Cubane derivatives
10*. Synthesis and molecular structures of nitroxymethylcubanes

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The reactions of hydroxymethylcubanes with nitric acid result in the respective nitroxymethylcubanes.

Key words: cubane derivatives, nitroxymethylcubanes, nitroesters, X-ray diffraction analysis, cardiac pharmacological activity, nitric acid.

The search for the drugs to treat cardiovascular and oncological diseases is currently highly topical. The preparation of new polyfunctional compounds, study of their structures and properties will allow expansion of the spectrum of exogenous NO donors as potential drugs.

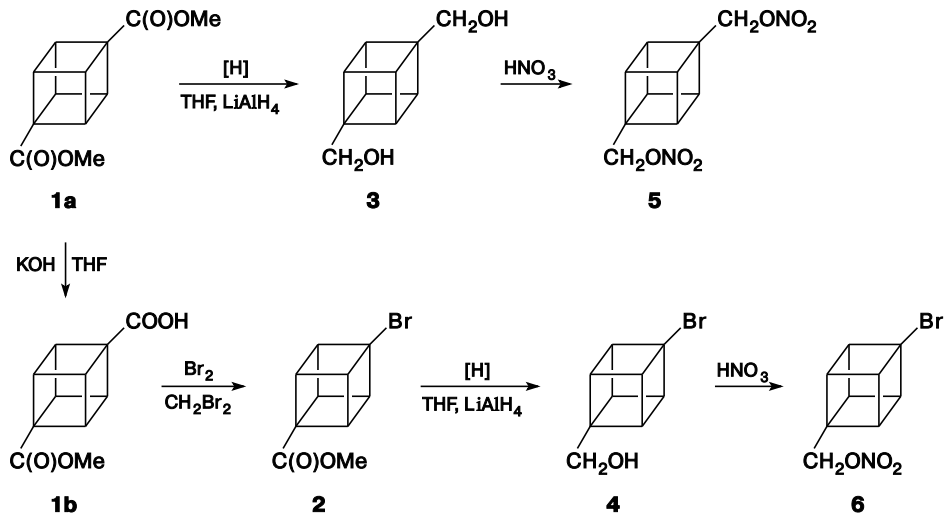
Nitrates (or nitroesters) are a well-known class of organic substances the pharmacological activity of which is determined by their metabolism with NO liberation (see Ref. 2). They include such compounds as Nitroglycerin, Nitrosorbide, Erinite, and others, which are commonly used to treat ischemic cardiovascular diseases, for example, stenocardia. It is known that cubane derivatives also show rather high anti-ischemic activity.[3,4]

With the aim of search for new anti-ischemic drugs, we performed the synthesis of nitroesters of the cubane series.

Previously,[5,6] it has been shown that the reduction of dimethyl cubane-1,4-dicarboxylate (**1a**) and methyl 4-bromocubane-1-carboxylate (**2**) afforded 1,4-bis(hydroxymethyl)cubane (**3**) and 4-bromo-1-hydroxymethylcubane (**4**). In the present work, 1,4-bis(nitroxymethyl)cubane (**5**) and 4-bromo-1-nitroxymethylcubane

* For Part 9, see Ref. 1.
† Deceased.

Scheme 1



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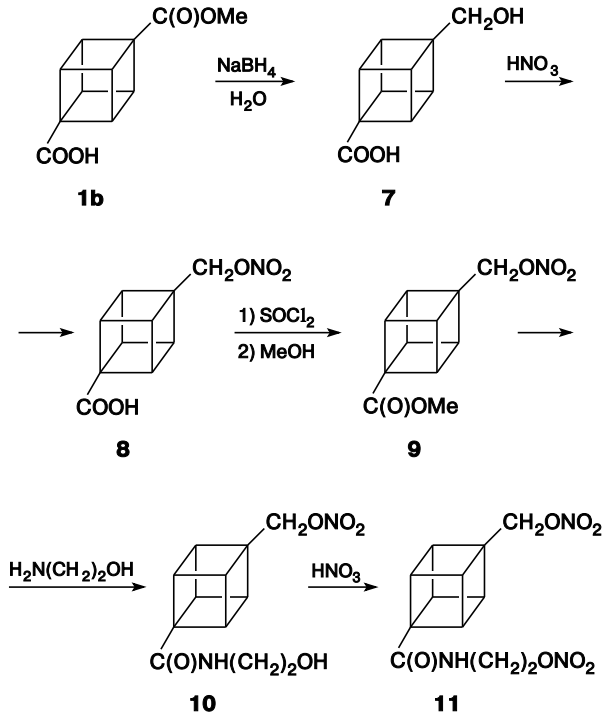
(**6**) (Scheme 1) were synthesized for the first time and characterized.

