Synthesis, NMR Spectra and X-ray Data of Chloro and Dichloro Derivatives of 3-Hydroxy-2-phenylquinolin-4(1*H*)-ones and their Cytostatic Activity

Pavel Hradil*,[a], Petr Krejčí[a], Jan Hlaváč[a], Iveta Wiedermannová[a], Antonín Lyčka[b], and Valerio Bertolasi[c]

[a] Department of Organic Chemistry, Palacky University, Tř. Svobody 8, 771 46 Olomouc, Czech Republic, Fax:++420-68-5634405, E-mail: ph.1@tiscali.cz
[b]Research Institute for Organic Syntheses, Pardubice, 532 18 Czech Republic; Antonin.Lycka@vuosas.cz
[c]Università di Ferrara, Dipartimento di Chimica, Via L. Borsari, 46, 44100 Ferrara, Italy; m38@dns.unife.it

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As known, some derivatives of quinolin-4(1*H*)-one possess interesting biological properties. The biological and cytostactic activity of 2-substituted 3-hydroxyquinolin-4(1*H*)-ones has not been reported yet. In this paper the synthesis of a series of chloro and dichloro 2-phenyl-3-hydroxyquinolin-4(1*H*)-ones and their characterization by NMR spectra and X-ray data is described. Their cytostatic properties have been evaluated and the results are reported.

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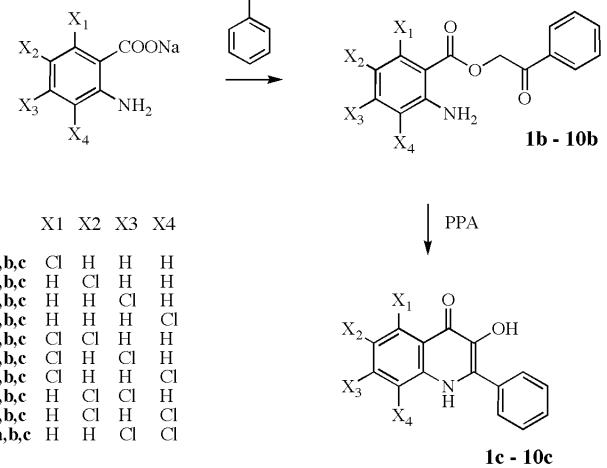
2-Phenyl-3-hydroxyquinolin-4(1*H*)-ones are a group of compounds isosteric with natural flavonoids - natural compounds exhibiting cytostatic and antileukemic properties. Biological activity of flavonoids is intensively studied, on the other hand, biological activity of substituted 3-hydroxyquinolin-4(1*H*)-ones has not been described yet. As a part of our work at this theme we have synthesized series of dichloro and monochloroderivatives. Their structures and their cytostacic activity were studied.

Chloro and dichloro derivatives of 3-hydroxy-2-phenylquinolin-4(1*H*)-ones were synthesized from commercially available chloro and dichloro anthranilic acids **1a-10a**, according to methods of preparation and cyclization of phenacyl anthranilates previously described [1,2]. These acids were treated with phenacyl bromide to give phenacyl anthranilates **1b-10b**. After their cyclization in polyphosphoric acid, the titled quinolones **1c-10c** were received (Scheme 1, Table 1 and 2).

Scheme 1



	X1	X2	X3	X4
1a,b,c	Cl	H	H	H
2a,b,c	H	Cl	H	H
3a,b,c	H	H	Cl	H
4a,b,c	H	H	H	Cl
5a,b,c	Cl	Cl	H	H
6a,b,c	Cl	H	Cl	H
7a,b,c	Cl	H	H	Cl
8a,b,c	H	Cl	Cl	H
9a,b,c	H	Cl	H	Cl
10a,b,c	H	H	Cl	Cl

1c - 10c

Table 1

Characteristic Data of Chloro and Dichloro Derivatives of Phenacyl Anthranilates **1-10b**

