

## Lagoden dimethylformamide hemisolvate dihydrate: absolute configuration, dipolar interactions and hydrogen-bonding interactions

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Received 29 July 2009

Accepted 22 August 2009

Online 5 September 2009

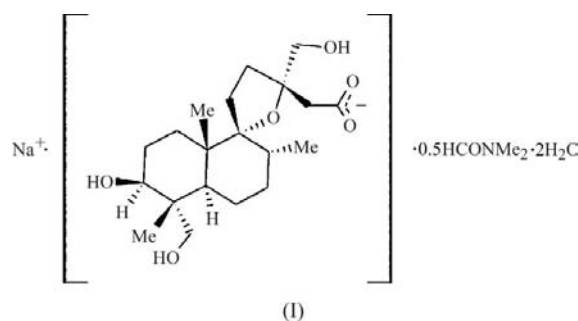
Lagoden ( $L \cdot 3H_2O$ , where  $L$  is  $Na^+ \cdot C_{20}H_{33}O_6^-$ ; sodium  $3\beta,16,18$ -trihydroxy- $8,13$ -*epi*- $9,13$ -epoxylabdan- $15$ -oate trihydrate) is widely used as an effective haemostatic agent. It has been crystallized from dimethylformamide (DMF) as sodium  $3\beta,16,18$ -trihydroxy- $8,13$ -*epi*- $9,13$ -epoxylabdan- $15$ -oate dimethylformamide hemisolvate dihydrate,  $Na^+ \cdot C_{20}H_{33}O_6^- \cdot 0.5C_3H_7NO \cdot 2H_2O$  or  $L_2 \cdot DMF \cdot 4H_2O$ , and the asymmetric unit contains two of the latter formulation. The four symmetry-independent  $Na^+$  cations and lagoden anions, one DMF molecule and six of the eight symmetry-independent water molecules assemble into a one-dimensional polymeric structure *via* dipolar and hydrogen-bonding interactions. The lagoden anions coordinate to the  $Na^+$  cations *via* the carboxylate groups and the two primary hydroxy groups, whereas the secondary OH groups are solely involved in hydrogen bonding. Two of the four symmetry-independent lagoden anions act in a chelating mode, forming seven-membered chelate rings. The absolute structure, based on anomalous dispersion data collected at 130 K with Cu  $K\alpha$  radiation, confirms an inverted configuration at chiral centres C8 and C13 (labdane numbering) relative to the labdane skeleton.

### Comment

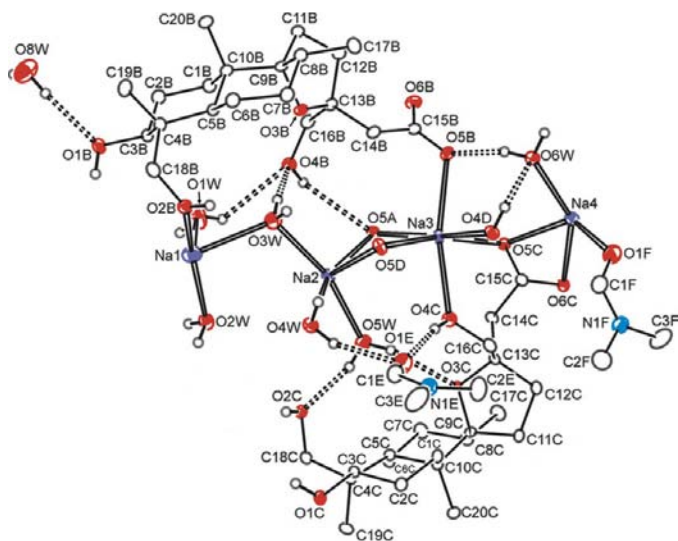
Plants of the *Lagochilus* genus (family Lamiaceae), native to Central Asia and the Middle East, have long been used in traditional medicine and are reputed to possess anti-haemorrhagic and haemostatic properties. The components responsible for these effects are labdane-type diterpenoids, many of which have been isolated from these plants and have shown haemostatic properties. Lagoden is a synthetic derivative of the naturally occurring diterpenoid lagochirsin (Zainutdinov *et al.*, 1994), which has been isolated from three

plants, *viz.* *L. gypsaceus*, *L. hirsutissimus* and *L. setulosus*. It has been developed and approved for public use in Russia, Uzbekistan and some other former Soviet republics. Lagoden is produced as a white crystalline powder that is odourless and nonhygroscopic, and is sold as a 0.5% water solution in ampoules for internal introduction.