The presence of different pharmacophoric groups in a molecule is valuable as regards the biological activity.[2,7,8] Therefore, the preparation of cubane derivatives bearing both nitroxymethyl and nitroxyethylamide moiety was of great interest. The anti-ischemic activity of the nitroxyethylamide group has been demonstrated by us previously.[3,4]

The reduction of 4-methoxycarbonylcubane-1-carboxylic acid (**1b**) with sodium borohydride led to 4-hydroxymethylcubane-1-carboxylic acid (**7**) in 88—90% yield, the nitration of that resulted in 4-nitroxymethylcubane-1-carboxylic acid (**8**) (Scheme 2). The choice of a nitration system and reaction conditions was problematic due to intermolecular hydrogen bonds in compound **7** caused by the presence of the carboxylic groups. Good yield of compound **8** (93%) was achieved in the reaction performed at −20 °C with the use of 90—95% nitric acid. Coupling of methyl 4-nitroxymethylcubane-1-carboxylate (**9**) with aminoethanol afforded *N*-(2-hydroxyethyl)-4-nitroxymethylcubane-1-carboxamide (**10**), subsequent nitration of which with 90—95% nitric acid at −10÷−15 °C resulted in the target *N*-(2-nitroxyethyl)-4-nitroxymethylcubane-1-carboxamide (**11**) in 85—90% yield (see Scheme 2).

The structures of the new compounds were established by elemental analysis, IR and NMR spectroscopy and by X-ray diiffraction analysis (compounds **5**, **6**, and **8**).

Scheme 2



The presence of substitutents in positions 1 and 4 of the cubane fragments practically does not affect their geometry, in all four structures it is virtually identical. Molecule **5** (see Fig. 1) has 2/*m* symmetry, in other compounds (see Fig. 2—5) the molecules are located in general position. In the strucrute of **8** (see Fig. 3), the

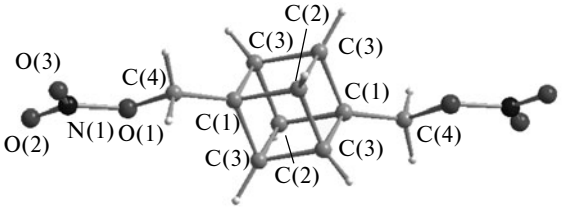


Fig. 1. The structure of compound **5**.

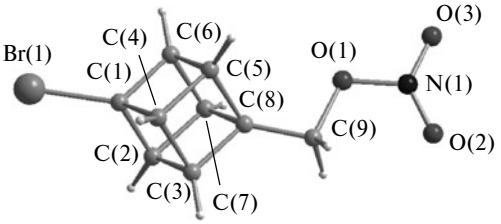


Fig. 2. The structure of compound **6**.

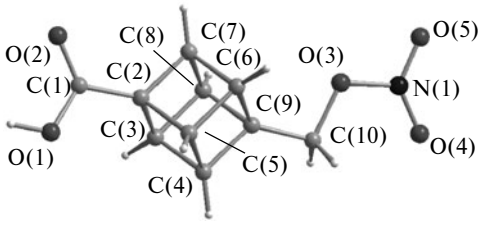


Fig. 3. The structure of compound **8**.

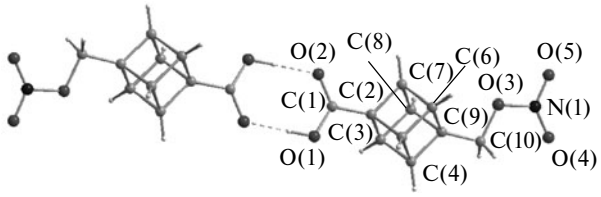


Fig. 4. H-bonded dimers in structure **8**.

