorganisms Growth inhibitory effect on arthropods	32a
2006	Penigequinolone A (**3**) Penigequinolone B (**4**) Quinolinone B (**5**) Peniprequinolone (**7**)	Toxic to brine shrimp	32a
2009	Yaequinolones A1, A2, B-F, J1 and J2 (**13-16**; **22-26**)	Ectoparasiticide activity against ticks and fleas	33a
2012	Aflaquinolones A (**27**) and B (**28**)	Antiproliferative (inactive)	34
2013	Aniduquinolones B (**35**) and C (**36**) Aflaquinolone A (**27**)	Toxic to brine shrimp	35
2013	Peniprequinolone (**7**)	Antioxidant and radical scavenger	36
2014	22-*O*-(*N*-Me-L-valinyl)-21-*epi*-aflaquinolone B (**41**) Aflaquinolone D (**30**)	Anti-RSV	38