Novel Approach to Isoindolo[2,1-*a*]quinolines: Synthesis of 1- and 3-Halo-Substituted 11-Oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acids

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Abstract: A series of 1- and 3-halo-substituted isoindolo[2,1-*a*]quinolines were obtained by means of electrophilic cyclization of methallyl- and allyl-substituted isoindolo-7-carboxylic acids. The influence of halogen atoms on the stereochemistry of the formation of key intermediates, 3a,6-epoxyisoindoles, was studied.

Key words: furans, intramolecular Diels–Alder reactions, cyclizations, electrophilic aromatic substitutions, isoindolo[2,1-*a*]quinolines

Only a few synthetic approaches to isoindolo[2,1-*a*]quinolines have been reported.[1–13] As a rule they require poorly available starting materials and involve a multi-step synthesis. Polycyclic nitrogen heterocycles with isoindolo[2,1-*a*]quinoline moiety have been shown to have important biological properties. In particular, it was found in the last ten years that analogs of berberine alkaloids[4,10] had effect against nitrogen-induced hypoxia and were inhibitors of human topoisomerase II.

1,2,3,4-Tetrahydroquinolines possessing halogen substituents in the aromatic ring are also known to show a wide range of biological activities. Ofloxacin (**1**) possesses topoisomerase inhibiting activity,[10] (±)-4-*trans*-2-carboxy-5,7-dichloro-4-[^{3}H]phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline (**2**) is a potent NMDA antagonist,[14] 6-halo-4-methyl-2-pyrido-1,2,3,4-tetrahydroquinolines **3** have antifungal activity,[15] and halogen-substituted 2-(1*H*-indol-3-yl)tetrahydroquinoline derivatives **4** possess *in vitro* activity against methicillin-resistant *Staphylococcus aureus*[16] (Figure 1).

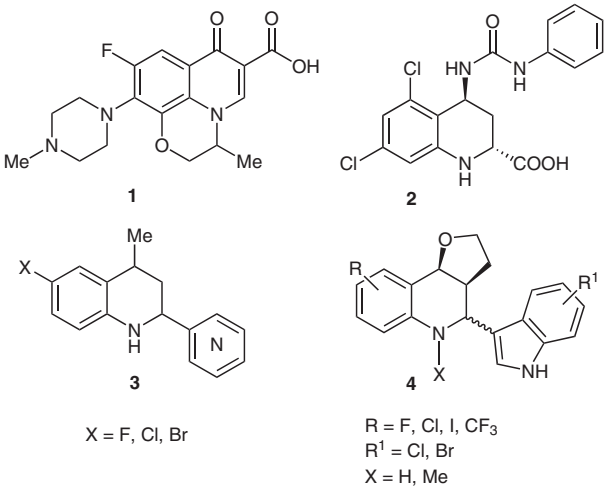
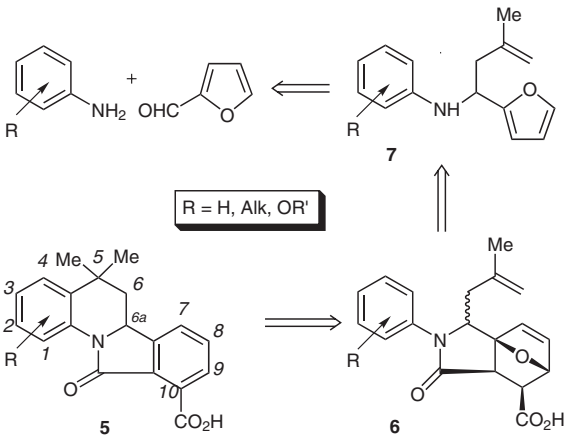


Figure 1 1,2,3,4-Tetrahydroquinolines **1**–**4** of biological interest.

We have recently reported[17] a new preparation of 11-oxo-isoindolo[2,1-*a*]quinoline-10-carboxylic acids **5**, possessing electron-donating substituents R in the quinoline fragment using 4-(*N*-aryl)amino-4-(2′-furyl)but-1-enes **7**[18,19] as starting compounds. Intramolecular electrophilic cyclization of 3-allyl-2-arylisoindole-7-carboxylic acids **6**, derived from furfurylamines **7** and maleic anhydride is a key step of this synthetic methodology[17,20] (Scheme 1).



Scheme 1

As a part of our research program directed toward the development of synthetic methodologies to prepare polycyclic nitrogen heterocycles on the basis of homoallylamines, we were interested in developing a synthetic route to isoindolo[2,1-*a*]quinolines possessing halogen substituents in the quinoline moiety.

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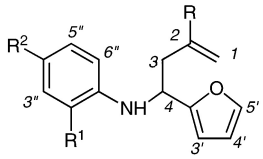
The required halo-substituted homoallylamine precursors **9a–h** and **10a–g** were readily synthesized via a two-step process (Scheme 2).[17–19] The condensation of halo-substituted anilines and furfural gave the corresponding Schiff bases **8a–h**, which were treated with Grignard reagents to give amines **9** and **10** in 46–83% yields (Tables 1–3).

Table 1 4-*N*-Arylamino-4-(2′-furyl)but-1-enes **9a–h**, **10a–g**

Product[a]	MS, M^+, *m/z*		R_f		IR (cm^{-1})		
	Found	Calcd	(Silufol UV_{254})	Bp (°C)/Torr or Mp (°C)	$\nu_{C=C}$	ν_{NH}	Yield (%)
9a	261 (^{35}Cl)	261.5	0.35[b]	49.5–50.5[c,d]	1640	3430	69
9b	307 (^{81}Br)	306	0.44[b]	51.5–52.5[c,d]	1639	3385	83
9c	245	245	0.54[e]	148–152/3	1658	3387	60
9d	261 (^{35}Cl)	261.5	0.33[f]	159–160/4	1638	3386	61
9e	307 (^{81}Br)	306	0.44[g]	oil[c]	1647	3410	46
9f	245	245	0.59[b]	142/3	1638	3410	47
9g	353	353	0.31[g]	oil[c]	1642	3420	78
9h	367	367	0.28[g]	oil[c]	1645	3440	68
10a	247 (^{35}Cl)	247.5	0.30[b]	163–166/4	1640	3406	79
10b	293 (^{81}Br)	292	0.44[b]	160/3	1642	3400	73
10c	231	231	0.52[b]	129–133/1.5	1631	3400	68
10d	247 (^{35}Cl)	247.5	0.20[f]	144/5	1638	3400	62
10e	293 (^{81}Br)	292	0.60[g]	oil[c]	1642	3398	59
10f	231	231	0.62[b]	145–147/9	1640	3405	48
10g	339	339	0.26[g]	oil[c]	1645	3400	64

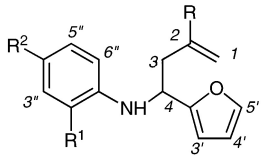
[a] Satisfactory microanalyses obtained: C,H,N: ±0.3%.
[b] EtOAc–hexane (1:10).
[c] Purification by chromatography over Al_2O_3 (hexane).
[d] Recrystallization from pentane.
[e] EtOAc–hexane (1:1).
[f] EtOAc–hexane (1:2).
[g] EtOAc–hexane (1:100).

Table 2 ^1H NMR Spectra ($CDCl_3$/TMS, 400 MHz) of 4-*N*-Arylamino-4-(2′-furyl)but-1-enes **9a–h**, **10a–g**; Chemical Shifts



Product	Chemical shifts, δ														
	1-*cis*	1-*trans*	R	3A	3B	4	Furyl			Aryl					NH
							3′	4′	5′	R^1	3″	R^2	5″	6″	
9a	4.83 br d	4.91 br t	1.70 s (CH_3)	2.67 br dd	2.56 ddd	4.54 m	6.17 dt	6.31 dd	7.36 dd	6.54 AA′	7.09 BB′	Cl	7.09 BB′	6.54 AA′	4.01 br s
9b	4.83 br d	4.91 br t	1.70 s (CH_3)	2.68 dd	2.56 ddd	4.54 dt	6.17 dt	6.31 dd	7.36 dd	6.49 AA′	7.23 BB′	Br	7.23 BB′	6.49 AA′	4.02 br d
9c	4.85 br s	4.91 br s	1.72 s (CH_3)	2.68 dd	2.57 dd	4.53 dd	6.19 br d	6.32 dd	7.37 dd	6.56 AA′F	6.87 BB′F	F	6.87 BB′F	6.56 AA′F	3.89 br s

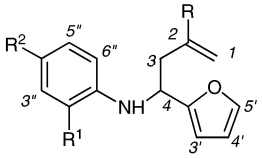
Table 2 ^{1}H NMR Spectra ($CDCl_3$/TMS, 400 MHz) of 4-*N*-Arylamino-4-(2′-furyl)but-1-enes **9a–h**, **10a–g**; Chemical Shifts (continued)



Product	Chemical shifts, δ														
	1-*cis*	1-*trans*	R	3A	3B	4	Furyl			Aryl					NH
							3′	4′	5′	R^1	3″	R^2	5″	6″	
9d	4.88 m	4.93 m	1.71 s (CH_3)	2.72 br dd	2.64 ddd	4.62 dt	6.18 dd	6.30 dd	7.37 dd	Cl	7.26 dd	6.63 dt	7.07 ddd	6.61 dd	4.73 br d
9e	4.91 m	4.95 m	1.71 s (CH_3)	2.73 br dd	2.65 ddd	4.63 ddd	6.18 dd	6.31 dd	7.43 dd	Br	7.43 ddd	6.58 m	7.11 td	6.58 m	4.76 br d
9f	4.82 br s	4.88 br s	1.68 s (CH_3)	2.67 dd	2.58 dd	4.57 m	6.17 br d	6.27 dd	7.33 br d	F	6.94 dd	6.60 m	6.90 dd	6.62 d	4.27 br s
9g	4.81 br s	4.91 br s	1.69 s (CH_3)	2.66 dd	2.54 dd	4.53 m	6.16 br d	6.29 dd	7.34 br d	6.39 AA′	7.38 BB′	I	7.38 BB′	6.39 AA′	4.02 br s
9h	4.86 m	4.91 m	1.69 s (CH_3)	2.71 dd	2.60 ddd	4.56 dd	6.15 dt	6.30 dd	7.36 dd	I	7.33 br d	2.11 s (CH_3)	7.30 dd	6.31 d	3.94 br s
10a	5.17 dd	5.21 dd	5.78 m (H)	2.68 m		4.54 t	6.17 br d	6.32 dd	7.38 dd	6.55 AA′	7.12 BB′	Cl	7.12 BB′	6.55 AA′	4.04 br s
10b	5.12 m	5.16 m	5.72 ddt (H)	2.61–2.66 m		4.49 t	6.12 dt	6.27 dd	7.33 dd	6.46 AA′	7.20 BB′	Br	7.20 BB′	6.46 AA′	4.00 br s
10c	5.16 m	5.20 m	5.78 ddt (H)	2.67 m		4.50 t	6.17 dd	6.31 dd	7.37 dd	6.56 AA′F	6.87 BB′F	F	6.87 BB′F	6.56 AA′F	3.91 br s
10d	5.25 ddt	5.30 dq	5.85 ddt (H)	2.78 m		4.66 q	6.23 dt	6.35 dd	7.43 dd	Cl	7.32 ddd	6.67–6.71 m	7.13 dt	6.67–6.71 m	4.82 br d
10e	5.17 dd	5.22 dd	5.76 ddt (H)	2.70 t		4.57 q	6.13 br d	6.27 dd	7.35 dd	Br	7.40 dd	6.55 dt	7.08 dt	6.56 d	4.73 br d
10f	5.20 br d	5.24 ddd	5.82 ddt (H)	2.74 ddt		4.61 t	6.22 dt	6.34 dd	7.40 dd	F	7.02 ddd	6.64 m	6.98 ddt	6.71 br dt	4.34 br s
10g	5.15 dd	5.19 dd	5.76 ddt (H)	2.66 m		4.52 t	6.15 dd	6.30 dd	7.36 dd	6.40 AA′	7.40 BB′	I	7.40 BB′	6.40 AA′	4.05 br s