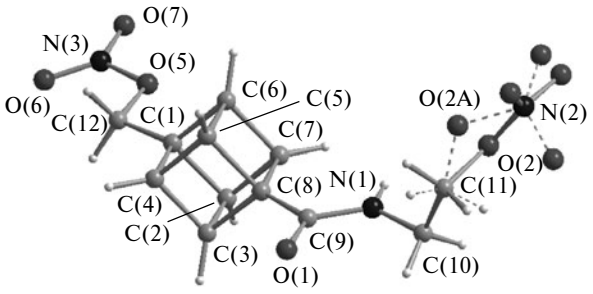


Fig. 5. The structure of compound **11**.

molecules are linked to each other by strong intermolecular hydrogen bonds (O(1)—H...O(2), angle 167°, O...O 2.671(5) Å, H...O 1.76(3) Å) with formation of centrosymmetric dimers (see Fig. 4). In molecule **11** (see Fig. 5), the disordered nitro group N(2)O(3) is linked with the atom C(11) and occupies two equivalent positions with ~0.5 population for the O atoms (O(2)—O(4); O(2a)—O(4a)), and the orientation of these positions is characterized by the torsion angles N(2)—O(2A)—C(11)—C(10) 107.8(12)°; N(2)—O(2)—C(11)—C(10) 168.4(7)°.

Compounds **5**, **6**, and **11** were investigated for antiischemic activity at the National Research Center for the Safety of Biologically Active Compounds (NRC BAC) and showed significant coronary-dilatatory activity. The activity of compound **5** appeared to be equal to that of the well-known cardioprotective drug nicorandil, compound **6** was 2 times as potent as nicorandil, and compound **11** was 5 times as potent as nicorandil.

Experimental

^{1}H (200.13 MHz) and ^{13}C (50.3 MHz) NMR spectra were recorded on a Bruker DPX-200 spectrometer using Me_4Si as the internal standard. IR spectra were recorded on a Specord M 82 spectrometer (KBr pellets).

Compounds **1a,b** and **2—4** were prepared according to decribed methods.[4—6,9] The characteristics of the newly prepared compounds was given in Tables 1 and 2.

Table 1. Elemental analysis data of nitroxymethylcubanes **5—11**

Compound	Molecular formula	Found / Calculated (%)			
		C	H	N	Br
5	$C_{10}H_{10}N_2O_6$	47.13 / 47.25	3.80 / 3.97	11.00 / 11.02	—
6	$C_9H_8O_3BrN$	41.93 / 40.80	3.27 / 3.12	5.60 / 5.43	31.77 / 30.96
7	$C_{10}H_{10}O_3$	66.90 / 67.41	5.75 / 5.66	—	—
8	$C_{10}H_9NO_5$	52.75 / 53.82	3.97 / 4.06	6.10 / 6.28	—
9	$C_{11}H_{11}NO_5$	55.40 / 55.70	4.60 / 4.67	5.90 / 5.90	—
10	$C_{12}H_{14}N_2O_5$	54.40 / 54.13	5.10 / 5.30	10.50 / 10.52	—
11	$C_{12}H_{13}N_3O_7$	47.00 / 46.31	4.10 / 4.21	13.56 / 13.50	—

1,4-Bis(nitroxymethyl)cubane (5). 1,4-Bis(hydroxymethyl)-cubane (**3**) (1 g, 6 mmol) was slowly added to a cooled (0 °C) mixture of 99% HNO_3 (3.8 g, 60 mmol) and Ac_2O (6.1 g, 60 mmol), and the reaction mixture was stirred at this temperature for 30 min. Then it was poured onto crushed ice. The precipitate was filtered off, washed with cold water and 1% $NaHCO_3$ until neutral, dried over P_2O_5, and recrystallized from CCl_4. Yield 1.2 g (80%), m.p. 123—124 °C (decomp.).