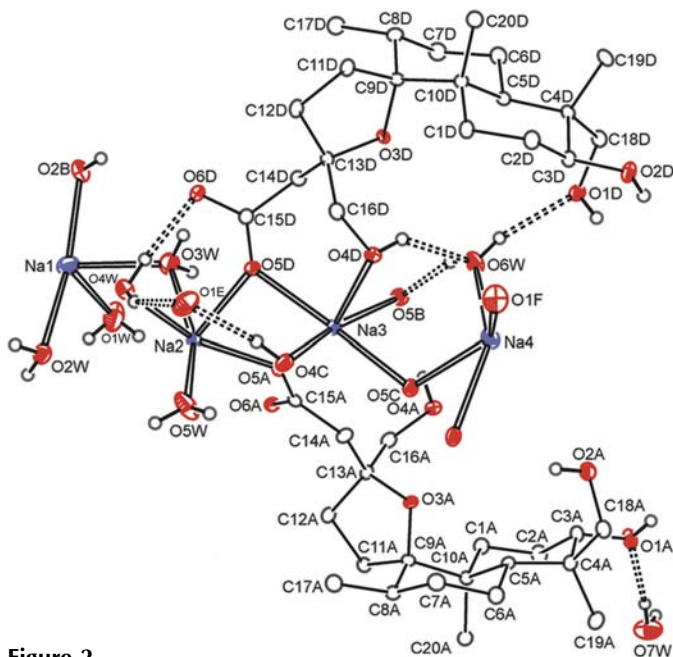
The crystal structures of lagochilin in its anhydrous and hydrated forms (Izotova *et al.*, 1997; Vorontsova *et al.*, 1975), lagochirsin (Izotova *et al.*, 2004) and several other labdane-type diterpenoids isolated from plants of the *Lagochilus* genus, or their derivatives, have been reported over the years (Talipov *et al.*, 2001; Izotova *et al.*, 2000; Zainutdinov *et al.*, 1999). Recently, we succeeded in growing single crystals of lagoden from a dimethylformamide (DMF) solution and we report its crystal structure here as the title compound, (I). Owing to the presence of  $Na^+$  ions, the absolute structure of (I) could be determined reliably using Cu  $K\alpha$  radiation.



Single crystals of lagoden proved very difficult to grow, despite many attempts over a long period. In most cases, crystallizations resulted in amorphous glassy materials, but from a water–*n*-butanol mixture well shaped thin plates could be obtained repeatedly, although they diffracted very poorly. Serendipitously, a large prism of compound (I) was found in a small-scale crystallization from a DMF solution that had been left unattended for several months. The structure was initially determined at 100 K using Mo  $K\alpha$  radiation. As revealed by X-ray analysis, this crystal was a pseudomerohedral twin, with a twin law corresponding to a  $180^\circ$  rotation about the direct-space [100] direction (the twin matrix in reciprocal space is  $100/0\bar{1}0/-0.991,0,\bar{1}$ ). The structure refined well, revealing most of the important features of the crystal structure except the absolute configuration of lagoden, which was one of the objectives of the X-ray analysis. The anomalous signal originating mostly from Na ( $\Delta f'' = 0.025$ ) and O atoms ( $\Delta f'' = 0.006$ ) was too weak for reliable absolute structure determination, as reflected by the high s.u. value of the Flack parameter [ $x = 0.1$  (3); Flack, 1983]. Nevertheless, we noticed that the enantiomer indicated by the Flack parameter as the most probable had the expected chirality, with the C5, C9 and C10 centres corresponding to those of labdane, and the stereochemistry of the C8 and C13 centres being inverted. The Hooft parameter  $\gamma$  (Hooft *et al.*, 2008) for this enantiomerically pure crystal was 0.25 (9). As the anomalous dispersions of Na ( $\Delta f'' = 0.124$ ) and O ( $\Delta f'' = 0.032$ ) are significantly stronger