The homoallylamines **9a**,**b** are colorless crystals, **9c–h** and **10a–g** are viscous oils, and were purified either by distillation in vacuo or by column chromatography (Table 1). It is worth noting that *ortho*-bromo- and *ortho*-iodo-substituted furfurylamines **9e**, **10e** and **9g**, **9h**, **10g**, respectively, are thermally unstable (explosive during vacuum distillation). Condensation of *ortho*-bromo- or *ortho*-fluoro-substituted anilines and furfural is completed over a longer period (4 h) compared with their *para*-substituted analogues (1–2 h). This can be explained in terms of steric hindrance of amino group with the bulky bromine atom and its reduced nucleophilic activity due to the strong electron-withdrawing effect of fluorine.

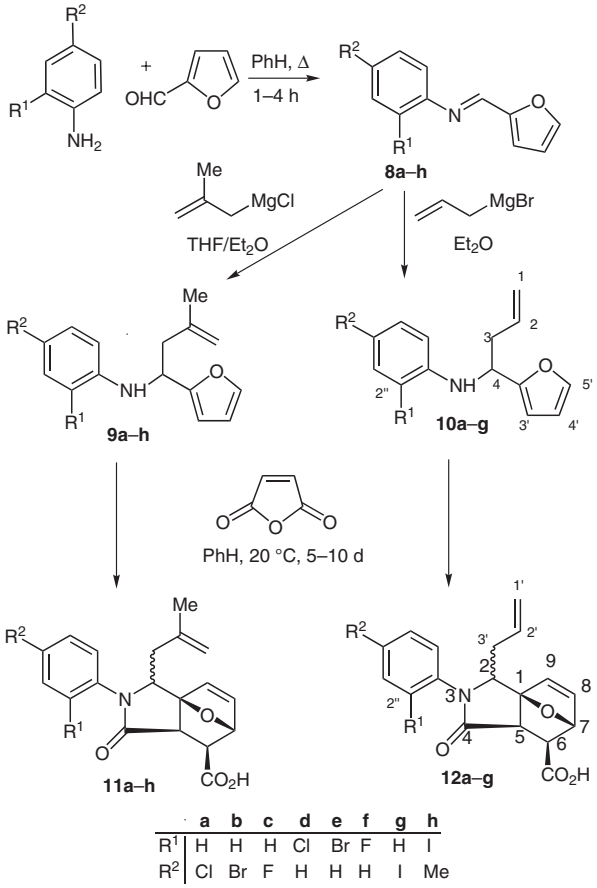
Table 3 ^{1}H NMR Spectra ($CDCl_3$/TMS, 400 MHz) of 4-*N*-Arylamino-4-(2′-furyl)but-1-enes **9a–h**, **10a–g**; Coupling Constants



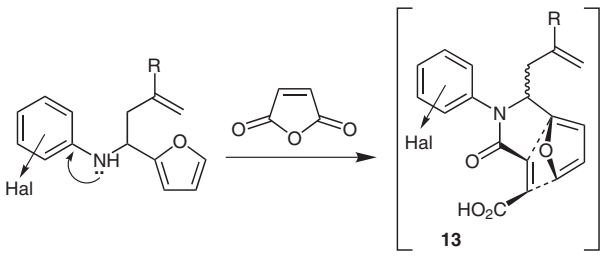
Product	Coupling Constants, *J* (Hz)																
	1-*cis*,2	1-*trans*,2	1-*cis*, 1-*trans*	2,3A	2, 3B	3A,4	3B,4	3A,3B	3′,4′	3′,5′	4′,5′	3″,4″	3″,5″	4″,5″	4″,6″	5″,6″	Other Constants
9a	–	–	0.7	–	–	5.5	8.7	14.1	3.2	0.7	1.8	–	–	–	–	~8.9	$J_{1\text{-}cis,3B}$ = 0.8, $J_{3',NH}$ = 0.7, $J_{2'',3''}$ = ~8.9
9b	–	–	–	–	–	5.5	8.7	14.1	3.0	0.8	1.8	–	–	–	–	~8.7	$J_{1\text{-}cis,3B}$ = 0.8, $J_{3',NH}$ = 0.8, $J_{4,NH}$ = 5.5, $J_{2'',3''}$ = ~8.7
9c	–	–	–	–	–	5.7	8.6	14.0	3.1	–	1.5	–	–	–	–	–	–
9d	–	–	–	–	–	5.5	8.4	14.0	3.2	0.7	1.8	7.5	1.5	7.5	1.4	8.2	$J_{1\text{-}cis,3B}$ = 0.7, $J_{1\text{-}trans,3B}$ = $J_{1\text{-}trans,3A}$ = 1.5, $J_{4,NH}$ = 4.8
9e	–	–	–	–	–	5.3	8.4	13.9	3.2	0.8	1.8	7.7	1.5	7.7	1.5	7.7	$J_{1\text{-}cis,3B}$ = 0.8, $J_{4,NH}$ = 5.6, $J_{3'',6''}$ = 0.5
9f	–	–	–	–	–	5.6	8.5	14.0	2.9	–	1.7	8.2	–	7.4	–	7.4	$J_{3'',F}$ = 11.3
9g	–	–	–	–	–	5.5	8.5	14.1	3.2	–	1.8	–	2.7	–	–	~8.5	$J_{2'',3''}$ = 1.8, $J_{2'',6''}$ = 2.7
9h	–	–	–	–	–	5.2	8.8	13.9	3.2	0.8	1.7	–	2.1	–	–	8.4	$J_{1\text{-}cis,3B}$ = 0.8, $J_{3'',6''}$ = 0.7
10a	10.4	17.1	1.8	6.1	6.1	6.1	6.1	–[a]	3.1	0.6	1.8	–	–	–	–	~8.5	–
10b	10.1	17.2	~1.5	7.1	7.1	6.2	6.2	–[a]	3.2	0.8	1.8	–	–	–	–	~8.5	$J_{3',NH}$ = 0.8
10c	10.2	17.2	1.7	7.1	7.1	6.4	6.4	–[a]	3.2	0.7	1.8	–	–	–	–	–	–
10d	10.1	17.0	1.5	7.1	7.1	6.0	6.0	–[a]	3.2	0.9	1.8	7.7	1.6	7.5	–	7.5	$J_{1\text{-}cis,3}$ = 1.0, $J_{1\text{-}trans,3}$ = 1.5 $J_{3',NH}$ = 0.8, $J_{4,NH}$ = 6.0, $J_{3'',6''}$ = 0.4
10e	10.1	17.2	1.5	7.2	7.2	6.3	6.3	–	3.2	0.7	1.8	7.7	1.5	7.7	1.3	7.7	$J_{4,NH}$ = 7.2
10f	10.1	17.1	1.9	7.1	7.1	6.3	6.3	–	3.2	0.8	1.8	8.0	1.4	8.2	1.4	8.2	$J_{1\text{-}cis,3}$ = 1.1, $J_{1\text{-}trans,3}$ = 2.3, $J_{3'',F}$ = 11.8, $J_{5'',F}$ = 0.8
10g	10.2	17.2	0.8	7.0	7.0	5.7	5.7	–	2.9	0.8	1.6	–	–	–	–	8.7	$J_{2'',3''}$ = ~8.7

[a] Coupling constants cannot be determined due to overlap of the corresponding signals.

The reaction of furfurylamines **9a–h** and **10a–g** with maleic anhydride[17,20] was carried out at 20 °C and the corresponding oxoepoxyisoindolocarboxylic acids **11a–h** and **12a–g** were isolated in moderate to quantitative yields (30–97%, Tables 4– 7). In the case of halo-substituted furfurylamines **9** and **10**, the reaction rate was slow (5–10 days) and the yields were lower compared to the alkyl- and alkoxy-substituted amines **7**.[17] Providing that the acylation at nitrogen with maleic anhydride leading to the formation of corresponding maleaimide **13** (Scheme 3) is the initial step of the described process, it was supposed that the slower reaction rate could be explained by the reduced nucleophilic activity of the amino group due to the steric and electronic influence of aromatic halogens.



Scheme 2



Scheme 3

The cycloaddition reaction was highly stereoselective, and only the Diels–Alder *exo*-adducts **11a–h** and **12a–g** were formed, as confirmed by comparing the values of spin-spin coupling constants of oxabicycloheptene moiety H-atoms with the literature data.[21] The H-atoms in position 6 of the tricycles **11** and **12** have the *endo*-orientation and gave a doublet signal at δ 2.55–3.24 with $J_{5,6}$ = 9.0–9.3 Hz in ^{1}H NMR spectra (in the case of *exo*-orientation 6-H atom would give a doublet of doublet signal with $J_{6,7}$ = 1.5–2.0 and $J_{5,6}$ = 8.5–10 Hz) (Tables 5 and 6).

Exo-epoxyisoindolones **11a–c**,**f**,**g** and **12a–c**,**f**,**g** were isolated as mixtures of two geometrical isomers based on the orientation of the allyl (for **12**) and methallyl (for **11**) groups in relation to the 1,7-epoxy bridge. The ratio of isomers varies depending on the reaction conditions, but in common it is ca. 1:1. Tricycles **11d**,**e**,**h** and **12d**,**e** possessing bulky substituents (Cl, Br, or I) in the *ortho*-position of the aryl radical were isolated as mixtures of three geometrical isomers. We suppose that this fact can be explained by the impossibility of the rotation of the aryl fragment around C–N bond. Isomers of compounds **11** and **12** could not be separated due to poor solubility in the commonly used organic solvents (chloroform, alcohol, ethyl acetate).