Compound	M.P. °C Yield. %	Formula M.W.	Calculated /Found %C	%H	%N
1b	84-86	$C_{15}H_{12}ClNO_3$	62.18	4.17	4.83
	52	289.73	61.93	3.86	4.79
2b	157-160	$C_{15}H_{12}ClNO_3$	62.18	4.17	4.83
	82	289.73	62.85	4.20	4.52
3b	135-140	$C_{15}H_{12}ClNO_3$	62.18	4.17	4.83
	70	289.73	62.39	3.84	4.74
4b	146-148	$C_{15}H_{12}ClNO_3$	62.18	4.17	4.83
	81	289.73	61.87	4.02	4.82
5b	127	$C_{15}H_{11}Cl_2NO_3$	55.57	3.42	4.32
	82	324.18	55.25	3.06	4.24
6b	124-126	$C_{15}H_{11}Cl_2NO_3$	55.57	3.42	4.32
	83	324.18	55.55	3.69	4.43
7b	118-121	$C_{15}H_{11}Cl_2NO_3$	55.57	3.42	4.32
	85	324.18	55.54	3.56	4.44
8b	195-198	$C_{15}H_{11}Cl_2NO_3$	55.57	3.42	4.32
	91	324.18	55.54	3.56	4.44
9b	191-192	$C_{15}H_{11}Cl_2NO_3$	55.57	3.42	4.32
	86	324.18	55.67	3.03	4.18
10b	139-140	$C_{15}H_{11}Cl_2NO_3$	55.57	3.42	4.32
	66	324.18	55.61	2.99	4.24

Structures of the compounds were confirmed by NMR. The ^1H and ^{13}C chemical shifts were assigned using gs (gradient selected)-H, H-COSY, gs-HSQC (optimised for $^1J(^{13}C,H)$ *ca* 145 Hz) gs-HMBC [3] (optimised for $^3J(^{13}C,H)$ *ca* 5 - 10 Hz). H,H-COSY provided proton-proton connectivity. A correlation of proton H(6) with carbon of C(7)OO group in HMBC spectra was key information for the assignment of proton and carbon resonances in compounds **1b – 10b** and, similarly, a correlation of proton H(5) with carbon of C(4)=O group in HMBC spectra was

Table 2

Characteristic Data of Chloro and Dichloro Derivatives of 3-Hydroxy-2-phenylquinolin-4(1*H*)-ones **1-10c**

Compound	M.P. °C Yield. %	Formula M.W.	Calculated /Found %C	%H	%N
1c	308-312.5	$C_{15}H_{10}ClNO_2$	66.30	3.71	5.15
	82	271.71	66.51	3.85	5.31
2c	300-303	$C_{15}H_{10}ClNO_2$	66.30	3.71	5.15
	53	271.71	66.65	4.01	5.32
3c	>350	$C_{15}H_{10}ClNO_2$	66.30	3.71	5.15
	95	271.71	66.22	3.76	5.18
4c	272-274	$C_{15}H_{10}ClNO_2$	66.30	3.71	5.15
	65	271.71	65.98	4.13	4.87
5c	314-319	$C_{15}H_9Cl_2NO_2$	58.84	2.96	4.57
	45	306.16	58.53	2.64	4.55
6c	297-300	$C_{15}H_9Cl_2NO_2$	58.84	2.96	4.57
	47	306.16	58.80	2.63	4.36
7c	171-174	$C_{15}H_9Cl_2NO_2$	58.84	2.96	4.57
	45	306.16	58.51	3.17	4.70
8c	342-346	$C_{15}H_9Cl_2NO_2$	58.84	2.96	4.57
	93	306.16	58.74	2.56	4.25
9c	212-215	$C_{15}H_9Cl_2NO_2$	58.84	2.96	4.57
	90	306.16	58.64	3.28	4.62
10c	262-4	$C_{15}H_9Cl_2NO_2$	58.84	2.96	4.57
	65	306.16	59.30	2.31	4.55

key information for the assignment of proton and carbon resonances in compounds **1c – 10c** (Table 4, 5, 6 and 7 in the experimental part).