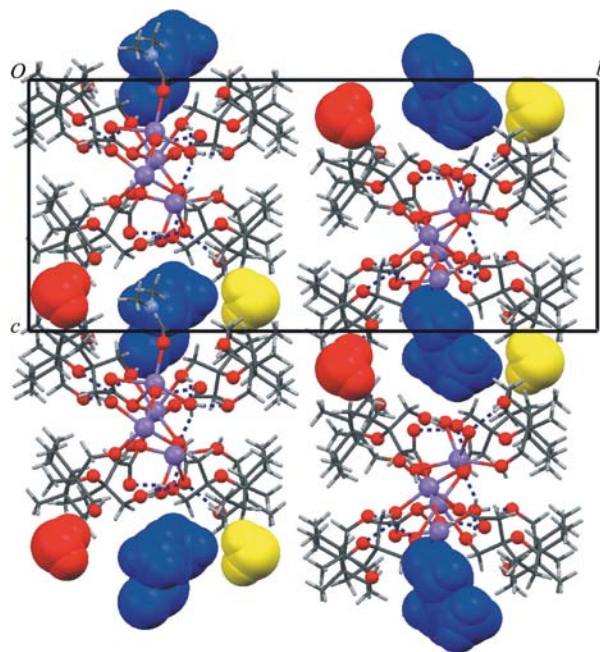


**Figure 1**  
The asymmetric unit of compound (I), with ligands *A* and *D* and water molecule *O7W* omitted. Displacement ellipsoids are drawn at the 40% probability level. C-bound H atoms have been omitted. Double-dashed lines represent hydrogen bonds.



**Figure 2**  
The asymmetric unit of compound (I), with ligands *B* and *C*, the DMF molecule and water molecule *O8W* omitted. Displacement ellipsoids are drawn at the 40% probability level. C-bound H atoms have been omitted. Double-dashed lines represent hydrogen bonds.

for Cu  $K\alpha$  radiation, the measurements were repeated with an Oxford Diffraction Nova Cu  $K\alpha$  source with a small single crystal cut from the twinned specimen. The Flack parameter  $x = 0.03$  (3) and the Hooft parameter  $y = 0.030$  (8) for Cu  $K\alpha$  radiation indicated that the configurations of the C8 and C13 chiral centres of lagoden are *R* and *S*, respectively, and that the remaining centres correspond to the labdane stereochemistry. This feature is typical of all known structurally characterized

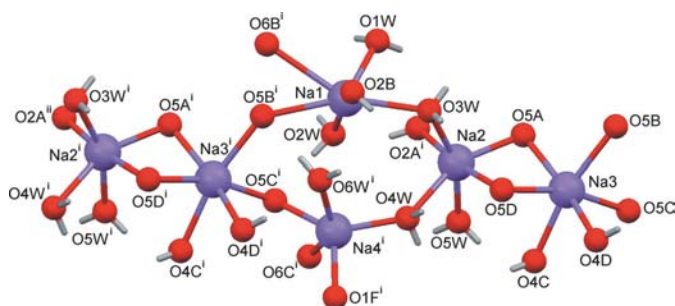


**Figure 3**  
The crystal packing of compound (I), viewed along the *a* axis. Solvent molecules are represented by van der Waals radii and small spheres represent Na, O and N atoms.

diterpenoids of the *Lagochilus* genus, including its most popular member lagochilin.

The asymmetric unit of compound (I) is shown in Figs. 1 and 2. It consists of four  $\text{Na}^+$  cations, four carboxylate anions, one DMF molecule and six water molecules coordinating to the  $\text{Na}^+$  ions, and three solvent molecules (one DMF and two water). The numbering scheme of the diterpenoid follows the IUPAC recommendation for the labdane skeleton (IUPAC Commission on Nomenclature of Organic Compounds, 1999). The four diterpenoid anions (*A*, *B*, *C* and *D*) exhibit similar conformations, with the largest differences found in the region of the spiro tetrahydrofuran ring and its substituents at C13. Analysis of the endocyclic torsion angles of the five-membered ring indicates a twist form, with the twist axis through atom O3 of the furanoid ring. The methyl substituents on the ring system at C4 and C10 are positioned axially, whereas the O1 hydroxy group and the C17 methyl group are in equatorial positions.