Table 4 Compounds **11**, **12**, and **14–17** Prepared

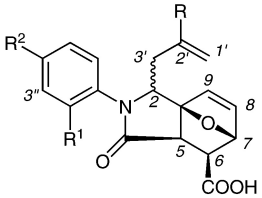
Product[a]	MS, M$^+$, *m*/*z*		R_f (Silufol, UV_{254})	Mp (°C)	IR (cm^{-1})		Yield (%)
	Found	Calcd			$\nu_{C=O}$	$\nu_{NC=O}$	
11a	359 (^{35}Cl)	359.5	0.32[b]	180.5–181	1730	1680[c]	75
11b	403 (^{79}Br)	404	0.34[b]	180–181	1726	1669[c]	62
11c	343	343	0.32[b]	162–162.5	1726	1680[c]	92
11d	359 (^{35}Cl)	359.5	0.34[b]	224–225	1738	1661[c]	64
11e	403 (^{79}Br)	404	0.35[b]	227.5–228	1740	1674[c]	21
11f	343	343	0.28[b]	210–212	1750	1682[c]	85
11g	451	451	0.32[b]	181.5–182	1740	1680[c]	83
11h	465	465	0.30[b]	200	1745	1673[c]	48
12a	345 (^{35}Cl)	345.5	0.42[d]	165–166.5	1729	1673[c]	90
12b	389 (^{79}Br)	390	0.32[b]	158–160	1737	1680[c]	75
12c	329	329	0.28[b]	124.5–126	1702	1608[c]	92
12d	345 (^{35}Cl)	345.5	0.35[b]	153–155	1730	1675[c]	97

Table 4 Compounds **11**, **12**, and **14–17** Prepared (continued)

Product[a]	MS, M^+, *m/z*		R_f (Silufol, UV_{254})	Mp (°C)	IR (cm^{-1})		Yield (%)
	Found	Calcd			$\nu_{C=O}$	$\nu_{NC=O}$	
12e	389 (^{79}Br)	390	0.32[b]	160–164	1745	1699[c]	45
12f	329	329	0.30[b]	167–169	1735	1680[c]	52
12g	437	437	0.27[b]	151–153	1740	1685[c]	85
14a	341 (^{35}Cl)	341.5	0.54[e]	288.5–290[f]	1712	1610	41
14b	385 (^{79}Br)	386	0.46[e]	292–293.5[f]	1710	1608	51
14c	325	325	0.52[e]	259–260.5[f]	1740	1632	62
14d	341 (^{35}Cl)	341.5	0.56[e]	268–270[f]	1715	1660	50
14e	385 (^{79}Br)	386	0.48[e]	279.5–280[f]	1725	1621	31
14f	325	325	0.50[e]	246–248[f]	1718	1608	40
14g	433	433	0.47[e]	300–301.5[f]	1720	1612	36
15a, **16a**	327 (^{35}Cl)	327.5	0.54[e]	166–167[f]	1722	1618	41
15b, **16b**	371 (^{79}Br)	372	0.48[e]	266–268[f]	1719	1620	63
15c, **16c**	311	311	0.50[e]	237.5–239[f]	1719	1620	54
15d, **16d**	327 (^{35}Cl)	327.5	0.56[e]	202–204[f]	1715	1616	44
15e, **16e**	371 (^{79}Br)	372	0.52[e]	254.5–256[f]	1715	1615	40
15f, **16f**	311	311	0.33[e]	222.5–226[f]	1719	1625	30
15g, **16g**	419	419	0.47[e]	258.5–259[f]	1725	1621	26
17a	327 (^{35}Cl)	327.5	0.56[e]	169.5–171[f]	1702	1621	65
17c	311	311	0.52[e]	146–148[f]	1701	1603	70
17g	419	419	0.51[e]	149.5–152[f]	1712	1621	60

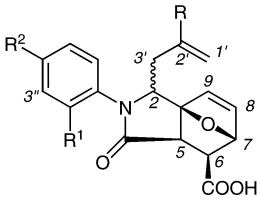
[a] Satisfactory microanalyses obtained: C, H, N ±0.3%.
[b] EtOAc–$CHCl_3$ (1:2).
[c] Absorption band of C=C bond is overlapped by absorption band of NCO group.
[d] EtOAc.
[e] EtOAc–$CHCl_3$ (1:10).
[f] Recrystallized from *i*-PrOH–DMF.

Table 5 ^1H NMR Spectra (DMSO-d_6[a] or $CDCl_3$[b]/TMS, 400 MHz) of 3-Aryl-3-aza-6-carboxy-4-oxo-10-oxatricyclo[5.2.1.$0^{1,5}$]dec-8-enes **11a–h** and **12a–g**; Chemical Shifts



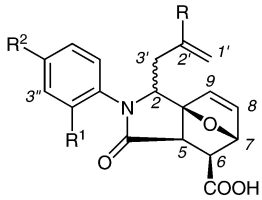
Product		Chemical Shifts, δ											
		2	5	6	7	8	9	1′-*cis*	1′-*trans*	R	3′A	3′B	CO_2H	Aryl
11a[a] (2.5:1)	maj	5.04 t	2.95 d	2.57 d	5.07 d	6.36 dd	6.52 d	4.75 and 4.77 br s		1.71 s (CH_3)	2.19 d		12.21 br s	7.28 (AA′, 2 H), 7.47 (BB′, 2 H)
	min	4.80 dd	3.23 d	2.56 d	5.00 d	6.47 dd	6.57 d	4.83 and 4.84 m		1.69 s (CH_3)	2.39 dd	2.59 dd	12.21 br s	7.42 (AA′, 2 H), 7.58 (BB′, 2 H)

Table 5 ^{1}H NMR Spectra (DMSO-d_6[a] or $CDCl_3$[b]/TMS, 400 MHz) of 3-Aryl-3-aza-6-carboxy-4-oxo-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **11a–h** and **12a–g**; Chemical Shifts (continued)



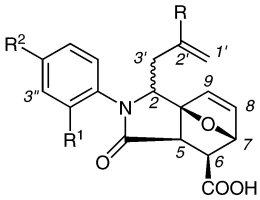
Product		Chemical Shifts, δ											
		2	5	6	7	8	9	1′-*cis*	1′-*trans*	R	3′A	3′B	CO_2H	Aryl
11b[a] (1.1:1)	maj	4.77–4.84	3.24 d	2.58 d	5.06 d	6.48 dd	6.58 d	4.77–4.84 m		1.71 s (CH_3)	2.20 and 2.40 m		12.23 br s	7.55 (br s, 4 H)
	min	5.01–5.08 m	2.96 d	2.57 d	5.01 d	6.37 dd	6.52 d	5.01–5.08 m		1.72 s (CH_3)	2.20 and 2.40 m		12.23 br s	7.24 (AA′, 2 H), 7.61 (BB′, 2 H)
11c[b] (1.3:1)	maj	4.73 dd	3.01 d	2.85 d	5.31 d	6.37 dd	6.47 d	4.78 and 4.85 br s		1.72 s (CH_3)	2. 26 ddq	2.39–2.48 m	–[c]	7.08 (AA′F, 2 H), 7.23 (BB′F, 2 H)
	min	4.66 dd	3.15 d	2.84 d	5.25 d	6.45 dd	6.59 d	4.83 and 4.92 br s		1.73 s (CH_3)	2.55 ddq	2.39–2.48 m	–[c]	7.08 (AA′F, 2 H), 7.40 (BB′F, 2 H)
11d[a] (2.1:1.8:1)	maj	4.56 dd	3.18 d	2.59 d	5.05 d	6.39 dd	6.58 d	4.63 and 4.70 br s		1.57 s (CH_3)	2.34 m	2.66 dd	12.18 br s	7.32–7.59 (m, 4 H)
	mid	4.94 dd	3.01 d	2.54 d	5.09 d	6.39 dd	6.60 d	4.69 and 4.76 br s		1.65 s (CH_3)	1.90–1.97 m	2.27 dd	12.18 br s	7.32–7.59 (m, 4 H)
	min	4.92 dd	2.94 d	2.54 d	5.09 d	6.48 dd	6.54 d	4.65 and 4.69 br s		1.62 s (CH_3)	1.90–1.97 m	2.27 dd	12.18 br s	7.15 (m, 1 H), 7.32–7.59 (m, 4 H)
11e[a,d] (6:3.5:1)	maj	4.92 dd	2.98 d	2.57 d	5.08 d	6.39 dd	6.60 d	4.61 and 4.67 br s		1.64 s (CH_3)	1.93 dd	2.27 dd	12.21 br s	7.12 (dd, 1 H, H-6″), 7.32 (td, 1 H, H-4″), 7.43 (td, 1 H, H-5″), 7.73 (dd, 1 H, H-3″)
	mid	4.92 dd	2.92 d	2.51 d	5.08 d	6.39 dd	6.53 d	4.61 and 4.63 br s		1.60 s (CH_3)	1.93 dd	2.39 dd	12.21 br s	7.26 (t, 1 H, H-5″), 7.35 (d, 1 H, H-6″), 7.49 (td, 1 H, H-4″), 7.66 (dd, 1 H, H-3″)
11f[a] (1.1:1)	maj	4.57 dd	3.21 d	2.55 d	5.04 d	6.49 dd	6.59 d	4.66 and 4.75 br s		1.55 s (CH_3)	2.35 dd	2.62 dd	12.16 br s	7.19–7.43 (m, 4 H)
	min	4.91 dd	2.99 d	2.57 d	5.08 d	6.37 dd	6.56 d	4.66 and 4.71 br s		1.66 s (CH_3)	2.02 dd	2.26 dd	12.16 br s	7.19–7.43 (m, 4 H)
11g[a] (1.1:1)	maj	4.79 dd	2.94 d	2.56 d	5.06 d	6.35 dd	6.51 d	4.78 and 4.84 br s		1.71 c (CH_3)	2.18 m		12.23 br s	7.08 (AA′, 2H), 7.76 (BB′, 2 H)
	min	5.03 m	3.23 d	2.54 d	5.00 d	6.46 dd	6.56 d	4.75 and 4.84 br s		1.70 s (CH_3)	2.37 m		12.23 br s	7.39 (AA′, 2 H), 7.70 (BB′, 2 H)
11h[a,d] (5:4:1)	maj	4.93 dd	2.90 d	2.54 d	5.07 d	6.36 dd	6.52 d	4.65 and 4.70 br s		1.63 s (CH_3)	1.88 dd	2.22 dd	12.19 br s	2.10 (s, 3 H, CH_3-4″), 7.10 (d, 1 H, H-6″), 7.60 (dd, 1 H, H-5″), 7.63 (d, 1 H, H-3″)