Derivatives **1c**, **7c** and **9c** were isolated in the form of monocrystal and their structure was confirmed by X-ray diffraction. It is the definitive confirmation of 2-phenyl-3-hydroxy-4(1*H*)-quinoline as a product of anomalous cyclization of phenacyl esters of anthranilic acid in polyphosphoric acid instead of 2-aryl-1*H*-benz[*e*][1,4]oxazepin-5-ones described in previous papers [4]. Structure of quinolones is drawn in Figure **1a, 1b, 2a, 2b** and **3**.

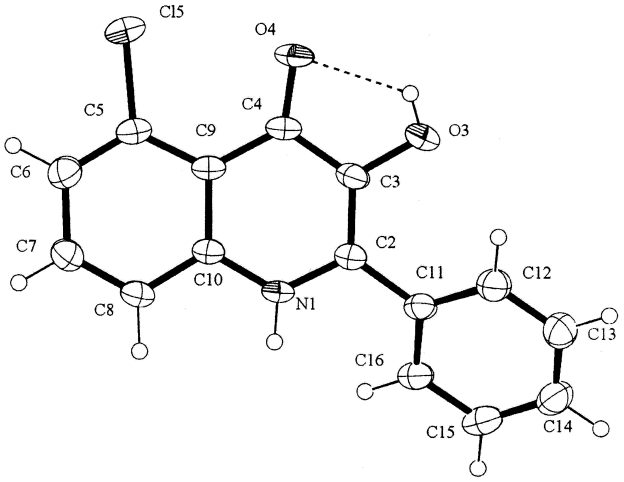


Figure 1a. ORTEP view of compound **1c** showing the thermal ellipsoids at 40% probability level.

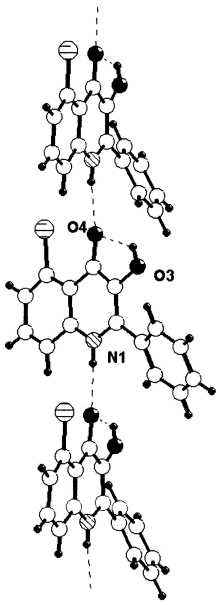


Figure 1b. Chain of hydrogen-bonded molecules in crystal packing of compound **1c**.

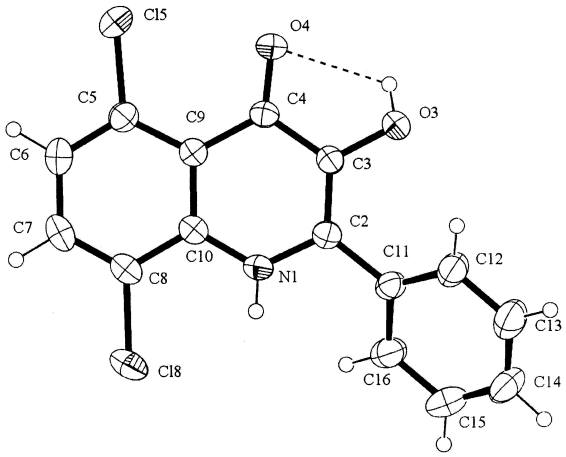


Figure 2a. ORTEP view of compound **7c** showing the thermal ellipsoids at 40% probability level.

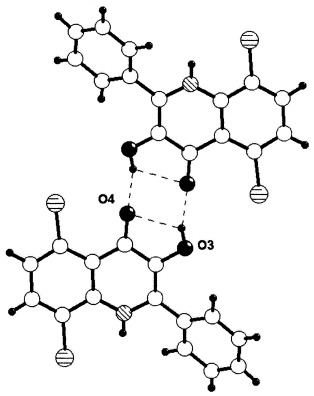


Figure 2b. Dimer of hydrogen-bonded molecules in crystal packing of compound **7c**.