All of the symmetry-independent  $\text{Na}^+$  cations and lagoden anions, and some of the neutral ligands (one DMF and six water molecules) are assembled *via* dipolar interactions [ $\text{Na}-\text{O}$  distances in the range 2.2610 (16)–2.9399 (15) Å; Table 1] and  $\text{O}-\text{H}\cdots\text{O}$  hydrogen bonds (Table 2) into a one-dimensional polymeric structure propagating along the *a* axis. The hydrophobic parts of the diterpenoid cover the polymer surface on two opposite sides, leaving deep grooves on the remaining two sides. Adjacent polymeric chains along the *c* axis are bridged by the two remaining symmetry-independent water molecules, *viz.* *O7W* and *O8W*, which are involved as donors in  $\text{O}-\text{H}\cdots\text{O}$  hydrogen bonds to the secondary O1 hydroxy groups of the four symmetry-independent anions. In



**Figure 4**  
A view of the  $\text{Na}^+$  cations, together with the coordinating groups [symmetry codes: (i)  $x - 1, y, z$ ; (ii)  $x - 2, y, z$ .]

effect, the grooves on opposite sides of the polymer meet to form a channel accommodating both the coordinated and hydrogen-bonded DMF molecules (Fig. 3).

The  $\text{Na}^+$  cations and their coordinating groups are shown in Fig. 4. The coordination environments of Na2 and Na3 are distorted octahedral, with carboxylate atoms O5D and O5A bridging the two metal centres. Na3 has in its coordination environment exclusively O atoms from four symmetry-independent lagoden anions, whereas Na2 has three water molecules and O atoms from anions A and D. These two  $\text{Na}^+$  ions, together with Na1 and Na4, carboxylate atoms O5C and O5B, and the water molecules O3W and O4W, form a cyclic  $\text{Na}_4\text{O}_4$  structure (Fig. 4). Na1 and Na4 are basically penta-coordinated, with Na1 additionally including in its coordination environment atom O6B from the asymmetrically chelating carboxylate group of anion B [Na1—O6B( $x - 1, y, z$ ) = 2.9399 (15) Å]. The closest distances between the  $\text{Na}^+$  ions along the polymeric chain are 3.4807 (8) Å within the  $\text{Na}_2\text{O}_2$  cyclic structures and 3.9845 (9) Å in the  $\text{Na}_4\text{O}_4$  ring. The Na—O—Na angles at the bridging O atoms range from 94.48 (5)° in the smaller ring up to 138.21 (6)° in the eight-membered cycle.

Lagoden anions C and D act as chelating ligands by coordinating Na3 *via* a carboxylate O atom and the primary hydroxyl group at C16. The seven-membered chelate rings that are formed are strongly puckered. The other two ligands coordinate to  $\text{Na}^+$  cations *via* a carboxylate group and the primary hydroxy group at C18. The coordination mode of the carboxylate groups of ligands B and C is asymmetric chelating and bridging, whereas in the remaining cases it is only bridging. The secondary OH groups at C3 do not interact with the  $\text{Na}^+$  ions but act as donors in O—H...O hydrogen bonds to carboxylate groups within the same polymeric structure, and as acceptors of hydrogen bonds from water molecules that bridge adjacent polymeric chains *via* O—H...O interactions (Table 2).

## Experimental

Lagoden (Zainutdinov *et al.*, 1994) (1.2 mg) was dissolved in DMF (1 ml) and placed in a 1.5 ml closed plastic vial. After approximately three months, one colourless prism-shaped crystal of (I) was obtained.