Table 5 ^{1}H NMR Spectra (DMSO-d_6[a] or $CDCl_3$[b]/TMS, 400 MHz) of 3-Aryl-3-aza-6-carboxy-4-oxo-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **11a–h** and **12a–g**; Chemical Shifts (continued)



Product		Chemical Shifts, δ												
		2	5	6	7	8	9	1′-*cis*	1′-*trans*	R	3′A	3′B	CO_2H	Aryl
	min	4.93 dd	3.18 d	2.51 d	5.02 d	6.45 dd	6.55 d	4.74 and 4.76 br s		1.57 s (CH_3)	2.39 m	2.63 dd	12.19 br s	2. 04 (s, 3 H, CH_3-4″), 7.10 (d, 1 H, H-6″), 7.56 (dd, 1 H, H-5″), 7.65 (d, 1 H, H-3″)
12a[b] (2.6:1)	maj	4.60 t	3.06 d	2.83 d	5.25 d	6.49 dd	6.62 d	5.18 m	5.16 m	5.75 m (H)	2.61 br t		9.40 br s	7.30–7.45 (m, 4 H)
	min	4.55 dd	2.97 d	2.84 d	5.31 d	6.40 dd	6.46 d	5.08 m		5.75 m (H)	2.41 m		9.40 br s	7.20–7.35 (m, 4 H)
12b[a] (1.3:1)	maj	4.86 dd	2.99 d	2.59 d	5.09 d	6.42 dd	6.54 d	5.00 dd	5.03 dd	5.73 ddt (H)	2.15–2.23 and 2.33–2.39 m		12.25 br s	7.25 (AA′, 2 H), 7.61 (BB′, 2 H)
	min	4.77 dd	3.09 d	2.58 d	5.01 d	6.52 dd	6.75 d	5.10–5.13 m		5.80 ddt (H)	2.15–2.23 and 2.33–2.39 m		12.25 br s	7.59 (s, 4 H)
12c[a] (1.3:1)	maj	4.81 dd	2.96 d	2.60 d	5.06 d	6.42 dd	6.55 d	4.95–5.20 m		5.73 m (H)	2.20–2.35 m		–[c]	7.15–7.35 (m, 4 H)
	mid	4.68 dd	3.05 d	2.59 d	5.02 d	6.53 dd	6.73 d	4.95–5.20 m		5.73 m (H)	2.20–2.35 m		–[c]	7.15–7.35 (m, 4 H)
12d[a] (3:1.8:1)	maj	4.41 dd	3.07 d	2.59 d	5.04 br s	6.52 dd	6.68 d	4.95 m	5.19 dd	5.79 ddt (H)	1.97–2.06 m		12.11 br s	7.34–7.59 (m, 4 H)
	mid	4.70 dd	3.01 d	2.55 d	5.10 br s	6.43 dd	6.61 d	4.89–5.00 m		5.62 ddt (H)	2.27–2.40 m		12.11 br s	7.34–7.59 (m, 4 H)
	min	4.73 dd	2.95 d	2.57 d	5.06 br s	6.43 dd	6.55 d	4.89–5.00 m		5.62 m (H)	2.45–2.64 m		12.11 br s	7.16 (m, 1 H), 7.34–7.59 (m, 3 H)
12e[a] (2.1:1.5:1)	maj	4.69 dd	2.99 d	2.56 d	5.10 br s	6.43 dd	6.61 d	4.99 dd	5.19 dd	5.61 m (H)	1.96–2.05 m		12.10 br s	7.26–7.35 (m, 2 H, H-4″ + H-6″), 7.45 (dt, 1 H, H-5″), 7.73 (dd, 1 H, H-3″)
	mid	4.42 dd	3.06 d	2.59 d	5.04 d	6.51 dd	6.68 d	4.89–5.08 m		5.80 m (H)	2.42–2.61 m		12.10 br s	7.14 (dd, 1 H, H-6″), 7.26–7.35 (m, 1 H, H-4″), 7.44 (dt, 1 H, H-5″), 7.70 (dd, 1 H, H-3″)
	min	4.72 dd	2.95 d	2.58 d	5.06 br s	6.42 dd	6.54 d	4.89–5.08 m		5.58 m (H)	2.27–2.35 m		12.10 br s	7.26–7.35 (m, 2 H, H-4″ + 6″), 7.44 (m, 1 H, H-5″), 7.67 (m, 1 H, H-3″)

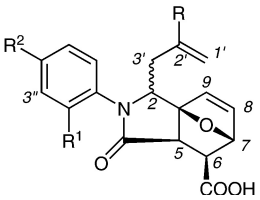
Table 5 ^{1}H NMR Spectra (DMSO-d_6[a] or $CDCl_3$[b]/TMS, 400 MHz) of 3-Aryl-3-aza-6-carboxy-4-oxo-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **11a–h** and **12a–g**; Chemical Shifts (continued)



Product		Chemical Shifts, δ												
		2	5	6	7	8	9	1′-*cis*	1′-*trans*	R	3′A	3′B	CO_2H	Aryl
12f[a] (1.1:1)	maj	4.70 dd	3.05 d	2.55 d	5.09 d	6.52 dd	6.71 d	5.04 m	5.15 dd	5.75 ddt (H)	2.12 m		12.19 br s	7.22–7.41 (m, 4 H)
	min	4.46 dd	3.00 d	2.58 d	5.03 d	6.42 dd	6.57 d	4.96 m	4.99 m	5.66 ddt (H)	2.27 m		12.19 br s	7.22–7.41 (m, 4 H)
12g[a] (1.05:1)	maj	4.75 dd	3.07 d	2.57 d	5.08 d	6.41 dd	6.74 d	5.07–5.13 m		5.72 ddt (H)	2.17 m		12.25 br s	7.43 (AA′, 2 H), 7.71 (BB′, 2 H)
	min	4.85 dd	2.97 d	2.56 d	5.00 d	6.51 dd	6.53 d	4.99–5.04 m		5.79 m (H)	2.34 m		12.25 br s	7.10 (AA′, 2 H), 7.76 (BB′, 2 H)

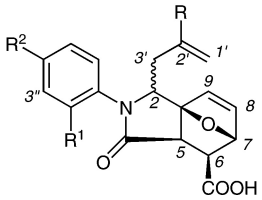
[a] EtOAc–$CHCl_3$ (1:2).
[b] EtOAc.
[c] CO_2H proton gets exchanged with DMSO-d_6.
[d] The signals of minor isomer protons are of extremely low intensity.

Table 6 ^{1}H NMR Spectra (DMSO-d_6 or $CDCl_3$/TMS, 400 MHz) of 3-Aryl-3-aza-6-carboxy-4-oxo-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **11a–h** and **12a–g**; Coupling Constants



Product		Coupling Constants, *J* (Hz)										
		1′-*cis*,2′	1′-*trans*,2′	2′,3′A	2′,3′B	3′,3′	2,3′A	2,3′B	5,6	7,8	8,9	Other Constants
11a	maj	–	–	–	–	–[a]	7.3	7.3	9.1	1.6	5.7	–
	min	–	–	–	–	15.5	4.5	9.8	9.1	1.6	5.8	–
11b	maj	–	–	–	–	–[a]	–[a]	–[a]	9.2	1.4	5.6	–
	min	–	–	–	–	–[a]	–[a]	–[a]	9.2	1.4	5.6	–
11c	maj	–	–	–	–	14.0	4.0	10.8	9.0	1.6	5.9	$J_{3'A,Me} = J_{3'B,Me} = 0.6$
	min	–	–	–	–	14.8	4.1	9.8	9.1	1.7	5.8	$J_{3'A,Me} = J_{3'B,Me} = 0.6$
11d	maj	–	–	–	–	15.4	–[a]	8.5	9.1	1.6	5.7	–
	mid	–	–	–	–	13.7	–[a]	10.0	9.1	1.5	5.7	–
	min	–	–	–	–	13.7	–[a]	10.0	9.2	1.7	5.6	–
11e	maj	–	–	–	–	14.0	4.5	9.9	9.0	1.3	5.7	$J_{3'',4''} = J_{4'',5''} = J_{5'',6''} = 7.8$
	mid	–	–	–	–	14.0	4.5	9.9	9.0	1.3	5.7	$J_{3'',4''} = J_{4'',5''} = J_{5'',6''} = 8.0$
11f	maj	–	–	–	–	15.3	6.6	7.8	9.1	1.6	5.7	–
	min	–	–	–	–	13.5	4.0	10.3	9.1	1.6	5.7	–

Table 6 ^{1}H NMR Spectra (DMSO-d_6 or $CDCl_3$/TMS, 400 MHz) of 3-Aryl-3-aza-6-carboxy-4-oxo-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **11a–h** and **12a–g**; Coupling Constants (continued)



Product		Coupling Constants, *J* (Hz)										
		1′-*cis*,2′	1′-*trans*,2′	2′,3′A	2′,3′B	3′,3′	2,3′A	2,3′B	5,6	7,8	8,9	Other Constants
11g	maj	–	–	–	–	–[a]	4.0	9.7	9.2	1.7	5.7	$J_{2'',3''} = J_{5'',6''}$ = ~8.7
	min	–	–	–	–	–[a]	4.9	4.9	9.2	1.7	5.8	$J_{2'',3''} = J_{5'',6''}$ = ~8.9
11h	maj	–	–	–	–	13.5	4.0	10.3	9.1	1.5	5.6	$J_{3'',5''}$ = 1.7, $J_{5'',6''}$ = 8.2
	min	–	–	–	–	15.5	4.0	9.5	9.1	1.5	5.6	$J_{3'',5''}$ = 1.7, $J_{5'',6''}$ = 8.2
12a	maj	10.4	16.5	5.8	5.8	–[a]	4.9	4.9	9.2	1.5	5.8	–
	min	10.4	16.5	–[a]	–[a]	–[a]	4.6	7.9	9.2	1.5	5.8	–
12b	maj	10.2	17.1	7.0	7.0	–[a]	3.9	10.6	9.2	1.7	5.7	–
	min	10.7	17.7	7.3	7.3	–[a]	3.8	6.4	9.1	1.7	5.9	–
12c	maj	10.1	17.1	7.0	7.0	–[a]	5.2	9.5	9.2	1.5	5.8	$J_{1',1'}$ = 1.6, $J_{2'',3''} = J_{5'',6''}$ = ~8.7
	min	10.1	17.1	7.0	7.0	–[a]	4.6	5.8	9.2	1.5	5.8	–
12d	maj	10.6	17.2	7.0	7.0	–[a]	4.9	6.9	9.2	1.5	5.8	$J_{1',1'}$ = 1.5
	mid	10.3	17.4	7.1	7.1	–[a]	5.4	10.1	9.1	1.8	5.7	–
	min	–[a]	–[a]	–[a]	–[a]	–[a]	5.0	10.1	9.3	1.8	5.8	–
12e	maj	10.2	17.5	7.0	7.0	–[a]	5.1	10.1	9.1	1.6	5.7	$J_{3'',4''}$ = 8.0, $J_{3'',5''}$ = 1.3, $J_{5'',4''} = J_{5'',6''}$ = 7.6
	mid	10.2	17.0	6.7	6.7	–[a]	4.9	7.0	9.2	1.7	5.8	$J_{3'',4''}$ = 8.4, $J_{3'',5''}$ = 1.3, $J_{5'',4''} = J_{5'',6''}$ = 7.7
	min	10.3	16.4	5.7	5.7	–[a]	4.9	10.0	9.3	1.7	5.6	–
12f	maj	10.4	17.3	7.2	7.2	–[a]	4.9	10.1	9.2	1.7	5.8	$J_{1',1'}$ = 0.9
	min	10.4	17.3	7.4	7.4	–[a]	5.0	5.3	9.2	1.7	5.7	$J_{1',1'}$ = 0.9
12g	maj	10.1	17.1	7.0	7.0	–[a]	3.7	6.3	9.2	1.7	5.8	$J_{2'',3''} = J_{5'',6''}$ = ~8.8
	min	10.6	17.6	7.0	7.0	–[a]	4.0	10.7	9.2	1.7	5.8	$J_{1',1'}$ = 1.6, $J_{2'',3''} = J_{5'',6''}$ = ~8.6