Table 2. The spectral characteristics of nitroxymethylcubanes **5—11**

Compound	^{1}H NMR: Solvent	^{1}H NMR: δ (*J*/Hz)	^{13}C {^{1}H} NMR (DMSO-d_6—CCl_4), δ	IR, ν/cm^{-1}
5	CD_2Cl_2	3.89 (s, 6 H, CH); 4.61 (s, 4 H, CH_2ONO_2)	—	1611, 1279, 1274, 883 (ONO_2); 3007, 1325 (CH_{cub}); 2949, 2867, 1377 (CH_2)
6	$CDCl_3$	~4.08 (m, 3 H, CHCCH$_2$ONO$_2$, A-part AA′A″BB′B″, Δν ≈ 28); ~4.21 (m, 3 H, CHCBr, B-part AA′A″BB′B″); 4.65 (s, 2 H, CH_2ONO_2); 3.76 (s, 4 H, CH_2CCl); 3.79 (s, 6 H, CH)	72.81 (s, 1 C, CH_2ONO_2); 63.83 (s, 1 C, CCBr); 54.26 (s, 3 C, CHCBr); 45.83 (s, 3 C, CHCCH$_2$ONO$_2$)*	1624, 1612, 1279, 885 (ONO_2); 820 (C—Br); 2999, 2990, 1318 (CH_{cub}); 2946, 2883, 1448 (CH_2)
7	DMSO-d_6—CCl_4	3.28 (br.s, C(O)OH); 3.50 (d, 2 H, CH_2OH, $^3J_{CH_2OH} \approx 4.0$); 3.76 (m, 3 H, CHCCH$_2$OH, B-part AA′A″BB′B″, $\Delta\nu_{A,B} = 45$); 4.00 (m, 3 H, CHCC(O), A-part AA′A″BB′B″); 4.46 (br.t, 1 H, CH_2OH, $^3J_{CH_2OH} \approx 4.0$)	—	3252, 1000 (OH); 2569, 2511, 1662, 1306, 1226 (COOH); 2990, 1321 (CH_{cub}); 2914, 2861, 1457 (CH_2)
8	DMSO-d_6—CCl_4	~3.93 (m, 3 H, CHCC(O), A-part AA′A″BB′B″, $\Delta\nu_{A,B} \approx 30.0$); ~4.08 (m, 3 H, CHCCH$_2ONO_2$, B-part AA′A″BB′B″, $\Delta\nu_{A,B} \approx 30.0$); 4,72 (s, 2 H, CH_2ONO_2); ~7.00 (br.s, 1 H, C(O)OH)	172.44 (s, 1 C, C(O)); 73.30 (s, 1 C, CH_2ONO_2); 55.87 (s, 1 C, CCH$_2$ONO$_2$); 53.56 (s, 1 C, CC(O)); 45.89 (s, 3 C, CHCCH$_2$ONO$_2$); 44.15 (s, 3 C, CHCC(O)	2900, 2705, 2596, 1678, 1418, 1222 (COOH); 1629, 1274, 865 (ONO_2); 3002, 1315 (CH_{cub}); 2944, 2888, 1456 (CH_2)

(*to be continued*)

Таблица 2 (*continued*)