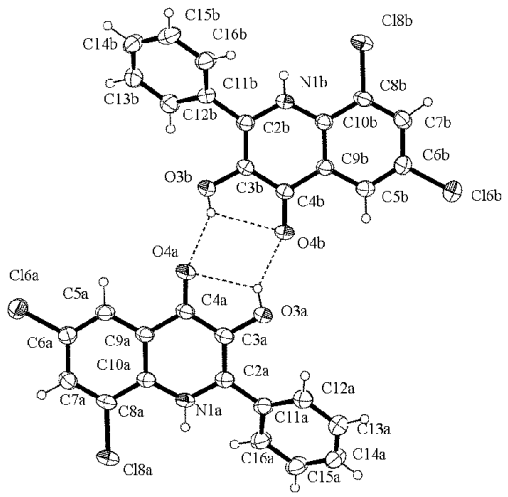


Figure 3. Dimer of hydrogen-bonded molecules in crystal packing of compound **9c**.

As mentioned previously, biological properties of 2-substituted 3-hydroxy-2-phenylquinolin-4(1*H*)-ones are not known. The cytotoxic properties of some substituted 2-phenylquinolin-4(1*H*)-ones and their affinity to colchicin binding place were descr recently[5].

The cytostatic properties of prepared quinolinones have been evaluated in the National Cancer Institute Bethesda. All compounds have been screened in the 3-cell line – breast cancer MCF7, non-small cell lung cancer NCI-H460 and CNS cancer SF-268.

Each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration and the culture incubated for 48 hours. End-point determination is made with alamar blue. Results of each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells (Table 3). Compounds which reduce the growth of any one of the cell lines to approximately 32% or less are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range.

In our case, three compounds (**6c**, **7c**, **9c**) which passed NCI's criteria were evaluated against the 60 tumor cell lines.

These compounds have limited effects on cancer lines in lower concentration. The most active was compound **7c**. It has the most notable effects in the screen on some lines from the colon panel and on some lines from the breast cancer panel.

These compounds have limited effects on cancer lines in the lower concentration. Activity of these three compounds was characterized by log GI_{50}, where GI_{50} is the concentration which causes growth inhibition of 50%.

The most active compound of this series of quinolinone derivatives was compound **7c**. Compound **9c** did not exhibit any activity where log GI_{50} is smaller than –5.

Table 3

Percent of Growth of the Cells Treated with 1.10^{-4} mol Compound Compared to the Untreated Cells

Compound	M-CF7	NCI-H460	SF-268
1c	63	84	84
2c	46	59	55
3c	61	72	47
4c	66	84	55
5c	33	70	71
6c	29	70	73
7c	12	11	20
8c	61	89	81
9c	65	27	86
10c	61	91	74

Activity against Breast Cancer exhibit compounds **6c** and **7c**. Both of these compounds were active against the cell line MCF7, log GI_{50} was -5.68 and –5.77.

Activity against melanoma was similar for both these compounds. These compounds were active against the cell line M147. Activity of both compounds was very similar, log GI_{50} was approximately -5.50.

Both compounds **6c** and **7c** exhibit some activity against Ovarian Cancer. The compound **6c** was active against the cell line IGROV1 log GI_{50} = -5.48. The compound **7c** exhibits activity against the cell line OVCAR-8 log GI_{50} = -5.50.

Different activity of these compounds was observed against Renal cancer. The compound **7c** was not active. Compound **6c** exhibits activity against the cell lines CAKI-1 and UO-31 log GI_{50} = -5.44 and log GI_{50} = -5.45.

The compound **6c** was not active against leukemia. Compound **7c** was active against most of tested leukemia lines. Especially against the cell lines CCRF-CEM, HL-60(TB), MOLT-4 and K-562; Log GI_{50} was between -5.48 to -5.81.

The compound **7c** exhibits moderate activity against Non-Small Cell Lung Cancer. Higher activity of this compound was observed against the cell lines HOP-62, NCI-H322M, NCI-H460. Logarithm of the concentration GI_{50} was between -5.64 to -5.93.

The compound **7c** was also active against the Colon Cancer cell line HCC-2998 and the cell line HCT-116. There was log GI_{50} = -5.77 and log GI_{50} = -5.62.

EXPERIMENTAL

Melting points were determined on a Boetius stage. Infrared spectra (KBr disks) were taken with an ATI Unicam Genesis FTIR instrument. NMR spectra of solutions in DMSO-d_6 (TMS as internal standard) were measured on a Bruker Avance 300 spectrometer (300 MHz). Elemental analyses were obtained with an EA 1108 Elemental Analyzer (Fison Instrument).