[a] Coupling constants cannot be determined because of the overlap of the corresponding signals.

Table 7 Mass Spectral Data of Compounds **11, 12,** and **14–17** (EI, 70 eV)

Product	*m*/*z*, rel. intensity (%)
11a	359 ([M$^+$] (for ^{35}Cl), 3), 304 (12), 260 (10), 206 (100), 204 (10), 135 (19), 127 (5), 117 (12), 111 (11), 99 (17), 91 (11), 77 (5), 55 (10), 44 (14), 39 (9), 28 (15)
11b	403 ([M$^+$] (for ^{79}Br), 4), 350 (8), 338 (14), 304 (5), 250 (80), 41 (220), 204 (16), 182 (16), 171 (21), 155 (25), 143 (8), 135 (49), 125 (100), 117 (45), 105 (23), 99 (93), 91 (80), 77 (46), 71 (26), 65 (49), 55 (89), 39 (76)
11c	343 ([M$^+$], 13), 288 (30), 270 (3), 258 (2), 244 (11), 226 (2), 214 (2), 190 (100), 161 (2), 135 (3), 117 (2), 99 (10), 55 (5)

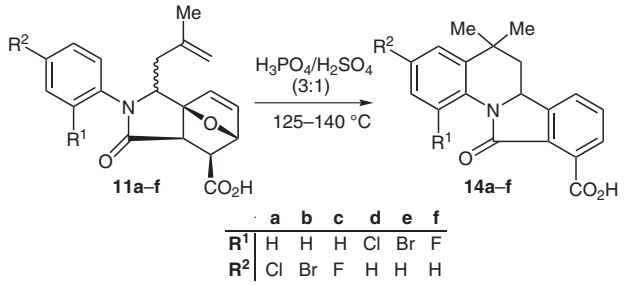
Table 7 Mass Spectral Data of Compounds **11, 12,** and **14–17** (EI, 70 eV) (continued)

Product	*m*/*z*, rel. intensity (%)
11d	359 ([M$^+$] (for ^{35}Cl), 5), 304 (15), 260 (12), 206 (100), 135 (21), 127 (5), 117 (12), 111 (10), 99 (20), 91 (12), 79 (6), 75 (5), 65 (5), 55 (10), 44 (12), 39 (9), 28 (15)
11e	403 ([M$^+$], 1), 350 (20), 304 (10), 250 (100), 190 (7), 170 (5), 155 (4), 135 (13), 117 (7), 99 (12), 91 (7), 81 (5), 69 (7), 44 (4)
11f	343 ([M$^+$], 4), 299 (3), 288 (16), 244 (11), 190 (100), 135 (8), 122 (14), 99 (10), 91 (6), 79 (4), 55 (5), 28 (16)
11g	451 ([M$^+$] (12), 396 (26), 352 (11), 298 (100), 171 (13), 135 (25), 117 (12), 99 (11), 91 (9), 76 (6), 55 (5)
11h	465 ([M$^+$] (4), 433 (54), 418 (14), 410 (40), 389 (27), 366 (9), 312 (100), 256 (9), 217 (5), 185 (18), 135 (17), 128 (5), 117 (14), 99 (16), 91 (10), 55 (6)
12a	345 ([M$^+$] (for ^{35}Cl) (15), 304 (17), 260 (9), 246 (23), 153 (6), 140 (5), 138 (11), 127 (8), 121 (30), 111 (13), 103 (17), 99 (21), 91 (17), 77 (16), 65 (7), 55 (11), 44 (19), 41 (7)
12b	389 ([M$^+$] (for ^{79}Br) (7), 373 (4), 348 (12), 304 (9), 290 (23), 250 (100), 223 (3), 190 (5), 184 (12), 171 (13), 157 (21), 145 (6), 121 (57), 103 (42), 91 (45), 65 (19), 55 (28), 39 (20), 27 (15)
12c	329 ([M$^+$], 4), 288 (12), 244 (9), 230 (15), 190 (100), 149 (9), 137 (5), 121 (27), 103 (14), 91 (24), 77 (10), 65 (7), 55 (12), 44 (18), 39 (18), 26 (6)
12d	345 ([M$^+$] (for ^{35}Cl), 1), 310 (6), 304 (13), 260 (5), 246 (20), 206 (100), 190 (5), 138 (10), 121 (10), 111 (8), 103 (8), 99 915), 91 (12), 77 (11), 55 (7), 44 (11), 39 (10), 28 (14)
12e	389 ([M$^+$] (for ^{79}Br), 7), 348 98), 310 (13), 292 (9), 250 (100), 190 (32), 170 (7), 155 (13), 121 (46), 91 (35), 77 (39), 55 (25), 39 (44)
12f	329 ([M$^+$], 3), 288 (14), 244 (5), 230 (24), 190 (100), 122 (13), 103 (7), 99 (12), 95 (7), 77 (8), 55 (6), 44 (6), 39 (7), 27 (5)
12g	437 ([M$^+$], 12), 396 (13), 352 (10), 338 (20), 298 (100), 219 (6), 203 (12), 171 (28), 142 (5), 121 (37), 91 (26), 77 (22), 55 (13), 39 (15)
14a	341 ([M$^+$] (for ^{35}Cl), 90), 326 (47), 308 (18), 297 (100), 282 (26), 266 (6), 252 (11), 238 (6), 217 (9), 178 (5), 141 (10), 115 (10), 108 (9), 102 (6), 44 (13), 36 (7), 28 (12)
14b	385 ([M$^+$] (for ^{79}Br), 31), 370 (11), 354 (5), 341 (51), 326 (18), 297 (24), 276 (6), 262 (11), 247 (14), 232 (36), 217 (39)
14c	325 ([M$^+$], 88), 310 (42), 292 (18), 281 (100), 266 (30), 250 (11), 236 (16), 222 (13), 162 (6), 133 (13), 117 (6), 44 (7), 28 (6)
14d	341 ([M$^+$] (for ^{35}Cl), 13), 306 (59), 297 (100), 282 (10), 262 (45), 254 (26), 241 (10), 232 (10), 217 (23), 204 (14), 190 (12), 178 (23), 164 (16), 151 (12), 141 (26), 123 (24), 115 (57), 102 (48), 96 (25), 89 (42), 82 (6), 73 (39), 63 (29), 55 (8), 51 (27), 44 (55), 39 (34)
14e	343 ([M$^+$ – 44] (for ^{81}Br), 2), 306 (100), 262 (3), 217 (1), 109 (2), 95 (2), 81 (2), 69 (4), 43 (4)
14f	325 ([M$^+$], 7), 310 (6), 281 (100), 266 (15), 238 (8), 226 (6), 197 (7), 170 (5), 128 (10), 115 (7), 77 (6)
14g	433 ([M$^+$], 100), 418 (27), 389 (52), 374 (9), 262 (6), 232 (7), 217 (8), 204 (5), 128 (3), 115 (6), 109 (4), 77 (2), 44 (2)
15a, **16a**	327 ([M$^+$] (for ^{35}Cl), 28), 311 (6), 294 (4), 283 (100), 268 (25), 254 (9), 232 (7), 217 (5), 204 (13), 178 (9), 164 (11), 151 (8), 140 (4), 128 (6), 115 (16), 102 (31), 89 (20), 75 (30), 63 (15), 51 (16), 39 (17)
15b, **16b**	373 ([M$^+$] (for ^{79}Br), 66), 371 (69), 356 (7), 329 (100), 312 (13), 298 (7), 284 (15), 248 (19), 232 (23), 217 (9), 204 (33), 177 (6), 146 (5), 129 (4), 115 (9), 102 (19), 77 (9), 51 (4), 39 (3)
15c, **16c**	311 ([M$^+$]; 63), 296 (5), 279 (9), 267 (100), 252 (26), 238 (11), 222 (21), 178 (5), 162 (6), 146 (6), 101 (5), 75 (5), 44 (6)
15d, **16d**	327 ([M$^+$] (for ^{35}Cl), 42), 312 (10), 294 (6), 283 (100), 268 (18), 232 (8), 204 (11), 194 (6), 178 (7), 164 (9), 151 (7), 134 (9), 123 (8), 109 (9), 102 (38), 96 (11), 89 (13), 82 (13), 75 (18), 63 (11), 58 (29), 51 (13), 36 (19)
15e, 16e	371 ([M$^+$] (for ^{79}Br), 19), 327 (10), 292 (100), 248 (13), 204 (8), 115 (7), 89 (7), 77 (9), 63 (6), 51 (7), 39 (8)
15f, **16f**	311 ([M$^+$], 23), 267 (100), 238 (7), 224 (14), 222 (11), 162 (6), 133 (4), 44 (7), 28 (4)
15g, **16g**	419 ([M$^+$], 100), 375 (60), 248 (11), 232 (6), 204 (10), 128 (7), 102 (6), 44 (6), 41 (7)

Table 7 Mass Spectral Data of Compounds **11, 12,** and **14–17** (EI, 70 eV) (continued)