Compound	^{1}H NMR		^{13}C {^{1}H} NMR (DMSO-d_6—CCl_4), δ	IR, ν/cm^{-1}
	Solvent	δ (*J*/Hz)		
9	DMSO-d_6—CCl_4	3.62 (s, 3 H, OCH_3); 4.03 (m, 6 H, CH, AA´A″BB´B″, $\Delta\nu_{A,B} \approx 37.0$); 4.72 (s, 2 H, CH_2ONO_2)	~170 (s, 1 C, C(O)); 73.13 (s, 1 C, $\underline{CH_2}ONO_2$); 65.36 (s, 1 C, $\underline{C}CH_2ONO_2$); 53.53 (s, 1 C, $\underline{C}C(O)$); 51.06 (s, 1 C, $O\underline{CH_3}$); 45.91 (s, 3 C, $\underline{CH}CCH_2ONO_2$); 44.49 (s, 3 C, $\underline{CH}CC(O)$)	1716, 1209, 1088 [C(O)O]; 1618, 1274, 955, 867 (ONO_2); 3001, 1328 (CH_{cub}); 2949, 2884, 2849, 1451, 1436 (CH_3, CH_2)
10	DMSO-d_6—CCl_4	3.11 (dt, 2 H, $NH\underline{CH_2}CH_2$, $^3J_{CH_2CH_2} \approx {}^3J_{CH_2NH} \approx 6.0$); 3.39 (t, 2 H, $\underline{CH_2}OH$, $^3J_{CH_2CH_2} \approx 6.0$); ~3.87 (m, 3H, CH, A-part AA´A″BB´B″, $\Delta\nu_{A,B} \approx 37.0$); ~4.06 (m, 3H, CH, B-part AA´A″BB´B″, $\Delta\nu_{A,B} \approx 37.0$); ~4.59 (br.s, 1 H, OH); 4.71 (s, 2 H, CH_2ONO_2); 7.61 (br.t, 1 H, C(O)NH, $^3J_{NHCH_2} \approx 6.0$)	170.63 (s, 1 C, C(O)); 73.41 (s, 1 C, $\underline{CH_2}ONO_2$); 59.82 (s, 1 C, $\underline{CH_2}OH$); 57.50 (s, 1 C, $\underline{C}CH_2ONO_2$); 53.25 (s, 1 C, $\underline{C}C(O)$); 45.85 (s, 3 C, $\underline{CH}CCH_2ONO_2$); 44.00 (s, 3 C, $\underline{CH}CC(O)$); 41.26 (s, 1 C, $N\underline{CH_2}$)	3380, 1070 (OH); 3344 pl, 1621, 1534 [C(O)NH]; 1630 pl, 1276, 957, 870, 757 (ONO_2); 3001, 1325 (CH_{cub}); 2949, 2884, 2848, 1433 (CH_2)
11	DMSO-d_6—CCl_4	3.41 (dt, 2 H, $NH\underline{CH_2}CH_2$, $^3J_{CH_2CH_2} \approx {}^3J_{CH_2NH} \approx 5.5$); ~3.89 (m, 3 H, $\underline{CH}CC(O)$, A-part AA´A″BB´B″, $\Delta\nu_{A,B} \approx 34.0$); ~4.06 (m, 3 H, $\underline{CH}CCH_2ONO_2$, B-part AA´A″BB´B″, $\Delta\nu_{A,B} \approx 34.0$); 4.52 (t, 2 H, CH_2ONO_2, $^3J_{CH_2CH_2} = 5.5$); 4.71 (s, 2 H, CH_2ONO_2); 7.99 (br.t, 1 H, C(O)NH, $^3J_{NHCH_2} \approx 5.5$)	170.29 (s, 1 C, C(O)); 73.37 (s, 1 C, $\underline{CH_2}ONO_2$); 72.01 (s, 1 C, $\underline{CH_2}ONO_2$); 57.31 (s, 1 C, $\underline{C}CH_2ONO_2$); 53.34 (s, 1 C, $\underline{C}C(O)$); 45.88 (s, 3 C, $\underline{CH}CCH_2ONO_2$); 44.12 (s, 3 C, $\underline{CH}CC(O)$); 35.93 (s, 1 C, $N\underline{CH_2}$)	1630 pl, 1277, 869 (ONO_2); 3360, 1620, 1522 [C(O)NH]; 3000, 1327 (CH_{cub}); 2944, 2886, 1457, 1417 (CH_2)

* Solvent $CDCl_3$.

4-Bromo-1-nitroxymethylcubane (6). 4-Bromo-1-hydroxymethylcubane (**4**) (2.1 g, 10 mmol) was slowly added to a cooled (0 °C) mixture of 99% HNO_3 (3.2 g, 50 mmol) and Ac_2O (5.1 g, 50 mmol), the mixture was stirred at this temperature for 30 min. Then it was poured onto crushed ice. The precipitate was filtered off, washed with cold water and 1% $NaHCO_3$ until neutral, dried over P_2O_5, and recrystallized from methanol. Yield 2.2 g (87%), m.p. 108—109 °C (decomp.).

4-Hydroxymethylcubane-1-carboxylic acid (7). A suspension of 4-methoxycarbonylcubane-1-carboxylic acid (1.02 g, 5 mmol) (**1b**) in 15 mL of water was added with stirring over 30 min to a cooled (0 °C) solution of $NaBH_4$ (0.84 g, 22 mmol) in 18 mL of water. The reaction mixture was stirred at room temperature for 2 h. The solution was cooled to 0 °C and 3 *M* HCl (7.0 mL) was slowly added with stirring. The precipitate was filtered off, washed with cold water, cold methanol, dried over P_2O_5, and recrystallized from a mixture methanol—ether. Yield 0.78 g (89%), m.p. 200—201 °C (decomp.).