General Procedure of Preparation of Chloro Phenacyl Anthranilates (**b**).

Acid **a** (13 mmol) was dissolved in dimethylformamide (10 ml) and sodium carbonate (0.69 g, 6.5 mmol) was added to the solution. The reaction mixture was stirred for 10 minutes at laboratory temperature and then the reaction mixture was heated at 65 °C for 45 min. The mixture was cooled to 25 °C and phenacyl bromide (2.59 g, 13 mmol) was added. The reaction temperature increased spontaneously to 30 °C. The mixture was heated up to 70 °C for 60 minutes. The hot mixture was poured onto crushed ice and the precipitated solid was collected by suction, thoroughly washed with water and dried at 60 °C. The dried product was crystallized from hot acetone and dried at 60 °C.

General Procedure of Preparation of Chloro and Dichloro 2-Phenyl-3-hydroxyquinolin-4(1*H*)-ones (**c**).

Phenacyl anthranilate **b** (2.03 g, 7.2 mmol) was stirred with polyphosphoric acid (30 g) at 100 to 110 °C for 2 h. Then the reaction mixture was poured into water (100 ml) and the precipitated solid was collected by filtration and washed with water to neutral pH. The solid was dried at 80 °C and crystallized from 2-methoxyethanol. The product was collected by filtration and washed with cold acetone.

NMR Spectra.

The ^{1}H (500.13 MHz) and ^{13}C (125.76 MHz) and NMR spectra of compounds **1b,1c - 10b,10c** were measured on a Bruker Avance 500 spectrometer equipped with 5 mm broadband probe with z-shielding and a SGI O2 computer in hexadeuteriodimethyl sulfoxide at ambient temperature. The ^{13}C and ^{1}H chemical shifts were referred to the central peak of DMSO-d_6 ($\delta(^{13}C)$ = 39.60, $\delta(^{1}H)$ = 2.55). Positive values of chemical shifts denote high frequency shifts with respect to standards. Two dimensional gs (gradient selected)-H,H-COSY, gs-HSQC and gs-HMBC [6,7] spectra were measured using standard microprograms provided by Bruker [3].

Scheme 2

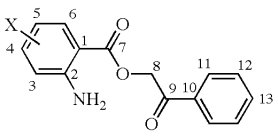


Table 4

^{1}H Chemical Shifts of Phenacyl anthranilates **1-10b** in DMSO-d_6

No	1b	2b	3b	4b	5b	6b	7b	8b	9b	10b
2	6.21	6.85	6.94	6.80	6.30	6.50	6.30	6.99	6.92	7.08
3	6.70	6.90	6.96	-	6.84	6.89	-	7.14	-	-
4	7.21	7.38	-	7.61	7.43	-	6.78	-	7.88	-
5	6.81	-	6.65	6.71	-	6.79	7.44	-	-	6.91
6	-	7.81	7.87	7.93	-	-	-	7.96	7.78	7.90
8	5.88	5.74	5.74	5.79	5.91	5.88	5.94	5.75	5.80	5.79
11	8.10	8.06	8.06	8.07	8.11	8.10	8.11	8.06	8.06	8.06
12	7.63	7.63	7.63	7.62	7.64	7.63	7.65	7.63	7.64	7.62
13	7.77	7.74	7.76	7.75	7.78	7.77	7.79	7.76	7.77	7.75