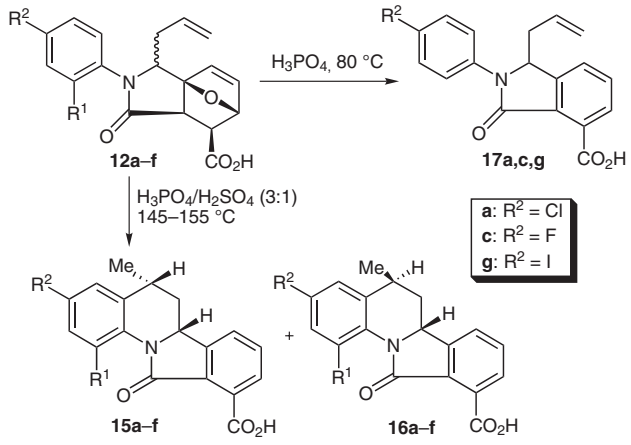
Product	*m/z*, rel. intensity (%)
17a	327 ([M$^+$] (for ^{35}Cl), 9), 286 (100), 283 (22), 244 (5), 243 (5), 242 (15), 214 (12), 178 (5), 152 (10), 151 (5), 138 (6), 111 (11), 77 (9), 75 (8)
17c	311 ([M$^+$], 5), 270 (100), 226 (14), 198 (12), 170 (5), 95 (8), 77 (6), 28 (7)
17g	419 ([M$^+$], 12), 378 (100), 334 (8), 306 (7), 179 (10), 152 (4), 76 (8)

The intramolecular cyclization of isoindolones **11a–f** and **12a–f** leading to isoindolo[2,1-*a*]quinoline-10-carboxylic acids **14a–f**, **15a–f** and **16a–f** was carried out at 125–155 °C in the presence of concentrated *ortho*-phosphoric and sulfuric acids (3:1 by volume) (Schemes 4 and 5 and Tables 4, 7–9). Intramolecular cyclization of allyl-substituted epoxyisoindolones **12a–f** required more drastic reaction conditions (145–155 °C, Scheme 5) compared to their methallyl substituted analogs **11a–f** (125–140 °C, Scheme 4).[17] It can be explained by the poor stability of the intermediate secondary carbocation formed by protonation of the allyl fragment in comparison with the tertiary one formed from the methallyl fragment.



	a	b	c	d	e	f
R^1	H	H	H	Cl	Br	F
R^2	Cl	Br	F	H	H	H

Scheme 4



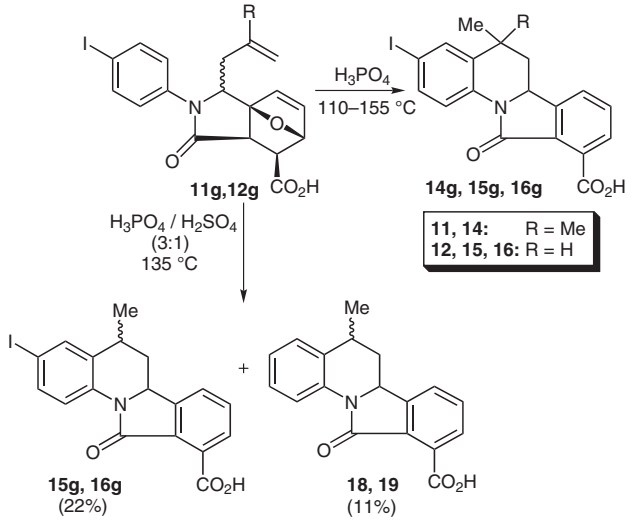
Scheme 5

The intramolecular cyclization of fluoro-substituted adducts **11c**,**f** required a higher temperature (135–140 °C) as compared to their chloro- and bromo-substituted analogs (125–130 °C). The cyclization reaction rate in the case of *ortho*-substituted adducts **11d–f** is lower (2 h) compared to their *para*-analogs **11a–c** (1 h). Oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acids **14a–f** were obtained in moderate yields (31–62%, Table 4) as colorless crystals.

In contrast to the 5,5-dimethylisoindolo[2,1-*a*]quinolines **14**, their 5-monosubstituted homologues were formed as mixtures of two geometrical isomers **15** and **16** according to the orientation of the hydrogen atoms at the C-5 and C-6a positions (Scheme 5). In all the cases isomer **15** with pseudoequatorial orientation of 5-Me group was predominating. The stereochemistry of isomers **15a–f** and **16a–f** was determined based on the spin-spin coupling constants of the H-5 and H-6a atoms. Thus, for the prevailing isomer **15** with pseudoaxial orientation of the 5-H atom, the coupling constants were $J_{5ax,6ax}$ = 9.5–12.5 Hz and $J_{5ax,6eq}$ = 5.6–6.9 Hz, while for the minor isomer **16** with the pseudoequatorial orientation of the same H-atom the constants were much smaller ($J_{5eq,6ax}$ = 5.5–6.2 Hz and $J_{5eq,6eq}$ = 2.4–6.2 Hz) (Table 9).

Using allyl-substituted epoxyisoindolones **12a**,**c**,**g** as model compounds we have shown (Scheme 5) that the aromatization of the oxabicycloheptene fragment was a preliminary step in the formation of isoindolo[2,1-*a*]quinolines **14–16**. Heating compounds **12a**,**c**,**g** in phosphoric acid alone at 80 °C initiated the epoxide opening and aromatization reaction sequence to give 3-allylisoindolones **17a**,**c**,**g** in good yields (53–70%, Table 4).

In the presence of sulfuric acid, the iodo-substituted adduct **12g** underwent reduction leading to a mixture of 3-iodo-substituted (**15g**, **16g**) and unsubstituted (**18**, **19**) oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acids in 33% total yield (molar ratio 2:1). Molecular iodine was evolved during the reaction. The desired cyclization of **11g**, **12g** into the corresponding 3-iodo-substituted oxoisoindolo[2,1-*a*]quinolines **14g**, **15g** and **16g** was carried out in the presence of phosphoric acid at 110–155 °C (Scheme 6).



Scheme 6

We did not manage to find out any suitable conditions for the cyclization of *ortho*-iodo-substituted oxoepoxyisoindolone **11h**. Thus, adduct **11h** forms a resin in the presence of phosphoric acid even at low (60–80 °C) temperatures.

In all the tetracyclic acids **14–16, 18** and **19**, the 6a-H-atom has a pseudoaxial orientation and the spin-spin coupling constant values confirm its orientation ($J_{6a,6ax}$ = 10.3–13.0 Hz and $J_{6A,6eq}$ = 1.8–4.4 Hz) (Table 9).

In conclusion, this work demonstrates a new two-step synthesis of 1- and 3-halo-substituted isoindolo[2,1-*a*]quinoline-10-carboxylic acids interesting as potentially biologically active compounds. It was demonstrated that the insertion of an electron-withdrawing substituent did not have any sufficient effect on the key step of this synthetic approach – intramolecular electrophilic cyclization of 2-allyl(methallyl)oxoepoxyisoindolones.

Melting points are uncorrected. IR spectra were obtained in KBr pellets for solids or as thin film for oils. NMR spectra ^{1}H (400 MHz) and ^{13}C (100.6 MHz) were recorded for solutions (2–5%) in $CDCl_3$ or DMSO-d_6 at 30 °C and traces of $CHCl_3$ (^{1}H NMR, δ = 7.26), DMSO-d_5H (^{1}H NMR, δ = 2.49) and DMSO-d_6 (^{13}C NMR, δ = 39.43) present in the solvents were used as the internal standard. Chemical shifts are reported in ppm units, coupling constants (*J*) are reported in Hz. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC silufol UV_{254} plates. The separation of the final products was carried out by column chromatography on Al_2O_3 (activated, neutral, 50–200 mm) or by recrystallization.

Compounds 9a–h, 10a–g; General Procedure

The corresponding aldimine **8a–h** (0.30 mol) was slowly added dropwise at reflux to a stirred solution of allylmagnesium bromide [prepared from allyl bromide (39 mL, 0.45 mol) and Mg turnings (22.0 g, 0.90 mol) in Et_2O (300 mL)] for amines **10**, or to a solution of methallylmagnesium chloride [prepared from methallyl chloride (41 mL, 0.45 mol) and Mg (22.0 g, 0.90 mol) in a mixture of THF–Et_2O (1:1, 300 mL)] for amines **9**. After the addition of the Schiff base, the reaction mixture was stirred for 1 h at r.t. The cooled mixture was poured into sat. aq NH_4Cl solution (300 mL) under ice cooling and extracted with Et_2O (3 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was distilled in vacuo or purified by Al_2O_3 (Tables 1– 3).

Compounds 11a–h, 12a–g; General Procedure

The appropriate homoallylamine **9**, **10** (0.10 mol) was dissolved in benzene (250 mL). An equimolar amount of maleic anhydride (0.10 mol, 9.8 g) was added in one portion to the solution. The reaction mixture was stirred for 5–10 days at r.t. The crystalline product was collected by filtration, washed with toluene (2 × 100 mL) and Et_2O (2 × 80 mL), and dried in air to give the desired products **11**, **12** as colorless solids. Their physical properties and spectral characteristics are given in Tables 4– 7.

Compounds 14a–f, 15a–f, 16a–f; General Procedure

The appropriate adduct **11a–f**, **12a–f** (0.01 mol) was stirred with a mixture of 85% H_3PO_4 and 96% H_2SO_4 (45 mL, 3:1 by volume) at 125–155 °C for 1 h (TLC monitoring). At the end of the reaction, the mixture was diluted with H_2O (200 mL). The precipitate obtained was collected by filtration, washed with cold H_2O (5 × 80 mL), and dried in air. The crude product was purified by recrystallization to give the desired isoindoloquinolines **14a–f**, **15a–f**, **16a–f** as colorless crystals. Their physical properties and ^{1}H NMR and mass spectral data are given in Tables 4, 7–9. Their ^{13}C and ^{19}F data are given below.

3-Chloro-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14a)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.4 (s) and 165.0 (s) (CO_2H and NC=O), 148.3 (s), 141.8 (s), 133.0 (d), 130.9 (d), 130.1 (s), 128.9 (s), 128.2 (d), 127.8 (s), 127.6 (d), 126.9 (s), 126.5 (d), 125.3 (d), 56.6 (d, C-6a), 44.9 (t, C-6), 34.6 (d, C-5), 31.9 (q) and 29.7 (q, CH_3-5).

3-Bromo-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14b)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.0 (s) and 165.6 (s) (CO_2H and NC=O), 146.3 (s), 139.2 (s), 133.0 (d), 132.7 (s), 131.0 (d), 130.1 (d), 129.8 (s), 129.5 (d), 128.6 (s), 126.3 (d), 122.2 (d), 117.7 (s), 56.1 (d, C-6a), 41.5 (t, C-6), 33.9 (d, C-5), 31.4 (q) and 30.3 (q, CH_3-5).