4-Nitroxymethylcubane-1-carboxylic acid (8). Conpound **7** (1 g, 5.6 mmol) was slowly added to a cooled (−20 °C) 91% HNO_3 (8 mL) and the mixture was stirred at this temperature for 30 min. Then the reaction mass was poured onto crushed ice. The precipitate was filtered off, washed with cold water, dried over P_2O_5, and recrystallized from dichloroethane. Yield 0.93 g (93%), m.p. 140 °C (decomp.).

Methyl 4-nitroxymethylcubane-1-carboxylate (9). Compound **8** (1.1 g, 5 mmol) was treated with $SOCl_2$ (10 mL) for 1 h at −20 °C. The excess of $SOCl_2$ was evaporated *in vacuo*. Methanol (10 mL) was added to the freshly prepared acid chloride and the mixture was stirred for 2 h at room temperature. The solvent was evaporated, the solid residue was recrystallized from CCl_4. Yield 1.1 g (94%), m.p. 102—104 °C.

***N*-(2-Hydroxyethyl)-4-nitroxymethylcubane-1-carboxamide (10).** A mixture of compound **9** (1.2 g, 5 mmol) and monoethanolamine (1.5 g) in methanol (20 mL) was stirred at 50 °C for 6 h, then the reaction mixture was cooled to room temperature, methanol and the excess of monoethnolamine was evaporated under reduced pressure. The solid residue was recrystallized from ethanol. Yield 1.0 g (73%), m.p. 124—125 °C.

***N*-(2-Nitroxyethyl)-4-nitroxymethylcubane-1-carboxamide (11).** Compound **10** (0.8 g, 3 mmol) was slowly added to a cooled (−10 °C) 91% HNO_3 (5 mL). The reaction mixture was stirred at this temperature for 30 min and poured onto crushed ice. The precipitate was filtered off, washed with cold water and 1% $NaHCO_3$ until neutral, dried, and recrystallized from CH_2Cl_2. Yield 0.6 g (64%), m.p. 102.5—103 °C (decomp.).

X-ray diffraction study. The experimental X-ray diffraction data for compounds **5** and **8** were collected on an automated Enraf-Nonius Cad-4 diffractometer (graphite monochromator, ω-scanning technique), and for compounds **6** and **11** on an

Table 3. Crystallographic parameters of compounds **5**, **6**, **8**, **11**

Parameter	**5**	**6**	**8**	**11**
Molecular formula	$C_{10}H_8N_2O_6$	$C_9H_8BrNO_3$	$C_{10}H_9NO_5$	$C_{12}H_{13}N_3O_7$
Molecular weight	252.18	258.07	223.18	311.25
T/K	296(2)	110(2)	296(2)	296(2)
Crystal system	Rhombic	Monoclinic	Monoclinic	Monoclinic
Space group	*Cmca*	$P2(1)/n$	$P2(1)/c$	$P2/c$
a/Å	6.178(3)	8.5212(19)	5.9760(10)	15.9757(12)
b/Å	10.362(4)	11.462(3)	9.995(2)	5.2872(4)
c/Å	17.307(8)	9.867(2)	16.517(3)	16.3633(12)
α/deg	90	90	90	90
β/deg	90	109.846(5)	100.07(3)	101.794(2)
γ/deg	90	90	90	90
V/Å^3	1107.9(9)	906.5(4)	971.4(3)	1352.97(18)
Z	4	4	4	4
d_{calc}/g cm^{-3}	1.512	1.891	1.526	1.528
μ/mm^{-1}	0.128	4.512	0.125	0.128
Radiation λ (MoKα)	0.71073	0.71073	0.71073	0.71073
Number of measured reflections	882	4854	3086	2437
Number of reflections with $I > 2\sigma(I)$	605	1853	1990	1721
R_1	0.0483	0.0381	0.0543	0.0584
wR_2	0.2059	0.0954	0.2072	0.1923

automated Bruker AXS SMART diffractometer equipped with a CCD detector (graphite monochromator, ω-scanning technique with a step of 0.3°, exposure time per frame was 30 s) using a standard procedure.[10] The structures of compounds were solved by direct method and refined by the full-matrix least-squares method with anisotropic displacement parameters for all non-hydrogen atoms. The hydrogen atoms were located in the difference Fourier maps and refined isotropically using the riding model. The calculations were carried out using the program package.[11,12]

The crystallographic parameters and the main refinement statistics for compounds **5**, **6**, **8**, **11** are given in Table 3.

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