Table 5

^{13}C Chemical Shifts of Phenacyl anthranilates **1-10b** in DMSO-d_6

No	1b	2b	3b	4b	5b	6b	7b	8b	9b	10b
1	114.4	109.1	107.3	110.5	116.3	113.0	116.5	108.5	110.9	108.8
2	148.8	150.5	152.5	147.0	147.1	149.7	143.8	150.9	146.1	148.3
3	116.4	118.8	115.5	119.4	115.9	113.6	117.2	117.8	120.5	117.2
4	132.1	134.4	139.1	134.5	132.3	136.2	131.8	136.9	129.1	137.5
5	114.5	118.0	115.0	115.5	117.6	115.8	117.0	115.9	118.0	116.1
6	131.5	129.6	132.9	130.2	128.8	132.9	129.8	131.9	133.8	130.5
7	165.3	165.9	166.1	166.4	164.8	164.5	164.5	165.2	165.4	165.9
8	67.4	66.9	66.7	67.0	67.7	67.5	67.8	67.0	67.4	67.1
9	193.9	193.1	193.1	193.0	193.9	193.7	193.9	192.9	192.8	192.8
10	133.6	134.0	134.0	134.0	133.5	133.5	133.4	134.0	133.9	133.9
11	128.1	127.9	127.9	127.9	128.2	128.1	128.2	127.9	128.0	127.9
12	129.1	129.0	129.0	129.0	129.1	129.1	129.1	129.1	129.1	129.0
13	134.4	134.1	134.1	134.1	134.6	134.4	134.6	134.2	134.3	134.1

Scheme 3

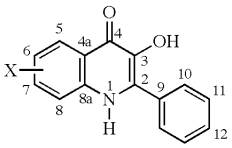


Table 6

^{1}H Chemical Shifts of Substituted 2-Phenyl-3-hydroxyquinolinones **1-10c** in DMSO-d_6

No	1c	2c	3c	4c	5c	6c	7c	8c	9c	10c
1	-	8.67	-	8.65	8.45	8.52	8.78	-	8.80	8.82
3	11.72	11.83	11.55	11.55	11.93	11.70	10.34	11.81	10.75	10.62
5	-	8.15	8.21	8.22	-	-	-	8.27	8.14	8.19
6	7.73	-	7.31	7.34	-	7.32	7.32	-	-	7.57 [b]
7	7.51	7.66	-	7.85	7.71	-	7.76	-	7.86	-
8	7.26	7.81	7.82	-	7.75	7.77	-	7.96	-	-
10	7.84	7.85	7.86	7.81	7.84	7.85	7.82	7.83	7.84	7.84
11	7.60	7.60	7.61	7.60	7.61	7.62	7.60	7.61	7.58	7.57 [b]
12	7.54	7.55	7.57	7.55	7.56	7.59	7.55	7.57	7.54	7.57 [b]

[b] Middle of the multiplet.

X-Ray crystal Structure Analysis.

Crystal data for **1c**: $C_{15}H_{10}ClNO_2$; monoclinic, space group $P2_1/a$, a = 13.7745(6), b = 6.4125(3), c = 14.1271(8) Å, β = 102.538(2)°, V = 1218.1(1) Å^3, Z = 4, D_c = 1.482 g cm^{-3}. Intensity data collected with θ ≤ 28° using Mo-Kα radiation (λ = 0.71073 Å) on a Nonius Kappa CCD diffractometer; T = 295 K, 2911 independent reflections measured; 2146 reflections observed [I ≥ 2σ(I)]; solution by direct methods [SIR92] [8]; full matrix least-squares refinement, on F^2, using SHELXL-97 [9] with anisotropic non-H atoms and isotropic hydrogens. Final R index = 0.044 (observed reflections). An ORTEP view [10] of the molecule is shown in Figure 1a. The molecules form intramolecular hydrogen bond: O3-H3…O4 [O3…O4 = 2.584(2) Å, O3-H3…O4 = 124(3)°] and chains linked by intermolecular hydrogen bonds assisted by resonance [11,12]: N1-H1…O4 [N1…O4 = 2.905(2) Å, N1-H1…O4 = 159(2)°] (Figure 1b).