## Crystal data

$\text{Na}^+ \cdot \text{C}_{20}\text{H}_{33}\text{O}_6^- \cdot 0.5\text{C}_3\text{H}_7\text{NO} \cdot 2\text{H}_2\text{O}$	$V = 4594.32 (15) \text{ \AA}^3$
$M_r = 465.04$	$Z = 8$
Monoclinic, $P2_1$	Cu $K\alpha$ radiation
$a = 10.7614 (2) \text{ \AA}$	$\mu = 1.01 \text{ mm}^{-1}$
$b = 31.0703 (5) \text{ \AA}$	$T = 130 \text{ K}$
$c = 14.7131 (3) \text{ \AA}$	$0.3 \times 0.2 \times 0.2 \text{ mm}$
$\beta = 110.948 (2)^\circ$	

## Data collection

Oxford Diffraction SuperNova diffractometer	70056 measured reflections
Absorption correction: multi-scan (CrysAlis Pro; Oxford Diffraction, 2009)	18050 independent reflections
$T_{\min} = 0.655, T_{\max} = 0.818$	17865 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.030$

**Table 1**

Selected bond lengths (Å).

Na1—O2B	2.3488 (16)	Na3—O5D	2.3479 (12)
Na1—O1W	2.3917 (18)	Na3—O5C	2.3640 (12)
Na1—O2W	2.4151 (16)	Na3—O5A	2.4036 (13)
Na1—O3W	2.5605 (16)	Na3—O4C	2.5108 (14)
Na1—O5B <sup>i</sup>	2.6656 (14)	Na3—O4D	2.5130 (13)
Na1—O6B <sup>i</sup>	2.9399 (15)	Na3—O5B	2.5358 (14)
Na2—O5A	2.2860 (12)	Na4—O1F	2.2610 (16)
Na2—O5W	2.3124 (16)	Na4—O4W <sup>ii</sup>	2.2782 (14)
Na2—O2A <sup>i</sup>	2.3841 (13)	Na4—O6W	2.3304 (15)
Na2—O5D	2.3928 (13)	Na4—O5C	2.3856 (13)
Na2—O3W	2.4779 (15)	Na4—O6C	2.4619 (14)
Na2—O4W	2.5377 (14)		

Symmetry codes: (i)  $x - 1, y, z$ ; (ii)  $x + 1, y, z$ .

**Table 2**

Hydrogen-bond geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O2A—H2OA...O2W <sup>ii</sup>	0.82	2.14	2.8513 (17)	145
O1A—H1A...O6A <sup>ii</sup>	0.82	1.98	2.7797 (16)	166
O4A—H4A...O6B	0.82	1.89	2.7066 (17)	173
O2B—H2OB...O2D <sup>i</sup>	0.82	1.99	2.7717 (17)	160
O1B—H1B...O6B <sup>i</sup>	0.82	2.02	2.8395 (18)	174
O4B—H4B...O6A	0.82	1.84	2.6347 (16)	164
O2C—H2OC...O6C <sup>i</sup>	0.82	2.03	2.8200 (17)	162
O1C—H1C...O6C <sup>i</sup>	0.82	2.02	2.8198 (17)	165
O4C—H4OC...O1E	0.82	1.94	2.7494 (18)	169
O2D—H2OD...O6D <sup>ii</sup>	0.82	1.90	2.6949 (17)	162
O1D—H1D...O6D <sup>ii</sup>	0.82	2.06	2.8563 (17)	166
O4D—H4OD...O6W	0.82	2.14	2.8013 (17)	138
O1W—H1W1...O4A <sup>i</sup>	0.85	1.97	2.717 (2)	146
O2W—H2W1...O3A <sup>i</sup>	0.85	2.25	3.0748 (17)	163
O2W—H2W1...O4A <sup>i</sup>	0.85	2.57	3.1303 (18)	125
O2W—H2W2...O5C <sup>i</sup>	0.85	1.94	2.7856 (17)	176
O3W—H3W1...O4B	0.85	1.95	2.7824 (18)	166
O4W—H4W1...O6D	0.85	1.96	2.8022 (18)	169
O4W—H4W1...O5D	0.85	2.55	3.0552 (16)	119
O4W—H4W2...O1E	0.85	2.11	2.9033 (19)	156
O5W—H5W1...O4C	0.85	2.22	2.8571 (19)	131
O5W—H5W1...O3C	0.85	2.50	3.2706 (18)	152
O5W—H5W2...O2C	0.85	2.00	2.8224 (18)	163
O6W—H6W2...O2D	0.85	2.13	2.9575 (17)	163
O6W—H6W1...O5B	0.85	2.00	2.7872 (17)	154
O7W—H7W1...O1A	0.85	2.09	2.9366 (19)	175
O7W—H7W2...O1C <sup>iii</sup>	0.85	2.11	2.9577 (19)	175
O8W—H8W2...O1B	0.85	2.17	3.023 (2)	176
O8W—H8W1...O1D <sup>iv</sup>	0.85	2.19	3.027 (2)	171