3-Fluoro-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14c)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.9 (s) and 165.3 (s) (CO_2H and NC=O), 159.25 (d, $^1J_{C,F}$ = 242.8 Hz, C-3), 146.2 (s), 139.41 (d, $^3J_{C,F}$ = 6.3 Hz, C-4a), 132.9 (d), 131.3 (d), 129.57 (d, $^4J_{C,F}$ = 2.7 Hz, C-11b), 129.52 (s), 128.7 (s), 126.4 (d), 122.15 (d, $^3J_{C,F}$ = 8.3 Hz, C-1), 113.8 (d, $^2J_{C,F}$ = 23.5 Hz), 113.5 (d, $^2J_{C,F}$ = 23.5 Hz), 56.3 (d, C-6a), 41.6 (t, C-6), 34.0 (d, C-5), 31.3 (q) and 30.3 (q, CH_3-5).

^{19}F NMR (DMSO-d_6, 376.5 MHz, external standard: 0.2 M C_6H_5F in DMSO): δ = –2.76.

1-Chloro-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14d)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.9 (s) and 165.5 (s) (CO_2H and NC=O), 146.1 (s), 138.8 (s), 132.9 (d), 132.2 (s), 131.0 (d), 129.7 (s), 129.4 (s), 128.5 (s), 127.1 (d), 126.4 (d), 126.2 (d), 121.8 (d), 56.0 (d, C-6a), 41.4 (t, C-6), 33.8 (d, C-5), 31.3 (q) and 30.2 (q) (CH_3-5).

1-Bromo-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14e)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.8 and 164.9 (C=O), 148.4 (s), 142.4 (s), 133.2 (d), 132.4 (s), 131.6 (d), 130.8 (d), 130.2 (s), 128.2 (d), 127.8 (s), 126.8 (d), 126.0 (d), 118.0 (s), 56.7 (C-6a), 44.9 (t, C-6), 40.5 (d, C-5), 32.0 and 29.7 (CH_3-5).

1-Fluoro-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14f)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.4 (s) and 165.0 (s) (CO_2H and NC=O), 154.32 (d, $^1J_{C,F}$ = 251.4 Hz, C-3), 147.8 (s), 140.6 (br d, C-4a), 132.8 (d), 130.9 (d), 130.0 (s), 127.8 (s), 127.08 (d, $^3J_{C,F}$ = 8.1 Hz, C-3), 126.4 (d), 122.5 (d, $^4J_{C,F}$ = 2.7 Hz, C-4), 120.85 (d, $^2J_{C,F}$ = 12.7 Hz, C-11b), 114.5 (d, $^2J_{C,F}$ = 19.9 Hz, C-2), 55.9 (d, C-6a), 44.4 (t, C-6), 33.9 (d, C-5), 32.2 (q) and 29.9 (q, CH_3-5).

^{19}F NMR (DMSO-d_6, 376.5 MHz, external standard: 0.2 M C_6H_5F in DMSO): δ = 0.60.

3-Chloro-5-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (15a)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.1 and 165.6 (C=O), 145.9 (s), 134.7 (s), 133.3 (s), 133.1 (d), 131.4 (d), 129.7 (s), 129.4 (s), 128.5 (s), 127.6 (d), 126.7 (d), 126.4 (d), 121.71 (d), 59.1 (C-6a), 35.5 (C-6), 31.0 (C-5), 20.5 (CH_3-5).

16a

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.1 and 165.6 (C=O), 146.3 (s), 135.2 (s), 133.1 (d), 133.0 (s), 131.2 (d), 129.8 (s), 129.0 (s), 128.6 (s), 127.6 (d), 126.7 (d), 126.4 (d), 121.66 (d), 55.0 (C-6a), 33.1 (C-6), 30.4 (C-5), 23.8 (CH_3-5).

3-Bromo-5-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (15b)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.4 and 165.2 (C=O), 146.0 (s), 135.6 (s), 135.2 (s), 133.0 (d), 131.6 (d), 130.4 (d), 130.0 (s), 129.9 (s), 129.6 (d), 126.3 (d), 122.1 (d), 117.7 (s), 59.3 (C-6a), 36.0 (C-6), 31.0 (C-5), 20.6 (CH_3-5).

16b

^{13}C NMR: Not recorded on account of the extremely low concentration of the solution.

3-Fluoro-5-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (15c)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.1 (s) and 165.5 (s) (CO_2H and NC=O), 159.5 (d, $^1J_{C,F}$ = 242.6 Hz, C-3), 146.0 (s), 135.30 (d, $^3J_{C,F}$ = 7.2 Hz, C-4a), 133.1 (d), 131.67 (d), 130.85 (d, $^4J_{C,F}$ = 2.2 Hz, C-11b), 129.6 (s), 128.8 (s), 126.6 (d), 122.06 (d, $^3J_{C,F}$ = 8.3 Hz, C-1), 114.5 (d, $^2J_{C,F}$ = 23.0 Hz), 113.5 (d, $^2J_{C,F}$ = 22.4 Hz), 59.4 (d, C-6a), 35.7 (t, C-6), 31.2 (d, C-5), 20.6 (q, CH_3-5).

^{19}F NMR (DMSO-d_6, 376.5 MHz, external standard: 0.2 M C_6H_5F in DMSO): δ = –3.10.

16c

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.3 (s) and 165.5 (s) (CO_2H and NC=O), 159.5 (d, $^1J_{C,F}$ = ~242 Hz, C-3), 146.4 (s), 135.70 (d, $^3J_{C,F}$ = 7.2 Hz, C-4a), 133.1 (d), 131.5 (d), 130.5 (d, $^4J_{C,F}$ = 2.2 Hz, C-11b), 129.7 (s), 128.9 (s), 126.6 (d), 122.06 (d, $^3J_{C,F}$ = 8.3 Hz, C-1), 116.1 (d, $^2J_{C,F}$ = 22.6 Hz), 113.7 (d, $^2J_{C,F}$ = 22.5 Hz), 55.3 (d, C-6a), 33.3 (t, C-6), 30.7 (d, C-5), 23.9 (q, CH_3-5).

^{19}F NMR (DMSO-d_6, 376.5 MHz, external standard: 0.2 M C_6H_5F in DMSO): δ = –3.71.

1-Chloro-5-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (15d)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.7 and 165.0 (C=O), 148.3 (s), 137.9 (s), 133.2 (d), 131.7 (s), 130.9 (d), 130.2 (s), 128.5 (d), 128.3 (s), 127.72 (d), 127.65 (s), 126.6 (d), 126.4 (d), 58.8 (C-6a), 38.5 (C-6), 31.3 (C-5), 21.1 (CH_3-5).

16d

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.7 and 165.0 (C=O), 148.5 (s), 140.1 (s), 133.7 (s), 133.3 (d), 132.1 (s), 130.9 (d), 128.6 (s), 128.2 (d), 128.03 (d), 127.96 (s), 126.9 (d), 125.9 (d), 56.4 (C-6a), 37.3 (C-6), 29.7 (C-5), 21.0 (CH_3-5).

1-Bromo-5-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (15e)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.7 and 165.0 (C=O), 148.49 (s), 138.6 (s), 133.2 (s), 133.2 (d), 131.7 (d), 131.0 (d), 130.2 (s), 128.2 (d), 127.6 (s), 127.0 (d), 126.6 (d), 118.1 (s), 58.8 (C-6a), 38.3 (C-6), 31.6 (C-5), 21.2 (CH_3-5).

16e

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.9 and 165.7 (C=O), 148.55 (s), 141.1 (s), 134.0 (s), 133.4 (d), 131.3 (d), 131.0 (d), 130.0 (s), 128.6 (d), 128.0 (s), 127.1 (d), 125.9 (d), 118.6 (s), 56.9 (C-6a), 37.4 (C-6), 29.7 (C-5), 19.9 (CH_3-5).

1-Fluoro-5-methyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (15f)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 165.7 (s) and 165.2 (s) (CO_2H and NC=O), 154.7 (d, $^1J_{C,F}$ = 252.6 Hz, C-3), 147.8 (s), 136.5 (br d, C-4a), 133.1 (d), 131.2 (d), 130.1 (s), 127.9 (s), 127.25 (d, $^3J_{C,F}$ = 8.1 Hz, C-3), 126.7 (d), 123.27 (d, $^4J_{C,F}$ = 2.3 Hz, C-4), 121.96 (d, $^2J_{C,F}$ = 12.8 Hz, C-11b), 114.5 (d, $^2J_{C,F}$ = 20.2 Hz, C-2), 58.6 (d, C-6a), 38.4 (t, C-6), 30.7 (d, C-5), 20.9 (q, CH_3-5).

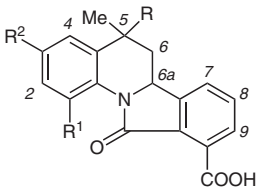
^{19}F NMR (DMSO-d_6, 376.5 MHz, external standard: 0.2 M C_6H_5F in DMSO-d_6): δ = 0.58.

16f

^{13}C NMR: Not recorded on account of the extremely low concentration of the solution.

^{19}F NMR (DMSO-d_6, 376.5 MHz, external standard: 0.2 M C_6H_5F in DMSO-d_6): δ = 0.41.

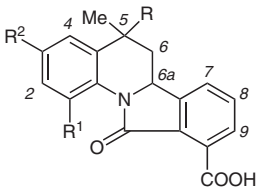
Table 8 ^{1}H NMR Spectra (DMSO-d_6/TMS, 400 MHz) of 5,6,6a,11-Tetrahydroisoindolo[2,1-*a*]quinolines **14a–g**, **15a–g** and **16a–e**; Chemical Shifts