Table 7

^{13}C Chemical Shifts of Substituted 3-Hydroxy-2-phenylquinolin-4(1*H*)-ones **1-10c** in DMSO-d_6

No	**1c**	**2c**	**3c**	**4c**	**5c**	**6c**	**7c**	**8c**	**9c**	**10c**
2	129.8	132.2	131.6	132.5	129.1	129.7	131.0	132.7	[a]	[a]
3	138.9	138.4	138.5	138.6	138.8	139.6	139.0	138.7	138.8	[a]
4	169.6	169.0	169.7	170.2	168.9	169.2	169.8	168.9	168.9	169.5
4a	117.5	122.7	120.3	118.5	118.5	116.2	120.9	121.7	[a]	[a]
5	131.5	123.3	126.9	124.2	129.8	133.3	130.1	125.9	[a]	[a]
6	118.1	126.7	122.4	122.4	126.5	123.8	124.5	124.9	[a]	[a]
7	130.3	130.8	135.2	131.1	131.2	134.1	131.8	133.2	[a]	[a]
8	124.4	121.1	117.5	121.8	119.4	117.0	118.8	120.3	[a]	[a]
8a	140.3	136.6	138.2	134.5	139.7	140.4	136.2	136.9	[a]	[a]
9	131.7	132.4	132.0	132.3	131.6	131.6	131.8	132.0	[a]	[a]
10	129.2	129.4	129.2	129.7	129.3	129.2	129.5	129.4	129.4	129.6
11	128.4	128.4	128.4	128.3	128.5	128.5	128.3	128.5	128.3	128.2
12	129.5	129.5	129.5	129.4	129.6	129.6	129.4	129.7	[a]	129.3

[a] Broad and overlaying signals.

Crystal data for **7c**: $C_{15}H_9Cl_2NO_2$; orthorhombic, space group *Pbca*, a = 15.8452(3), b = 6.9292(1), c = 24.3340(5) Å, V = 2671.74(8) Å^3, Z = 8, D_c = 1.522 g cm^{-3}. Intensity data collected with $\theta \leq 28°$ using Mo-Kα radiation (λ = 0.71073 Å) on a Nonius Kappa CCD diffractometer; T = 295 K, 3185 independent reflections measured; 2266 reflections observed [$I \geq 2\sigma(I)$]; solution by direct methods [SIR92][8], full matrix least-squares refinement, on F^2, using SHELXL-97 [9] with anisotropic non-H atoms and isotropic hydrogens. Final *R* index = 0.039 (observed reflections). An ORTEP view [10] of the molecule is shown in Figure 2a. The molecules form intramolecular hydrogen bond: O3-H3…O4 [O3…O4 = 2.668(2) Å, O3-H3…O4 = 112(2)°] and dimers linked by intermolecular hydrogen bonds: O3-H3…O4 [O3…O4 = 2.786(2) Å, O3-H3…O4 = 160(3)°] (Figure 2b).

Crystal data for **9c**: $C_{15}H_9Cl_2NO_2$; monoclinic, space group $P2_1/c$, a = 9.8478(2), b = 13.1654(2), c = 20.3946(6) Å, β = 94.016(1)°, V = 2637.7(1) Å^3, Z = 8, D_c = 1.542 g cm^{-3}. Intensity data collected with $\theta \leq 28°$ using Mo-Kα radiation (λ = 0.71073 Å) on a Nonius Kappa CCD diffractometer; T = 295 K, 5973 independent reflections measured; 3842 reflections observed [$I \geq 2\sigma(I)$]; solution by direct methods [SIR92] [8], full matrix least-squares refinement, on F^2, using SHELXL-97 [9] with anisotropic non-H atoms and isotropic hydrogens. Final *R* index = 0.047 (observed reflections). An ORTEP view [10] of the asymmetric unit built up by two independent molecules is shown in Figure 3. These molecules form intramolecular hydrogen bond: O3-H3…O4 [O3A…O4A = 2.728(3) Å, O3A-H3A…O4A = 114(3)°; O3B…O4B = 2.751(3) Å, O3B-H3B…O4B = 115(3)°] and are linked in dimers by means of intermolecular hydrogen bonds: O3-H3…O4 [O3A…O4B = 2.637(2) Å, O3A-H3A…O4B = 143(3)°; O3B…O4A = 2.661(2) Å, O3B-H3B…O4A = 147(3)°].

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 202132, 202133, 202134. Copies of the data can be obtained, free of charge, on application to CCDC, Union Road, Cambridge CB2 1EZ, UK [fax: +(44)(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]

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