Symmetry codes: (i)  $x - 1, y, z$ ; (ii)  $x + 1, y, z$ ; (iii)  $x + 1, y, z - 1$ ; (iv)  $x - 2, y, z - 1$ .

## Refinement

$$R[F^2 > 2\sigma(F^2)] = 0.032$$

$$wR(F^2) = 0.086$$

$$S = 1.03$$

18050 reflections

1143 parameters

1 restraint

H-atom parameters constrained

$$\Delta\rho_{\max} = 0.55 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.29 \text{ e } \text{\AA}^{-3}$$

Absolute structure: Flack (1983),

with 8192 Friedel pairs

Flack parameter: 0.03 (3)

C-bound H atoms were placed in idealized positions, with C–H = 0.93–0.98 Å. O-bound H atoms were located in difference electron-density maps and refined with distance restraints of O–H = 0.82 (2) Å for hydroxy groups and 0.85 (2) Å for water molecules. The H···H distances in the water molecules were restrained to 1.35 (2) Å. In the final cycles of refinement, all the H atoms were treated as riding on their parent atoms, with  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}, \text{O})$ .

Data collection: *CrysAlis Pro* (Oxford Diffraction, 2009); cell refinement: *CrysAlis Pro*; data reduction: *CrysAlis Pro*; program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SU3037). Services for accessing these data are described at the back of the journal.

## References

- Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., De Caro, L., Giacovazzo, C., Polidori, G. & Spagna, R. (2005). *J. Appl. Cryst.* **38**, 381–388.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.
- Hooft, R. W. W., Straver, L. H. & Spek, A. L. (2008). *J. Appl. Cryst.* **41**, 96–103.
- IUPAC Commission on Nomenclature of Organic Compounds (1999). *Revised Section F: Natural Products and Related Compounds*, World-Wide Web version by G. P. Moss. URL: <http://www.chem.qmul.ac.uk/iupac/sectionF/>.
- Izotova, L. Y., Beketov, K. M., Talipov, S. A. & Ibragimov, B. T. (1997). *Pol. J. Chem.* **71**, 1037–1044.
- Izotova, L. Y., Talipov, S. A., Ibragimov, B. T., Bekbulatova, B. & Zainutdinov, U. N. (2000). *Chem. Nat. Compd USSR*, **36**, 181–184.
- Izotova, L. Y., Talipov, S. A., Ibragimov, B. T., Bekbulatova, B. & Zainutdinov, U. N. (2004). *Chem. Nat. Compd USSR*, **40**, 484–487.
- Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.
- Oxford Diffraction (2009). *CrysAlis Pro*. Oxford Diffraction Ltd, Yarnton, Oxfordshire, England.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.
- Talipov, S. A., Izotova, L. Y., Bekbulatova, B., Ibragimov, B. T., Islamov, R. & Zainutdinov, U. N. (2001). *Chem. Nat. Compd USSR*, **37**, 322–325.
- Vorontsova, L. G., Chizhov, O. S., Tarnopolskii, B. L. & Andrianov, V. I. (1975). *Latv. PSR Zinat. Akad. Vestis Kim. Ser.* **2**, 338–343.
- Zainutdinov, U. N., Khaitboev, K., Safaev, M. A., Isalnov, R. & Aslanov, K. A. (1994). *Chem. Nat. Compd USSR*, **30**, 31–32.
- Zainutdinov, U. N., Talipov, S. A., Kamaev, F. G., Ibragimov, B. T., Izotova, L. Y., Bekbulatova, B. & Safaev, M. A. (1999). *Chem. Nat. Compd USSR*, **35**, 308–313.