Product	Chemical Shifts, δ												
	R^1	2	R^2	4	R	CH_3-	6*ax*	6*e*	6a	7	8	9	CO_2H
14a	8.30 d	7.38 dd	Cl	7.64 d	1.38 s (CH_3)	1.47 s	1.59 t	2.50 dd	5.16 dd	7.99 br d	7.85 t	8.04 br d	9.95 br s
14b	8.24 d	7.51 dd	Br	7.75 d	1.38 s (CH_3)	1.46 s	1.59 t	2.49 dd	5.16 dd	7.99 d	7.85 t	8.03 br d	14.73 br s
14c	8.29 dd	7.17 ddd	F	7.46 dd	1.37 s (CH_3)	1.46 s	1.59 t	2.51 dd	5.16 dd	8.00 d	7.85 t	8.07 d	–[a]
14d	Cl	7.55 dd	7.33 t	7.44 dd	1.39 s (CH_3)	1.28 s	1.55 dd	2.45 dd	5.23 dd	7.98 br d	7.85 t	8.00 br d	14.45 br s
14e	Br	7.61 d	7.27 t	7.60 d	1.24 s	1.40 s	1.60 dd	2.46 dd	5.25 dd	8.00 d	7.87 t	8.03 d	–[a]
14f	F	7.22 m	7.33 m	7.42 d	1.37 s (CH_3)	1.42 s	1.50 t	2.49 br d	5.21 br d	8.01 d	7.86 t	8.03 d	15.87 br s
14g	8.09 d	7.66 dd	I	7.88 d	1.36 s (CH_3)	1.45 s	1.58 t	2.47 dd	5.15 dd	7.98 d	7.85 t	8.03 d	9.92 br s
15a	8.37 d	7.40 dd	Cl	7.54 d	3.29 m (H)	1.40 d	1.39 q	2.82 ddd	5.11 dd	7.99 br d	7.87 t	8.09 br d	14.74 br s
15b	8.30 d	7.51 dd	Br	7.67 d	3.30 m (H)	1.39 d	1.38 q	2.80 ddd	5.10 dd	8.00 d	7.86 t	8.07 d	–[a]
15c	8.43 dd	7.06 td	F	7.14 dd	3.32 m (H)	1.47 d	1.51 ddd	2.75 ddd	4.88 dd	7.75 dd	7.82 t	8.51 dd	–[a]
15d	Cl	7.44–7.47 m	7.32 t	7.44–7.47 m	3.27 m (H)	1.25 d	1.39 dt	2.75 ddd	5.17 dd	7.97 d	7.86 t	8.02 br d	14.51 br s
15e	Br	7.62 d	7.25 t	7.50 d	3.27 m (H)	1.20 d	1.45 dt	2.75 ddd	5.19 dd	7.96–8.03 m	7.85–7.90 m	7.96-8.03 m	10.16 br s
15f[b]	F	7.21–7.36 m			3.28 m (H)	1.36 d	1.28 q	2.77 dd	5.13 dd	7.98 t	7.86 dd	8.04 br d	10.11 br s
15g[b]	8.13 d	7.68 dd	I	7.81 d	3.29 m (H)	1.36 d	1.36 dd	2.76 ddd	5.09 dd	7.85 t	7.98 d	8.05 d	9.90 br s
16a	8.37 d	7.38 dd	Cl	7.48 d	3.30 m (H)	1.48 d	1.78 dt	–[c]	5.14 dd	8.00 br d	7.87 t	8.06 br d	14.74 br s
16b	8.30 d	7.49 dd	Br	7.61 d	3.30 m (H)	1.46 d	1.76 dt	2.49 m	5.13 dd	8.00 d	7.86 t	8.05 d	–[a]
16c	8.43 dd	7.06 td	F	7.13 dd	–[c]	1.45 d	1.90 dt	2.42 ddd	4.96 dd	7.75 dd	7.82 t	8.50 dd	–[a]
16d	Cl	7.44–7.47 m	7.34 t	7.44–7.47 m	3.27 m (H)	1.34 d	2.28 dt	2.88 q	5.21 t	7.97 d	7.87 t	8.00 br d	14.51 br s
16e	Br	7.64 d	7.29 t	7.39 d	3.27 m (H)	1.31 d	2.07–2.26 m		5.22 t	7.96–8.03 m	7.85–7.90 m	7.96–8.03 m	10.16 br s

[a] Proton of CO_2H group are lacking owing to the exchange with DMSO-d_6.
[b] The signals overlap with the signals of the corresponding protons of the major isomer.
[c] The signals of minor isomer protons are of extreme low intensity.

Table 9 ^{1}H NMR Spectra (DMSO-d_6/TMS, 400 MHz) of 5,6,6a,11-Tetrahydroisoindolo[2,1-*a*]quinolines **14a–g**, **15a–g** and **16a–e**; Coupling Constants



Product	Coupling constants, *J* (Hz)												
	5,6*ax*	5,6*eq*	5,Me	6a,6*ax*	6a,6*eq*	6*ax*,6*eq*	1,2	1,3	2,3	2,4	3,4	7,8	8,9
14a	–	–	–	12.5	2.3	12.7	8.8	–	–	2.4	–	7.6	7.6
14b	–	–	–	12.6	2.5	12.8	9.1	–	–	2.9	–	7.6	7.6
14c[a]	–	–	–	12.6	2.6	12.8	8.8	–	–	2.3	–	7.7	7.7
14d	–	–	–	10.9	3.9	13.3	–	–	7.9	1.2	7.9	7.6	7.6
14e	–	–	–	10.2	3.8	13.1	–	–	7.9	–[b]	7.9	7.7	7.7
14f	–	–	–	12.0	1.8	13.0	–	–	7.6	–	7.6	8.0	8.0
14g	–	–	–	13.0	2.0	13.0	8.7	–	–	2.0	–	7.6	7.6
15a	12.2	5.9	7.2	12.6	2.6	12.8	8.7	–	–	2.0	–	7.5	7.5
15b	12.5	5.6	6.7	12.1	2.5	12.6	8.8	–	–	2.1	–	7.6	7.6
15c[c]	12.4	6.1	7.0	12.8	3.1	13.4	9.0	–	–	3.0	–	7.6	7.6
15d	~10.3	6.3	7.0	10.3	4.4	13.2	–	–	7.8	–	7.8	7.6	7.6
15e	9.5	6.9	7.0	13.0	4.8	13.0	–	–	8.0	–	8.0	7.6	7.6
15f	12.0	5.7	6.8	12.0	2.8	12.8	–	–	–[b]	–[b]	–[b]	7.7	7.7
15g	12.2	5.8	6.8	13.0	2.5	13.0	8.7	–	–	2.0	–	7.7	7.7
16a	5.9	–[b]	7.2	11.8	2.6	13.1	8.5	–	–	2.0	–	7.5	7.5
16b	5.5	–[b]	7.2	13.0	2.3	13.0	8.8	–	–	2.2	–	7.6	7.6
16c	5.8	1.2	7.0	12.8	3.4	13.0	9.0	–	–	–[b]	–	7.6	7.6
16d	–[b]	–[b]	7.0	~7.1[b]	~7.1[b]	13.2	–	–	7.6	–	7.6	7.6	7.6
16e	–[b]	–[b]	6.9	6.5	6.5	–[b]	–	–	8.2	–	8.2	7.6	7.6

[a] $J_{1,F}$ = 5.6, $J_{2,F}$ = 11.0 and $J_{4,F}$ = 10.5 Hz.
[b] Coupling constants cannot be determined due to overlap of the corresponding signals.
[c] $J_{1,F}$ = 5.5, $J_{2,F}$ = 9.0, $J_{4,F}$ = 9.5 and $J_{7,9}$ = 1.5 Hz.

Compounds 14g, 15g, 16g; General Procedure

A mixture of corresponding adduct **11g**, **12g** (0.01 mol) and 85% H_3PO_4 (40 mL) was stirred at 110–155 °C for 45 min (TLC monitoring). At the end of the reaction, the mixture was diluted with H_2O (200 mL). The precipitate obtained was collected by filtration, washed with cold H_2O (5 × 80 mL), and dried in air. The crude product was recrystallized to give the desired isoindoloquinolines **14g**, **15g**, **16g** as colorless crystals. Their physical properties and spectral characteristics are given in Tables 4, 7–9).

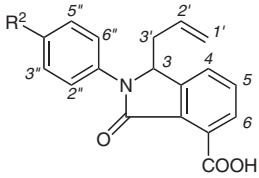
3-Iodo-5,5-dimethyl-11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (14g)

^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 166.1 and 165.7 (C=O), 146.4 (s), 139.3 (s), 136.0 (d), 135.4 (d), 133.3 (s), 133.1 (d), 131.2 (d), 129.9 (s), 128.7 (s), 126.4 (d), 122.4 (d), 90.4 (s, C-3), 56.1 (C-6a), 41.6 (C-6), 33.8 (C-5), 31.5 and 30.4 (CH_3-5).

Compounds 17a,c,g; General Procedure

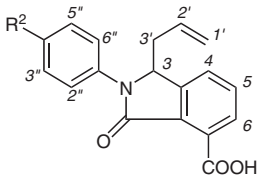
A mixture of corresponding adduct **12a**,**c**,**g** (0.01 mol) and 85% H_3PO_4 (40 mL) was stirred at 80 °C for 1.5 h (TLC monitoring). At the end of the reaction, the mixture was diluted with H_2O (200 mL). The precipitate obtained was collected by filtration, washed with cold H_2O (5 × 80 mL), and dried in air. The crude product was purified by recrystallization to give the desired products **17a**,**c**,**g** as colorless crystals. Their physical properties and spectral characteristics are given in Tables 4, 10, 11).

Table 10 ^{1}H NMR Spectra ($CDCl_3$/TMS, 400 or 200 MHz) of 7-Carboxyisoindoles **17a**,**c**,**g**; Chemical Shifts



Product	3	4	5	6	1′*cis*	1′*trans*	2′	3′A	3′B	2″	3″	R^2	5″	6″
17a	5.40 dd	7.77 m		8.41 m	4.98 d	4.83 d	5.19 m	2.80 ddd	2.60 dd	7.47 s		Cl	7.47	
17c	5.33 dd	7.85–7.75 m		8.50 m	5.02 br d	4.87 br d	ca. 5.25 m	2.80 m	2.63 m	7.22 AA′F		F	7.49 BB′F	
17g	5.38 dd	7.79 br d	7.78 t	8.46 ddd	4.99 br d	4.84 dq	5.21 m	2.80 ddd	2.62 m	7.29 AA′		I	7.84 BB′	

Table 11 ^{1}H NMR Spectra ($CDCl_3$/TMS, 400 or 200 MHz) of 7-Carboxyisoindoles **17a**,**c**,**g**; Coupling Constants



Product	Coupling Constants, *J* (Hz)											
	3,3′A	3,3′B	4,5	5,6	1′-*cis*, 1′-*trans*	1′-*cis*,2′	1′-*trans*,2′	2′, 3′A	2′, 3′B	3′A, 3′B	2″,3″	5″,6″
17a	3.4	5.8	–[a]	–[a]	–[a]	10.4	17.4	5.4	8.1	14.1	–[a]	–[a]
17c[b]	3.4	6.0	–[a]	7.0	–[a]	10.1	17.1	–[a]	–[a]	–[a]	8.7	8.7
17g[c]	3.1	6.0	7.4	7.4	0.8	10.1	16.9	3.1	8.2	14.7	~8.8	~8.8

[a] Coupling constants cannot be determined due to overlap of the corresponding signals.
[b] $J_{2'',F} = J_{6'',F} = 5.6$ and $J_{3'',F} = J_{5'',F} = 8.7$ Hz.
[c] $J_{1',3'B}$ = ca. 0.8, $J_{1',3'A} = 1.4$, $J_{3,6} = 0.4$ and $J_{4,6} = 1.4$ Hz.

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